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ReMAPping the Microtubule Landscape: How Phosphorylation Dictates the Activities of Microtubule-Associated Proteins

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Abstract

Classical microtubule associated proteins (MAPs) were originally identified based on their co-purification with microtubules assembled from mammalian brain lysate. They have since been found to perform a range of functions involved in regulating the dynamics of the microtubule cytoskeleton. Most of these MAPs play integral roles in microtubule organization during neuronal development, microtubule remodeling during neuronal activity, and microtubule stabilization during neuronal maintenance. As a result, mutations in MAPs contribute to neurodevelopmental disorders, psychiatric conditions, and neurodegenerative diseases. MAPs are post-translationally regulated by phosphorylation depending on developmental time point and cellular context. Phosphorylation can affect the microtubule affinity, cellular localization, or overall function of a particular MAP and can thus have profound implications for neuronal health. Here we review MAP1, MAP2, MAP4, MAP6, MAP7, MAP9, Tau and DCX, and how each is regulated by phosphorylation in neuronal physiology and disease.

Keywords

Kinases; cytoskeleton; neuronal development; neurodegeneration

INTRODUCTION

Neuronal development and function is governed by the underlying architecture of the cytoskeleton, which includes the microtubule, actin and intermediate filament networks. The microtubule cytoskeletal network is organized into stable and dynamic arrays that provide structural support, serve as tracks for molecular motor transport, and function as signaling platforms during neuronal development and plasticity (Keating and Borisy, 1999; Bartolini and Gundersen, 2006; Witte and Bradke, 2008; Hoogenraad and Bradke, 2009; Stiess et al., 2010; Dent and Baas, 2014). It is therefore essential to understand the regulatory mechanisms of microtubule cytoskeleton organization as a neuron develops, changes, or maintains its internal structure, because altering these processes can disrupt neuronal function and ultimately lead to pathological conditions (Kaufmann and Moser, 2000; Jan and Jan, 2010). For example, mutations in proteins affecting the assembly of microtubules can lead to neurodevelopmental disorders such as Lissencephaly (Pilz et al., 1998; Viot et

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al., 2004; Tsai et al., 2016), mutations in proteins involved in the remodeling of the microtubule cytoskeleton are correlated with neuropsychiatric disorders such as schizophrenia (Arnold et al., 1991; Cotter et al., 2000; Somenarain and Jones, 2010), and mutations in proteins important for microtubule stability or microtubule-based transport can cause neurodegenerative pathologies, such as motor neuron disease and Alzheimer's disease (Tolnay and Probst, 1999; Lewczuk et al., 2004; Harms et al., 2012). Therefore, the precise regulation of the microtubule cytoskeleton is critical for neuronal health at all stages of life.

Microtubules are composed of alpha- and beta-tubulin heterodimers that assemble into protofilaments, which then form lateral contacts with one another to form a tubule (Borisy et al., 1974; Kirschner et al., 1974; Olmsted and Borisy, 1975; Downing and Nogales, 1998). Both alpha and beta-tubulin bind, but only beta-tubulin hydrolyzes, GTP. Beta-tubulin must be in the GTP-bound state in order for the heterodimer to assemble onto a protofilament. Once assembled, beta-tubulin is exposed at the "plus end" and alpha-tubulin is exposed at the "minus end". This structural polarity results in growth rate differences of each end, and it has been observed that the plus end grows much more rapidly than the minus end both in vivo and in vitro (Howard and Hyman, 1993; Howard and Hyman, 2003; Bieling et al., 2007; Bieling et al., 2010). Microtubules can be remodeled within the cell by switching between states of assembly and disassembly in a process known as dynamic instability (Mitchison and Kirschner, 1984). There are numerous microtubule associated proteins (MAPs) that can bind the microtubule lattice, tubulin heterodimers, or both, and regulate these dynamics to properly organize and remodel the microtubule cytoskeleton during neuronal development and activity (Papasozomenos et al., 1985; Caceres and Kosik, 1990; Bulinski et al., 1997; Gleeson et al., 1999a; Gordon-Weeks and Fischer, 2000; Volle et al., 2013; Tymanskyj et al., 2017).

Different types of MAPs perform various functions. Proteins that associate with the growing plus end of the microtubule, or plus-end tracking proteins (+TIP s), regulate microtubule growth and catastrophe (reviewed in (Akhmanova and Steinmetz, 2010)). There are also proteins that associate with the minus ends of the microtubule and protect them from depolymerization (Goodwin and Vale, 2010; Jiang et al., 2014). Many MAPs are molecular motors that utilize the energy of nucleotide hydrolysis to produce force along microtubule, including the long-distance transport motors, cytoplasmic dynein and kinesin-1, the microtubule sliding motors, kinesin-5 and −12, and microtubule depolymerizing or severing proteins, such as mitotic centrosome-associated kinesin (MCAK), spastin, and katanin (Andersen and Wittmann, 2002; Vale, 2003; Walczak, 2003; Myers and Baas, 2007; Roll-Mecak and McNally, 2010; Vallee et al., 2012). There are also tubulin-modifying enzymes that exert control over many aspects of microtubule biology through post-translational modification of alpha and beta-tubulin (reviewed in (Verhey and Gaertig, 2007; Janke and Bulinski, 2011; Yu et al., 2015)). Finally, there are structural or classical MAPs that bind along the microtubule lattice and have various effects on microtubule polymerization, stability, and bundling (Figure 1 and Figure 2) (Vallee and Borisy, 1978). Many of these MAPs are abundantly expressed in the nervous system and some may have overlapping roles within neurons in order to maintain the microtubule cytoskeletal architecture (Baas et al., 2016).

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Microtubule organization within cells can be governed by the association and dissociation of different MAPs that can have opposing or synergistic activities (Heins et al., 1991; Vandecandelaere et al., 1996; McNally et al., 2002; Szebenyi et al., 2005). It is well documented that the interaction of MAPs with the microtubule cytoskeleton is affected by posttranslational modifications (Drewes et al., 1997). In particular, the phosphorylation state of MAPs can have a pronounced effect on microtubule dynamics, and subtle changes in MAP phosphorylation patterns accompany major rearrangements of the microtubule network during neuronal outgrowth, differentiation, and plasticity (Table 1 and Figure 2) (Ikegami et al., 2000; Biernat et al., 2002; Szebenyi et al., 2005). This review focuses on the known kinase regulators of classical MAPs and the downstream effect these modifications have on the microtubule cytoskeleton during neuronal development and maintenance. We also review how phosphorylation of tubulin heterodimers can directly affect microtubule dynamics.

MAP1 FAMILY (MAP1A, MAP1B, MAP1S)

The MAP1 family members were originally identified as high molecular weight protein complexes, consisting at least one heavy chain and one light chain, that co-purified with microtubules prepared from mammalian brain lysate, and were predominantly enriched in brain white matter (Kuznetsov et al., 1981; Vallee, 1982; Bonifacino et al., 1985). All MAP1 subtypes are expressed in the nervous system, where they function in neuronal development and overall maintenance (Hanley et al., 1999; Meixner et al., 2000). Each of the MAP1 complexes are composed of a heavy chain and at least one light chain, which can modulate their interactions with microtubules and actin, among other intracellular partners (Noiges et al., 2002).

MAPlA is expressed abundantly throughout development and into adulthood, where it is enriched specifically in dendrites (Fink et al., 1996). MAP1B is highly expressed during neuronal development where it is localized to axons, then expression decreases after neuronal differentiation, but increases again in adulthood where MAP1B has both dendritic and axonal functions (Kutschera et al., 1998; Gonzalez-Billault et al., 2001; Bodaleo et al., 2016). The shortest and least studied MAP1 member, MAP1S, is expressed in a variety of tissues including the brain, liver, spleen, heart and other organs (Orban-Nemeth et al., 2005), and recent studies indicate that it is involved in cell division, autophagy and phagocytosis (Eriksson et al., 2007; Xie et al., 2011a; Xie et al., 2011b; Liu et al., 2012c; Tegha-Dunghu et al., 2014).

All three MAP1 proteins, MAP1A, MAP1B and MAP1S, associate with both microtubules and actin (Noiges et al., 2002; Tegha-Dunghu et al., 2014). The heavy chains of MAP1A and MAP1B have either one or two microtubule binding domains, respectively. The light chains for MAP1A, MAP1B and MAP1S contain non-overlapping microtubule and actin binding domains, and it is speculated that MAP1 proteins can simultaneously bind and crosslink microtubules and actin (Noiges et al., 2002; Halpain and Dehmelt, 2006). All MAP1 proteins bind the microtubule lattice and are thought to stabilize microtubules (Vandecandelaere et al., 1996; Bondallaz et al., 2006; Tegha-Dunghu et al., 2014; Liu et al., 2015).

