

REVIEW

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Tau in neurodegenerative diseases: molecular mechanisms, biomarkers, and therapeutic strategies

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Abstract

The deposition of abnormal tau protein is characteristic of Alzheimer's disease (AD) and a class of neurodegenerative diseases called tauopathies. Physiologically, tau maintains an intrinsically disordered structure and plays diverse roles in neurons. Pathologically, tau undergoes abnormal post-translational modifications and forms oligomers or fibrous aggregates in tauopathies. In this review, we briefly introduce several tauopathies and discuss the mechanisms mediating tau aggregation and propagation. We also describe the toxicity of tau pathology. Finally, we explore the early diagnostic biomarkers and treatments targeting tau. Although some encouraging results have been achieved in animal experiments and preclinical studies, there is still no cure for tauopathies. More in-depth basic and clinical research on the pathogenesis of tauopathies is necessary.

Keywords Tau, Alzheimer's disease, Tauopathies, Aggregation, Propagation, Biomarkers

Introduction

Tau is a microtubule-associated protein encoded by the *MAPT* gene, which is located on chromosome 17q21 and contains 16 exons [1]. Tau can be subdivided into the N-terminal projection domain and the C-terminal assembly domain. The N-terminal projection domain sticks away from microtubules, while the C-terminal assembly domain contains the repeat domains and flanking regions that bind to microtubules and contribute to

the aggregation of tau. Between amino acids 151 and 243, several Thr-Pro and Ser-Pro motifs can be phosphorylated [2]. There are six main isoforms of tau expressed in the adult human brain. The variants vary based on the 29-residue inserts near the amino terminus: the variants with 0, 1, or 2 inserts are referred to as 0N, 1N, and 2N, respectively. The isoforms can also be classified according to the inclusion of three or four repeat domains, known as 3R or 4R, respectively [1]. In the brain, tau is predominantly expressed in neurons, while glial cells contain only trace amounts of tau [3]. Furthermore, tau has been detected extracellularly [4]. The cellular localization of tau is controlled by developmental processes [5]. In immature neurons, tau is evenly distributed in the cell body and cell extensions. Later, as axons emerge and neurons become polarized, tau is enriched in axons, with small quantities present in dendrites and the nuclei [6, 7].

Physiologically, tau plays diverse roles in various parts of neurons. In healthy neurons, tau in axons regulates the stability of microtubules and microtubule dynamics, and influences axonal transport [8]. A small quantity of

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tau is also present in dendrites, where it may play a role in mediating excitotoxicity and regulating synaptic plasticity, post-synaptic microtubule dynamics, and neuronal physiology [9]. Tau in the nucleus may contribute to the preservation of genomic DNA integrity [7, 10]. Recent studies have revealed various abnormal changes in tau knockout mice, suggesting that tau might be involved in the control of neurogenesis, neuronal function, and long-term depression [1].

Pathologically, tau abnormalities are implicated in various tauopathies, including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), frontotemporal dementia with parkinsonism-17 (FTDP-17), corticobasal degeneration (CBD), chronic traumatic encephalopathy (CTE), argyrophilic grain disease (AGD), Pick's disease, and Huntington's disease. Over 80 mutations of the *MAPT* gene have been discovered to be associated with tauopathies [11, 12]. In this review, we extensively discuss the role of tau in neurodegenerative diseases, with a focus on the mechanisms of tau aggregation or propagation, the toxicity of tau pathology, and early diagnostic biomarkers and treatments targeting tau.

Tau pathology in neurodegenerative diseases

The term "tauopathy" was initially described as a specific condition known as frontotemporal lobar degeneration (FTLD) [13]. Soon after, the term "tauopathies" was adopted to encompass a diverse array of degenerative disorders affecting the nervous system, both sporadic and hereditary. These disorders are characterized by the presence of tangled accumulations of hyperphosphorylated tau, which can be found in neurons or both neurons and glial cells. Tauopathies encompass more than 20 distinct neurodegenerative disorders and can be further divided into primary and secondary tauopathies. In primary tauopathies such as PSP, FTDP-17, CBD, Pick's disease, and AGD, tau pathology is considered the primary cause of neurodegeneration, whereas in secondary tauopathies such as AD and CTE, tau pathology is considered as having diverse driving force [14].

Pick's disease predominantly features three-repeat (3R) tau aggregates with round, well-defined inclusions in the neuronal cytoplasm. In contrast, PSP and CBD present diverse neuronal and glial inclusions composed of four-repeat (4R) tau. CTE is characterized by clusters of twisted neurofibrillary tangles (NFTs) composed of both 3R and 4R tau, noticeable tangled fibers within the neuropil, and astroglial tau pathology [15]. In AD, a mix of 3R and 4R tau aggregates exists in the affected brain area. These observations support the concept that the presence of different pathogenic tau strains may cause distinct tauopathy subtypes.

AD

AD is a progressive neurodegenerative disease and is the most common cause of dementia worldwide. Clinically, AD is characterized by gradual declines in memory and cognitive function, and difficulties in daily tasks [16]. Neuropathologically, AD is characterized by the presence of amyloid plaques and NFTs [17]. NFTs are primarily composed of truncated and aberrantly hyperphosphorylated tau, forming paired helical filaments (PHFs) or straight filaments. Importantly, the density and distribution of NFTs are consistently related to the extent of brain atrophy, cognitive decline, and memory impairment [18–20], suggesting that tau pathology may play a pivotal role in the development of dementia in AD patients.

