Molecular Interactions among Protein Phosphatase 2A, Tau, and Microtubules

IMPLICATIONS FOR THE REGULATION OF TAU PHOSPHORYLATION AND THE DEVELOPMENT OF TAUOPATHIES*

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Hyperphosphorylated forms of the neuronal microtubule (MT)-associated protein tau are major components of Alzheimer’s disease paired helical filaments. Previously, we reported that ABc, the dominant brain isoform of protein phosphatase 2A (PP2A), is localized on MTs, binds directly to tau, and is a major tau phosphatase in cells. We now describe direct interactions among tau, PP2A, and MTs at the submolecular level. Using tau deletion mutants, we found that ABc binds a domain on tau that is indistinguishable from its MT-binding domain. ABc binds directly to MTs through a site that encompasses its catalytic subunit and is distinct from its binding site for tau, and ABc and tau bind to different domains on MTs. Specific PP2A isoforms bind to MTs with distinct affinities in vitro, and these interactions differentially inhibit the ability of PP2A to dephosphorylate various substrates, including tau and tubulin. Finally, tubulin assembly decreases PP2A activity in vitro, suggesting that PP2A activity can be modulated by MT dynamics in vitro. Taken together, these findings indicate how structural interactions among ABc, tau, and MTs might control the phosphorylation state of tau. Disruption of these normal interactions could contribute significantly to development of tauopathies such as Alzheimer’s disease.

The axonal microtubule (MT)-associated protein (MAP) tau (1, 2) is encoded by one alternatively spliced gene that directs the synthesis of six tau isoforms in human brain (3). The C-terminal half of brain tau encompasses three or four contiguous MT-binding repeats that act synergistically with regions flanking both sides of the repeats to support higher affinity MT binding (4–6). All tau isoforms in human brain contain 21 serine/threonine phosphorylation sites (7), some of which modulate MT binding of tau (8–11). Only a few sites on tau are phosphorylated at any moment in normal adults (12, 13). In Alzheimer’s disease brain, however, tau is more heavily phosphorylated (12, 13), due in part to decreased tau phosphatase activity (13, 14). Hyperphosphorylated tau is the principal component of Alzheimer’s disease paired helical filaments and neurofibrillary lesions present in several other neurodegenerative disorders (15) and has very low affinity for MTs (16, 17). Although non-phosphorylated tau can assemble into paired helical filament-like filaments in vitro (18–21), it is reasonable to hypothesize that changes in tau phosphorylation are decisive events in paired helical filament biogenesis in vivo.

To study how tau phosphorylation is regulated, we have been focusing on protein phosphatase 2A (PP2A), a heterotrimeric enzyme that comprises one catalytic C subunit, one non-catalytic A subunit, and one of several structurally distinct, regulatory B subunits (22). We previously reported that PP2A is likely to be a major tau phosphatase in vitro (23). Initially, we found that a pool of ABc, the major PP2A isoform in brain (22), is associated with MTs in brain and cultured cells (17). Subsequently, we determined that tau binds with high affinity to ABc and AB βC; less tightly to AC; and poorly, if at all, to AC or individual PP2A subunits (23). Finally, we found that the relative affinities of PP2A isoforms for tau correlated with their tau phosphatase activities, and suppression of PP2A activity in cells stimulated Alzheimer’s disease-like phosphorylation of tau and prevented tau from binding MTs (23).

Here, we describe the use of tau deletion mutants, specific PP2A enzymes, and intact and proteolyzed MTs to define binding sites on tau for PP2A, on PP2A for tau and MTs, and on MTs for PP2A. When considered collectively, the results indicate how structural interactions among PP2A, tau, and MTs can control the phosphorylation of tau. The results suggest, moreover, that disruption of the normal interactions could contribute significantly to the development of tauopathies such as Alzheimer’s disease.