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The role of MAP1A in dendrites during neuronal development and maintenance has been studied extensively. Not only is MAP1A important for dendritic outgrowth and morphology, but it is also essential in remodeling the dendritic arbor in response to neuronal activity (Szebenyi et al., 2005; Liu et al., 2015). MAP1A localizes to excitatory synapses where it transiently interacts with post-synaptic density proteins, PSD-93 and PSD95, and is important for the localization of NMDA receptors (Brenman et al., 1998; Ikeda et al., 2002; Takei et al., 2015). As a result of its role at synapses, MAP1A knockout mice exhibit learning and memory defects with impaired long-term potentiation and long-term depression (Takei et al., 2015). A mouse model with *MAP1A* mutations develops ataxia, tremors, and late-onset degeneration of Purkinje neurons (Liu et al., 2015). MAP1A has a number of other interacting partners that it may tether to the microtubule or actin cytoskeletons, including calcium and potassium channels, indicating that loss of MAP1A could cause a number of neurological abnormalities depending on neuronal cell type. For a comprehensive review of MAP1A, MAP1B and MAP1S function and interacting partners, please refer to Halpain and Delnert (2006).

As expected based on its expression and localization patterns, knockdown of MAP1B inhibits both axon outgrowth and dendritic spine formation (Riederer, 2007; Tortosa et al., 2011). Intriguingly, deletion of the *MAP1B* gene region results in the absence of corpus callosum, along with other defects in neuronal migration and neuronal activity (Meixner et al., 2000). In regenerating adult mouse dorsal root ganglion neurons, knockdown of MAP1B results in enhanced axonal branching, but impaired axonal turning behavior (Bodaleo et al., 2016). MAP1B therefore has distinct roles in microtubule-based processes, such as neuronal migration and growth cone turning, and actin-based processes, such as dendritic spine maturation. Considering MAP1B interacts either directly or indirectly with numerous neurotransmitter receptors, including GABAc, NMDA, AMPA, and mGluR, receptor regulatory proteins, and various channels, it is unsurprising that it has been implicated in a variety of neurological diseases including Parkinson’s disease (Chan et al., 2014; Shah and Lahiri, 2017), Alzheimer’s Disease (Ulloa et al., 1994; Good et al., 2004; Gevorkian et al., 2008), and schizophrenia (Davidkova and Carroll, 2007; Lebeau et al., 2011; Tortosa et al., 2011; Benoist et al., 2013). Whether MAP1B acts an anchor for these proteins to either the actin or the microtubule cytoskeletons, or whether it is involved in the proper transport and localization of these proteins remains to be more fully elucidated.

MAP1S appears to have roles during mitosis and autophagy. MAP1S decorates the mitotic spindle and knockdown of MAP1S results in the formation of an unstable metaphase plate, leading to improper chromatid separation and mitotic defects (Dallol et al., 2007; Liu et al., 2012c; Tegha-Dunghu et al., 2014). As a result, although MAP1S knockout mice do not manifest any developmental or behavioral phenotypes, they are at a higher risk to develop cancer (Xie et al., 2011b). Furthermore, MAP1S plays a role in suppressing tumorigenesis in mouse cancer models and in pancreatic cancer patients (Liu et al., 2012c). It has been shown that MAP1S also positively regulates autophagy from biogenesis to degradation via its interaction with LC3 (Liu et al., 2012c), and may facilitate the interaction between autophagosomes and damaged mitochondria as well (Xie et al., 2011a).

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MAP1A and MAP1B are regulated by phosphorylation, but there is little known about the post-translational regulation of MAP1S (Halpain and Dehmelt, 2006). It has been shown that MAP1A can be activated through the mitogen-activated protein kinase (MAPK) pathway during dendritic remodeling, but whether MAP1A is phosphorylated during this process is unknown (Szebenyi et al., 2005). Dual-specificity tyrosine phosphorylated-regulated kinase-1a (DYRK1a) phosphorylates MAP1A and MAP2 and causes their release from clathrin-coated vesicles, but the effect on microtubule binding has not been assessed (Murakami et al., 2012). In addition, it is unknown why MAP1A and MAP2 are associated with clathrin-coated vesicles. There are three potential DYRK1a phosphorylation sites in MAP1A (Thr2059, Ser2221, and Ser2546) based on the consensus sequence for DYRK1a, but none have been confirmed as direct targets of DYRK1a.

MAP1B is a target for phosphorylation by a number of different kinases (Tymanskyj et al., 2010). Phosphorylated MAP1B is highly enriched in growing axons while non-phosphorylated MAP1B is present in the somatodendritic compartment (Sato-Yoshitake et al., 1989; Riederer et al., 1993; Gordon-Weeks and Fischer, 2000; Riederer, 2007). Glycogen synthase kinase III β (GSKIIIβ) has been shown to phosphorylate MAP1B at Ser1260 and Thr1265 in growing axons, especially in the distal growth cone (Goold et al., 1999; Goold and Gordon-Weeks, 2003; Trivedi et al., 2005). DYRK1a phosphorylates MAP1B at one residue, Ser1392, which primes MAP1B for phosphorylation by GSKIIIβ at Ser1388 as well (Scales et al., 2009). These phosphorylation events enhance the ability of MAP1B to maintain a dynamic microtubule population. The role of MAP1B in facilitating dynamic microtubules is counter to the original hypothesis that MAP1B stabilizes microtubules, but indicates that MAP1B could have multiple roles in regulating the microtubule cytoskeleton depending on its phosphorylation state, and may maintain a balance between microtubule stability and catastrophe. Jun N-terminal kinase 1 (JNK1) has also been shown to phosphorylate MAP1B in the growing axons to promote microtubule dynamicity, and when JNK1 is knocked down, MAP1B is hypophosphorylated and microtubules become highly stable in the axons (Chang et al., 2003; Kawauchi et al., 2005). MAP1B can be phosphorylated in vitro by other kinases such as cdc2, MARK, and casein-kinase II, and dephosphorylated by protein phosphatase 2B (calcineurin) and protein phosphatase 2A (Ulloa et al., 1993; Ulloa et al., 1994). Phosphorylation of MAP1B is likely to be highly regulated, because it dictates the functions of MAP1B depending on neuronal context. Rather than regulating the microtubule binding affinity of MAP1B, phosphorylation appears to affect the function of MAP1B in manipulating cytoskeletal dynamics, which are remodeled extensively during neuronal outgrowth and after neuronal activity.

MAP2

Similar to the MAP1 family, MAP2 proteins were also identified as high affinity microtubule associated proteins in preparations from mammalian brain. In contrast to MAP1, MAP2 proteins were found to be enriched in grey brain matter, suggesting a specific localization to neuronal dendrites (Murphy et al., 1977; Vallee and Borisy, 1978; Bulinski and Borisy, 1980; Hernandez et al., 1986). Since its discovery, MAP2 has become a widely used marker for dendrites both in vivo and ex vivo due to its consistent expression in neurons and localization to dendrites (Cumming et al., 1984; Vouyiouklis and Brophy,

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1995). There are four isoforms of MAP2: the high molecular weight proteins (~1830 kDa), MAP2A and MAP2B, and the low molecular weight proteins (~470 kDa), MAP2C and MAP2D (Hernandez et al., 1986). MAP2D is predominantly expressed during development, while MAP2C and MAP2B are expressed throughout development and into adulthood, and MAP2A is expressed in adulthood (Cumming et al., 1984; Nunez, 1988; Doll et al., 1993; Ferhat et al., 1998). In addition, MAP2A appears to have compensatory roles, and has been shown to be upregulated when MAP2C levels are low (Chung et al., 1996).

There have been numerous functions ascribed to the MAP2 family of proteins. They have been shown to stabilize microtubules by rescuing catastrophes and increasing microtubule stiffness (Gamblin et al., 1996), as well as to bundle microtubules and provide regular spacing between microtubules within dendrites (Chen et al., 1992; Dominguez et al., 1994; Cunningham et al., 1997; Itoh et al., 1997). Knockdown of MAP2 or deletion of the MAP2 microtubule-binding domain results in decreased microtubule density and impaired dendrite elongation, while overexpression of MAP2 leads to increased dendrite number and length (Harada et al., 2002; Tang et al., 2014). MAP2 can also bind actin and neurofilaments and may be able to mediate interactions between the three cytoskeletal filaments (Bloom and Vallee, 1983; Selden and Pollard, 1983; Papasozomenos et al., 1985; Pedrotti et al., 1994; Roger et al., 2004). The ability of MAP2 to crosslink microtubules with actin/neurofilaments has been shown to be important during neuronal morphogenesis and dendrite formation, during which the cytoskeletal networks are grossly reorganized (Dehmelt et al., 2011).

MAP2 also helps direct microtubule motor transport within dendrites. Not only is MAP2 important for proper localization of certain proteins and channels to the somatodendritic compartment (Theurkauf and Vallee, 1982; Obar et al., 1989; Rubino et al., 1989; Davare et al., 1999), but it is also known to be involved in the transport of endoplasmic reticulum membranes along microtubules (Heins et al., 1991; Farah et al., 2005). MAP2 may indirectly affect the transport of molecular motors such as kinesins and dynein by competing for the same binding sites on the microtubule lattice, or directly affect these motors by sterically hindering their progress with its projection domain (Heins et al., 1991; Lopez and Sheetz, 1993; Hagiwara et al., 1994). Interestingly, the levels of MAP2 are decreased in postmortem brains from patients with schizophrenia (Arnold et al., 1991; Cotter et al., 2000; Broadbelt et al., 2002; Rioux et al., 2003; Somenarain and Jones, 2010; Shelton et al., 2015), highlighting the importance of MAP2 function in dendrites, whether that is maintaining microtubule stability or directing motor transport of essential cargo. A recent study suggests that the two isoforms: MAP2C and MAP2B have very different roles in directing kinesin-based transport (Gumy et al., 2017). Gumy et al., (2017) shows that unlike MAP2C, MAP2B is not bound to the microtubule lattice, but is free in the cytoplasm where it binds and sequesters kinesin-1. This observed function allows for kinesin-3 motors to transport important cargo into the axons of neurons. These data provide a new mechanism for how MAP2 contributes to neuronal development and maintenance.

