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The Structure Biology of Tau and Clue for Aggregation Inhibitor Design

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Abstract
Tau is a microtubule-associated protein that is mainly expressed in central and peripheral nerve systems. Tau binds to tubulin and regulates assembly and stabilization of microtubule, thus playing a critical role in neuron morphology, axon development and navigation. Tau is highly stable under normal conditions; however, there are several factors that can induce or promote aggregation of tau, forming neurofibrillary tangles. Neurofibrillary tangles are toxic to neurons, which may be related to a series of neurodegenerative diseases including Alzheimer's disease. Thus, tau is widely accepted as an important therapeutic target for neurodegenerative diseases. While the monomeric structure of tau is highly disordered, the aggregate structure of tau is formed by closed packing of β-stands. Studies on the structure of tau and the structural transition mechanism provide valuable information on the occurrence, development, and therapy of tauopathies. In this review, we summarize recent progress on the structural investigation of tau and based on which we discuss aggregation inhibitor design.

Keywords Tauopathies · Protein aggregation · Fibril structure · Drug design · Neurodegenerative diseases

1 Introduction

Tau is a microtubule-associated protein that is mainly expressed in central and peripheral nerve systems. Tau binds to tubulin and regulates assembly and stabilization of microtubule, thus playing a critical role in neuron morphology, axon development and navigation [1, 2]. In addition to regulating microtubule assembly, recent studies show that tau has other functions [3–6]. For example, tau regulates the function of mitochondria, dynamics of RNA, formation of stress granules, integrity of neuronal DNA, motility of motor proteins, and the signaling pathway of brain insulin [7–12].

Under normal conditions, wild type tau protein is highly soluble, showing little tendency for aggregation; however, under pathological conditions, a variety of factors have been shown to induce or promote tau aggregation, including mutation, post-translational modification (PTM), metal ions, and interaction with polyanion or other molecules. Aggregation of tau into neurofibrillary tangles (NFTs) characterizes a series of neurodegenerative diseases termed as tauopathies, including Alzheimer's disease (AD), Parkinson's disease (PiD), Huntington's disease, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), agyrophilic grain disease, and frontotemporal dementia with parkinsonism-17 [13, 14]. Consequently, tau is widely considered as a potential target for the treatment of tauopathies [15–20].

So far, several strategies have been applied to reduce tau aggregation [2, 15–21]. Aggregation inhibitors directly bind to tau and block its aggregation. Molecules stabilizing microtubules enhance binding of tau to microtubules, thus reducing the concentration of free tau. Molecules targeting pathways involved in tau hyperphosphorylation or acetylation also suppress tau aggregation by reducing tau PTMs. Furthermore, anti-tau vaccines, via active or passive immunotherapies, enhance clearance of tau aggregates. In this review, we summarize recent progress on the structural characterization of tau, based on which tau targeted aggregation inhibitor design/discover is discussed.

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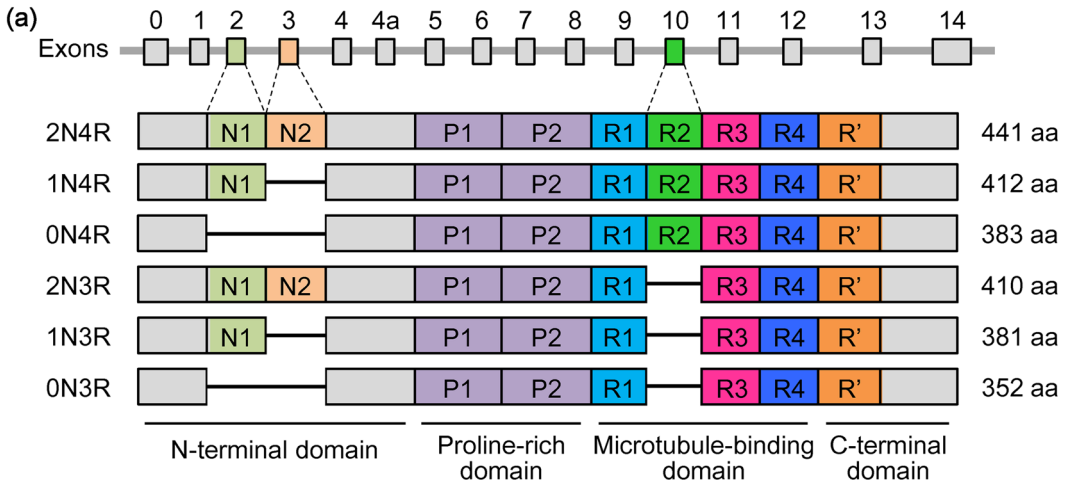
(a)
Exons
0 1 2 3 4 4a 5 6 7 8 9 10 11 12 13 14
2N4R N1 N2 P1 P2 R1 R2 R3 R4 R' 441 aa
1N4R N1 P1 P2 R1 R2 R3 R4 R' 412 aa
0N4R P1 P2 R1 R2 R3 R4 R' 383 aa
2N3R N1 N2 P1 P2 R1 R3 R4 R' 410 aa
1N3R N1 P1 P2 R1 R3 R4 R' 381 aa
0N3R P1 P2 R1 R3 R4 R' 352 aa
N-terminal domain
Proline-rich domain
Microtubule-binding domain
C-terminal domain