EXPERIMENTAL PROCEDURES

Binding of PP2A to Tau—Purified bovine brain or bovine cardiac (24, 25) or human recombinant (22) ABc (300 nm) in storage buffer (25 mm Tris, 1 mm dithiothreitol, 1 mm EDTA, and 50% glycerol, pH 7.5) was incubated for 15 min on ice in a final volume of 5 μl with a 600 nm concentration of either purified bovine brain tau (26) or any of several previously described human recombinant tau (rTau) fragments (27, 28). We also used one new recombinant tau fragment, rTau9 (see Fig. 1),
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Fig. 6. 200 nM radiolabeled soluble tau was mixed with 40 nM AB lower panel containing 20 mM EGTA, and 5 mM MgCl2) containing 1 mM GTP and 20 µM Taxol (provided by Nancita Lomax, NCI, National Institutes of Health). When used in PP2A enzymatic assays, MTs were first washed free of GTP by centrifugation at 100,000 rpm for 45 min at 30 °C with PEM buffer containing 2 mM phenylmethylsulfonyl fluoride and 20% glycerol, and immunoblotted with antibodies to the C or B subunits of PP2A (23). Immunoreactive proteins were detected using enhanced chemiluminescence reagents (ECL, Amersham Pharmacia Biotech). Blots were densitometrically scanned and quantitatively analyzed using a PhosphorImager and ImageQuant software (Molecular Dynamics, Inc.).

Assembly and Limited Proteolysis of Tubulin—Purified bovine brain tubulin (29) at 5 µM (equal to 0.5 mg/ml) was polymerized into MTs by incubation for 10 min at 37 °C in PEM buffer (0.1 MPIPES, pH 6.9, 2 mM EGTA, and 5 mM MgCl2) containing 1 mM GTP and 20 µM Taxol (provided by Nancita Lomax, NCI, National Institutes of Health). When used in PP2A enzymatic assays, MTs were first washed free of GTP by centrifugation at 100,000 rpm for 45 min at 30 °C with PEM buffer containing 2 mM phenylmethylsulfonyl fluoride and 20% glycerol, and immunoblotted with antibodies to the C or B subunits of PP2A (23). Immunoreactive proteins were detected using enhanced chemiluminescence reagents (ECL, Amersham Pharmacia Biotech). Blots were densitometrically scanned and quantitatively analyzed using a PhosphorImager and ImageQuant software (Molecular Dynamics, Inc.).

RESULTS

ABoC and MTs Bind to the Same Region within Tau—To localize the binding site on tau for ABoC, a gel mobility shift assay (23) coupled with immunoblotting (see "Experimental Procedures") was used to monitor binding of ABoC to 13 different r Tau proteins, all but one of which (r Tau9) have been previously described (27, 28). These recombinant proteins are derived from adult (r Tau1–r Tau6) or fetal (r Tau7–r Tau13) isoforms of human brain tau. The largest recombinant tau that was used, r Tau1, contains four MT-binding repeats (four-repeat tau) and two 29-mer N-terminal inserts. As shown in Fig. 1, each of the other r Tau proteins contained one or more unique deletions. Their N- and C-terminal amino acids and the boundaries of their deletions are numbered relative to the amino acid sequence of the largest isoform of brain tau (3), which is equivalent to r Tau1.

Fig. 1 summarizes the results of the binding assays in which ABoC and the pertinent r Tau proteins were used at 300 and 600 nM, respectively. Densitometry of the resulting immunoblots was used to estimate the percentage of PP2A that was bound to each r Tau protein. Maximal binding of ABoC (≥95%) was observed for every r Tau protein that contains all four MT-binding repeats plus extensive sequence contiguous with the N terminus of the repeats. Included in this group are r Tau1 and r Tau2, which do not have any C-terminal deletions, and r Tau6 and r Tau8, which are missing part or all of the C-terminal 45 amino acid residues of native tau. A modest decrease in binding (to ~80%) was observed for r Tau7, which is equivalent to the fetal isoform of brain tau (3), contains only three MT-binding repeats (three-repeat tau), and lacks the two N-terminal inserts. A similar level of ABoC binding (~75%) was observed for r Tau5, the C terminus of which is in the middle of the third MT-binding repeat, but contains no other deletions relative to r Tau1. By comparison, r Tau4, which contains a large internal deletion and includes just part of the last MT-binding repeat, was able to bind only ~45% of ABoC. The minimal protein that retained the ability to bind ABoC (~38%) was r Tau12, which lacks all four MT-binding repeats, but, near its C terminus, contains a proline-rich sequence that has MT-binding activity independent of the repeats (4, 5). In stark contrast, r Tau13, which lacks residues 221–242 of r Tau12, is otherwise identical, failed to bind any ABoC.

