Potential structure/function relationships of predicted secondary structural elements of tau

T. Chris Gamblin*

Department of Molecular Biosciences, University of Kansas, 1200 Sunnyside Ave. Lawrence, KS 66045, United States

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Abstract

The microtubule-associated protein tau is believed to be a natively unfolded molecule with virtually no secondary structure. However, this protein self-associates into filamentous forms in various neurodegenerative diseases. Since these filamentous forms show a remarkable degree of higher order due to their regular widths and periodicity, it is widely speculated that tau does contain secondary structures that come together to form tertiary and quaternary structures in the filamentous form. The purpose of this review is to use the primary sequence of tau along with predictive methods in an effort to identify potential secondary structural elements that could be involved in its normal and pathological functions. Although there are few predicted structural elements in the tau molecule, these analyses should lead to a better understanding of the structure/function relationships that regulate the behavior of tau.

Keywords: Tau; Alzheimer’s disease; Paired helical filament; Protein structure; Sequence analysis; Polymerization

Under normal conditions, the microtubule-associated protein tau demonstrates the properties of a highly soluble natively unfolded molecule, essentially devoid of secondary or tertiary structural elements (reviewed in Ref. [1]). However, in Alzheimer’s disease (AD) and other neurodegenerative disorders, this protein can accumulate in filamentous forms that demonstrate a remarkable degree of order. Paired helical filaments, the major filament type found in AD, consist of tau filaments that range in thickness from 8 to 20 nm with a regular periodicity of 80 nm [2]. Straight filaments, the major filament type found in Pick’s disease and the minor filament type found in AD, have a regular width of approximately 10–15 nm without any regular periodicity [3]. It is unlikely that the random aggregation of tau in the disease state could lead to creation of these highly ordered structures. Rather, it is much more likely that the tau molecule adopts specific secondary and tertiary structures which interact in an orderly fashion to produce the highly regular filaments found in disease.

However, the credibility of this proposition suffers from the seeming lack of regular structural elements in the tau protein that could contribute to this process.

Analyses of the structure of tau protein in its soluble state through conventional methods such as electron microscopy, spectroscopy, and X-ray diffraction have not provided detailed information about the regions of tau that may play a role in its ability to either bind to microtubules or to self-associate into the filaments found in neurodegenerative diseases [3–8]. Some structural details have been obtained from structural analyses of tau in its filamentous state. The current consensus in the field is that tau is capable of self-associating through β-strands formed by sequences in its microtubule-binding repeats [9–12], although analyses revealing little structure or a predominance of α-helical structure in tau filaments have also been reported [8,13,14]. With only a few exceptions (discussed below), the actual sequences of tau that are involved in creating secondary structure are unknown.

Since the tau molecule has proven resistant to structural analyses through direct methods, it is the purpose of this article to discuss the potential involvement of the primary
sequence of tau in the adoption of secondary structures that one could hypothesize would be necessary to generate filaments derived solely from tau protein. In order to make these predictions, current algorithms for assigning secondary structure to primary amino acids sequences were combined with known structural/functional relationships in the tau molecule in an attempt to identify regions of tau with a high potential for adopting secondary structure that could be involved in its normal or pathological roles.

1. Methods employed

Although the success rates of many algorithms designed to predict secondary structures from primary amino acid sequences have improved with growing databases of protein secondary structures, it must be noted that many algorithms only result in 60–70% accuracy, with many false-positives, an inability to correctly assign structure, or the incorrect assignment of the secondary structures. In an effort to reduce over-analysis of the primary sequence of tau, or perhaps the incorrect assignment of secondary structures, five different algorithms for predicting secondary structure from primary amino acid analysis were employed in this study, and only those sequences that exhibited agreement in at least three of the five methods were assigned secondary structures for the purpose of this review. Regions of the molecule that at least four of the five methods agree in their predictions for a high propensity for a particular type of secondary structure are referred to as being strongly predicted to adopt that structure. Regions of the molecule that have agreement between only three of the five methods are referred to as being weakly predicted to adopt structure.