All isoforms of MAP2 are highly phosphorylated at different stages of development by a number of kinases, but in most cases phosphorylation causes MAP2 to dissociate from the microtubule. There are a number of KXGS motifs within the microtubule binding repeats of MAP2, which have been shown to be targets of phosphorylation by cAMP-dependent

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protein kinase (PKA), protein kinase C (PKC), and MARK. PKA phosphorylates MAP2C at three serine residues, Ser319, Ser350, and Ser382, which causes MAP2C to release from the microtubule and associate with actin in peripheral membrane ruffles in vivo (Rubino et al., 1989; Ozer and Halpain, 2000). Non-phosphorylated MAP2 is able to bundle actin filaments, but phosphorylated MAP2 remains competent to interact with actin, though it is unable to generate actin bundles (Sattilaro, 1986). Therefore, the role of phosphorylated MAP2 in actin organization is complex and remains unclear. Phosphorylation by both MARK at Ser1713 and Ser1682 and PKC at Ser1703, Ser1711, Ser1728 causes MAP2 to dissociate from the microtubule (Ainsztein and Purich, 1994; Illenberger et al., 1996; Drewes et al., 1997; Ebneth et al., 1999). JNK1 phosphorylation of both MAP2 and MAP1B occurs during neuronal development and is thought to regulate microtubule assembly for proper dendrite outgrowth (Chang et al., 2003). Based on the functions of MAP2 during development, phosphorylation and release from the lattice could have profound implications not only for microtubule dynamics, but also for motor transport of essential dendritic cargo (Heins et al., 1991). Many other protein kinases can phosphorylate MAP2 proteins *in vitro* such as Ca2+/calmodulin-dependent protein kinase (CaMKII), extracellular signal-regulated kinase-1 (ERK), GSKIIIβ, and cdc2 kinase, but the targeted residues and the functional consequences of phosphorylation have yet to be determined (Brugg and Matus, 1991; Itoh et al., 1997). The phosphorylation state of MAP2 is also determined by neuronal activity, which correlates with changes in cytoskeletal architecture within dendrites (Halpain and Greengard, 1990; Diaz-Nido et al., 1993; Quinlan and Halpain, 1996; Philpot et al., 1997). Therefore, MAP2 function is regulated by phosphorylation not only during neuronal development, but also after differentiation during synaptic activity for maintenance of neuronal health (Diaz-Nido et al., 1993; Diez-Guerra and Avila, 1993; Dhamodharan and Wadsworth, 1995; Riederer et al., 1995).

MAP4/MAP3

Microtubule-associated protein 4 (MAP4, a.k.a. MAP3) is expressed in a variety of different cell types, where it has been shown to promote microtubule assembly, inhibit the binding of other MAPs, and potentially cross-link microtubules and actin/neurofilaments (Huber et al., 1985; Matsushima et al., 2012). During neuronal development, MAP4 is lowly expressed in the nervous system, but is subsequently upregulated in both neurons and glia in the adult brain (Bernhardt et al., 1985; Huber et al., 1985; Matsushima et al., 2012). Immunofluorescence studies on primary neurons reveal that MAP4 is mainly restricted to the axons (Matsushima et al., 2012), where it is concentrated at branching points (Tokuraku et al., 2010). Both in vivo and in vitro studies have revealed that MAP4 enhances tubulin polymerization and overall microtubule stability (Nguyen et al., 1997; Nguyen et al., 1998; Xiao et al., 2012). In *Xenopus* melanophores, muscle cells, and in vitro motility assays, MAP4 has been shown to inhibit dynein motility, but there are conflicting results as to its effects on kinesin (Bulinski et al., 1997; Tokuraku et al., 2010; Samora et al., 2011; Semenova et al., 2014; Mogessie et al., 2015). In *Xenopus* melanophores, MAP4 enhances kinesin-2-based transport and inhibits dynein-based transport (Semenova et al., 2014). In muscle myoblast cells, a MAP4 isoform, termed oMAP4, aligns microtubules into antiparallel bundles that withstand motor force, and prevents dynein-and kinesin-driven

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microtubule sliding (Mogessie et al., 2015). This newly identified oMAP4 isoform is necessary to establish and maintain microtubule bundles during polarization and elongation of myotubes. The presence of MAP4 on the microtubule also inhibits the association of the depolymerizing kinesin, MCAK (Holmfeldt et al., 2002), and the microtubule severing enzyme, katanin (McNally et al., 2002). Therefore, the regulation of MAP4 association with the microtubule lattice should have profound consequences for microtubule stability.

Based on the above studies, MAP4 could contribute to microtubule stability in two ways: 1) by bundling microtubules and promoting resistance to external forces, and 2) by binding the microtubule and sterically blocking proteins that actively disassemble the microtubule.

MAP4 can be regulated by a number of kinases, including PKC, MAPK, MARK, and cyclin-B-cdc2 (Mori et al., 1991; Hoshi et al., 1992; Illenberger et al., 1996; Ookata et al., 1997; Ebneth et al., 1999). Phosphorylation by all four of these kinases leads to the detachment of MAP4 from microtubules and subsequent destabilization of the microtubule cytoskeleton (Ebneth et al., 1999; Mandelkow et al., 2004), but they each exert their effects on MAP4 in different cellular contexts. The MAP4 phosphorylation sites, Ser696, Ser768, Ser787, and Ser815, located within the proline-rich region of its microtubule-binding domain are proposed to be the key residues regulating microtubule affinity (Mori et al., 1991; Ookata et al., 1997; Srsen et al., 1999). p38/MAPK phosphorylation of MAP4 is induced in cardiomyocytes under hypoxic conditions (Hu et al., 2010; Hu et al., 2014). Furthermore, p38/MAPK is an essential signal required for the cytoskeletal rearrangement that precedes endothelial barrier disruption (Li et al., 2015). Therefore, it is conceivable that a potential regulatory balance between MAP4 phosphorylation and dephosphorylation controlled by p38/MAPK may exist to maintain microtubule organization under high stress conditions.

Cyclin B-cdc2 phosphorylates MAP4 at Ser696 and Ser787 in vivo and in vitro, and causes microtubules to become more dynamic by decreasing the frequency of rescue (Ookata et al., 1995; Ookata et al., 1997). Phosphorylation of MAP4 by PKC and MARK has also been shown to disrupt microtubule stability and lead to cell death (Mori et al., 1991; Illenberger et al., 1996; Drewes et al., 1997; Ebneth et al., 1999). Taken together, phosphorylation and subsequent release of MAP4 from the microtubule affects microtubule stability in two ways: 1) by removing a stabilizing protein from the lattice that would otherwise prevent catastrophe, or 2) by allowing catastrophe factors, such as MCAK and katanin, to more easily access the microtubule surface and induce disassembly. Further studies will be necessary to determine the molecular basis for MAP4 inhibition of other MAPs and the functional output on microtubule growth and stability.

MAP6/STOP

MAP6, or STOP (Stable-Tubule-Only Polypeptide), is expressed in a range of tissues in vertebrate animals, and is known to protect microtubules from depolymerization in conditions such as low temperatures or treatment with depolymerizing drugs (Bosc et al., 2003; Arama et al., 2012; Delphin et al., 2012; Gory-Faure et al., 2014). There are three major MAP6 isoforms that have been described in the mouse nervous system: MAP6-E (E-

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STOP), which is expressed throughout neuronal development, as well as in the adult brain, and MAP6-N (N-STOP), and MAP6d1 (SL21), both of which are expressed in the brain and other tissues postnatally (Gory-Faure et al., 2014; Deloulme et al., 2015). Mice deficient in *MAP6* have lower synaptic vesicle pools, defects in synaptic plasticity, and altered neurotransmission, all of which are associated with behavioral disorders such as schizophrenia (Andrieux et al., 2002; Eastwood et al., 2007; Bouvrais-Veret et al., 2008; Fournet et al., 2012b; Volle et al., 2013; Daoust et al., 2014). In cultured neurons, MAP6 proteins are present in both axons and dendrites, where they are thought to interact with the microtubule cytoskeleton, but MAP6 proteins also show transient localization within both pre- and post-synaptic compartments, where they are thought to interact with the actin cytoskeleton (Andrieux et al., 2002; Baratier et al., 2006). There are several proteins that interact with both the actin and microtubule cytoskeletons to enable cross-talk between the two cytoskeletal networks (Bartolini and Gundersen, 2010). However, the interactions between MAP6 and microtubules or actin may be mutually exclusive and appear tightly regulated by phosphorylation (Baratier et al., 2006; Lefevre et al., 2013).

