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Tau - It's not what you think

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Summary

Tau is a multi-functional microtubule-associated protein in the neuron. For decades, tau's main function in neurons has been broadly accepted as stabilizing microtubules in the axon; however, this conclusion was reached mainly on the basis of studies performed *in vitro* and on ectopic expression of tau in non-neuronal cells. The idea has become so prevailing that some disease researchers are even seeking to use MT-stabilizing drugs to treat diseases in which tau dissociates from microtubules. Recent work suggests that tau is not a stabilizer of microtubules in the axon, but rather enables axonal microtubules to have long labile domains, in part by outcompeting genuine stabilizers. This new perspective on tau challenges long-standing dogma.

Keywords

microtubule; axon; neuron; MAP6; microtubule stability; Alzheimer's disease

Tau

Tau (see Glossary) was discovered in the 1970s as a protein that co-purifies with tubulin from brain preparations and promotes microtubule assembly in the test tube [1]. Since then, tau has become one of the most studied proteins in the biological sciences because of its relevance to the normal functioning of neurons (and a few other cell types) and because of its relevance to several neurodegenerative diseases [2, 3]. Tau consists of multiple splice variants, over 80 potential phosphorylation sites, and domains that have been documented to interact with various proteins and structures [3, 4]. Tau is considered to be enriched in axons, where it binds microtubules, but tau is also present at lower levels in the neuron's soma and dendrites, where it is generally not microtubule-bound [5–7]. There is broad consensus that tau is multi-functional, contributing to microtubule-related features of nerve cells such as microtubule-actin interactions, motor-driven transport of organelles along microtubules, and flexural rigidity of microtubules, and also contributing to non-microtubule features of these cells, such as properties of dendritic spines [8–15]. Tau's many phosphorylation sites are

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regulated by an array of kinases and phosphatases, which in turn are regulated by signaling cascades relevant to various cellular functions [16–18].

Although it has many functions, tau is best known as a protein that confers stability to the microtubules of the axon. Decades of research have led to the claim that the primary function of tau is to stabilize microtubules in the axon. On the basis of this broadly accepted claim, some disease researchers are even seeking to use microtubule-stabilizing drugs to treat diseases in which tau dissociates from microtubules [19–21]. The idea that tau is a stabilizer of microtubules has its basis in test tube studies and overexpression studies conducted in non-neuronal cells, both of which demonstrate that at sufficient levels and under certain conditions, tau can indeed stabilize microtubules [22–24]. But is this actually the case in the axon?

Despite the prevailing dogma on tau, there have been reasons to be skeptical. Microtubule researchers have long observed that proteins with microtubule-binding sites that may not physiologically stabilize microtubules can stabilize them if overexpressed in cells or if exposed in excess to microtubules *in vitro*. In addition, it has been known for over two decades that tau is most enriched on the especially labile microtubules that occupy the distal region of the axon and the growth cone [6, 25]. Finally, the normal on-off rate of tau's association with the microtubules in the axon is 40 milliseconds [26], which seems rather fast for a protein that supposedly stabilizes the microtubule against disassembly. For these and other reasons, a fresh look at tau's role in microtubule stability in the axon is long overdue.

Microtubule stability in the axon of cultured neurons

In the early 1990s, it was reported that individual microtubules in the axon of cultured rat sympathetic neurons consist of a stable domain toward the minus end of the microtubule and a labile domain toward the plus end of the microtubule [27, 28]. The labile domain was shown to depolymerize rapidly in the presence of nocodazole, a drug that binds free tubulin subunits, while the stable domain was shown to depolymerize much more slowly. These studies took advantage of the fact that post-translational detyrosination (and also acetylation) of alpha tubulin usually accumulates in the more stable microtubule fraction of cells, leaving the more labile fraction richer in tyrosinated (and unacetylated) tubulin (see Box 1). Using immuno-electron microscopy, it was shown that the labile domain labels heavily for tyrosinated tubulin, while the stable domain shows no labeling at all. This domain structure was later also demonstrated with immunofluorescence microscopy, using a strong extraction protocol that enables individual domains to be visualized as they splay away from the axonal microtubule bundle [28]. In neurons treated with nocodazole for just 15 minutes, almost all of the labeled microtubule profiles were no longer present, demonstrating a tight correlation between staining for tyrosinated tubulin and the identity of the microtubule profile as a labile domain. In cultured rat sympathetic neurons, roughly half the microtubule mass of the axon was determined to be stable and the other half labile. The half-lives for depolymerization in the presence of nocodazole were a few minutes for the labile domains and over 100 minutes for the stable domains [27, 29]. Similar findings were later obtained in studies on cultured rat hippocampal and cortical neurons, but with a greater fraction of the microtubule mass