(b)
1 MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQT
51 PTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEG
101 TTAEEAGIGDTPSLEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTK
151 IATPRGAAPPGQKGQANATRIPAKTPPAPKTPPSSGEPPKSGDRSGYSSP
201 GSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRL
244 QTAPVPMPDLK NVKSKIGSTENLKHQPGGGK
275 VQIINKKLDLS NVQSKCGSKDNIKHVPGGGS
306 VQIVYKPVDLS KVTSKCGSLGNIHHKPGGGQ
337 VEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN
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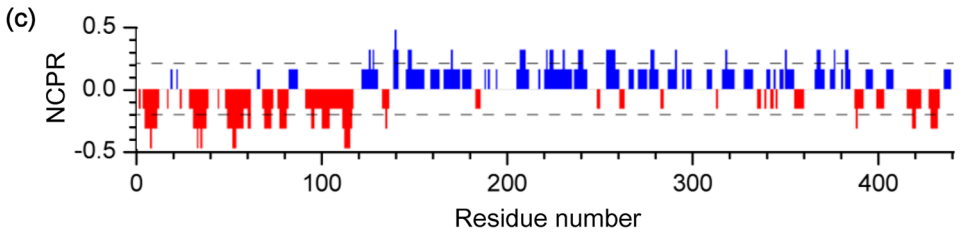
(c)
NCPR
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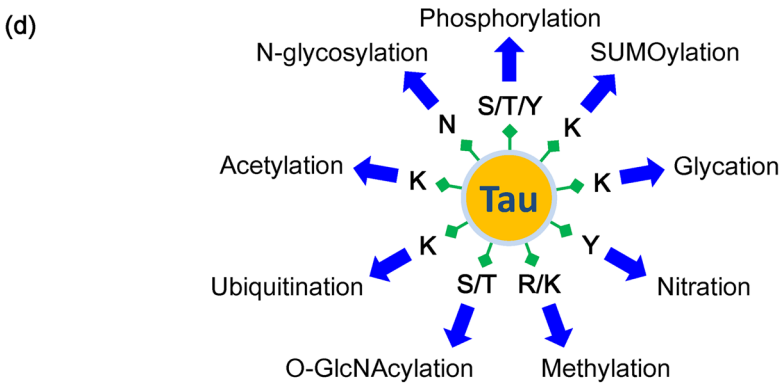
0.0
-0.5
0
100
200
300
400
Residue number


(d)
Phosphorylation
N-glycosylation
SUMOylation
N
S/T/Y
K
Acetylation
K
Tau
K
Glycation
K
Y
Ubiquitination
S/T
R/K
Nitration
O-GlcNAcylation
Methylation

◂**Fig. 1** Primary structure of tau protein. **a** Human *MAPT* gene encodes six tau isoforms that are resulted from alternative splicing of exons 2, 3, and 10. N1 and N2 are the N-terminal inserts. P1 and P2 are the two proline rich regions. R1 to R4 are the four microtubule-binding repeats. R' is the C-terminal repeat-like region. **b** Amino acid sequence of 2N4R tau isoform. Individual region is indicated by the same color as in (**a**). The two hexapeptide motifs and the two cysteine residues are highlighted in yellow. **c** Net charge per residue (NCPR) distribution of 2N4R tau. NCPR was analyzed by CIDER [182]. **d** Residue type specific post-translational modifications of tau (Color figure online)