FTLD

FTLD is a group of neurodegenerative diseases characterized by atrophy of the frontal and temporal lobes [21]. FTLD is one of the most common causes of dementia, only next to AD and dementia with Lewy bodies (DLB). FTLD is characterized by changes in social behavior and personality, speech and language. FTLD can occur either independently or in conjunction with motor disorders [22]. Neuropathologically, FTLD is characterized by the presence of aberrant protein aggregates formed by tau, TDP-43, or FUS (fused in sarcoma protein) [23]. Nearly 95% of clinical FTD cases are FTLD-tau and FTLD-TDP.

PSP

PSP, a type of neurodegenerative disease, was initially described by Steele and his team in 1964 [24]. It typically starts after the age of 40 and has an average survival time of six years from the onset of symptoms. Clinically, individuals with PSP exhibit impairments in motor skills, gait control, balance, swallowing, speech production, and vision. Patients also display symptoms of parkinsonism, sensitivity to light, sleep and emotional disturbances, depression, anxiety, and dementia [23, 24].

Neuropathologically, PSP is characterized by the presence of tufted astrocytes, accompanied by the existence of NFTs and threads within the basal ganglia and brainstem [25]. While the proportion of 3R and 4R isoforms in the healthy brain is 1:1, protein aggregates formed by 4R tau are found in patients with PSP [26]. Injecting brain extracts from patients with PSP into tau transgenic mice can recapitulate PSP-like tau inclusions, suggesting the presence of template-dependent amplification of tau aggregates [27].

CBD

CBD refers to a neurodegenerative disease characterized by pathological tau deposition in various cell types

and anatomical regions [28]. Clinically, the symptoms of CBD include behavioral, dysexecutive, and visuospatial syndromes; nonfluent, agrammatic primary progressive aphasia syndrome; and progressive supranuclear palsy-like syndrome. Neuropathologically, CBD is characterized by the presence of a glial pathology that encompasses hyperphosphorylated 4R tau [28]. Other tau-related abnormalities are also found in the CBD, including neuronal inclusions, threads, and coiled bodies [28–30].

CTE

CTE is a disease caused by long-term exposure to repeated hits to the head. Symptoms of CTE include memory impairment, cognitive confusion, compromised decision-making, difficulties in controlling impulses, aggressive behavior, depression, anxiety, suicidal thoughts, parkinsonism, and, ultimately, progressive dementia. The manifestation of these symptoms is often delayed by years or even decades following the occurrence of the last head injury or the cessation of active sports engagement [31]. Neuropathologically, CTE is characterized by the accumulation of phosphorylated tau, the formation of NFTs, astrocytic tangles, and neurites around small blood vessels in the cortex, which are typically located at the depths of the sulci. Severe cases of CTE display widespread tau pathology throughout the entire brain [32]. Most individuals with CTE exhibit abnormal levels of phosphorylated TDP-43. Additionally, amyloid- β (A β) aggregates are found in 43% of cases. The tau isoform profile and phosphorylation state in CTE resemble those observed in AD, which involve both 3R and 4R tau [33].

Tau pathology in synucleinopathies

Synucleinopathies refer to a group of neurodegenerative diseases in which abnormal accumulation of misfolded α -synuclein protein occurs, resulting in diseases such as Parkinson's disease (PD), DLB, and multiple system atrophy (MSA) [34–36]. Tauopathies and synucleinopathies exhibit overlapping clinical, pathological, and genetic features. Clinically, cognitive decline and parkinsonism are frequently observed in PD, DLB, MSA, PSP, and CBD patients. Pathologically, tau pathology may also manifest as Lewy bodies and glial cytoplasmic inclusions within synucleinopathies. Furthermore, the presence of *MAPT* H1 haplotype is associated with an increased risk of synucleinopathies such as PD and potentially DLB and MSA [37, 38]. These shared characteristics between synucleinopathies and tauopathies suggest the possibility of interactions or common pathways contributing to neurodegeneration.

The mechanisms mediating tau aggregation

Posttranslational modifications (PTMs) of tau

Tau undergoes various PTMs, including phosphorylation, acetylation, methylation, ubiquitination, SUMOylation, DOPAGEL, and truncation. These PTMs may affect the function and aggregation propensity of tau by altering its charge, hydrophobicity, and structural properties.

Tau phosphorylation

Phosphorylation is the most common PTM of tau and usually involves three types of amino acids: serine (S), threonine (T) and tyrosine (Y). 2N4R tau has 85 potential phosphorylation sites [39]. Tau phosphorylation is regulated by various kinases and phosphatases. The kinases are divided into three groups: (1) protein kinases PDPKs (proline-directed protein kinases), including GSK3 β , CDK5, and MAPKs; (2) protein kinases non-PDPKs, including TTBK1/2, CK1a/1e/2, PKA, PKB/Akt, PKC, PKN, and CaMKII; and (3) tyrosine kinases, including Src, Lck, Syk, Fyn, and c-Abl kinase [39]. Several tau kinases, such as GSK3 β , CDK5, DYRK1A, and CK1, have been reported to be involved in the abnormal phosphorylation of tau in the AD brain [39–42]. The dephosphorylation of tau is mediated by phosphatases such as protein phosphatase (PP)-1, PP5, PP2A, PP2B, and PTEN (phosphatase and tensin homolog deleted on chromosome 10) [43]. The activity or expression of these phosphatases is disrupted in AD brains [44].