being labile [30]. The domain structure of axonal microtubules is important throughout the life of the neuron because each domain, by virtue of its differences in composition, interacts differently with molecular motors, microtubule-severing proteins, and proteins called +TIPs that interact preferentially with the plus end of rapidly elongating microtubules. Individual microtubules in adult neurons also consist of stable and labile domains, as was shown several years ago in studies on intact nerves from animals [31].

The current tau dogma would predict greater levels of tau associated with the stable domain of the microtubule compared to the labile domain, with the stable domain becoming less stable when tau is depleted. However, when a tau antibody was microinjected into cultured neurons to sequester tau in the cell body prior to axon outgrowth, the microtubules in the tau-free axons that rapidly grew from these neurons were no more less stable than the microtubules in control axons [32]. Despite this work calling into question tau dogma, only recently have there been follow-up studies, with the results suggesting that axonal microtubules become more stable in the absence of tau.

Tau and microtubule stability

A new study [33] set forth to ascertain the effects of depleting tau on axonal microtubule stability in cultured rat cortical or sympathetic neurons using more quantitative and multi-faceted approaches than those used in the earlier work [32], with special attention to the effects on stable and labile microtubule domains. After four days of tau depletion by pan-tau-isoform RNA interference, the axons were not markedly different in their length or morphology from control counterparts, but contained less microtubule mass, per unit length of axon. Tau dogma would predict that this microtubule loss was due to destabilization of the microtubules, meaning that the stable domains of the microtubules become less stable. However, quantitative immunofluorescence revealed that the tau-depleted axons contained higher levels of detyrosinated tubulin, per unit length of axon, than controls axons, despite having less microtubule mass. In addition, far fewer labile (i.e., tyrosinated-tubulin-rich) domains of microtubules can be visualized in tau-depleted axons relative to control axons. These observations suggest that the microtubule diminution after tau depletion is not from stable domains becoming less stable but rather is due to the partial loss of the labile domains. In fact, the remaining portions of the labile domains become more stable as tau is lost.

The kinetics of microtubule loss in the presence of nocodazole were consistent with the results on microtubule detyrosination. More microtubule mass was stable in tau-depleted axons than controls with the remaining portion of the labile fraction not as labile (i.e., more stable) than the labile fraction of controls. Live-cell imaging of rates of microtubule assembly also revealed that that labile domains had become less dynamic (i.e., less labile) than control counterparts.

Live-cell imaging also revealed dramatically fewer microtubule assembly excursions in tau-depleted axons compared to control axons. Each stable domain should theoretically be able to assemble a new labile domain from its plus end, and there are no fewer stable domains after tau depletion than before. There would only be fewer assembly excursions if tau has an

additional role in not only protecting the labile domain from being stabilized but also in promoting its assembly. In fact, the ability of tau to promote microtubule assembly was its original hallmark [34], even before the notion of it stabilizing microtubules became so prevalent.

When studying microtubule dynamics in non-neuronal cells or *in vitro* with limited accessory proteins present, the stability of the microtubule is often defined as how long it assembles before it undergoes a bout of disassembly. Thus, one might wonder, in considering these results, if tau provides some level of stability to the labile domain in the sense that tau enables the labile domain to grow longer than it otherwise would in the absence of tau. However, in the absence of tau, the labile domain is shorter, more detyrosinated, less dynamic and less sensitive to nocodazole. Thus, by these criteria, the labile domain is more labile in the presence of tau than in the absence of tau, which disqualifies tau's influence on the labile domain as a stabilizing effect. The reason for this, as explained later, is that in the absence of tau, other proteins can influence the labile domains of the microtubules in ways that these proteins do not when tau is present (Figure 1A).