2 Primary Structure of Tau

Human tau protein (UniProt ID P10636) is encoded by the *MAPT* gene which is located on chromosome 17q21 and comprises 16 exons [22]. Alternative splicing of exons 2, 3 and 10 generates six different tau isoforms, which contain zero, one or two N-terminal inserts (0 N, 1 N and 2 N) and three or four microtubule-binding repeats (3R and 4R) (Fig. 1a) [23, 24]. The amounts of 3R and 4R tau isoforms are approximately equal in normal brain [25], but their distributions can be uneven in tauopathies. Based on the biochemical properties and functions, the tau protein can be divided into four distinct domains: the N-terminal domain (NTD), the proline-rich domain (PRD), the microtubule-binding domain (MTBD), and the C-terminal domain (CTD) (Fig. 1a) [1, 26, 27]. The NTD and PRD form the projection domain which extends outward from the microtubule surface when tau associates with microtubule via the MTBD [28, 29]. Compared to 3R tau, 4R tau contains one more repeat. Consequently, 4R tau exhibits higher affinity for microtubule and promotes microtubule assembly more efficiently [2, 25]. As shown in Fig. 1b, the amino acid sequence of 2N4R tau is mostly hydrophilic, low complexity, and locally repetitive. 4R tau contains two aggregation-prone hexapeptide motifs, PHF6* (^{275}VQIINK^{280}) and PHF6 (^{306}VQIVYK^{311}), as well as two cysteine residues, Cys291 and Cys322. PHF6* and Cys291 are located on the R2 repeat of MTBD while PHF6 and Cys322 are located on the R3 repeat. PHF6 and PHF6* are critical for tau aggregation. Tau molecules lacking these two hexapeptide motifs cannot aggregate [30]. The two cysteine residues also regulate tau aggregation in a DTT dependent manner. In the presence of DTT, cysteine to alanine mutation delays the initial aggregation kinetics [31]. On the contrary, cysteine to alanine mutation promotes aggregation in the absence of DTT [32]. Charge distribution analysis reveals that the NTD and CTD are mainly negatively charged (Fig. 1c). On the contrary, the PRD and MTBD are highly positively charged. As discussed below, such a charge segregation feature has a critical impact on the structure and function of tau.

Tau can be subjected to a large number of PTMs (Fig. 1d) [33–35]. 2N4R tau contains 45 serine residues, 35 threonine residues, and 5 tyrosine residues. Within these 85 potential phosphorylation sites, phosphorylation on about 45 sites has been observed experimentally [36]. It has been found that phosphorylation plays a critical role in regulating the function of tau, and the phosphorylation state of tau is developmentally regulated [36]. Fetal tau and adult tau carry approximately seven and two phosphates per molecule on average, respectively [37]. Although the phosphorylation extent of tau is low in normal adults, it rises again in AD patients, with eight phosphates per molecule on average [38], indicating a correlation between tau phosphorylation and tauopathies [39, 40]. Besides phosphorylation, acetylation is another major PTM regulating the function and stability of tau. Tau contains 44 lysine residues and more than twenty of them can be acetylated [41–43]. Tau acetylation is detected in various transgenic mice and human tauopathies, suggesting that tau acetylation could be involved in the pathogenesis of neurodegenerative diseases [44, 45]. Similar to phosphorylation, acetylation can also impair tau–microtubule interactions and result in tau aggregation [41, 44–49]. Acetylation and phosphorylation may compete with each other or one PTM may promote the other [49, 50]. Ubiquitination usually drives protein degradation. It is surprised to find that tau filaments from CBD and AD brain tissues are ubiquitinated and ubiquitination of tau mediates the filament structures [51]. Recently, Kametani et al. investigated PTMs of tau associated with a wide range of tauopathies [52]. They identified 170 PTMs in total, among which disease-specific PTMs are usually found in the MTBD. Theses disease-specific PTMs may contribute to form the filaments, or they may occur after the filaments have been formed.

3 Secondary Structure of Tau

Although tau forms extensive β-strands in the aggregated filaments, free tau monomer is intrinsically disordered, with low propensity of forming secondary structures (Fig. 2a) [53]. Circular dichroism (CD) confirms that tau has very little secondary structure [54, 55]. The α-helix and β-strand contents are estimated to be less than 5% and 15%, respectively [55]. Nevertheless, nuclear magnetic resonance (NMR) reveals that dynamic and residual secondary structures are present in tau monomer [56–60] (Fig. 2b). Segments showing β-structure conformations include ^{86}GKQAAAQ^{92} (in N2), ^{161}GQKGQA^{166} (in P1), ^{224}KKVAVVR^{230} (in P2), ^{256}VKSKIG^{262} (in R1), ^{274}KVQIINKKLDL^{284} (in R2), ^{305}SVQIVYKPVDL^{315} (in R3), ^{336}QVEVKSEKLD^{345} and