Hyperphosphorylation of tau may lead to the dissociation of tau from microtubules and hamper its capacity to facilitate microtubule polymerization [45]. Despite extensive research, the impact of phosphorylation on tau aggregation remains controversial. It has been proposed that phosphorylation of S214, S258, S262, S293, S305, S324, and S356 inhibits tau aggregation [45–47], while phosphorylation of T149, T153, S199, S202, T205, and T212 increases aggregation [48–50]. Biophysical characterization has shown that phosphorylation regulates the aggregation propensity of tau by neutralizing charge interactions and inducing conformational transitions, including disruption of local turn and β -sheet structures, formation of transient α -helices, opening of transient folds, and reorganization of the dimer interface [51–55].

Acetylation

Tau lysine acetylation is mediated by the p300/CREB binding protein, HAT, and tau itself [56–60]. In patients with early and moderate Braak stages of tauopathy, tau acetylation levels are elevated and contribute to neurotoxicity, neuronal dysfunction, and cognitive

decline [61]. Tau acetylation reduces the binding of tau to microtubules, impairs its ability to promote tubulin assembly, and affects its degradation [61, 62].

The impact of acetylation on tau pathological aggregation also remains controversial. On the one hand, acetylation can induce the formation of β -sheet structures, thereby accelerating tau filament assembly [63, 64]. However, other studies have shown that acetylation inhibits tau aggregation [56, 65, 66]. Thus, the exact roles of tau acetylation under physiological and pathological conditions warrant further study.

Methylation

Tau has been reported to undergo mono- and dimethylation at 11 sites [67]. Methylated tau is widely present in AD brains and colocalizes with NFTs in late-stage AD [68]. Methylation has minimal effects on the affinity of tau for microtubules and on tau-mediated tubulin polymerization. Notably, the aggregation propensity of methylated tau is dramatically attenuated during both the nucleation and elongation steps, suggesting that lysine methylation protects tau from aggregation [67].

Ubiquitination and SUMOylation

Tau has a high propensity for ubiquitination [69]. The ubiquitination of tau enhances its clearance through the proteasome or lysosomal autophagy system [68–70]. However, ubiquitinated tau oligomers may impair proteasome function [71]. Furthermore, ubiquitination also inhibits tau-mediated microtubule assembly [72] and promotes tau aggregation [69]. Recently, Arakhamia et al. reported that the ubiquitination of tau may help stabilize interprotofilament packing and regulate polymorphisms in tauopathies [73].

SUMOylation is mainly related to protein interactions and subcellular localization and usually occurs on lysine residues. For tau, SUMOylation targets K340R via small ubiquitin-like modifier 1 (SUMO1) [74, 75]. The SUMOylation of tau is closely associated with its phosphorylation. SUMO1 is colocalized with phosphorylated tau in the cerebral cortex of the AD brain. Tau SUMOylation promotes tau hyperphosphorylation. Additionally, tau hyperphosphorylation stimulates its SUMOylation. In addition, tau SUMOylation inhibits tau degradation by decreasing the solubility and ubiquitination of tau [76]. Some animal experiments have suggested that SUMOylation may be related to age [77]. These results suggest that the ubiquitination and SUMOylation of tau may play a key role in the development of tau pathology.

Truncation

In the AD brain, tau is abnormally truncated by many proteases. Tau is cleaved by caspase 2 at Asp314, by caspase 3 at Asp25 and Asp421, by caspase 6 at Asp13 and Asp402, by chymotrypsin at Tyr197, by calpain at Lys44 and Arg230 [78], and by asparaginyl endopeptidase (AEP) at Asn255 and Asn368 [79]. Among these proteases, the activity of AEP in the brain increases in an age-dependent manner. AEP cleaves tau at residues Asn255 and Asn368, generating a tau (1-368) fragment that is more prone to phosphorylation and aggregation than full-length tau [79]. AEP deletion in tau P301S transgenic mice reduces tau pathology and ameliorates cognitive deficits. The tau (1-368) fragment enhances BACE1 expression and A β production, propagating AD pathology [80]. Furthermore, compound #11, a small-molecule inhibitor of AEP, attenuates AD pathology and partially rescues cognitive deficits in mouse models of AD [81].

3,4-Dihydroxyphenylacetaldehyde (DOPEGAL) modification

DOPEGAL is the aldehyde metabolite of norepinephrine. Accumulation of the catecholamine-derived aldehyde DOPEGAL within neurons is thought to be one of the mechanisms triggering neurodegeneration in AD [82]. In AD patients, the concentration of DOPEGAL in the locus coeruleus is elevated by approximately three folds [82]. Recently, it was reported that DOPEGAL activates AEP and subsequently cleaves tau, promoting tau aggregation in AD [83]. Furthermore, DOPEGAL covalently modifies the Lys353 residue of tau in the locus coeruleus and triggers tau aggregation, accelerating its pathology and spreading to interconnected brain regions [84].