Deletion of the N-terminal 29-mer inserts (r Tau8) or residues 84–161 (r Tau2), which include part of the second N-terminal repeat, did not impair binding of four-repeat tau to ABoC. Other deletions located near the N-terminal repeat to the MT-binding repeats yielded diminutable, albeit modest effects. A slight reduction in binding (to ~90%) was observed for r Tau3, which contains all four MT-binding domain located immediately N-terminal to those repeats. Likewise, binding to ABoC correlated roughly with protein length for the three-repeat proteins (r Tau9, r Tau10, and r Tau11) that have extensive N-terminal deletions.
AB\textalpha C binds to the MT-binding domain on tau. Purified bovine brain AB\textalpha C (300 nM) was incubated on ice for 15–30 min in the presence of various recombinant proteins (600 nM) derived from adult (rTau1–rTau6) or fetal (rTau7–rTau13) isoforms of human brain tau. For each combination of AB\textalpha C and a rTau species, non-denaturing gel electrophoresis was used to separate complexes containing both proteins from free AB\textalpha C and rTau. The resulting gels were immunoblotted with a monoclonal antibody specific for the C subunit of PP2A, and densitometry of the immunoblots was used to estimate the percentage of total AB\textalpha C that was bound to each rTau. Values shown are the means ± S.D. of at least three separate experiments. For each rTau species, the N- and C-terminal amino acids and the boundaries of deletions (indicated by black lines) are numbered relative to the 441-amino acid sequence of the largest human adult tau isoform (3), which is equivalent to rTau1.
Taken together, these data demonstrate that the overall PP2A-binding region on tau encompasses the MT-binding repeats and a short sequence N-terminal to the repeats. It is thus indistinguishable, within the limits of experimental resolution, from the MT-binding region on tau (4–6). Interestingly, lower affinity binding of ABoC can be achieved by proteins that contain only the extreme N-terminal (rTau12) or C-terminal (rTau4) part of the overall binding region on tau for AB. In addition, the binding affinity of PP2A for tau increases with the number of MT-binding repeats present in tau. It is also important to note that inclusion of 1 μM okadaic acid in the binding reactions completely suppressed PP2A activity, but had no effect on the extent of PP2A interaction with tau (data not shown).

To seek further evidence that sequences on tau immediately N-terminal to the MT-binding repeats actually bind ABoC, the synthetic peptide p224KKAVVRTPPKSP236, which corresponds to a portion of this region, was tested for its ability to compete with native tau for binding to ABoC. The sequence of this portion of tau is invariant among all isoforms of human, rat, mouse, and bovine tau. Bovine brain ABoC (300 nM) was pre-incubated with 1 or 10 μM concentration of the synthetic peptide p224KKAVVRTPPKSP236, corresponding to the 224–236-amino acid sequence of the longest human adult tau isoform, and then further incubated for 15 min with 600 nM native bovine brain tau or buffer alone. The samples were analyzed by nondenaturing gel electrophoresis, followed by immunoblotting with a polyclonal antibody to the Bo subunit of PP2A. Note the presence of ABoC-peptide complexes and a decreased amount of ABoC-tau complex in the presence of 10 μM peptide.

In the next series of experiments, increasing concentrations of ABoC were incubated with MTs and then centrifuged to generate MT-bound (pellet) and unbound (supernatant) fractions. As shown in Fig. 3 (lower panel), the binding of ABoC to tau, inclusion of 5 μM okadaic acid in the assays completely suppressed PP2A activity, but had no effect on the extent of interaction of ABoC with MTs (data not shown).

To assess whether ABoC is the only form of PP2A that can bind MTs, we compared the behavior of distinct PP2A enzymes in the MT co-sedimentation assay. As shown in Fig. 4, all enzymatically active proteins tested, including the AβC and AβC holoenzymes, the AC dimer, and the catalytic C subunit, were able to bind MTs to some extent. However, distinct PP2A isoforms appeared to have distinct affinities for MTs because at fixed molar concentrations of PP2A and polymerized tubulin, the ratio of MT-bound to soluble enzyme varied considerably...
Among the phosphatases tested. Based on the results presented in Fig. 4, the ability of PP2A to bind to MTs can be ranked as follows: ABαC > AC > ABβC > C > AB/C. When actin filaments were substituted for microtubules, virtually none of the PP2A enzymes pelleted, demonstrating that their binding to microtubules was specific (data not shown).