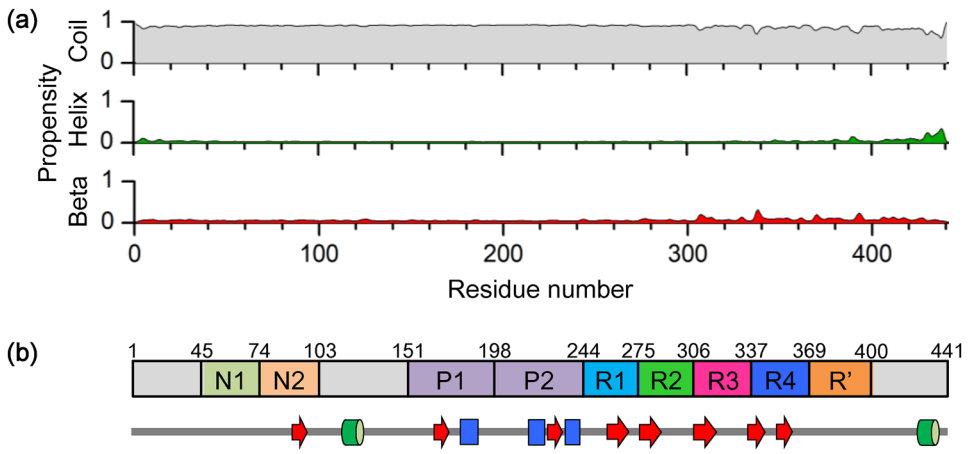


Fig. 2 Secondary structure of tau protein. **a** Secondary structure propensity of 2N4R tau predicted by PSSpred [183]. **b** Transient secondary structure elements in 2N4R tau identified from NMR characterization: β-structure (red), α-helical (green), polyproline II (blue) (Color figure online)

^{351}QSKIGSL^{357} (in R4), where segments comprising PHF6* and PHF6 exhibit the highest β-structure propensity [57]. α-Helical propensity is observed for ^{114}LEDEAAGHVT^{123} (between N2 and P2) and ^{428}LADEVSASLA^{437} (in CTD). Polyproline II helical conformation is identified for three segments within the PRD, i.e., ^{175}TPPAPKTPPS^{184} (in P1), ^{216}PTPPTREP^{223} and ^{232}PPKSPSSA^{239} (in P2). The formation of these secondary structure elements is transient. For example, the β-structure conformation is populated 12% of the time for ^{256}VKSKIG^{262} segment and the α-helical conformation is populated 25% of the time for ^{428}LADEVSASLA^{437} segment [57].

Solvent conditions, mutations, PTMs, metal ions as well as intermolecular interactions can remodel the conformational propensity of tau monomer. In the presence of 50% trifluoroethanol, the α-helix content of tau rises to 30% [55]. Inferred from NMR data, the ^{301}P-K^{311} segment forms nascent β-structure, where a type II β-turn is formed around ^{301}PGGG^{304} [59]. It has been found that Pro301 is critical in maintaining this β-hairpin since P301L mutation promotes conversion from collapsed hairpin to extended conformations [61]. C291R, a mutation with potential pathogenic function, is found to enhance the β-structure propensity of MTBD [62]. 2N4R tau contains two cysteine residues and twelve histidine residues, which provide coordination sites for metal ions. For example, tau binds Zn^{2+} and becomes more compacted globally [63]; however, structural changes around the MTBD may be subtle [64]. Tau interacts with various polyanions, such as heparin and poly-Glu. Three-dimensional (3D) heteronuclear NMR experiments demonstrate that interaction with heparin reinforces the β-strand structure as well as α-helical structure in several regions of tau [60].

4 Tertiary Structure of Tau

Due to its intrinsically disordered nature, it is extremely difficult to characterize the 3D conformation of tau in the free state. Small-angle X-ray scattering studies reveal that tau forms extended conformations comparable in size with random coils [55, 65]. The average radius of gyration of 2N4R tau is about 6.5 nm from small-angle X-ray scattering measurement or 5.1 nm from single molecule Förster resonance energy transfer (FRET) measurement [65, 66]. Spin relaxation rate measurement indicates that the NTD is highly mobile, whereas the PRD and MTBD are more rigid [57]. This is consistent with single-molecule force spectroscopy characterization which shows that the MTBD is more compact than the NTD [67]. Consequently, tau monomer forms extensive dynamic intramolecular interactions which can be captured by cross-linking mass spectrometry, FRET, and paramagnetic relaxation enhancement (PRE) of NMR signals [57, 58, 61, 68, 69]. Based on the distance information from FRET signals, Jeganathan et al. proposed a paperclip-like folded model for tau monomer, where the C-terminal end of tau folds over into the vicinity of the MTBD and the N-terminal end folds onto the C-terminal end (Fig. 3a) [68]. Although the NTD is outside the FRET distance of MTBD, PRE shows that the NTD is in close contact with PRD and MTDB [57, 69]. It is noted that the paperclip-like folded conformation does not restrain tau as tau remains highly mobile throughout [68].