Cross-seeding of tau with other prion-like proteins and cryo-EM structural analysis of different tau strains **Assembly model for tau**

The aggregation of tau follows a nucleation–elongation mechanism. The primary processes include dimerization, corresponding to filament nucleation (the rate-limiting nucleation event), and elongation (the addition of monomers to the ends of growing polymers). The secondary processes include filament fragmentation (increasing the number of filament ends available for elongation), secondary nucleation (producing small, highly diffusible aggregates associated with toxicity), and filament annealing [85]. The "nucleation phase" proceeds slowly with unfavorable thermodynamics, whereas the "elongation phase" proceeds rapidly with more favorable thermodynamics. Therefore, the kinetics of tau assembly display a sigmoidal growth curve with a lag phase followed by a rapid growth phase and a final plateau phase. The rate-limiting step in aggregation is the assembly of misfolded

proteins into nuclei (seeds). Amyloid formation can be significantly accelerated by adding preformed seeds. The seeds can reduce the lag time and promote amyloid formation by transforming normal proteins into fibrils (seeding).

Cross-seeding of tau with other prion-like proteins

Several studies have documented cross-seeding between tau and other misfolded proteins, including A β , α -synuclein, and IAPP.

The most representative cross-seeding studies in animal models involve A β and tau. The simultaneous accumulation of these proteins in the brain is a major hallmark of AD. A β has been found to accelerate tau aggregation, while tau aggregates do not have the same effect on A β [86, 87]. In human studies, advances in molecular positron emission tomography (PET) have enabled tracking of tau pathology and A β pathology in AD. A PET imaging study identified some converging areas of A β and tau pathology, particularly in the inferolateral temporal lobe, suggesting a physical interaction of these pathologies in disease progression [88]. Another PET imaging study revealed that tau pathology begins focally but progresses rapidly under the influence of A β pathology [89]. The interaction between A β and tau is linked to neurodegeneration and cognitive decline. These results indicate the synergistic role of A β and tau in the pathogenesis of AD.

In a subgroup of AD patients, tau and α -synuclein pathologies occur simultaneously. In addition, multiple studies have shown that tau and α -synuclein aggregate in PD and DLB brains [90–92]. These results suggest that α -syn and tau may synergistically promote fibrillation of each other. Tau interacts with α -syn directly via the microtubule-binding region of the tau protein and the C-terminus of α -syn [93]. This binding allows cross-seeding between tau and α -syn. In vitro, co-incubation of α -syn and tau synergistically promotes the aggregation of both proteins [94]. In vivo, α -syn preformed fibrils (PFFs) were shown to induce tau aggregation in cultured cells and in the brain [95–98]. On the other hand, tau PFFs also promote the aggregation and spread of α -syn in PD [99]. These results suggest that tau and α -syn accelerate the seeding and spreading of each other.

Patients with type 2 diabetes mellitus (T2DM) have an increased incidence of AD [100]. T2DM is characterized by the deposition of islet amyloid polypeptide (IAPP) in the pancreas [101]. IAPP interacts with tau to accelerate the formation of a more virulent strain that exhibits enhanced seeding activity and neurotoxicity. Intrahippocampal injection of tau fibrils formed in the presence of IAPP, into tau P301S transgenic mice, triggered the spread of tau pathology, synaptic loss, and cognitive deficits [102].

Cryo-EM structural analysis of different tau strains

The aggregation of tau is similar to that of prions, which transform from a soluble monomeric state to a state of self-propagating aggregates rich in β -sheet structures [103]. Prions adopt pathological conformations called "strains" to stably propagate in living systems and create unique neuropathological patterns. Data from multiple studies suggest that tau functions as a prion [104–106]. Diamond and colleagues isolated tau strains from 29 patients with 5 different tauopathies and found that different diseases are linked to distinct sets of strains [105]. Recent breakthroughs in electron cryo-microscopy have allowed the atomic structure of tau filaments to be extracted from the brains of individuals with various tauopathies. The characteristics of each disease are unique tau filament folding, which remains conserved among individuals suffering from the same disease [107].

In the brains of AD patients, tau inclusions have two types of cryo-EM structures, PHF and straight filaments, which consist of a common C-shaped ordered core [108]. PHFs and straight filaments are distinguished by different interprotofilament packing arrangements. The ordered core contains 306–378 amino acids (numbered by the 441-amino-acid tau isoform). The remaining amino acids at the N- and C-termini adopt random conformations termed the fuzzy coat [109]. Additional cases of AD or different brain regions from individual cases of AD show the same tau filament structures [110]. Since valine 306 at the beginning of the ordered core is the first amino acid of R3, 4R tau or 3R tau monomers can both be incorporated into filaments, which explains the presence of 3R and 4R tau PFFs in AD. If the ordered core includes amino acids containing R1 followed by R3 or R2 followed by R3, then such structures can recruit 3R or 4R tau isoforms, respectively [108].

In the past several years, the structure of tau fibrils in Pick's disease [111], CTE [112], CBD [28], PSP, and other tauopathies [113] has been determined by cryo-EM. Most R1s and no R2s are present in the ordered cores of Pick's disease filaments, explaining their selectivity for 3R tau. R2s are present in the ordered cores of tau filaments in CBD, PSP, and other diseases, explaining why they contain only 4R tau.