Tau's distribution on axonal microtubules

If it is keeping the labile domain labile, tau should theoretically be concentrated on the labile domain. It was known for decades that tau is enriched on the labile domains of microtubules that extend into the distal region of the axon, but whether the same is true of microtubules along the axon had yet to be explored. Visualizing this directly is problematic because stable and labile domains are staggered along the length of the axon, with individual microtubules taking on a range of lengths, and because the microtubules are spaced so closely together that individual microtubule domains cannot be resolved by conventional epi or confocal fluorescence techniques. As an indirect approach, it was reasoned that if there is more tau on labile domains than stable domains, then the ratio of microtubule-associated tau to microtubule mass in the axon should be lower after depolymerization of the labile domains with nocodazole. Indeed, such studies revealed that there is at least twice the density of tau on the labile domains compared to the stable domains. Moreover, newly assembling labile domains arising after rinsing out the nocodazole were especially rich in tau. Collectively, these findings are consistent with tau rapidly binding and concentrating on the labile domain of the microtubule as it assembles, with far less tau on the stable domain (Figure 1B).

How does tau prevent labile domains from being stabilized?

Might tau be enriched on labile domains to prevent genuine microtubule-stabilizing proteins from binding to the labile domain? If this is true, tau is not a stabilizer of the microtubule but a preventer of microtubule stabilization by other such proteins. Several years ago, it was reported that certain microtubules in lamellar regions of the axon are rich in doublecortin but deficient in tau, suggesting that these two microtubule-associated proteins may somehow exclude one another from the microtubule lattice [35]. However, total doublecortin levels in the axon are probably insufficient to account for a major shift in microtubule stability when tau is depleted, and indeed, investigation into this matter showed that doublecortin is not

responsible for the greater stability of microtubules in the absence of tau [33]. Moving on from doublecortin, MAP6 was considered a better candidate for conferring stability on tau-depleted axonal microtubules, because, unlike tau, MAP6 is richer on stable domains of axonal microtubules than labile domains [25] and because a number of studies had already documented that MAP6 has the appropriate properties to stabilize microtubules in cells [36]. In addition, MAP6, originally known as STOP (“stable tubule only protein”), was shown many years ago to slide along the lattice of the microtubule [37]. Most of the MAP6 in cells is not microtubule-associated but becomes microtubule-associated when cells are exposed to cold, in order to make the microtubule stable to cold-induced depolymerization [38]. Might the axon respond to tau depletion similarly to how it responds to cold by inducing greater levels of MAP6 to bind to the labile microtubule domains, perhaps in part by sliding out from the stable domain to bind to the labile domain? In support of this idea, not only was there more MAP6 bound to microtubules because of tau depletion, there were also higher levels of total MAP6 in the neuron [33].

Like tau depletion, depletion of MAP6 by siRNA resulted in loss of axonal microtubule mass. However, virtually everything else that was assayed in these experiments gave the inverse of the results of tau depletion. There was a diminution in the stable microtubule fraction, with the labile microtubule fraction becoming more labile (i.e., less stable) than control counterparts [33]. However, MAP6 cannot be the only microtubule stabilizer in the axon because the remaining portion of the stable microtubule fraction was no less stable after MAP6 depletion. A long list of other proteins has been implicated with microtubule stability in the axon [39], but whether any of the others share MAP6’s inverse relationship with tau remains an open question. One provocative aspect of these results is that loss-of-tau phenotypes in neurons might be just as attributable to more MAP6 binding to the microtubules as less tau.