The first algorithm employed is the method of Chou and Fasman [15], which relies on the propensities of certain amino acids to adopt particular secondary structures. This analysis was performed using the Omiga software package (MediaCybernetics). The second method is the refined GORII method that relies on preferences for a sequence of amino acids to adopt particular secondary structures, but with additional weight added to amino acids at a particular position within the secondary structure [16]. This analysis was also performed using the Omiga software package (MediaCybernetics). The third method, SSPAL, predicts secondary structures based on local alignments and nearest-neighbor algorithms applied to the primary sequence [17]. This analysis was originally performed on-line, and is now available at http://www.softberry.com/berry.phtml. The

![Primary structure and secondary structure prediction alignment of the tau molecule. The primary sequence of the longest human central nervous system isoform of tau is reproduced here with the variably spliced exon 2 (a.a. 41–73) in red letters, exon 3 (a.a. 74–103) in blue letters. The four microtubule-binding repeats (MTBR) are highlighted: MTBR1 in green (a.a. 241–274); the variable spliced exon 10 MTBR2 in pink (a.a. 275–304); MTBR3 in light blue (a.a. 305–335); and MTBR4 in orange (a.a. 336–367). The secondary structure predictions for each of the five methods are represented below the primary structure. Primary sequences predicted to form secondary structures are indicated by the types of structures they are predicted to form: cylinders depict predicted alpha helices and block arrows depict predicted beta strands. The primary sequences that have a consensus prediction by at least three of the five methods are underlined.](image-url)
fourth method, NNSSP, predicts secondary structures based on a neural-network and nearest-neighbor method developed by Yi and Lander [18] combined with a method for secondary structure prediction based on local structural secondary structures developed by Bowie et al. [19]. This analytical tool is available on-line at http://bioweb.pasteur.fr/seqanal/interfaces/nnssp-simple.html. The last method employed was NNPREDICT, a method for predicting secondary structure based on a two-layer, feed-forward neural network [20]. This analytical tool is available on-line at http://www.cmpharm.ucsf.edu/~nomi/nnpredict.html.

Overlaying the sequence analysis of the primary structure of tau obtained by the five different methods for predicting secondary structure reveals that only 12% of the molecule has consensus predictions for secondary structure (Fig. 1). Although this does not result in a large amount of secondary structure, it is our hypothesis that this small amount of information can lead to a more detailed analysis of the structural elements of tau that could be contributing to its formation of higher order aggregates. These predicted structures will be addressed in order beginning at the amino-terminus of tau and moving toward the carboxy-terminus. In addition, when these potential structural elements have functional roles in the properties of the tau molecule, they will be discussed in relationship to their predicted structure.

2. 7EFEVME12

The amino acids 7EFEVME12 in the amino-terminal region of tau are of a consensus prediction to form an alpha helix (Figs. 1 and 2). This region is believed to be involved in the ability of tau’s projection domain to interact with cellular components other than microtubules, including motor proteins and the plasma membrane [21–23]. In addition, this region has been implicated as being involved in the regular spacing of microtubules in axons [21–23]. The potential for forming structural elements could allow for the specific functions that have been postulated for this region.

This potential structural element could also be involved in the pathogenesis of Alzheimer’s disease. These amino acids form one of the discontinuous epitopes that comprise the antigen recognition motif of the conformationally sensitive antibody Alz50 [24–26]. Alz50 has been shown to have a higher affinity for tau in the aggregated state than for monomeric tau [24–26]. In addition, the levels of Alz50 reactivity is greatly increased in Alzheimer’s disease tissue as compared to age-matched controls [27].

The second discontinuous epitope involved in Alz50 reactivity has been shown to be in the microtubule-binding repeats region. There are potential structural elements in these that could form amphipathic alpha helices (although they do not have a consensus prediction to do so, as discussed below). These potential amphipathic alpha helices contain positively charged amino acids that could interact with the acidic side chains of 7EFEVME12 (Fig. 2), providing a structural basis for the Alz50 conformation.

This region of the molecule could also play an important role in the ordered aggregation of tau. Deletion of amino acids 2–18 resulted in a significant reduction of tau’s ability to aggregate in the presence of arachidonic acid (ARA) [28]. The addition of a peptide corresponding to this region of the molecule had no effect on the aggregation of tau in the presence of ARA, indicating that this region must be tethered in order to exert its influence on the reaction [28]. This information, combined with the aforementioned evidence obtained through Alz50 recognition of amino-terminal interactions with the microtubule-binding repeats in the disease state, has led to the postulation that tau aggregation is accompanied by a dramatic conformational change that brings the amino-terminus in close proximity to the microtubule-binding repeats [24]. In fact, it has been demonstrated through tryptophan mutagenesis of the microtubule-binding repeats and fluorescence resonance energy transfer that tyrosine residues in the amino-terminal region...
of the molecule come in close contact with the microtubule-binding repeats upon the formation of higher ordered tau structures [29].