Many studies have focused on the phosphorylation of MAP6 by CaMKII (Bosc et al., 2001; Bosc et al., 2003; Baratier et al., 2006). MAP6 is phosphorylated by CaMKII in vitro on at least three of the four potential CaMKII consensus sites found within its sequence: Ser139, Ser198, and Ser491 (Baratier et al., 2006; Lefevre et al., 2013). Phosphorylation of MAP6 by CaMKII causes MAP6 to dissociate from the microtubule (Lefevre et al., 2013). In vivo, phosphorylation is normally preceded by synaptic activation and causes a redistribution of MAP6 from primary branches to synaptic compartments (Baratier et al., 2006). It has also been shown that during synaptic activation, microtubule binding by MAP6 can be inhibited by Ca^{2+}-bound calmodulin, which binds and competes with the microtubule-binding domain of MAP6 to prevent microtubule association (Lefevre et al., 2013). These data suggest a model in which the microtubule association of MAP6 is regulated in two ways: 1) by binding Ca2+-calmodulin in response to transient Ca2+ influxes induced by synaptic activation, or 2) through phosphorylation by active CaMKII. The latter is a proposed mechanism for MAP6 regulation during short or long term synaptic potentiation, which both involve active CaMKII after Ca2+ levels return to basal levels (Baratier et al., 2006; Lefevre et al., 2013).

Phosphorylation by CaMKII could also be an important regulatory switch for MAP6 function. In vitro, phosphorylated MAP6 is unable to bind to microtubules, though it can still bind to polymerized actin (Baratier et al., 2006). In cultured neurons, phosphorylated MAP6 co-localizes with actin in pre- and post-synaptic compartments (Baratier et al., 2006). Actin is important for the localization and regulation of synaptic vesicle pools and MAP6 binding to actin may be important to maintain the vesicular pool (Hannah et al., 1999). It has been suggested that during synapse formation, there is increased actin polymerization events in both pre- and post-synaptic compartments (Fischer et al., 1998). It will be interesting to examine how MAP6 actually affects actin dynamics both in vivo and in vitro to further understand its role in these compartments during synaptic transmission.

As mentioned above, a hallmark of MAP6 deficiency is a dramatic depletion of synaptic vesicle pools in glutamatergic synapses, which could underlie the behavioral abnormalities

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observed in MAP6 mutant mice (Eastwood et al., 2007; Fournet et al., 2012b; Volle et al., 2013; Daoust et al., 2014). Taking all of this data together, the current model is that dephosphorylated MAP6 binds and stabilizes microtubules throughout the neuron, but upon synaptic activation, CaMKII phosphorylation of MAP6 facilitates its dissociation from the microtubule and relocalization to pools of actin within synapses. There is a controversy as to whether the behavioral alterations observed in the MAP6 null mice are attributed to the downstream effects on the microtubule or the actin cytoskeleton. Surprisingly, treatment of the MAP6 null mice with either antipsychotics or microtubule stabilizing drugs improves the observed behavioral phenotypes (Andrieux et al., 2002; Merenlender-Wagner et al., 2010; Fournet et al., 2012a), indicating that the role of MAP6 in stabilizing the microtubule cytoskeleton is essential during neuronal function. It will be interesting to further investigate the independent vs. concurrent roles of MAP6 in regulating the microtubule and actin cytoskeletons, and determine if MAP6 can facilitate cross talk between these two networks.

MAP7/Ensconsin/E-MAP-115

MAP7, also known as Ensconsin or E-MAP-115, was originally identified based on its tenacious association with microtubules (Bulinski and Borisy, 1980; Masson and Kreis, 1993; Bulinski and Bossler, 1994; Masson and Kreis, 1995; Fabre-Jonca et al., 1998; Bulinski et al., 1999; Faire et al., 1999). In vivo, MAP7 interacts with kinesin-1 to regulate cell polarity in *Drosophila* oocytes, organelle transport in S2 cells, and nuclear positioning in both *Drosophila* and mammalian muscle cells (Sung et al., 2008; Metzger et al., 2012; Barlan et al., 2013). In vitro, MAP7 competes with another MAP, tau, and directly enhances kinesin-1 binding to the microtubule, but inhibits kinesin-3 from accessing the microtubule (Monroy et al., 2017). Recently, MAP7 was found to be upregulated during collateral branch formation in dorsal root ganglion (DRG) neurons, and overexpression of MAP7 led to a dramatic increase in the number of collateral branches (Tymanskyj et al., 2017). Together these results suggest that MAP7 is involved both in kinesin-1-based transport and microtubule organization in a variety of cell types.

As with most MAPs, MAP7 is regulated by phosphorylation, but the extent to which phosphorylation regulates its function is less understood. Initial studies in HeLa cells reported that MAP7 was differentially localized depending on the stage of mitosis (Masson and Kreis, 1993). MAP7 is absent from microtubules during early prophase, but as mitosis progresses, MAP7 intensity increases at the spindle poles, then spreads to coat the mitotic spindle (Masson and Kreis, 1995; Gallaud et al., 2014). This localization pattern is consistent in the syncytial divisions of the *Drosophila* embryo (Gallaud et al., 2014). Interestingly, MAP7 was found to be hyperphosphorylated in mitotic cells and in microtubule co-pelleting assays from mitotic cell extract, MAP7 was enriched in the supernatant, suggesting that the hyperphosphorylated protein could not bind microtubules (Masson and Kreis, 1993). Fluorescent speckle microscopy used to analyze MAP7-microtubule binding dynamics also revealed an effect of phosphorylation. Treatment with a general kinase inhibitor, staurosporine, showed a decrease in MAP7 dynamics compared to untreated cells, indicating phosphorylation may regulate microtubule-binding dynamics by affecting MAP7 binding or dissociation rates (Faire et al., 1999; Bulinski et al., 2001).

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In *Drosophila* oocytes, polarity is established by the kinase, MARK (a.k.a. Par-1), and in its absence, MAP7 is no longer spatially restricted to the anterior region of the oocyte (Sung et al., 2008). MARK was found to phosphorylate MAP7 within both the N-terminal and the C-terminal regions (Sung et al., 2008). Deletion or alanine-mutations of six predicted phosphorylation sites within the MAP7 N-terminus did not affect the association of MAP7 with the microtubule, but did affect is localization pattern similar to loss of MARK. Mutating the only two residues conserved in mammalian MAP7, Ser168 and Ser198, reduced the ability of MARK to phosphorylate MAP7 and was sufficient to produce the same mislocalization phenotypes in *Drosophila* oocytes (Sung et al., 2008). This data suggests that the phosphorylation of MAP7 by MARK is required for its localization pattern, but does not affect microtubule affinity. Although this is in contrast to previous hypotheses about the regulation of MAP7 by phosphorylation, other kinases may phosphorylate MAP7 and differentially affect its function or localization. To date, MARK is the only kinase that has been shown to phosphorylate MAP7, and it could regulate the localization pattern of MAP7 during other cellular processes such as mitosis. There are three paralogs for the *MAP7* gene: *MAP7D1*, *MAP7D2* and *MAP7D3*. MAP7D1 exhibits the highest conservation with MAP7, and was recently identified as a phosphorylation substrate of DCLK1 in cortical neurons (Koizumi et al., 2017). DCLK1-mediated phosphorylation of MAP7D1 at Ser315 was shown to promote the elongation of growing axons within cortical neurons, but it is unknown how phosphorylation at this site modulates MAP7D1 activities (Koizumi et al., 2017). It is possible based on the original studies of MAP7 that other kinases could regulate the microtubule binding affinity of MAP7 to spatially or functionally control this protein during mitotic progression. Further investigation is necessary to determine how context dependent phosphorylation of MAP7 regulates its microtubule affinity versus its subcellular localization pattern.

MAP9/ASAP

MAP9, also termed ASAP (ASter-Associated Protein), is a microtubule-associated protein that localizes to the mitotic spindle and has important roles in bipolar spindle assembly and centrosome integrity (Saffin et al., 2005; Venoux et al., 2008b; Somenarain and Jones, 2010). MAP9 is expressed in the vertebrate nervous system throughout development, and depletion of MAP9 in the zebrafish embryo leads to a number of developmental defects that lead to early embryonic lethality (Fontenille et al., 2014). In cultured cells, MAP9 decorates the mitotic spindle and overexpression causes monopolar spindles, while knockdown leads to multipolar spindles and defects in cytokinesis (Saffin et al., 2005). MAP9 is also downregulated in certain types of cancers, such as colorectal cancer, and could be used as a valuable disease marker (Rouquier et al., 2014). These findings indicate that MAP9 has a crucial role in the organization of the bipolar mitotic spindle and in mitotic progression.