To construct the atomic conformations of tau monomer, molecular modeling or simulations have been performed using restrains from PRE, residual dipolar coupling, or chemical cross-linking [57, 58, 66, 69–71]. The resulted conformational ensembles show that tau monomer can adopt distinct topology with variable secondary structure elements (Fig. 3b). Since different experimental techniques capture different structure information, conformational ensembles constructed using different experimental information and

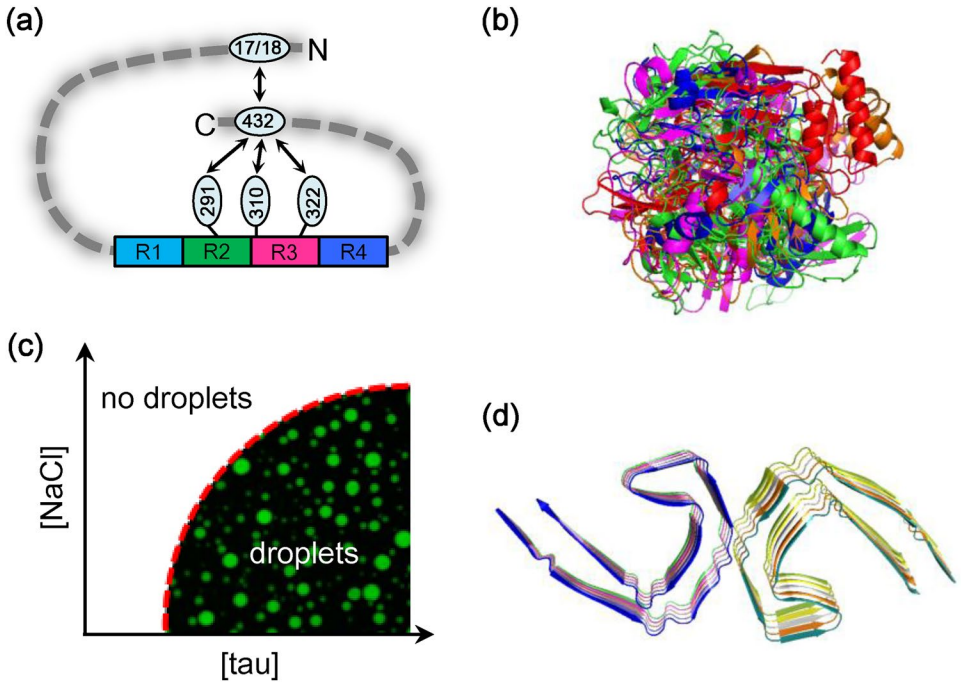


Fig. 3 Tertiary and assembly structure of tau. **a** Schematic illustration of the paperclip-like folded conformation of tau monomer. Residues within FRET distance are indicated by arrows. **b** Conformational ensemble of tau monomer based on cross-linking data [71]. Five conformers are shown by different colors. **c** LLPS of tau under the influence of salt concentration and tau concentration. **d** Packing of β-sheets in the filament core of tau from AD patients (Color figure online)

simulation methods may exhibit different secondary and tertiary structure properties.

Since the free energy landscape of tau conformational transition is not flat, some tau conformations may be trapped into local free energy minima. Indeed, distinct tau conformer species have been detected and isolated in experiments. Two groups of conformations with distinct degree of compactness and rotational dynamics have been identified from single molecule fluorescence anisotropy characterization using free tau molecules [72, 73]. Alternatively, two tau monomeric species are isolated by sonication treatment of tau fibrils [74, 75]. One tau form is inert and the other is seed-competent. A consensus of structural investigation on these tau species is that exposure of the PHF6* and PHF6 motifs in the MTBD is related to the formation of aggregation-prone conformations. This principle may be applicable to explain factors promoting or inhibiting tau aggregation. Pro301 mutation in the R3 region promotes tau aggregation. Recently, cross-linking mass spectrometry revealed that Pro301 mutation destabilizes local structures and extends the MTBD [61]. Phosphorylation also has remarkable influence on tau conformation. NMR derived ensembles indicate that AT8 phosphorylation expands tau [69].