Since an amino-terminal peptide by itself cannot recapitulate the effect of the tethered amino-terminus on tau aggregation, it is likely that it is the conformation of tau that is formed by the interaction of the amino-terminus and the microtubule-binding repeats, and not simply the interaction itself, that leads to tau’s increased ability to aggregate. This hypothesis is further strengthened by the observation that the modifications of the intervening regions between the amino-terminus and the microtubule-binding repeat regions through the elimination of exon 3 or exons 2 and 3 have a great effect on tau aggregation, even though these regions are not strongly predicted to contain structural elements [30].

3. **31MH**

The next region of tau to be predicted to form secondary structural elements is **31MH** which is relatively weakly predicted to form a beta strand through a consensus of three of the methods (Fig. 1). Very little is known about the contributions this region makes to the normal functions of tau or in its ability to aggregate into ordered structures. However, the fact that four of the five secondary structure prediction methods assigned secondary structure to this region indicates that some structural rigidity is likely for this region. Although the functional significance of this structural rigidity cannot be ascertained from primary sequence analysis, it could bear further investigation.

4. **117EAAGHVTQ**

The region **117EAAGHVTQ** is weakly predicted to form an alpha helix by three of the five secondary structure prediction algorithms. Although the functional significance of this region is unknown, this region is adjacent to the second most hydrophobic region of the molecule, which peaks at L114, as predicted by the Janin method (performed using the Omiga software package). In addition, this alpha helix is also predicted to be amphipathic by helical wheel analysis (Fig. 2), making it a candidate to interact with the microtubule-binding repeats or the carboxy-terminus of tau (see below).

5. **226VAVVR**

The region **226VAVVR** is strongly predicted to form a beta strand by four of the five secondary structure prediction algorithms (Fig. 1). This stretch of amino acids resides within the proline-rich region of tau, and represents a hydrophobic patch surrounded by basic amino acids. This region has been implicated in interacting with the microtubule-binding repeats to strengthen the interaction of tau with microtubules [31]. Synthetic peptides corresponding to this region were not capable of influencing microtubule binding on their own, but their addition to the microtubule-binding repeats greatly enhanced the ability of tau to influence microtubule dynamics, indicating that there could be a direct interaction of this region with the microtubule-binding repeats [31]. It is possible that this region could also be involved in the pathogenesis of AD. The sequence **226VAVVR** lies within the larger proline-rich region (155–244) which contains one part of the discontinuous epitope for the conformationally sensitive antibody Tau-66 [32]. The other part of the Tau-66 epitope lies in microtubule-binding repeat 3 (305–314, discussed below). This region is highly predicted to form a beta strand just as 226–230. Both of these beta strands are somewhat hydrophobic in nature, potentially providing a structural basis for their interaction in the enhancement of microtubule dynamics. In addition, Tau-66 reactive species are elevated in AD [32,33], indicating that this particular conformation of tau could represent one of the steps that lead to its formation of higher order aggregates that accumulate in this disease.

6. **275VQII** and **306VQIVY**

The predicted beta strands **275VQII** and **306VQIVY** are potentially the most important structural elements for tau’s ability to self-aggregate into ordered structures. These sequences have been shown to be capable of forming filamentous structures in the absence of the rest of the molecule and likely represent the core structural elements for filament elongation [9,34,35]. These sequences have also been shown to adopt a beta strand conformation upon aggregation by several methods, including FTIR, CD, and X-ray diffraction [9,34,35]. These beta strands would have a somewhat amphipathic nature (Fig. 3A and B), with several hydrophobic residues on one face, with a relatively polar face opposite. It has been previously suggested that this amphipathic nature could account for the strong association of these structural elements that lead to their aggregation [9,34]. In this situation, the amphipathic strands would form horizontal sheets that could then stack on top of one another to propagate the filament growth (Fig. 3C and D).