To date, studies have shown that MAP9 is phosphorylated by two mitotic kinases: Aurora A and Polo-like kinase 1 (PLK1) (Venoux et al., 2008a; Eot-Houllier et al., 2010). Aurora A is an important regulator of cell division and phosphorylates a number of MAPs throughout mitosis (Glotzer, 2009). MAP9 is phosphorylated by Aurora A on Ser625, and this one residue is necessary and sufficient to dictate the localization pattern of MAP9 within the mitotic spindle (Venoux et al., 2008a). Phosphorylated MAP9 localizes to the centrosome

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from G2 to telophase, then to the midbody during cytokinesis, and perturbing the phosphorylation of this residue leads to abnormal spindles and defects in mitotic progression (Venoux et al., 2008a). In the absence of Aurora A, MAP9 is degraded, highlighting the importance of phosphorylation in MAP9 protein stability. It is thought that MAP9 function, but not localization, is dependent upon Plk1 kinase (Eot-Houllier et al., 2010). Plk1 phosphorylates MAP9 at Ser289 after MAP9 has already been recruited to the centrosomes by the NEDD1-γ-tubulin pathway. This event may be important for subsequent microtubule nucleation from the centrosome, but further studies are necessary to dissect the functional interaction between MAP9 and the NEDD1-γ-tubulin pathway (Eot-Houllier et al., 2010). Taken together, Aurora A seems to be required to localize and stabilize MAP9 specifically to centrosomes during spindle formation, while Plk1 seems to be required for subsequent functions of MAP9 within the spindle pole, suggesting specific contributions of both kinases to MAP9 regulation.

TAU

Tau is one of the most widely studied MAPs due to its association with neurological diseases such as fronto-temporal dementia (FTD) and Alzheimer's disease (AD) (Tolnay and Probst, 1999; Del Carmen Alonso, 2010; Irwin et al., 2013; Ghetti et al., 2015; Gao et al., 2017; Kocahan and Dogan, 2017). Tau is now also a marker of brain damage following traumatic brain injury (TBI)(Zemlan et al., 1999; Zemlan et al., 2002; Franz et al., 2003; Smith et al., 2003; Tran et al., 2011a; Tran et al., 2011b; Hawkins et al., 2013; Kondo et al., 2015), highlighting the deleterious role of tau in neurodegeneration. Although tau was originally discovered to enhance microtubule stability and polymerization, it has subsequently been ascribed a number of other functions, which include controlling microtubule modifications, altering the stiffness and mechanical properties of the microtubule polymer, spacing microtubules at certain distances within the axon, and regulating microtubule motor transport (Cleveland et al., 1977; Drubin and Kirschner, 1986a; Drubin and Kirschner, 1986b; Fellous et al., 1986; Bre and Karsenti, 1990; Drechsel et al., 1992; Ebneth et al., 1998; Samsonov et al., 2004; Peck et al., 2011; Duan et al., 2017). Tau is expressed in the brain throughout development and into adulthood, and multiple isoforms of tau exist in the central nervous system due to alternative splicing of exons 2, 3, and 10 of the tau pre-mRNA (Kosik and Caceres, 1991; Goedert, 2015). There is one tau isoform expressed in the neonatal brain, and six tau isoforms expressed in the human adult brain. Of these six, three contain four microtubule-binding repeats (4R) and three contain three microtubule-binding repeats (3R) (Goedert et al., 1989). Within the brain, tau is predominantly expressed in neurons (Drubin and Kirschner, 1986b; Caceres and Kosik, 1990; Kosik and Caceres, 1991; Goode et al., 1997). Non-phosphorylated tau is restricted to the axon and is used as an axonal marker; however, antibodies against total tau have revealed that it is in both dendritic and axonal compartments (Mandell and Banker, 1996). During neuronal development, 3R-tau plays clear roles in neurite outgrowth, and in mature neurons, both 3R- and 4R-tau aids in the assembly of microtubules (Drubin and Kirschner, 1986a; Caceres and Kosik, 1990; Kosik and Caceres, 1991; Goode et al., 1997). Tau also contributes to the stability of microtubules by inhibiting katanin severing within the axon (Qiang et al., 2006). It has also been shown both in vivo and in vitro that tau inhibits kinesin-1 motility, but has less of an

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effect on dynein motility along microtubules (Ebneth et al., 1998; Seitz et al., 2002; Terwel et al., 2002; Vershinin et al., 2007; Dixit et al., 2008). Therefore, tau also directly impacts microtubule-based transport.

Tau has been reported to have a number of interacting partners, under normal and pathogenic conditions, which are comprehensively reviewed elsewhere (Mandelkow and Mandelkow, 2012; Bakota et al., 2017). Based on numerous studies, tau is an important MAP necessary for the development and maintenance of a neuron; however, tau null mice are viable and display increasing cognitive impairments with age (Harada et al., 1994; Ikegami et al., 2000; Fujio et al., 2007; Lei et al., 2012). This could be due to the compensatory effects of MAP1A, which is upregulated in the brains of tau null mice (Dawson et al., 2001), or MAP1B. Tau/MAP1B double knockout mice display more severe phenotypes in axonal elongation and neuronal migration compared to the single knockouts (Takei et al., 2000). The functional redundancy between MAPs that is observed in these studies highlights the importance of these classical MAPs during neuronal development.

Phosphorylation of tau contributes to a number of neuronal pathologies. Tau can be posttranslationally modified in a number of different ways: phosphorylation, glycosylation, ubiquitination, O-GlcNAcylation, and oxidation, among others (Avila et al., 2004; Avila, 2006; Avila et al., 2006; Avila, 2008). Phosphorylation of tau has been extensively studied, because hyperphosphorylated tau forms large aggregates called neurofibrillary tangles that contribute to the pathologies of FTD, AD, and neurodegeneration resulting from TBI (Mandelkow and Mandelkow, 1994; Trojanowski and Lee, 1995; Mandelkow and Mandelkow, 1998). Tau contains 80 potential serine/threonine and 5 potential tyrosine phosphorylation sites (Wang et al., 2007; Wang et al., 2013). In the brains of AD patients, tau is hyperphosphorylated at 20–40 sites (Duka et al., 2013). The kinases that have been shown to phosphorylate tau include: GSKIIIβ, MARK, MAPK, JNK1, PKA, ERKs, DYRK1a, casein kinase I, and cyclin-dependent kinase-5 (CDK5) (Avila, 2008; Hanger et al., 2009). Similar to other MAPs reviewed here, it has been demonstrated that tau phosphorylation reduces its affinity for microtubules or its ability to promote microtubule polymerization, resulting in overall microtubule instability (Avila et al., 2006). Phosphorylation at specific sites, such as Y18, regulates the dynamicity of tau on the microtubule and has significant effects on kinesin-1 motility (Stern et al., 2017). Whether neuronal cell death is a consequence of microtubule instability, transport, or tau neurofibrillary tangles is controversial (Dawson et al., 2010). However, it has been established that tau tangles are highly pathogenic and can cause neurodegeneration when introduced into healthy mice (Clavaguera et al., 2009; Zetterberg et al., 2013; Clavaguera et al., 2015; Wu et al., 2016; Fu et al., 2017). In addition, tau aggregates can transfer between neurons across synapses and can therefore spread and infect healthy neurons, causing a sweep of neurodegeneration (Liu et al., 2012b; Iba et al., 2013; Wu et al., 2016).

Most studies focus on the phosphorylation sites that cause tau to release from the microtubule and form aggregates, but thus far, there is one phosphorylation site on tau that does not affect microtubule affinity. Phosphorylation at Ser262 within tau does not cause tau to dissociate from the microtubule, but affects its ability to interact with and inhibit End-binding protein-1 (EB1) from tracking the plus end of the microtubule (Sayas et al., 2015;

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Ramirez-Rios et al., 2016). Therefore, phosphorylation of tau does not always cause tau to dissociate from the microtubule, but can affect other functions of this protein, which could contribute to neuronal alterations observed in neurodegenerative diseases.

DOUBLECORTIN FAMILY (DCX & DCLK)

The doublecortin (DCX) and doublecortin-like kinase (DCLK) proteins are part of the doublecortin-domain containing MAP family that have two tandem microtubule binding domains (DC1 and DC2)(Coquelle et al., 2006; Reiner et al., 2006). DCLK proteins contain an additional serine/threonine kinase domain at their C-terminal end that shares homology with the kinase domain of CaMKs (Kim et al., 2003; Dijkmans et al., 2010). DCX is expressed during the early stages of neuronal development and is predominantly localized to migrating neurons, followed by downregulation in differentiated neurons (Francis et al., 1999; Gleeson et al., 1999a; Liu et al., 2012a). The *DCX* gene has two paralogs: doublecortin-like kinase 1 and 2 (DCLK1 and DCLK2) (Reiner et al., 2006). In contrast to DCX, DCLK1 and DCLK2 are expressed in both developing and mature neurons (Burgess and Reiner, 2000; Tanaka et al., 2006; Liu et al., 2012a). DCLK1 preferentially localizes to the distal ends of dendrites and like DCX, DCLK1 is speculated to promote growth of dendrites. DCX and DCLK1-deficient neurons do not show dramatic defects in microtubule organization; however, they do display vesicular trafficking defects (Deuel et al., 2006). Both DCX and DCLK1 directly interact with kinesin-3 family members (KIF1A and KIF1C) to facilitate kinesin-3 transport of cargo within dendrites (Liu et al., 2012a; Lipka et al., 2016). This conserved function highlights the importance for DCX/DCLK1 in neuronal transport processes not only during development but also during neuronal maintenance.

Accumulating evidence suggests that DCLK1 is involved in a variety of cancers. DCLK1 is highly expressed in pancreatic cancer cells, where it promotes cell division and cell migration; however, its role during these two processes is unclear (Ito et al., 2016). In addition, a range of mutations throughout DCLK1 causes breast, colorectal, pancreatic and other cancers (Patel et al., 2016). A recent study has also identified a short isoform of DCLK1, termed DCLK1-S, which lacks the DCX microtubule-binding domains, but retains the entire kinase domain (Sarkar et al., 2017). This isoform is highly expressed in human colorectal tumors and colon cancer cells, and is currently being investigated as a potential biomarker for the detection cancer stem cells (Sarkar et al., 2017).