5 Structure of Tau Assemblies

Tau forms a variety of assemblies, including soluble oligomers, insoluble filaments, and liquid droplets. Their structures and assembling mechanisms have been subjected to extensive studies.

5.1 Structure of Tau Oligomers

Tau forms soluble oligomers with various molecular weights. Through a sensitive split-luciferase assay, Wegmann et al. detected the formation of tau oligomers in cells and they found that stable tau dimers are released and taken up by cells [76]. Although tau oligomers are known as the major toxic species in vivo, their structures remain elusive [77, 78]. Tau contains two cysteine residues. Therefore, intermolecular disulfide bond has been found as an important factor promoting formation of tau oligomers [79–82]. However, disulfide-independent oligomerization of tau has also been observed [82–84], where tau monomers are held together by electrostatic interactions between the negatively charged NTD and the positively charged PRD and MTBD [85–87]. Furthermore, several factors can promote tau oligomerization by changing tau conformation or serving as bridging molecules [88–90]. The conformations of tau oligomers are heterogeneous, since some oligomers can seed monomeric tau aggregation while others cannot grow into long filaments [80, 91, 92]. Although the atomic conformations of oligomeric tau are still lacking, immunodetection suggests that the conformations of oligomeric tau are different from those of monomeric tau and aggregated tau as monoclonal antibodies raised against tau oligomers show no reactivity toward monomeric tau and tau filaments [93–95]. This suggestion is further supported by biophysical studies. CD characterization shows that tau oligomers contain more β-sheets than tau monomer, but the β-sheets in tau oligomers are packed differently from those in filaments [92, 96]. Bis-ANS binding experiment shows that some hydrophobic

patches buried in tau monomer and fibrils are exposed in tau oligomers [96]. Molecular modeling using cross-linking restraints may be a promising strategy to construct the conformational ensembles of tau oligomers in the future.

5.2 Structure of Tau Filaments

Tau forms amyloid filaments in human brain. Different neurodegenerative diseases show distinct tau isoform compositions and filament structures [14, 97]. Many studies focus on tau filaments isolated from AD brains, indicating that the tau filament is composed of an amyloid core and a fuzzy coat. Limited proteolysis shows that the amyloid core is dominantly formed by the MTBD while the fuzzy coat consists of the N- and C-terminal domains [98–100]. Further spectroscopy characterization reveals that the filament core has clear cross-β structure and the fuzzy coat remains unstructured [101–104].

Tau NFTs are composed of paired helical filaments and straight filaments. Electron microscopy images show that the cross-section of tau filament core in AD has a C-shaped morphology [105, 106]. Cryo-EM structural studies reveal that paired helical filaments and straight filaments are made of two identical protofilaments comprising residues Val306–Phe378 with different inter-protofilament packing (Fig. 3d) [107, 108]. Besides AD, cryo-EM structures of filament cores from CTE, PiD and CBD have also been determined [51, 109–111], illustrating that different tauopathies have unique tau filament folds. R3, R4, and the N-terminal part of R' are involved in forming the filament cores of all tauopathies studied, while R1 and R2 are exclusively present in filament cores of PiD and CBD, respectively. Unidentified fuzzy cryo-EM densities are present adjacent to the structured core, some of which turn out to be (poly)-ubiquitin chains and the P2 region [51, 112]. Heparin is widely used to induce recombinant tau aggregation. Structures of heparin-induced tau filaments have also been determined and are found different from those in diseases [113, 114]. These results suggest that cofactors and PTMs influence the structures of tau filaments [115]. However, the detailed mechanism remains unknown and has to be explored in the future.

5.3 Structure of Tau Droplet

The newest identified assembly state of tau is liquid droplet, which is formed via liquid–liquid phase separation (LLPS) (Fig. 3c). To phase separate, tau molecules undergo extensive intermolecular interactions with each other, polyanions, metal ions, or tau-associated protein [116–127]. LLPS of tau is suppressed with increased salt concentration, suggesting that electrostatic interactions are critical for the formation of tau droplets [116, 117, 119, 123]. The involvement of hydrophobic interactions in driving tau droplets formation is also observed when tau droplets are dissolved with 1,6-hexanediol [117, 128, 129]. PTMs have a marked effect on regulating the LLPS of tau. Acetylation by histone acetyltransferase p300 or CREB suppresses LLPS of tau or tau/RNA complex [43, 122]. While phosphorylation either introduced by MARK2 or SF9 insect cells promotes LLPS of tau [117, 118], mouse brain extract phosphorylated tau shows a reduced propensity of LLPS with RNA [121].