The mechanisms mediating tau propagation and spreading

Transmission of tau pathology

During the progression of AD, tau pathology typically begins in the brainstem, including the locus coeruleus (LC), and then progresses to the transentorhinal cortex or the entorhinal cortex in the medial temporal lobe (Braak stages I and II), then to the hippocampal region (Braak stages III and IV), and finally to the neocortex or

the primary areas of the neocortex (Braak stages V and VI) [114]. An increasing number of studies have suggested that the LC may be the origin of tau pathology [114–116]. Jacobs et al. performed human-level neuroimaging research, including magnetic resonance imaging (MRI) measurements of LC integrity and tau PET imaging, and found that changes in LC integrity precede tau accumulation in the medial temporal lobe. In addition, the selective vulnerability of the LC to tau is related to specific genetic features [117]. Tau protein spreads in the brain through neuronal connections, which may involve multiple mechanisms, including spreading between strongly interacting brain regions (functional connectivity), through anatomical connections (structural connectivity), or simple diffusion. A study using magnetoencephalography/PET revealed that structural connections and functional connections play important roles in tau transmission [118].

In FTLT-Tau, this apparent aspect of tau diffusion is less well characterized. In PSP, an initial pallido-luysoneigral stage of tau deposition, progressing to the basal ganglia, the pontine and dentate nuclei, and the frontal and parietal lobe, has been reported [119]. In AGD, the initial sites of deposition are the ambient gyrus and its vicinity, the anterior and posterior medial temporal lobe, and the septum, insular cortex, and anterior cingulate gyrus, accompanied by spongy degeneration of the ambient gyrus [120]. These observations support the notion that pathological forms of tau spread between neurons and that the roots of tau transmission are distinct in different tauopathies.

Mechanisms that mediate neuron–neuron transmission of tau

Neuron–neuron transmission of tau is believed to be mediated by exocytosis and endocytosis. Exocytosis mechanisms include exosome release, secretion, and neuronal death. Wang et al. demonstrated that neurons can release tau via exosomes and that neuronal activity enhances the release of exosomes [121]. Notably, exosome-associated tau levels have been reported to be elevated in the cerebrospinal fluid (CSF) and blood of patients with AD and FTD [122, 123]. These findings suggest that exosomal processes are involved in the cell-to-cell spread of tau. Endocytosis mechanisms include micropinocytosis, phagocytosis, dynamin-mediated endocytosis, receptor-mediated endocytosis, and/or membrane fusion of exosomes. Macropinocytosis-mediated tau internalization in neurons is mediated by heparan sulfate proteoglycans (HSPGs) [124, 125], which bind to extracellular tau aggregates and promote their cellular uptake [126]. Low-density lipoprotein receptor-related protein 1 acts synergistically with HSPGs to

control tau entry into neurons [127], but its contribution to tau pathogenesis has not been determined. In addition, the dynamin-dependent endocytosis pathway also regulates tau endocytosis [128]. *BINI*/Amphiphyrin2, a genetic risk factor for late-onset AD, has also been shown to regulate clathrin-mediated endocytosis of pathological tau aggregates [129]. Another important mechanism mediating tau endocytosis is receptor-mediated endocytosis. One study screened for receptors of pathological tau and revealed that receptor for advanced glycation end products (RAGE) mediates neuronal uptake of pathological forms of tau [130]. RAGE deficiency reduces transsynaptic tau spread and inhibits microglial inflammatory responses. Furthermore, RAGE is needed for tau-induced memory loss, while blocking the interaction between RAGE and tau oligomers ameliorates cognitive impairment in rTg4510 mice [130]. These results suggest that RAGE plays an important role in tau pathogenesis. In addition, M1/M3 muscarinic receptors have also been reported to mediate tau uptake [131]. The muscarinic receptor antagonists atropine and pirenzepine block 80% of this uptake.

Microglia in the spread of tau pathology

Several studies have reported that microglia phagocytose free tau [132–135]. Microglial HSPGs, CX3CR1 and P2RY12 have been shown to bind tau [136–138]. Multiple mechanisms are involved in tau uptake by microglia, including phagocytosis, macropinocytosis, and micropinocytosis [139]. Microglia may release tau seeds through intracellular tau-mediated microglial cytotoxicity, resulting in the release of tau seeds that have not yet been degraded [140]. In addition, microglia can secrete tau through exosomes, which may be a way for microglia to directly transmit tau [141, 142]. Blocking exosome release or depleting microglia mitigates the spread of tau in a tau-inoculated mouse model [133]. In addition, microglia secrete factors that may exacerbate the spread of tau in neurons [143, 144]. Several studies have shown that microglia are able to degrade tau [132, 145, 146]. Thus, microglia may mediate the clearance of tau, but in advanced tauopathies, the degradation capacity of microglia may be overwhelmed by tau aggregates and the secretion of tau fibrils with enhanced seeding activity.