The doublecortin family is distinct from other MAPs in terms of its binding to microtubules. Classical MAPs such as MAP2 and Tau bind the ridges of the microtubule protofilament, while the DCX/DCLK proteins attach to the valleys between protofilaments (Al-Bassam et al., 2002; Moores et al., 2004; Bechstedt and Brouhard, 2012). Such binding between the grooves of the protofilaments is thought to provide both lateral and longitudinal stability to the microtubule filament and may regulate the 13-protofilament microtubules in vivo (Moores et al., 2004; Moores et al., 2006; Bechstedt and Brouhard, 2012; Bechstedt et al., 2014; Ettinger et al., 2016). Both DCX and DCLK1 potently stimulate microtubule polymerization in vitro, and it is proposed that they are required to specifically nucleate 13-protofilament microtubules (Bechstedt and Brouhard, 2012).

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DCX and DCLK1 are important during neurogenesis and neuronal migration (Mizuguchi et al., 1999; Mizuguchi et al., 2002; Shu et al., 2006; Jean et al., 2012; Liu et al., 2012a; Saaltink et al., 2012; Shin et al., 2013; Verissimo et al., 2013; Lipka et al., 2016). Certain mutations that cause the neuronal migration disorder, Lissencephaly, have been mapped to the *dcx* gene (Gleeson et al., 1998; Pilz et al., 1998; Gleeson et al., 1999b; Viot et al., 2004). Most patient missense mutations are located within the tandem microtubule binding domains of DCX, suggesting that the microtubule binding, polymerization and stabilizing activities of DCX may be important for neuronal migration (Gleeson et al., 1999b; Sapir et al., 2000; Taylor et al., 2000).

DCX is phosphorylated by a number of different kinases in the developing brain. CDK5 phosphorylates DCX at Ser297 (Tanaka et al., 2006), PKA and MARK phosphorylate Ser47 (Schaar et al., 2004), and JNK1 phosphorylates three different sites: Thr321, Thr331 and Ser334 (Gdalyahu et al., 2004). All of these sites are located within the tandem microtubule binding domains. DCLK1 autophosphorylates itself at a number of different sites both inside and outside the microtubule-binding domain (Patel et al., 2016). In general, phosphorylation of DCX/DCLK1 lowers their microtubule binding affinities, thereby reducing their effects on microtubule polymerization (Tanaka et al., 2006; Patel et al., 2016). CDK5-mediated phosphorylation alters the localization pattern of DCX within cultured migrating neurons from perinuclear regions to distal microtubule bundles (Tanaka et al., 2006). JNK1-mediated phosphorylation of DCX is critical for its role in growth cones and perturbation of this phosphorylation event affects neurite outgrowth and the velocity of migrating neurons (Gdalyahu et al., 2004). PKA and MARK phosphorylation of DCX are also necessary for DCX localization to the leading processes during neuronal migration, but negatively regulate the association of DCX with microtubules, highlighting the importance of MAP association and dissociation in controlling microtubule dynamics (Schaar et al., 2004). Interestingly, the PKA/MARK phospho-site on DCX, Ser47, is mutated in two individuals with Lissencephaly (Schaar et al., 2004). Collectively, these results underscore the importance of phosphorylation in regulating DCX during neuronal development.

TUBULIN

Most studies focus on how MAPs control microtubule dynamics and stability, but tubulin itself can be post-translationally modified and these modifications can have profound effects on microtubule dynamics and MAP association. For the purpose of this review, we will focus on what is known about the effects of phosphorylation on tubulin (Table 2). For comprehensive reviews on other tubulin post-translational modifications, please see: (Bulinski, 2009; Janke and Bulinski, 2011; Yu et al., 2015).

Phosphorylation of tubulin was reported by a number of groups over 30 years ago using total brain tubulin from either bovine or rat (Goodman et al., 1970; Murray and Froscio, 1971; Eipper, 1974). Brain tubulin was initially found to be phosphorylated by cAMP (Goodman et al., 1970; Murray and Froscio, 1971), then Eipper (1974) performed further experiments to show that beta-tubulin, in particular, was phosphorylated within its C-terminal tail. Gard and Kirschner (1985) also found that beta-tubulin was phosphorylated in neuroblastoma cell lines and that treatment with microtubule stabilizing drugs such as taxol induced tubulin

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phosphorylation, while treatment with depolymerizing drugs such as nocodazole decreased tubulin phosphorylation. Further work both in vivo in neuroblastoma lines and in vitro with purified components revealed that casein kinase II could phosphorylate beta-tubulin within the C-terminal tail at Ser444 or Ser446, and that this phosphorylation event did not inhibit microtubule assembly (Gard and Kirschner, 1985; Serrano et al., 1987; Luduena et al., 1988). It is unknown whether phosphorylation of this residue occurs on the tubulin heterodimer or within the lattice, or both. How phosphorylation of this particular residue affects other aspects of microtubule dynamics besides assembly, or the binding of MAPs, will be an interesting area of investigation. Beta-tubulin can also be phosphorylated at Ser172, and phosphorylation at this residue has been shown to inhibit microtubule assembly (Fourest-Lieuvin et al., 2006; Ori-McKenney et al., 2016). Ser172 is located near the GTP binding pocket of beta-tubulin and may prevent nucleotide exchange (Figure 3A). Only beta-tubulin in the GTP state is able to assemble onto the microtubule protofilament, thus if GTP binding is blocked, then microtubule polymerization will likely be inhibited. To date, CDK1 and DYRK1a have been shown to phosphorylate Ser172 to regulate microtubule growth during the cell cycle and during neuronal morphogenesis, respectively (Fourest-Lieuvin et al., 2006; Ori-McKenney et al., 2016).

Like beta-tubulin, phosphorylation of alpha-tubulin can also result in a range of effects within the cell. Unlike beta-tubulin, which is predominantly phosphorylated at serine and threonine residues, alpha-tubulin is phosphorylated at threonine and tyrosine residues, indicating that different types of kinases could act upon this subunit. In the presence of insulin, insulin receptor kinase phosphorylates alpha-tubulin at multiple tyrosine residues (Wandosell et al., 1987). The effect on microtubule growth varies depending on which tyrosine residue is phosphorylated. Phosphorylation of a tyrosine residue in the C-terminal tail of alpha-tubulin inhibits microtubule assembly, but phosphorylation of tyrosine residues in other regions of alpha-tubulin does not affect microtubule assembly (Wandosell et al., 1987). Upon T-cell activation, alpha-tubulin can be phosphorylated at a tyrosine residue, which prevents heterodimer assembly into microtubules (Ley et al., 1994). Similarly, after B-cell activation, the tyrosine kinase, Syk, phosphorylates alpha-tubulin on a tyrosine present near, but not within its C-terminal tail (Peters et al., 1996). Faruki et al. (2000) followed up on this work and showed that phosphorylation of alpha-tubulin at this tyrosine can occur on the heterodimer and on the microtubule polymer indicating that it does not affect microtubule assembly (Faruki et al., 2000). Interestingly, phosphorylation at one conserved site within alpha-tubulin inhibits the assembly of the heterodimer into the microtubule polymer: Thr349. An atypical MAPK phosphatase phosphorylates Thr349 within alpha-tubulin in response to osmotic stress in rice and Arabidopsis (Ban et al., 2013; Fujita et al., 2013). Thr349 is located at the exposed surface of alpha-tubulin that interacts with the beta-tubulin of another heterodimer (Figure 3A), and phosphorylation of this residue likely impairs this interaction and prevents microtubule assembly (Ban et al., 2013; Fujita et al., 2013).

Other studies have identified tyrosine phosphorylation of tubulin, but were unable to determine which subunit was specifically phosphorylated. The kinase, pp60c-src phosphorylates tubulin on tyrosine residues in neuronal growth cones (Matten et al., 1990). C-Fes tyrosine kinase phosphorylates tubulin on tyrosine residues, which actually stimulates

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microtubule assembly in vitro (Laurent et al., 2004). Finally, Jak2 phosphorylates tubulin on tyrosine residues, but the functional output of this modification is unknown (Ma and Sayeski, 2007). Considering that tyrosine phosphorylation has not been detected on beta-tubulin by previous groups, it is likely that these tyrosine phosphorylation sites are occurring on alpha-tubulin (Serrano et al., 1987; Luduena et al., 1988). By examining the PDB structure (1TUB) of the tubulin heterodimer, one potential tyrosine residue that may be exposed is Tyr261 (Figure 3B). Future studies are necessary to determine not only the precise residues targeted for phosphorylation by the tyrosine kinases, but their functional consequences on both microtubule assembly and MAP binding.