Structural characterization of tau droplets is challenging. Fusion, fission, fluorescence recovery after photobleaching and electron paramagnetic resonance spectroscopy indicate that tau droplets are in dynamic liquid state [119, 121, 122]. The level of β-structure content is increased upon LLPS [117, 123, 128]; however, the β-structure content in the droplets is still much smaller than that in the amyloid fibrils. Although the entire polypeptide chain of tau adopts more extended conformations in the droplet state [130], local conformation of the PHF6* region may remain unchanged [123].

There is mounting evidence showing that protein liquid droplets fulfill a range of biological functions and LLPS underlies the formation of membraneless compartments in living cells [131–136]. Some liquid droplets can convert into filaments or promote filaments formation, suggesting that LLPS are related to amyloid aggregation in some neurodegenerative diseases [137–140]. However, whether LLPS of tau is linked to fibril formation remains controversial. On one hand, some studies suggest that LLPS of tau mediates and facilitates aggregation. Aggregation enhancing factors, including polyanions, pro-aggregation mutations, and PTMs, promote LLPS of tau and tau droplets can turn into aggregates with elongated incubation [43, 118, 141]. On the other hand, other studies suggest that LLPS and amyloid aggregation of tau are independent processes although they occur in overlapping conditions [129]. Recently, Boyko et al. showed that tau LLPS greatly accelerates formation of fibrillar aggregates induced by heparin [124]. Since the conformations of PHF6 and PHF6* in the droplets are almost indistinguishable from those in the dilute state [123], LLPS may not accelerate tau aggregation by promoting aggregation-prone tau formation. However, the concentration of tau in the droplet is much higher than that in the dilute phase [118, 128], LLPS may promote the fibrillation reaction in a concentration-dependent regulatory mechanism [124]. Furthermore, phase separation of tau could facilitate the formation of soluble tau oligomers [142]. Consequently, although the connection between LLPS and tau fibrillation remains elusive, they may be able to influence each other.

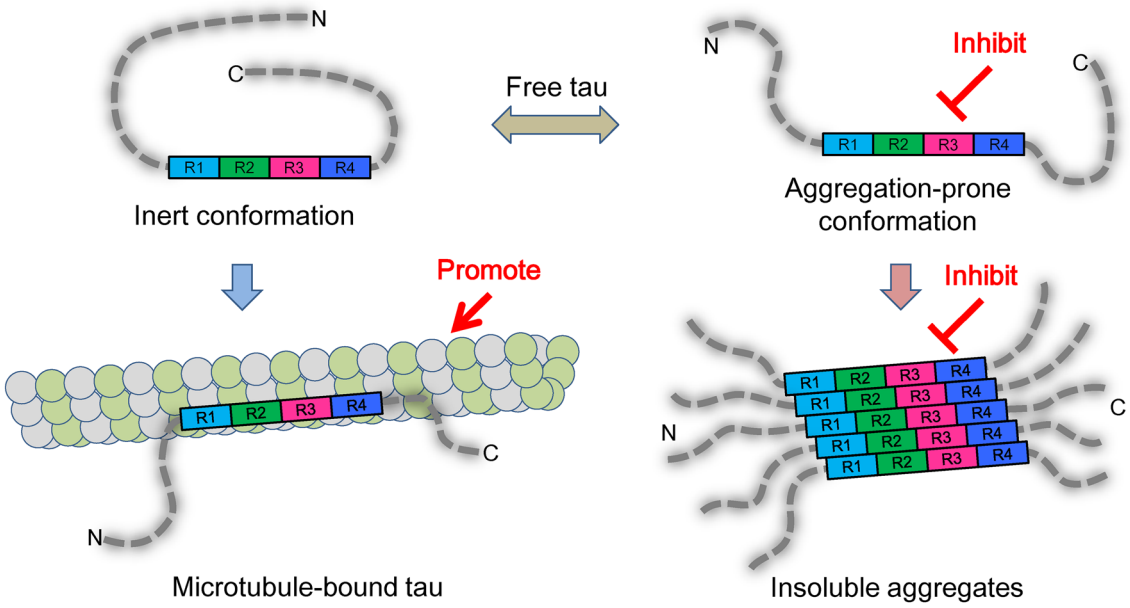


Fig. 4 Strategies for aggregation inhibitor design based on tau conformational transition