Relevant to the possibility that MAP6 is not alone in its inverse relationship with tau is recent work on a microtubule-associated protein called MAP7 (also called ensconsin), which is known to interact with kinesin-1, drawing it to the microtubule to enhance motile events along the microtubule [40, 41]. These studies demonstrate competition between tau and MAP7 for the microtubule lattice wherein tau binds abundantly first and then is gradually displaced by MAP7 [42]. MAP7 might be a genuine microtubule-stabilizing protein [40, 41], but even if it is not, these findings suggest a pattern (which includes doublecortin as well) by which tau impedes the binding of various different microtubule-associated proteins (with different microtubule-binding domains) to the microtubule lattice.

A new model

Understanding tau’s role in regulating the stability properties of axonal microtubules depends on the inverse role that tau has with genuine stabilizing proteins, such as MAP6. This kind of relationship would not likely be recapitulated in studies involving overexpression of tau in non-neuronal cells or in test tube studies – unless of course the experiments were designed specifically to test for such a relationship. In the context of the axon, it seems reasonable to posit a new model in which tau enables microtubules to assemble long labile domains while preventing them from being stabilized by proteins. How

might this work? The competition between tau and genuine stabilizers probably cannot be explained by different affinities for the same binding sites on the microtubule, because tau and these other proteins do not share the same kinds of microtubule-binding sites [43, 44]. It may be that tau's expression levels in neurons and tau's strong affinity for microtubules in the axon combine to overpower the capacity of genuine stabilizers to accumulate in sufficient numbers to stabilize the labile domain. When the labile domain assembles, tau immediately interacts with the lattice, associating and dissociating at a rapid rate, and this keeps down the number of molecules of MAP6 and other potential stabilizers that can bind to the labile domain. When a signaling event causes phosphorylation of tau's microtubule-binding sites, less tau is available to associate with the microtubule and hence genuine stabilizers such as MAP6 can then associate with the labile domain in higher numbers, rendering it more stable. This could be a partial stabilization, or it could lead to the labile domain becoming stabilized to the point of becoming part of the stable domain. Once the genuine stabilizers get a foothold, then tau becomes inefficient at outcompeting them, such that the stable domain does not revert to being labile. Interestingly, this model for tau and MAP6 (shown in Figure 2) is similar to a scenario described many years ago for MAP1b in which a phospho-variant of MAP1b binds to microtubules in the distal region of the axon to keep the non-phosphorylated version of MAP1b from stabilizing the microtubules [45]. Sequestration of MAP1b in the cell body of the neuron by the identical antibody injection approach as described earlier for tau demonstrated destabilization of microtubules in the distal region of the axon [46], consistent with a role for MAP1b as a genuine microtubule stabilizer.

Taken together, these results are relevant to emerging ideas about how various proteins such as traditional microtubule-associated proteins and molecular motor proteins might compete for association with the microtubule. These ideas, based mainly on studies conducted *in vitro*, suggest that the interaction of a particular protein with the microtubule might alter its lattice in such a way as to make it more or less amenable to the binding of other proteins [42]. This process, called "lattice gating," can also make the lattice more amenable to additional binding of the same protein, leading to high densities of that protein on discrete regions of the microtubule. This has been shown for tau, with vivid demonstration of tau "condensations" on individual microtubules [47].

Relevant also to these ideas are ground-breaking studies recently published at the near-atomic level, demonstrating via cryo-electron microscopy that tau binds along microtubule protofilaments, tethering together tubulin dimers [48]. The new model discussed here suggests that, at least in the context of microtubules in the axon, these interactions probably promote microtubule assembly without stabilizing the microtubule, perhaps because of the rapid on-off rate of tau. It is not difficult to fathom, however, that such tethers could stabilize the microtubule under less physiological conditions, thus leading to misleading results in overexpression studies.