The toxicity of pathological tau

The presence of pathological tau undoubtedly triggers a series of cellular dysfunctions, including mitochondrial dysfunction, endoplasmic reticulum stress, cytoskeletal instability, synaptic dysfunction, and disruption of axon transport, and eventually leads to neurodegeneration [147–151]. Tau is present in various forms, ranging from soluble monomers to insoluble fibrils. Insoluble

NFTs are considered classical toxic and pathogenic entities that parallel the duration and severity of the disease [152–154]. However, this perspective has been challenged in recent years. Some studies have shown that certain soluble forms of tau may play a more important role [155, 156]. Tau oligomers impair memory consolidation by inducing synaptic and mitochondrial dysfunction in wild-type mice [157]. Reducing soluble tau levels partially reversed cognitive impairments in animal models [158]. Tau oligomers also damage neuronal nuclei, impairing nucleocytoplasmic transport and altering pathogenic gene expression [159]. Compared with tau fibrils, tau oligomers have not been the subject of much research. In the future, more research is needed to explore the toxicity and pathogenic mechanism of tau oligomers.

Notably, tau not only exerts neurotoxicity but also indirectly affects other neurodegenerative proteins, such as A β , α -synuclein and IAPP [160]. The interaction between tau and other prion-like proteins may regulate the toxicity of tau aggregates [160–162]. Clinical studies have revealed greater cognitive decline in older adults with concurrent abnormalities in CSF A β and p-tau [163, 164]. Furthermore, A β and tau interactions in the inferotemporal neocortex exacerbate tau pathology and cognitive decline. Individuals with hypometabolism in the posterior cingulate gyrus, where tau–A β interactions are most closely related, show progressive memory decline [165]. These results suggest that synergy between A β and tau is associated with cognitive decline and brain dysfunction. Several studies have shown the synergistic effect of A β and tau on microglia, astrocytes, or organelles such as mitochondria [166, 167]. The copathology of α -syn and tau also promotes the pathological spreading of proteins more strongly than does the administration of tau or α -syn alone [168]. Administration of α -syn/tau oligomers derived from PD patients to the brains of tau transgenic mice accelerated the formation of tau oligomers and induced more severe neuronal loss than did administration of tau oligomers alone [169]. In addition, injection of tau/ α -syn mixed fibrils exacerbates the spread of tau pathology in a mouse model of tauopathy compared with injection of pure tau or α -syn fibrils [170]. The mixed fibrils of IAPP and tau also exhibit enhanced seeding activity and neurotoxicity both in vitro and in vivo. Compared with tau fibrils, intrahippocampal injection of IAPP-tau mixed strains into tau P301S transgenic mice significantly promoted the spread of tau pathology and induced more severe synaptic loss and cognitive deficits [102]. Thus, the synergistic effect of tau and other prion proteins deserves further study.

As we described previously, tau PTMs can also enhance tau toxicity. Hyperphosphorylation of tau can lead to mislocalization of tau to the somatogenic compartment,

reduce microtubule binding, and promote tau misfolding [171]. Tau acetylation impairs microtubule binding, reduces solubility, promotes cleavage, and impairs protein degradation [172–174]. The truncation of tau also affects tau toxicity by promoting tau aggregation, reducing microtubule binding, and promoting synaptic dysfunction [175].

Pathological tau as a diagnostic biomarker

Due to the crucial role of tau in the occurrence and development of this disease, a diagnosis based on tau pathology is urgently needed. At present, the diagnosis of pathological tau mainly includes CSF-based biomarkers, blood-based biomarkers, and tau-PET images [176].

CSF-based tau biomarkers

The elevation of p-tau in the CSF signifies the presence of pathology. For the past few decades, p-tau181 in the CSF has been found to be one of the core biomarkers of AD. Recently, the diagnostic capabilities of tau phosphorylated at other sites have begun to be recognized. It appears that p-tau217 is superior to p-tau181 as a CSF biomarker for the differential diagnosis of AD [177–179]. Recently, p-tau205 was also identified as a biomarker for AD [180]. Another study revealed that MTBR-tau243 is particularly specific to tau aggregates and is strongly associated with tau PET [181]. In addition to tau phosphorylation and aggregation, fragmentation of tau also plays a role in tau pathogenesis. AEP cleaves tau, thereby generating the tau (1-368) fragment, which is increased in patients with AD [79]. Blennow et al. showed that tau368 is a tangle-enriched fragment. The tau368/total-tau (t-tau) ratio in the CSF was decreased in patients with AD and negatively correlated with ¹⁸F-GTP1 retention [182]. In addition, they compared the levels of CSF p-tau 181, p-tau217, t-tau, and tau368 and their correlation with tau burden in cognitively unimpaired, mild cognitive impairment, non-AD cognitive disorder, and AD dementia patients. In symptomatic AD patients, tau368/t-tau was more strongly associated with tau-PET scanning and cognitive performance than other CSF tau biomarkers [183]. Although CSF-based biomarkers show high accuracy in the diagnosis of AD, blood-based biomarkers are needed because lumbar puncture is invasive.