CONCLUDING PERSPECTIVE

Phosphorylation of MAPs was originally shown to affect association with the microtubule, but advances in this field have revealed that phosphorylation can dictate intracellular MAP patterning and function. For the MAPs reviewed above, we find three general classes of phosphorylation effects (Table 1 and Figure 2): 1) MAP dissociation from the microtubule (MAP2, MAP4, MAP6, Tau, DCX), 2) MAP relocalization within the cell (MAP2, MAP6, MAP7, MAP9, DCX), or 3) altered MAP function (MAP1A, MAP1B, MAP9, Tau). The same MAPs can be classified into multiple groups indicating they can be modulated by phosphorylation in different ways. It is also apparent that a relatively few number of kinases are responsible for MAP phosphorylation (Table 1). The observations that the same kinases regulate multiple MAPs underscores the importance of these kinases during neuronal development and maintenance, but also raises an interesting question of how these kinases coordinate MAP binding and localization along the microtubule surface. MAPs bound to a particular microtubule could determine the growth rate or stability of the microtubule polymer, direct motor transport and/or dictate the binding of other MAPs. Many of these MAPs exhibit similar spatial and temporal patterns (Gumy et al., 2017). Some are dendrite-specific, such as MAP1A, MAP2, and DCX, or axon-specific, such as Tau, at certain developmental timepoints, but others localize to both the dendrites and the axons throughout development and into adulthood. MAP2 and Tau compete for the same binding site on the microtubule, but they are compartmentalized into dendrites and axons, respectively (Al-Bassam et al., 2002). Few studies have focused on how other MAPs compete for microtubule binding, but phosphorylation could be an important layer of regulation in coordinating MAPs that are localized to the same neuronal regions at the same time. Investigating the role of phosphorylation in directing MAP behavior will be essential in understanding the functions of MAPs, individually and as ensembles, on the organization of the microtubule cytoskeleton. This exciting research area will also provide greater insight into how MAPs are coordinated at the molecular and cellular level to ensure proper development and maintenance of neurons.

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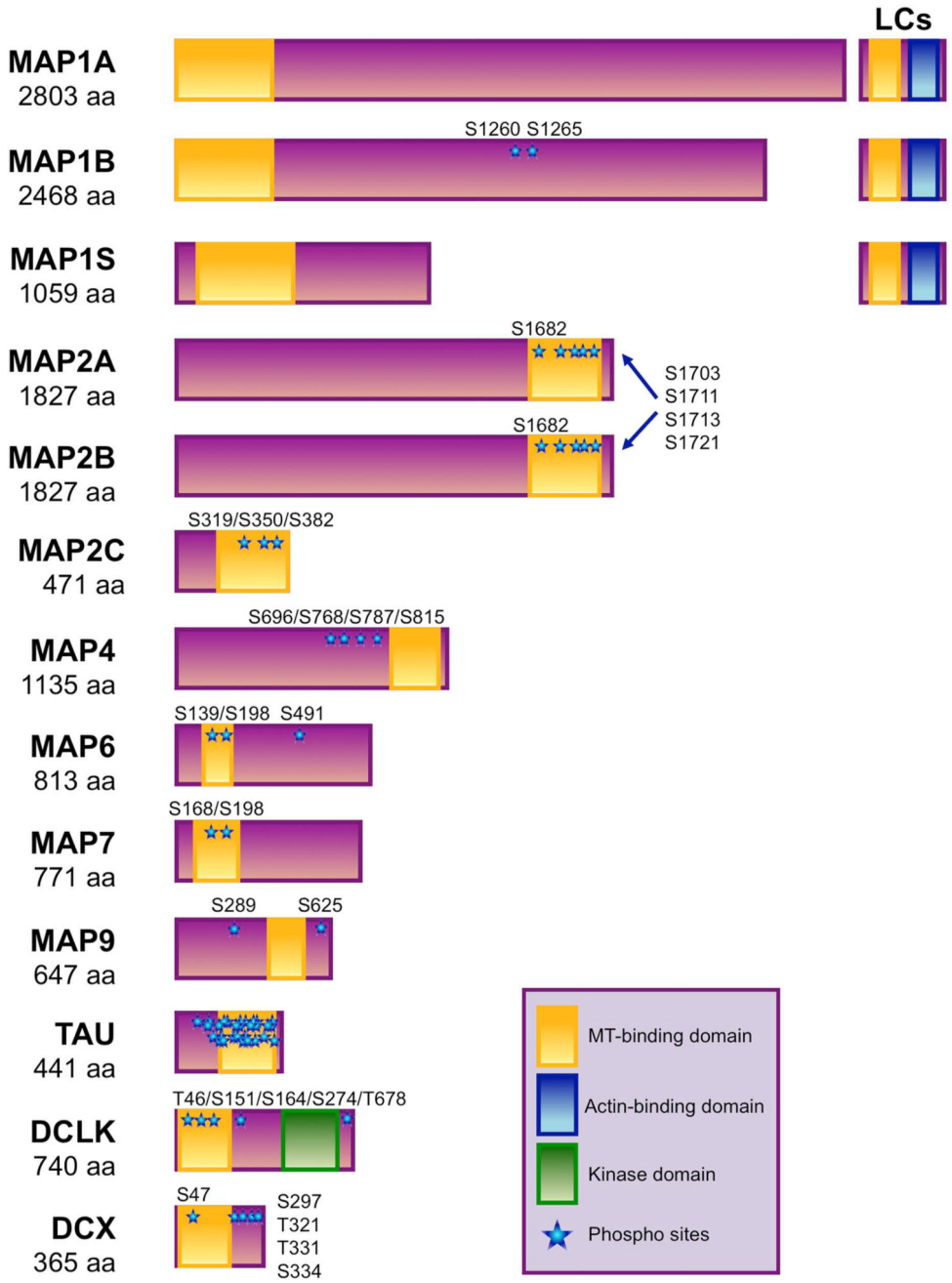

Figure 1. Domain organization of microtubule-associated proteins (MAPs)

The microtubule-binding domains (yellow), actin-binding domains (blue), kinase domains (green), and phosphorylation sites (blue stars) are illustrated for each MAP. Note that the phosphorylation sites of DCLK1 are proposed autophosphorylation sites. The following accession numbers for the protein sequences were used for this schematic: NP_002364.5 for MAP1A, NP_005900.2 for MAP1B, NP_060644.4 for MAP1S, NP_002365.3 for MAP2A/B, NP_114033.2 for MAP2C, NP_001127836.1 for MAP4, NP_149052.1 for MAP6, NP_001185537.1 for MAP7, NP_001034669.1 for MAP9, NP_005901.2 for tau, NP_001317001.1 for DCLK, and NP_835365.1 for DCX.

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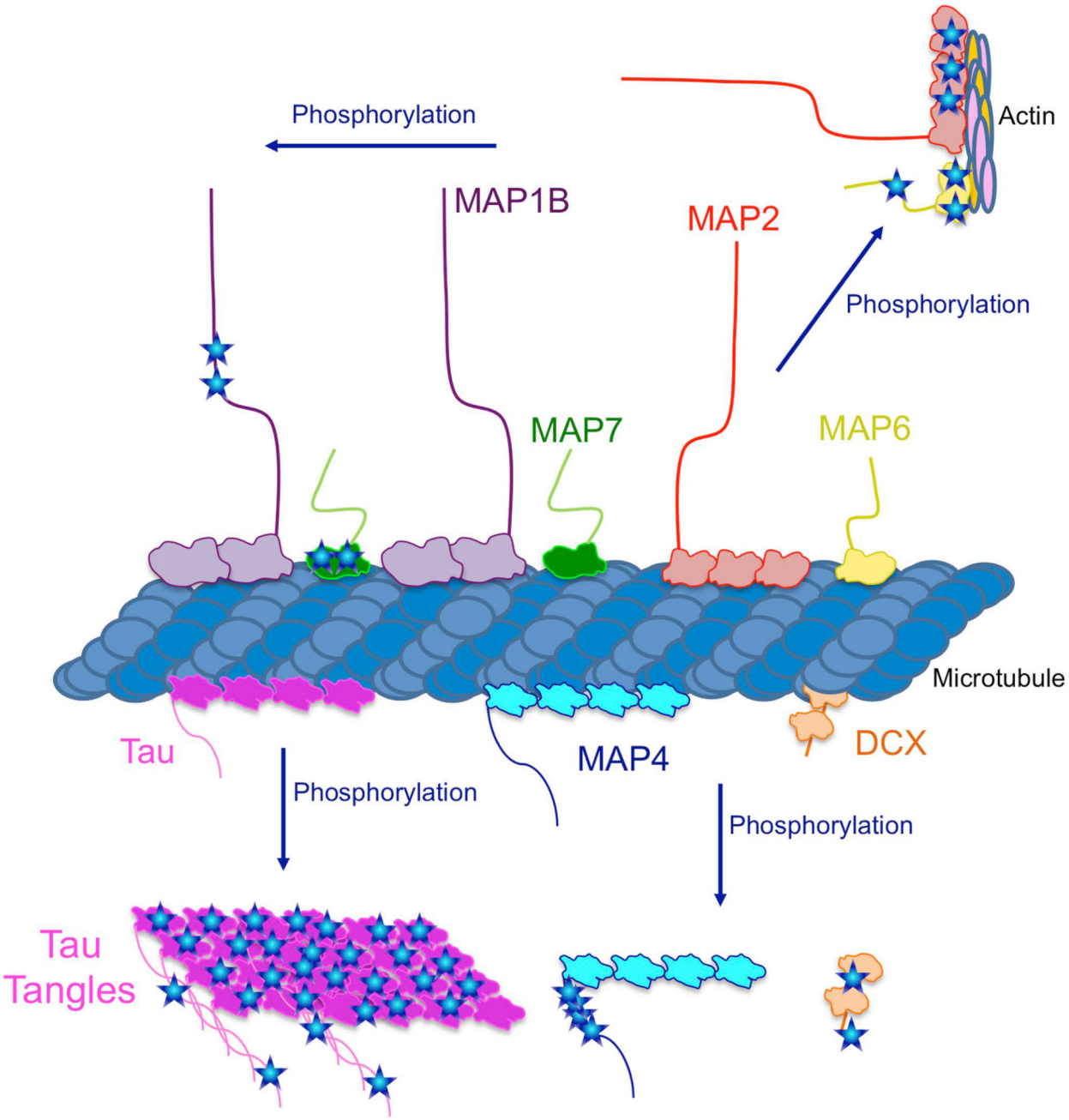