Adult neurons, disease and therapy

The most urgent next step is testing whether tau's role in adult neurons is the same as indicated by the work on developing neurons in culture. There are differences that may be

relevant, such as developing neurons express almost exclusively the 3R isoform of tau, which has three repeats of the microtubule-binding domain, whereas adult neurons also express the 4R isoform, which has four repeats of the microtubule-binding domain [49, 50]. There is also greater complexity to the phosphorylation status of tau in adult neurons, as well as the levels and complexity of other microtubule-related proteins with which tau may have inverse or redundant effects. In addition, features of the microtubules themselves might cause them to interact differently with tau and these other proteins; for example, polyamination of tubulin (which itself confers stability to microtubules) (See Box 1) is sparse in developing neurons but abundant in adult neurons [51]. Even so, the abundance of microtubule stabilizers in adult axons puts an even higher onus on tau to maintain a robust labile microtubule fraction. Some support for this view comes from work on post-mortem brain tissue from humans with tauopathies, in which the microtubule mass is diminished relative to normal brain samples, but more highly detyrosinated and/or acetylated [52–55]. This is consistent with the expectations from new findings discussed here, and the opposite of the expectations of tau dogma.

In tauopathies, the detachment of tau from the microtubule is generally considered to cause the loss of microtubule mass, as opposed to the toxic properties of the abnormally phosphorylated tau. Interestingly, when tau expression is experimentally reduced in adult mouse brain, the mouse displays memory loss and synaptic dysfunction, suggesting a major role for tau in maintenance of these brain functions [56]. This may suggest that the reduction and partial stabilization of labile domains of axonal microtubules is causative of these symptoms in patients with tauopathy. A popular idea in recent years has been that the microtubule loss in Alzheimer's disease and other tauopathies can be corrected by treatment with low levels of microtubule-stabilizing drugs [21]. While preclinical studies using such drugs on mouse disease models have produced some encouraging results, the studies discussed here on tau suggest that the mechanistic basis for such an approach needs re-thinking. Figure 3 shows one possible cascade (but not the only one) for how this might occur, starting with beta amyloid. Restoring lost labile microtubule mass may prove to be a more appropriate strategy than stabilizing microtubules. Whether low levels of microtubule-stabilizing drugs can substitute for tau in this regard remains to be seen. Germ line tau knockout mice are interesting to think about, in this context, because they appear to be relatively asymptomatic until old age [57], which suggests that compensatory mechanisms have prevented dramatic abnormalities in microtubule stability or tyrosination status from taking place in these animals, at least until old age. Perhaps understanding how other proteins compensate for the absence of tau in the younger tau knockout mice might prove useful toward the development of therapies for tauopathies. Along these lines, proteins that normally pare back labile domains of microtubules in the axon (Box 2) may be good targets for future drug discovery [30, 33, 58–63]. Another possibility is to pursue therapies that promote the binding of tau to microtubules, such that even under compromised tau conditions, available tau can be recruited to restore the labile microtubule domains [64, 65].

Concluding Remarks

It is remarkable that after hundreds of research papers from investigators around the world, there is still much to learn about tau, with dogma waiting to be challenged and surprises yet

to be revealed. Questions remain (see Outstanding Questions Box) such as whether similar results to those of the cell culture studies discussed here will be found in adult neurons *in vivo*. Tau's distribution on the stable and labile domains of the microtubules needs to be visualized directly, without the use of drugs, presumably by immuno-electron microscopy and/or expansion microscopy. Lattice gating as a mechanism to account for the competition between tau and genuine stabilizers makes sense but will require testing with quantitative techniques of greater resolution. Perhaps most pressing is what all of this means for treatment of tauopathies such as Alzheimer's disease.

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Glossary

Microtubules:

Polymers of tubulin subunits that act both as architectural struts for cells as well as railways along which molecular motor proteins convey cargo. They are polar structures that are highly dynamic until stabilized by tubulin modifications and microtubule-associated proteins.

Tau:

The best known and best studied of any microtubule-associated protein, which is enriched in the axon of neurons, where it binds along the lattice of the microtubule to influence various properties of the microtubule.

MAP6:

Originally known as STOP (stable tubule only peptide), MAP6 confers stability to microtubules when it binds to them and is known to bind more avidly to microtubules when cells are challenged with certain factors that would otherwise promote microtubule disassembly.