Blood-based tau biomarkers

Blood-based tau biomarkers are more economical, more accessible and less invasive. Among them, p-tau181, p-tau217 and p-tau231 are the most promising [184–188]. The plasma level of phosphorylated tau is correlated with the density of A β and tau [189–192]. Additionally, plasma markers can effectively differentiate AD from other neurodegenerative diseases and have certain

predictive power for the future development of AD [188, 193]. Notably, p-tau217 performs slightly better than others, possibly because of its higher levels in AD [190, 194]. The blood p-tau217 test is comparable or superior to the CSF p-tau217 test in the detection of AD pathology [195, 196]. Recent research has shown that the diagnostic accuracy of p-tau212 in blood is similar to that of p-tau217 [197]. In addition, blood-based brain-derived tau has been identified as a biomarker for identifying A β -positive individuals at risk of short-term cognitive decline and atrophy [198]. The development of blood-based biomarkers will aid in the early noninvasive diagnosis and treatment of tauopathy.

PET imaging of tau pathology

Tau-PET tracers are used to visualize tau aggregates and identify the distribution and stage of tau pathology. The first tau-PET tracer, [^{18}F]-flortaucipir, was approved by the U.S. Food and Drug Administration (FDA) in May 2020 for the clinical detection of AD. This tracer has good blood-brain barrier (BBB) permeability and excellent metabolism. This tracer is less sensitive to tau associated with tauopathies other than AD [199]. Second-generation tau-PET tracers, including [^{18}F]-MK6240, [^{18}F]-RO948, and [^{18}F]-PI2620, can more selectively bind to hippocampal tau. Tau-PET is predictive of cognitive disorders in AD patients [200]. Furthermore, the findings of tau-PET perfusion and [^{18}F]-FDG-PET metabolism are in strong agreement [201]. Recently, Isla et al. compared three tracers: [^{18}F]-Flortaucipir, [^{18}F]-MK-6240 and [^{18}F]-PI-2620. The three tracers showed similar autoradiographic binding characteristics. They all bind strongly to NFTs in AD

but do not significantly bind to tau aggregates in non-AD tauopathies, suggesting their limited utility in detecting non-AD tauopathies in vivo. None of them bind to A β , α -synuclein, or TDP-43 lesions, but they all bind strongly to neuromelanin and melanophore-containing cells and weakly to hemorrhage areas [202]. The off-target effects of PET tracers need to be further improved, and non-AD tauopathy PET tracers are also worthy of further study. Compared to fluid biomarkers, tau-PET is more accurate at the expense of high cost. Each of these approaches has advantages and disadvantages. It might be practical to use blood-based biomarkers as a screening index and then choose CSF and even tau-PET for further diagnosis.

Therapeutic strategies against tau pathology

Targeting tau production and aggregation

Targeting tau production is a way to inhibit tau pathology (Fig. 1). Cellular and animal experiments have shown that siRNAs targeting tau reduce tau pathology and neurodegeneration in tau P301S transgenic mice [203]. Intrathecal injection of antisense oligonucleotides (ASOs) targeting tau decreased the mRNA expression and protein level of tau in cynomolgus monkeys. The reduction of tau was observed in the frontal cortex, temporal cortex and hippocampus, indicating good transmission in the brain [204]. The results from a phase Ib trial (NCT03186989) indicated that the tau ASO MAPT Rx (also known as BIIB080) is safe and reduces t-tau and p-tau levels in the CSF of patients with mild AD [205]. Phase II trials have also been initiated in patients with MCI and AD (NCT05399888). A group of tau aggregation inhibitors has also been identified [206]. Methylene

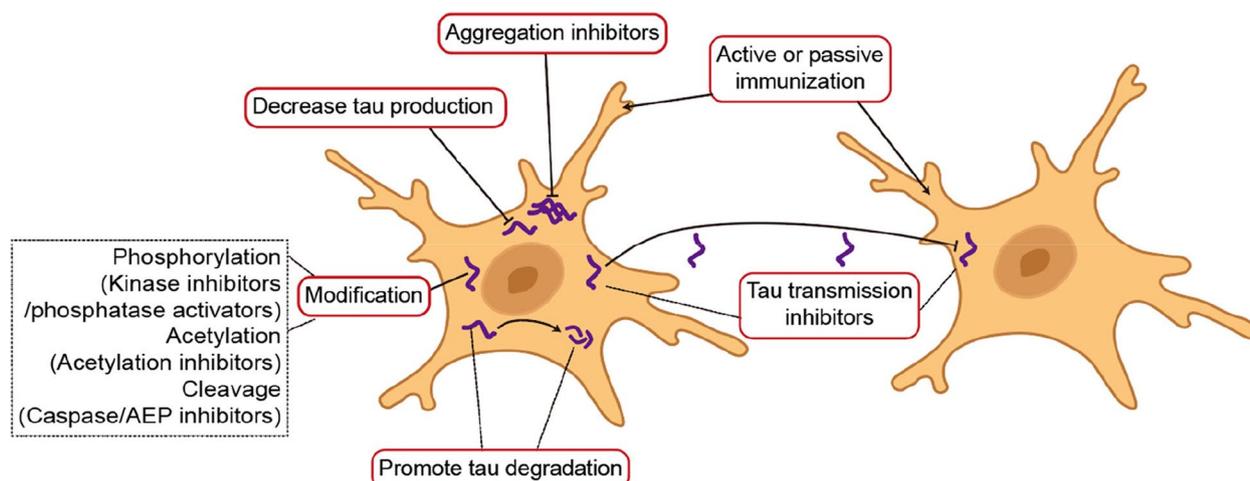


Fig. 1 Therapeutic strategies against tau pathology, including (1) inhibiting tau production, such as by siRNAs and ASOs; (2) inhibiting tau aggregation, such as the methylene blue derivatives LMTX and curcumin; (3) regulating the post-translational modifications of tau, such as kinase inhibitors/phosphatase activators, acetylation inhibitors, and caspase/AEP inhibitors; (4) promoting tau degradation, such as autophagy or proteasomal degradation regulators; (5) inhibiting tau transmission; and (6) active and passive immunotherapies