The fact that the monomeric C subunit co-sedimented with MTs indicates that it contains a binding site for MTs. However, our findings suggest that the presence of A and B subunits modulates interactions of the catalytic C subunit with MTs and that each type of B subunit does so in its own unique way. As reported previously for binding of various forms of PP2A to tau (23), the ABαC heterotrimer bound more tightly to MTs than any of the other forms of PP2A that were assayed. In addition, we found that neither ABαC nor AC forms detectable complexes with unpolymerized tubulin during nondenaturing gel electrophoresis (data not shown), implying that PP2A can efficiently interact with tubulin only when the tubulin has polymerized.

**Tau and PP2A Bind to Different Sites on MTs**—Binding to MTs of several MAPs such tau and MAP2 can be partially inhibited by prior exposure of either unassembled (32) or polymerized (30, 31) tubulin to the protease subtilisin, which removes a small C-terminal fragment from both α- and β-tubulin. To compare the binding sites on MTs for PP2A and tau, co-sedimentation experiments were therefore performed using untreated or subtilisin-treated MTs, bovine brain ABαC, and bovine brain tau. The resulting supernatants and pellets were analyzed by quantitative densitometric analysis of the immunoblots. The results shown are representative of a typical experiment.

The inhibitory effect of MTs on the tau phosphatase activity of PP2A was also analyzed by incubating 20 nM protein kinase A-phosphorylated bovine brain tau with 40 nM ABαC and a concentration series of MTs for 15 min. Fig. 6 (lower panel) shows that tau dephosphorylation by PP2A was inhibited by MTs in a concentration-dependent manner. In the absence of MTs, ~15% of the original 32P levels remained covalently bound to tau. In contrast, ~20% of 32P remained when 1 μM assembled tubulin was present, and ~45% remained at assembled tubulin concentrations of 2 μM or higher.

Although the MT-mediated inhibition of tau dephosphorylation by ABαC likely resulted, at least in part, from competition between MTs and ABαC for binding to tau, we hypothe-
sized that the direct interaction of PP2A with MTs may also affect its catalytic activity in general. To test this hypothesis, purified ABαC, AC, and C subunits were incubated with buffer alone or with buffer containing 5 μM unassembled or Taxol-polymerized tubulin. The phosphatase activity of each sample was then measured using either of two characterized PP2A substrates that do not bind MTs: phosphorylated myosin light chain or the synthetic RRREEE(pT)EEE peptide.

Fig. 7. MTs inhibit the catalytic activity of PP2A. Purified ABαC, AC, and C subunits (25 nM each) were incubated for 15 min in buffer alone or in buffer containing 5 μM soluble or Taxol-polymerized tubulin. Then, a 100 μM concentration of either of two phosphorylated substrates, myosin light chain (MLC) or the synthetic RRREEE(pT)EEE peptide, was added, and the samples were incubated for 5 min at 30 °C to allow substrate dephosphorylation. The data shown are the means ± S.E. of triplicate determinations from two separate experiments and are expressed as the percentage of PP2A activity measured with each substrate in the absence of tubulin (control).

Fig. 6. MTs inhibit dephosphorylation of tau by ABαC. Upper panel, bovine brain tau was phosphorylated by protein kinase A in the presence of [γ-32P]ATP. ~1000 cpm (400 nM) of MT-bound (+ MTs) and soluble (−MTs) tau were incubated for the indicated times at 30 °C with ~14 nM purified bovine brain ABαC. Samples were then resolved by SDS-PAGE, and 32P levels in tau were measured on dried gels using a PhosphorImager. Error bars indicate the S.D. values for data from two independent experiments. Lower panel, radiolabeled, protein kinase A-phosphorylated tau (200 nM) was incubated with or without Taxol-stabilized MTs at the indicated concentrations of polymerized tubulin, after which bovine brain ABαC was added to 40 nM. The dephosphorylation reactions were performed for 5 min at 30 °C as described above. The data shown are the means ± S.D. of results from three separate experiments and are expressed as the percentage of phosphate on tau that was not exposed to ABαC (control).
Taxol-polymerized bovine brain tubulin, which includes naturally phosphorylated tubulin in cultured cells and in vivo, has been tested to date (37). Based on these results, we measured but not by any of several other protein phosphatases that have been reported previously that the neuron-specific βIII-tubulin isoform, which represents ~25% of neuronal β-tubulin, is phosphorylated in cultured cells and in vivo (37–39). Remarkably, phosphorylated βIII-tubulin can be dephosphorylated by PP2A, but not by any of several other protein phosphatases that have been tested to date (37). Based on these results, we measured dephosphorylation of unassembled or Taxol-polymerized brain tubulin by bovine brain AB and AC. As shown in Fig. 8, both forms of tubulin were dephosphorylated by AB and AC.