Since these structural elements lie in the second and third microtubule-binding repeats, respectively, the three repeat isoforms of tau would only contain one of these elements (since they lack the second microtubule-binding repeat) and the four repeat isoforms of tau would contain both structural elements. This structural difference could account for the increased propensity for the aggregation of four repeat isoforms of tau at low (75 μM) ARA concentrations in vitro [30]. This potential structural difference is also observed using the polyanion heparin to induce tau polymerization. Peptides consisting of three microtubule-binding repeats
(MTBR 1, 3, and 4; K19 [36]) consistently polymerize more slowly than peptides consisting of four microtubule-binding repeats (MTBR 1, 2, 3, and 4; K18 [36]) in the presence of heparin and reducing agents. In the absence of cysteine oxidation, four repeat peptides (K18) polymerized at a faster rate and to a greater extent than three repeat peptides (K19) in the presence of heparin [36]. Together, these results suggest that having both of the potential structural elements represented by 275VQII278 and 306VQIVY310 present can enhance tau polymerization, although equal amounts of polymerization can be observed with only 306VQIVY310 present under oxidizing conditions [36].

The nature of these structural elements may also provide insight into the mechanism behind the ability of polyanions and anionic detergent-like molecules to induce the aggregation of tau in vitro. Amphipathic beta strands have a high propensity for self-association, especially if they are arranged in a parallel configuration. However, charged amino acids in such strands reduce this tendency to self-associate [37]. The amphipathic beta strands in the microtubule-binding repeats of tau have positively charged lysine residues in close proximity to the predicted strands: 275KVQINK280 and 305SVQIVY311. These charged residues should inhibit or greatly reduce the tendency of these strands to interact [37]. However, it is possible that negatively charged molecules such as heparin, polyglutamate, RNA, and fatty acids could help offset this electrostatic repulsion, explaining their ability to facilitate tau aggregation in vitro. In fact, this proposition would also explain why fatty acids have such a greater propensity for facilitating tau aggregation than do the other polyanions [36]. The amphipathic nature of fatty acids could potentially have two sites of interaction: with the positively charged lysine residues and with the hydrophobic side chains (Fig. 4A). This would explain why uncharged or cationic detergents were incapable of inducing tau aggregation [38], although more recent evidence suggests that the hydrophobic portion of the fatty acids are less involved in the induction of tau polymerization than is the negatively charged surface of fatty acid micelles [39]. In this case, it is likely that a sequence such as 305SVQIVYK311 would interact with the surface of a negatively charged micelle, leaving the other face of the proposed beta strand solvent exposed (Fig. 4B). This would provide sites for interaction for other solvent exposed beta strands with hydrophobic faces. Such interactions could result in the formation of filaments by the repeated lateral and vertical interactions of beta strands nucleating from the surface of the negatively charged particle. Evidence for such a mechanism has been directly observed using negatively charged particles to induce tau polymerization [39].

Further support for the importance of beta strand aggregation and inhibition of this process by the presence of positively charged lysine residues comes from experiments in which one of the lysine residues was removed from the second microtubule-binding repeat in a tau construct that
corresponded to the microtubule-binding repeats only (K19–D280, [36]). This construct is capable of aggregation, even in the absence of negatively charged inducer molecules. However, it should be noted that peptides corresponding to the sequences VYK, IVYK, QIVYK, and VQIVYK were capable of polymerization into filamentous structures containing two protofilaments in the absence of polyanion-inducer molecules [35]. Thus, the positively charged lysine residue does not completely inhibit the aggregation of this region, at least in the absence of the rest of the molecule.

It should be noted that the sequence KVQINKK could potentially adopt an alpha helical structure in the microtubule bound state even though they are not predicted to do so by any of the methods employed for this review. Lysines 275 and 281 are vital for the binding of four repeat tau to microtubules. In an alpha helix, these amino acids would be on the same face and ideally placed for interactions with the negatively charged surfaces of microtubules. If they were in the extended conformation of a beta strand, it is less likely that they would be so strongly involved in microtubule interactions due to distance considerations. Taken together, in vitro polymerization data [9] and the microtubule-binding data [40] suggest that this region could potentially adopt an alpha helical structure in the normal state, but convert to a beta strand in the aggregated disease state. Such a pathological conversion of structure is a common feature of amyloidogenic proteins [41].