Figure 2. Model for the effect of phosphorylation on each MAP

Based on the literature reviewed here, there are different classes of phosphorylation effects on MAP activity. Phosphorylation of MAP1B and MAP7 do not seem to affect their ability to bind the microtubule, while phosphorylation of DCX, MAP4, Tau, MAP2, and MAP6 all release from the microtubule upon phosphorylation. MAP2 and MAP6 re-localize to actin-rich regions with the cell, but how these MAPs bind actin is unknown.

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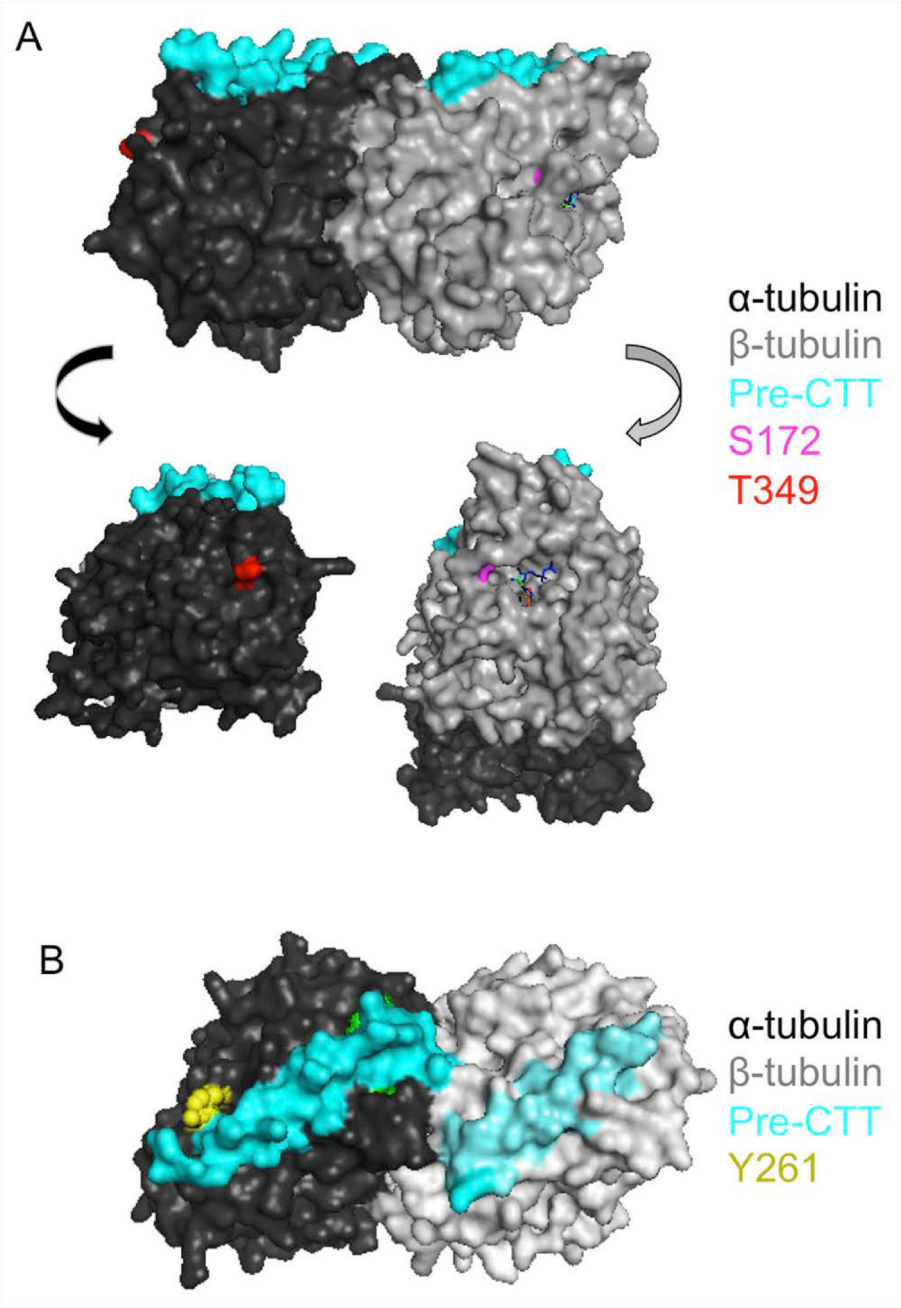

Figure 3. Phosphorylated residues in tubulin using the PDB structure, 1TUB

(A) The structure of the tubulin heterodimer highlighting the two residues that, upon phosphorylation, inhibit microtubule polymerization. S172 (in pink) is located near the GTP binding pocket of beta-tubulin (in gray). T349 (in red) is located within alpha-tubulin at the binding interface. The sequence that precedes the C-terminal tails (CTTs) is colored in cyan. **(B)** The structure of the tubulin heterodimer highlighting one potential tyrosine residue that is exposed on alpha-tubulin that could be a target of phosphorylation.

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Table 1

Effects of phosphorylation on each MAP.

MAP	Phospho-Site(s)	Kinase(s)	Phospho-Effects	References
MAP1A	Unknown	DYRKIa	Release from clathrin coated vesicles	Szebenyi et al., 2005; Murakami et al., 2012
MAP1B	S1260, T1265	GSKIIIB,JNK1, CKII, cdc2, MAPK, DYRKIa	Maintains dynamic MT pool and localizes to growing axons	Trivedi et al., 2005; Chang et al., 2003; Scales et al., 2009
MAP1S	Unknown	Unknown	Unknown	N.A.
MAP2	**MAP2C**:S319,S350, S382 **MAP2A/B**: S1682, S1703, S1711, S1713, S1721	PKA,PKC,MARK, cdc2,CaMKII,GSK IIIB, JNK1, ERK, CDKs	Dissociation from MTs and association with actin	Ozer&Halpain, 2000; Rubino et al., 1999; Ebneth et al., 1999; Drewes et al., 1997; Satillaro, 1986
MAP4	S696,S768,S787,S815	PKC, MAPK, MARK, cyclin-B-cdc2	Dissociation from MTs	Ookata et al., 1997; Mori et al., 1991; Hoshi et al., 1992; Illenberger et al. 1996
MAP6	S139,S198,S491	CaMKII	Dissociation from MTs and localization to actin-rich synapses	Baratier et al., 2006 Lefevre et al., 2013 Bosc et al., 2001 Bosc et al., 2003
MAP7	S168,S198	MARK	Phosphorylation affects localization and/or MT binding	Masson&Kreis, 1993; Faire et al., 1999; Sung et al., 2008
MAP9	S625 S289	Aurora A Plk1	Spindle localization and function	Venoux et al., 2008; Eot-Houllier et al., 2010
TAU	≥40 residues including: T69,T181,S184,S198, S199,S202,T212,S214,T231	MARK, MAPK, JNK1, CDK5, GSKIIIβ, ERK DYRKIa, CKI, PKA	Dissociation from MTs or EB1	Hanger et al., 2009; Wang et al., 2013; Duka et al., 2013
DCX	S47,S297,T321,T331, S334	CDK5, PKA, MARK, JNK1	Dissociates from MTs; altered localization	Tanaka et al., 2006; Schaar et al., 2004; Gdalyahu et al., 2004

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Table 2

Effects of phosphorylation on the tubulin heterodimer.

Tubulin Subunit	Phospho-Site(s)	Kinase(s)	Phospho-Effects on Function	References
Beta-tubulin	S444/446	cAMP casein kinase II	No effect on MT assembly	Gard&Kirschner, 1985; Luduena et al., 1988; Serrano et al., 1987
	S172	CDK1, DYRKIa	Inhibits MT assembly	Fourest-Lieuvin et al., 2006; Ori-McKenney et al., 2016
Alpha-tubulin	Tyrosine Residues	Syk and others	May or may not affect MT assembly	Wandosell et al., 1987; Peters et al., 1996; Faruki et al., 2000
	T349	MAPK Phosphatase	Inhibits MT assembly	Ban et al., 2013; Fujita et al., 2013
Not Determined	Tyrosine residues	Pp60c-src	Unknown	Matten et al., 1990
		Jak2	Stimulates MT assembly	Ma&Sayeski, 2007
		c-Fes	Unknown	Laurent et al., 2004