During the 30 min in which the reactions were allowed to proceed, however, polymerized tubulin was dephosphorylated to just 40% the level of unassembled tubulin.

**DISCUSSION**

Previously, we reported that a pool of AB is localized on intracellular MTs and binds to tau in vitro (23). A question that naturally arose from those observations was, “Does tau anchor PP2A to neuronal MTs?” There is precedent for MAPs acting as bridges between MTs and enzymes that control protein phosphorylation. For example, tau and MAP2 anchor PP1 (40) and protein kinase A (41) to MTs, respectively. As far as PP2A is concerned, however, the results presented here demonstrate that tau cannot be responsible for linking the enzyme to MTs. Instead, the data presented in Figs. 1 and 2 imply that PP2A and MTs bind to tau in a mutually exclusive manner. The interaction site on tau for PP2A corresponds approximately to amino acid residues 221–396 of adult human tau and thus encompasses the MT-binding repeats and nearby flanking regions that form the overall MT-binding domain on tau (4–6). Interestingly, AB (Fig. 1), like MTs (5, 6), was able to bind tau variants containing truncated MT-binding regions as small as only one repeat or the proline-rich domain located immediately N-terminal to the repeats. Since the C subunit of PP2A does not bind to tau alone (23), the MT-binding domain on tau can be viewed as a site that anchors the PP2A holoenzyme and enables its catalytic subunit to dephosphorylate residues located predominantly elsewhere on tau. This might explain why the tau phosphatase activities for various forms of PP2A are correlated with their affinities for tau (23) and why okadaic acid, which binds tightly to the catalytic site on PP2A and abolishes its enzymatic activity (42), does not interfere with binding of PP2A to tau.

One mechanism that apparently can account for the MT-binding activity of PP2A is direct association via the C subunit. This conclusion is supported by the finding that three distinct PP2A holoenzymes, the AC complex, and free C subunits all bound to MTs, albeit with varying affinities (Fig. 4). These in vitro data should not be assumed to mean that all PP2A enzymes efficiently interact with MTs in vivo, however. For example, in contrast to AB, the AC enzyme showed very low affinity for MTs in our in vitro assays (17) and is not known to be associated with MTs in vivo (43). Our finding that the affinity for MTs of PP2A holoenzymes varied according to their regulatory B subunits (Fig. 4) is consistent with the model that distinct PP2A isoforms are differentially targeted to specific subcellular compartments through their regulatory subunits (17, 22, 23, 43). It also must be noted that although direct binding of PP2A to MTs has now been shown to occur, other possible binding mechanisms cannot be formally excluded. For example, perhaps PP2A can also be linked to MTs indirectly through a MAP intermediate, as has been described for PP1 and tau (40).

One potential physiological consequence of the binding of PP2A to MTs is reduced phosphatase activity of the enzyme (Figs. 6 and 7). In the case of tau, this phosphatase inhibition could result from at least two factors: immobilization of the catalytic subunit of PP2A on MTs and competition between MTs and PP2A for tau binding. It is likely that inhibition of catalytic activity occurs subsequent to direct binding of the C subunit to MTs. Such an interaction may induce conformational changes in PP2A, which partially or completely conceal the catalytic site, preventing efficient access to substrates. The inhibition of PP2A activity by MTs also provides an explanation for reports that MT depolymerization induces okadaic acid-sensitive dephosphorylation of tau in cultured cells (11, 44). Together, these results underscore the possible importance of MT dynamics in the regulation of the phosphorylation state of PP2A-sensitive substrates, including tau. In addition to the control of PP2A activity by regulatory proteins, post-translational modifications, and biochemical factors (22, 25, 43), selective anchoring of PP2A to MTs may represent a novel way to regulate specific subcellular pools of PP2A.