7. Measured structural element 315LSKVTSKCGSL325

Another structural element that should be considered in the tau molecule is the stretch of amino acids in MTBR3 315LSKVTSKCGSL325 which has a high propensity for forming alpha helical structure in hydrophobic environments [42], although it is not strongly predicted to do so. This alpha helix also has an amphipathic nature as predicted by helical wheel analysis (Fig. 2, first reported in Ref. [42]). The amphipathic nature of the alpha helix would make it a candidate to interact with the amphipathic C-terminal tail. In addition, its amphipathic nature also makes it a candidate as a structural element that participates in tau–tau interactions in the aggregated state, as has been previously suggested [42]. Indeed, deletion of half this sequence greatly diminishes the ability of tau to aggregate in the presence of ARA [43]. Tau constructs containing amino acids 1–320 are capable of aggregation in the presence of ARA, whereas tau constructs containing amino acids 1–313 are not, emphasizing the importance of 314DLSKVTS for the aggregation of tau.

8. 338EVK340 and 361TH362

Microtubule-binding repeat 4 contains two potential secondary structural elements: 338EVK340 and 361TH362. These elements are only weakly predicted to form secondary structure, but their positioning in MTBR4 suggests that they could contribute to microtubule binding. MTBR4 is generally believed to have only a small influence on microtubule binding or the aggregation of tau, but the structural rigidity provided by the predicted propensity of these elements to
form secondary structures could suggest that they could play some role, although that role is not immediately clear from the analysis of their primary structure. Similar short beta strand elements $^{372}KLT^{377}$ and $^{391}EIVYK^{395}$ are present in the region between the MTBR and the C-terminus of tau. $^{391}EIVYK^{395}$ has a predicted structure similar to those beta strands predicted in MTBR2 and MTBR3 (see above) and deletion of the carboxy-terminus containing these residues reduces three-repeat tau binding to microtubules by approximately 10-fold [40]. Therefore, it is possible that this potential structural element could be interacting with the microtubule-binding repeats in a fashion similar to $^{226}VAVVR^{230}$. Although little is known about the contribution $^{391}EIVYK^{395}$ makes to the aggregation of the tau molecule, this region has been shown to be cleaved in some cases of AD. An antibody, MN423, recognizes tau that has been specifically truncated at E391 [44]. Many cases of AD show an elevation in MN423 reactivity, indicating that this site could be significant [45]. In addition, cleavage of tau at this site in vitro results in greatly enhanced kinetics of tau aggregation in the presence of ARA [43], indicating that this region could be interacting with the microtubule-binding repeats where it enhances microtubule binding and disfavors tau aggregation.

9. $^{426}ATLADEVSA^{437}$

The last strongly predicted element for forming secondary structure is a carboxy terminal alpha helix $^{426}ATLADEVSA^{437}$. This element has been shown to have a propensity for forming alpha helical structures in a hydrophobic environment [14,46,47]. Helical wheel analysis predicts that this element would have a strong amphipathic nature (Fig. 2 and Ref. [46]). This region of tau has been shown to inhibit the aggregation of tau molecules in the presence of ARA [43,46]. Removal of this region results in greatly enhanced polymerization kinetics [43,46] and peptides corresponding to this stretch of amino acids can strongly inhibit tau aggregation, suggesting that this structural element can directly bind to some other element of tau and prevent the aggregation of the molecules. This element is capable of inhibiting the aggregation of a tau construct containing amino acids 1–375, but is not capable of inhibiting the aggregation of a tau construct containing amino acids 1–320. Therefore, it has been predicted that the site of interaction of the carboxy terminal tail resides in the region of 320–375, and this binding partner is likely directly involved in the aggregation process [46].

10. Summary and conclusions

The function of regions of tau that have been identified as being important for its ability to bind microtubules or to self-associate can best be explained if these regions adopt a secondary structure. However, the best current data suggest that very little secondary structure exists in tau monomers alone in solution. Therefore, it is likely that the presence of a binding partner is responsible for the conversion of these regions from a natively unfolded state to a stable folded state, and that conversion is functionally important. Thus, “induced fit” conformational changes could explain the ability of tau to assume soluble, microtubule binding, and self-association states.

The microtubule-binding repeats and the inter-repeat regions are predicted to have a propensity for forming secondary structures that would arrange the amino acids in an optimal position for interacting with the relatively electronegative surface of the microtubule (Fig. 5). In addition, these predicted structural elements would, in theory, be capable of interacting with their nearest neighbors, and strengthen their binding through noncovalent interactions. Such a phenomenon has been observed with tau molecules “overloading” on the surface of microtubules [48]. This potential interaction could also contribute to the microtubule stability observed in the presence of tau by generating regions of microtubules that have a matrix of structural support proteins associated with them. However, it is important for tau solubility that these interactions do not occur off the surface of the microtubule. Without the correct binding partner, i.e., the electronegative surface of the microtubule, this region could be much less likely to adopt these secondary structures that contribute to a propensity for self-association. The positively charged lysines in this region, in addition to other regions, such as the amphipathic carboxy-terminal tail, could also prevent tau self-interactions, and thus keep it in a soluble state.