Axon:

One of two types of elongated processes extended by neurons (dendrites being the other) that is specialized to grow until it reaches an appropriate target and to transmit information over long distances.

Neurons:

Principal information-conveying cells of the nervous system that are terminally post-mitotic cells and that utilize their microtubules to extend and maintain axons and dendrites.

Microtubule stability:

Composed of tubulin subunits, microtubules are dynamic structures that undergo rapid bouts of assembly and disassembly. When a microtubule or a region of a microtubule is stabilized, the dynamics of assembly and disassembly slow considerably and sometimes completely.

Tauopathy:

Human diseases involving pathological alterations in tau. Tau, one of the most vulnerable proteins in the nervous system, is prone to becoming abnormally phosphorylated, leading to its dissociation from axonal microtubules. When this happens, the microtubules undergo changes due to loss of tau, but additional effects are elicited by the abnormally phosphorylated tau, which can form abnormal filaments such as neurofibrillary tangles. Alzheimer's disease is the best known tauopathy, but others include Parkinson's disease, traumatic brain injury, Supranuclear Palsy, and Frontotemporal Dementia.

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Box 1:**Tubulin post-translational modifications.**

Detyrosination, *acetylation*, and *polyamination* are three different modifications of tubulin associated with *microtubule stability*. All three (and there are also others) are regulated by enzymes. *Detyrosination* is the removal of the C-terminal tyrosine residue of alpha tubulin. *Acetylation* is the addition of an acetyl group to alpha tubulin.

Polyamination is the addition of amine groups to tubulin. *Polyamination* confers stability directly to microtubules, while the other two modifications do not. *Detyrosination* and *acetylation* accumulate in microtubules as a result of their stability. However, different microtubule-related proteins interact with microtubules differently as a result of these modifications, and these proteins can alter the stability of the microtubule. In the axon, *detyrosinated tubulin*, *acetylated tubulin*, and *polyaminated tubulin* are concentrated in the stable domain relative to the labile domain of individual microtubules.

Box 2:**Proteins that normally pare back labile microtubule domains – potential targets for tauopathy**

- *Fidgetin*: Microtubule-severing enzyme that preferentially severs microtubules in the labile domain; documented to function in this manner in the axon
- *Fidgetin-like-2*: Microtubule-severing enzyme similar in sequence and structure to fidgetin; presumably functions similarly to fidgetin, but not yet studied in the axon
- *Stathmin*: Sequesters tubulin subunits, thereby inducing disassembly of microtubules according to their dynamic properties
- *SCG10*: Similar to stathmin but neuron-specific
- *Kinesin-13*: Class of molecular motor proteins that induces loss of tubulin subunits from the microtubule by energy-dependent walking of the motor along the microtubule lattice
- *UNC-45A*: Cochaperone protein recently shown to induce microtubule severing and disassembly by an ATP-independent mechanism

Outstanding Questions Box

- What new information on tau's role in regulating axonal microtubule stability will be revealed by studies on adult neurons in their *in vivo* environment?
- What new information on tau's distribution on axonal microtubule might be revealed by higher resolution approaches such as immuno-electron microscopy, and/or by contemporary live imaging approaches, both in cells and *in vitro*?
- What is the mechanism by which tau outcompetes genuine microtubule-stabilizers for the labile domain of the microtubule, and how is this mechanism regulated by signaling pathways to convert labile domains to stable domains when and where functionally appropriate?
- Will strategies that restore lost labile domains of axonal microtubules provide effective treatments for tauopathies?
- What insights can be gleaned from tau knockout mice on the appropriate strategies for therapeutically overcoming the diminution of functional tau in tauopathies?