6 Clues for Aggregation Inhibitor Design

Based on the structural knowledge of tau, aggregation inhibitors can be designed by stabilizing tau in the inert conformations or blocking the propagation of aggregation (Fig. 4). PTMs are critical factors converting tau monomers from the inert conformations to the aggregation-prone conformations. Therefore, regulating the PTMs of tau is a therapeutic approach to tauopathies. Glycogen synthase kinase 3β (GSK3β) is a major tau kinase. It phosphorylates tau at 42 sites [143]. Inhibiting the activity of GSK3β by lithium reduced the phosphorylation of tau and levels of aggregated insoluble tau [144, 145]. Novel GSK3β inhibitors include memantine and ifendropil, indirubin, BIO-acetoxime, and NP12 [146–148]. The acetyltransferase p300 acetylates tau a multiple sites. Salsalate treatment has been found to inhibit p300 activity and lower levels of acetylated tau [45]. However, recent studies showed that salsalate has little effect on the disease progression in PSP [149]. The major function of tau is to bind to microtubule and promote microtubule assembly. Increasing the stability of microtubule reduces tau dissociation from microtubules and the consequent aggregation. Microtubule stabilizing molecules tested includes davunetide and abeotaxane [150]. Unfortunately, clinical trials showed that both drugs are not efficient treatments for PSP or AD [151–153].

Tau aggregation can be inhibited by binding to various molecules, including molecular chaperones, antibodies, and small molecules [15, 154–165]. Most of these molecules bind to the MTBD, mainly around the PHF6* and PHF6 motifs. Therefore, shielding these two motifs or interrupting their intermolecular interactions may be a general mechanism to inhibit tau aggregation. The conformational ensembles of tau monomer and the structures of tau filaments provide valuable information for tau aggregation inhibitor design/discovery. Small molecule binding sites are found by analyzing the conformational ensembles of tau K18 construct [166, 167]. Recently, Baggett and Nath identified novel tau aggregation inhibitors through a combination of molecular dynamics simulations, ensemble docking, and virtual screen of compound libraries [168]. Based on the atomic structures of amyloid fibrils formed by PHF6 and PHF6*, peptides have been designed to inhibit the aggregation of tau by capping the ends of tau fibrils [169–173]. Methylene blue (MB) and its derivative leuco-methylthioninium (LMTM) are efficient tau aggregation inhibitors [174]. Structural investigations suggest that MB and LMTM bind to the MTBD of tau and trap it in aggregation-incompetent conformations [32, 166]. Although LMTM effectively reduced tau pathology and improved cognition in transgenic mouse models of AD, it failed to show effects on the primary cognitive endpoints in two phase III trials [175–177]. Recently, it was found that while MB efficiently inhibits tau fibrils formation, it increases the number of granular tau oligomers [90]. This study provides a possible mechanistic explanation for the poor performance of LMTM in the Phase III clinical trials. Recently, Gorantla et al. designed cobalt(II)-complexes for effective inhibition of tau and disaggregation of preformed tau fibrils, illustrating potential application of metal-based therapeutics for tauopathies [178].

Antibodies can be raised to target tau fragments, monomers, oligomers, or filaments. By binding to these tau species, antibodies may inhibit the formation or propagation of aggregation-prone tau, or promote clearance of tau aggregates. Antibodies are able to cross the blood–brain barrier and reside for much longer in the body than small molecules. Consequently, immunotherapies are promising strategies for tauopathies treatment [179, 180]. Active immunization has been shown to reduce pathology of tauopathies. Two tau vaccines (i.e., AADvac1 and ACI-35) have been developed and are currently in clinical trials [181]. However, the risk of adverse immune reactions raises safety concerns on active immunization. Alternatively, the effect of passive immunization is transient and its specificity is higher. To date, several clinical trials have been conducted for various monoclonal tau antibodies in patients with AD or PSP [179].

7 Conclusions

As a major target for tauopathies treatment, tau protein has been subjected to extensive investigations. Although free tau monomer is intrinsically disordered and contains low secondary structure propensity, its conformations could be divided into two distinct classes: compacted inert conformation and extended aggregation-prone conformation. Several factors, including post-translational modifications, amino acid mutations, and interacting molecules, can modulate the conformational ensemble of tau monomer, thus inhibiting or promoting tau aggregation. Recently, 3D structures of tau filaments from several tauopathies have been determined by cryo-EM, revealing that different tauopathies have unique tau filament folds. Structural information on tau monomer and filaments provides important clues for tau aggregation inhibitor design/discovery through suppressing the formation of aggregation-prone conformations or blocking the propagation of aggregates. So far, structural knowledge on tau oligomers is very limited, although tau oligomers are toxic and can be spread between cells. Determining the 3D conformations of tau oligomers is urgent for a deeper understanding of tau aggregation and tauopathies. Novel tau aggregation inhibitors may be designed or discovered by targeting tau oligomers in the future.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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