It is conceivable that in Alzheimer’s disease and other neurodegenerative tauopathies the self interactions that are likely to occur on the surface of the microtubule may be induced while tau is no longer bound to the microtubule. Although the mechanism responsible for this change is not known with any certainty, one prediction is that it may involve phosphorylation. Phosphorylation can have profound functional and structural effects. Not only can it result in the release of tau from the surface of the microtubule (reviewed in Ref. [49]), but at specific sites, phosphorylation appears capable of preventing the adoption of particular conformations that tend to keep tau soluble in solution [43]. In fact, highly phosphorylated forms of tau purified from AD brain have a tendency to bind to other tau molecules, even those that are not themselves in a highly phosphorylated form [50]. The negative charges resulting from phosphate addition at specific sites in tau could overcome the electrostatic repulsion present in the predicted structural elements in the microtubule-binding repeats, leading to their association and subsequent aggregation into larger filaments that accumulate in disease.

At this point, one cannot rule out other possibilities that could lead to the interaction and aggregation of tau molecules. The potential involvement of various negatively
charged cofactors exists, since molecules of this type can be found in close association with tau pathology. For example, fatty acids are capable of driving tau aggregation in vitro, and fatty acid-containing glycolipids can be co-purified from AD PHFs \[51–53\].

The secondary structure predictions made above can be used to model the interactions leading to tau aggregation (Fig. 5). As previously mentioned, it is likely that the \(\beta\)-strand forming elements in microtubule-binding repeats 2 and 3 form the “core” repeating element of the tau aggregate. This ability to aggregate is likely due to the amphipathic nature of the \(\beta\)-strands in this region. However, it is likely that other elements are involved in the process as well. Although short peptides consisting of the vital \(306\)\text{VQIVYK}^{311}\) sequence are

Fig. 5. Summary of structural elements predicted by sequence analysis and how they could influence microtubule binding and/or tau aggregation. (A) The primary sequence of the longest human central nervous system isoforms of tau is reproduced using the color scheme in Fig. 1. The consensus structural elements from the five methods in Fig. 1 are shown here as cylinders for \(\alpha\)-helix and block arrows for \(\beta\)-strands. (B) A cartoon of the predicted secondary structures and how they might interact with microtubules and each other for microtubule binding. (C) A cartoon of the predicted secondary structures and how they might interact with one another in the aggregation of tau. Please see text for more details.
capable of adopting β-strand conformation and aggregating in vitro, the resulting fibrils formed are irregular in size and shape [9,35]. However, when the peptide 315LSKVTSKCGSL325, which has been shown to have a propensity for adopting an amphipathic α-helical structure is included in the reaction, the resulting fibrils are much more regular in size and shape and more closely resemble those found in disease [9]. Therefore, it is likely that 315LSKVTSKCGSL325 also makes an important contribution to the formation of tau filaments. The combination of 306VQIVYK311 and 315LSKVTSKCGSL325 most likely results in a beta–turn–helix motif that is capable of aggregating through the hydrophobic interactions of the beta strands, while the helix provides sites for stabilization of the beta strands through additional hydrophobic interactions. Lastly, the predicted amphipathic alpha helix 315LSKVTSKCGSL325 would place a cysteine residue present on the hydrophobic face of the helix (Fig. 2). Therefore, if two of these amphipathic alpha helices were to interact with one another through their hydrophobic faces, it is possible that the cysteine residues could be in close enough proximity to form disulfide bonds, and this could impart the apparent structural stability that AD PHFs possess.

In summary, tau contains very few predicted structural elements, but these small structural units, whether predicted or measured through biochemical/biophysical methods, are likely responsible for the normal and abnormal functions of tau by providing sites for specific interactions either with microtubules or other tau molecules. Detailed analysis of these potential structural elements should provide future directions for understanding the molecular mechanisms responsible for the metamorphosis of tau from a soluble natively unfolded molecule to an amyloidogenic entity that contributes to neurodegeneration.

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