Highlights

- Tau is concentrated on the labile domain of the axonal microtubule, not the stable domain, which is contrary to the expectation of tau dogma.
- Contrary to tau dogma, when tau is depleted from neurons, the stable domain is no less stable, but the labile domain becomes shorter and more stable.
- When tau is depleted, MAP6, a genuine stabilizer of microtubules, is expressed more highly and binds to microtubules more avidly, providing an explanation for why the labile domain becomes more stable when tau is depleted.
- Competition between tau and MAP6 for binding to the microtubule is consistent with trending ideas on a process called “lattice gating,” by which the binding of one protein to the microtubule changes the lattice of the microtubule in a manner that makes it more or less amenable to the binding of another protein (or the same protein).
- The real role of tau in regulating microtubule stability in the axon is not to stabilize axonal microtubules, but rather to enable them to have long labile domains.
- Microtubule stabilization is likely achieved through signaling pathways that lead to tau phosphorylation, which leads to less tau affiliated with the labile domain of the microtubule, and hence greater propensity for genuine stabilizers such as MAP6 to stabilize the microtubule.
- Microtubule-stabilizing drugs may not be a logical choice for treatment of tauopathies in human patients.
- More rational microtubule-based strategies for treating tauopathies would restore labile domains of axonal microtubules that are diminished as a result of tau detachment.

Figure 1 (Key Figure). Recent experimental results are not consistent with tau dogma.

Each microtubule in the axon consists of a stable domain (dark blue) and a labile domain (lighter blue). Panel **A** shows repercussions of tau depletion from the axon. The cluster of microtubules on the lower left of the panel shows the expectations of tau dogma, in which depletion of tau results in microtubule destabilization, in turn leading to loss of microtubule mass. The cluster of microtubules on the lower right of the panel shows the experimental results, in which depletion of tau results in no change in the stability of the stable domain, but rather a shortening and partial stabilization of the labile domain. Shades of blue indicate levels of stability, with lighter shades indicating less stability. Panel **B** shows the distribution of tau (pink thread-like structures) on axonal microtubules. The panel on the left shows the

expectations of tau dogma, in which tau is concentrated on the stable domain to endow it with stability. The panel on the right reflects recent experimental results, which suggest that tau is concentrated on the labile domain to prevent it from being stabilized while also promoting its assembly.

Figure 2. Model for tau's role in regulating microtubule stability in the axon.

The upper panel shows tau enriched on the labile domain (light green) of the microtubule and MAP6 enriched on the stable domain (dark green). Shades of green indicate levels of stability, with lighter shades indicating less stability. Lower panels indicate the effects of tau depletion (on the left) and MAP6 depletion (on the right). When tau (pink thread-like structures) is depleted, MAP6 (blue thread-like structures) spreads out along the microtubule, binding more to the labile domain than it normally does, thus partially stabilizing it. When MAP6 is depleted, the stable domain becomes no less stable, suggesting that other stabilizing proteins contribute to its stability, but the labile domain becomes even more labile than it normally is, indicating that the small amount of MAP6 normally on the labile domain makes it slightly less labile than it would otherwise be. Tau depletion leads to shortening of the labile domain, while MAP6 depletion leads to shortening of both domains.

Figure 3. Proposed new role for tau in tauopathies.

Represented in the figure is one possible cascade (but not the only one) for Alzheimer's disease, wherein amyloid beta (Aβ) (yellow triangles) overproduction leads to tau being abnormally phosphorylated (clusters of purple hexagons), which leads to tau (dark brown thread-like structures) detachment from the microtubules. In other tauopathies, abnormal tau phosphorylation is caused by factors such as tau mutations. The effects on the microtubules displayed here reflect new findings on the actual role of tau in the regulation of microtubule stability in the axon. Microtubule loss occurs, but it is not due to microtubule destabilization.

Rather, the labile domains shorten and become somewhat more stable. Shades of magenta indicate levels of stability, with lighter shades indicating less stability. This is contrary to tau dogma and suggests that therapeutics should be based on restoring labile domains of the microtubules, as opposed to stabilizing them. The abnormally phosphorylated tau is toxic, and so too are the neurofibrillary tangles (and other abnormal tau filaments) formed from the abnormally phosphorylated tau. The toxicity of the abnormal tau contributes to axonal degeneration, further complicating the disease beyond the effects of detachment of tau from the microtubules.