Whereas MT assembly dynamics may regulate PP2A activity, PP2A, in turn, might modulate MT stability in axons by regulating the MT-binding and -stabilizing activities of tau (23, 45). Moreover, cycles of tubulin phosphorylation and dephosphorylation have been proposed to regulate MT functions during neuronal differentiation and to mediate interactions of MTs with other cellular components (38, 46). Interestingly, AB and AC preferentially dephosphorylated depolymerized as compared with polymerized brain tubulin (Fig. 8). This difference may result from the binding of PP2A to MTs, but not to soluble tubulin. The neuron-specific βIII-Tubulin is the only known form of phosphorylatable brain tubulin and is found primarily in the assembled pool of tubulin in vivo (37–39). Because phosphate can turn over rapidly on βIII-tubulin, it was hypothesized that higher levels of phosphorylation in assembled MTs likely resulted from slower dephosphorylation of tubulin phosphate in polymers rather than in monomers (38). Since AB is the only known phosphatase capable of dephosphorylating βIII-tubulin (37, 46), this hypothesis is supported by our in vitro data showing the preferential dephosphorylation of unassembled tubulin by AB. Thus, AB may be an important modulator of MT phosphorylation levels and functions in neurons. Yet, the lack of effect of okadaic acid on the ability of PP2A to co-sediment with MTs and the presence of AB on non-neuronal MTs both suggest that the interactions between PP2A and MTs are not simply restricted to dephosphorylation of tubulin. Their functional significance for the regulation of the cytoskeleton remains to be defined.
Based on the collective results presented here and in related reports from our laboratories and others, we propose a model in which AβεC regulates the phosphorylation state of tau by a complex mechanism involving structural interactions as well as enzyme-substrate interactions among AβεC, tau, and MTs (Fig. 9). Because AβεC binds to the MT-binding domain of tau and MTs inhibit the tau phosphatase activity of PP2A, the model presumes that AβεC can dephosphorylate tau primarily, if not exclusively, when tau is dissociated from MTs. Depolymerization of MTs or dissociation of PP2A from MTs thus potentiates the phosphatase activity of PP2A for soluble tau. In contrast to PP2A, other tau phosphatases such as PP1 (40) may be able to dephosphorylate both MT-bound and soluble tau. As long as the tau kinases and phosphatases remain in proper balance, the phosphorylation state of tau will remain within limits that favor binding of tau molecules to MTs, as opposed to other tau molecules. If the balance becomes altered in favor of the kinases, however, phosphates may accumulate on tau at specific sites such as serine 214 or serine 262, which, when phosphorylated, dramatically diminish the MT-binding activity of tau (48). The elimination of MTs as favored binding partners for tau may then contribute to an environment that permits tau to self-assemble into paired helical filaments. Disruption of the normal structural interactions between PP2A and tau may also lead to tau hyperphosphorylation. PHFs, paired helical filaments.

Based on the collective results presented here and in related reports from our laboratories and others, we propose a model in which AβεC regulates the phosphorylation state of tau by a complex mechanism involving structural interactions as well as enzyme-substrate interactions among AβεC, tau, and MTs (Fig. 9). Because AβεC binds to the MT-binding domain of tau and MTs inhibit the tau phosphatase activity of PP2A, the model presumes that AβεC can dephosphorylate tau primarily, if not exclusively, when tau is dissociated from MTs. This is in stark contrast to the tau phosphatase activity of PP1 because tau acts as a bridge between PP1 and MTs; PP1 binds to a portion of tau that is distinct from the MT-binding site on tau; and PP1 has the potential to dephosphorylate both soluble and MT-bound tau (40). For simplicity’s sake, however, the model does not take into account other factors that are involved in the regulation of PP2A and MTs. Many neurodegenerative disorders besides Alzheimer’s disease are characterized by the presence of filaments assembled from hyperphosphorylated tau. The recent discovery of a direct link between tau mutations and neurodegenerative disorders such as FTDP-17 has underscored the importance of functional tau for neuronal integrity and survival (15). In this context, tau mutations, especially those occurring within the MT-binding domain of tau, could affect its ability to bind to PP2A. Although it has been proposed earlier that a decrease in tau phosphatase activity, especially that contributed by PP2A, could underlie the biogenesis of hyperphosphorylated tau in Alzheimer’s disease (23, 44, 47), the data we present here and in a prior report (17) suggest specific molecular mechanisms by which this could occur, namely, any alteration of the MT-binding site on tau, by mutation or post-translational modification, might compromise the ability of PP2A to bind and thereby dephosphorylate tau. It is easy to imagine how such a situation could lead to the accumulation of highly phosphorylated tau, as occurs in Alzheimer’s disease. Likewise, deregulation of MT dynamics could indirectly affect endogenous levels of PP2A activity and deregulate PP2A-controlled signaling pathways. The fate of tau thus appears to be intimately linked to the complex interrelationships existing among tau, MTs, and PP2A. Disruption of the normal structural and enzymatic interactions among these factors might be a major underlying cause of the development of tauopathies.
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