blue (MB) hinders the aggregation of tau [207, 208]. A customized intranasal hydrogel delivering MB was developed to ameliorate cognitive dysfunction [209]. LMTX (TRx0237) is a derivative of MB. TRx0237 is currently being evaluated in the LUCIDITY Phase III trial. The interim results showed that the improvements in the treatment group were less than expected. The natural product curcumin also binds to β -sheets and prevents aggregation [210]. Recently, Wang et al. identified a set of aptamer candidates, including BW1c, which has a high binding affinity for tau and significantly inhibits tau oligomerization and aggregation [211]. In addition, Yao et al. synthesized a group of isatin-pyrrolidinylpyridine compounds that inhibit tau self-aggregation and even depolymerize tau aggregates [212]. These promising compounds deserve further clinical study.

Targeting tau degradation and transmission

Promoting the degradation of tau is another therapeutic strategy (Fig. 1). Tau is cleared through the ubiquitin-proteasome system, the endosomal-lysosomal system, and the autophagy-lysosome system. The phosphorylation of 26S proteasomes induced by cAMP/PKA promotes the degradation of tau [213]. Some phosphodiesterase inhibitors are currently undergoing clinical trials [214]. Anti-tau scFv chimeras were developed to direct tau to the proteasome or lysosome, reducing intracellular tau levels [215]. Tau-targeting proteolysis-targeting chimeras (PROTACs), which can lead to polyubiquitination and proteasome-mediated degradation of the protein, were developed to reduce t-tau and p-tau levels in tauopathy mouse models [216, 217]. Lysosome-targeting chimeras and antibody-based PROTACs were also designed to promote lysosomal targeting and clearance of tau [218, 219]. The autophagy-targeting chimera complex was developed to clear tau through the autophagy-lysosomal system [220]. Recently, a study revealed pathogenic tau-specific autophagy based on a customized nanochaperone that enhanced autophagic flux and pathological tau clearance, alleviating the tau burden and cognitive deficits in AD mice [221]. However, this strategy requires further clinical validation. There are currently several antibodies designed to prevent the transmission of tau, such as BIIB076 [222], Tilavonemab, and PRX005. Nevertheless, further clinical studies are needed to validate these antibodies in the future.

Targeting tau modification

Several drugs have been developed to target tau hyperphosphorylation, including lithium [223, 224], phosphatase modifiers, and synthetic small molecules [225, 226]. Lithium is an inhibitor of GSK3- β [227]. The long-term administration of lithium reduces amyloid

plaque formation, reduces tau hyperphosphorylation, and improves learning and memory in transgenic mice that overproduce A β and tau [227–229]. However, the cognitive outcomes did not improve in a phase 2 clinical trial [230]. Another phase II trial (NCT02862210) to assess the effects of lithium on the behavioral symptoms of FTD was completed, but the results have yet to be reported. Sodium selenite has been shown to reduce tau phosphorylation in animal models [231, 232]. However, in a clinical trial of patients with mild to moderate AD, diffusion MR images were slightly improved. In a phase Ib open-label study (ACTRN12617001218381) in patients with FTD, MRI and cognitive and behavioral measures were slightly reduced. Two phase IIB trials in patients with FTD (ACTRN12620000236998) and PSP (ACTRN12620001254987) are ongoing. Salsalate and diflunisal were shown to reduce tau acetylation by inhibiting p300 acetyltransferase [233]. Pieper et al. reported that patients receiving salsalate or diflunisal exhibited a decreased incidence of AD [61]. However, a phase I open-label study (NCT02422485) in PSP patients showed that the drug was well tolerated but failed to improve disease progression in PSP patients [234]. A second phase I trial (NCT03277573) involving AD patients has been completed, but the results have not yet been reported. Minocycline and VX-765 are caspase inhibitors that also play a positive role in AD [235–237]. A multicenter phase II study (ISRCTN16105064) of minocycline in AD patients showed that minocycline increased adverse effects and failed to slow disease progression. The AEP inhibitor compound 11 reduced tau cleavage and resulted in the amelioration of tau pathology and protection of cognitive function in tau P301S and 5 \times FAD transgenic mice [81]. However, further clinical research on compound 11 is needed.

Tau immunotherapies

Immunotherapies have achieved remarkable progress in recent years. Active immunization involves the induction of antigen-antibody reactions with low doses of tau fragments. The initial attempt at active immunization was to treat C57 mice with full-length human tau protein, which resulted in various side effects, including axonal damage and encephalomyelitis. Researchers subsequently turned to tau fragments [206, 238]. To date, active immunization therapies including AADvac1 (targeting phosphorylation-independent conformational epitope) and ACI-35 (targeting Ser396/Ser404 epitope) are in clinical trials [239–242]. Four clinical studies of AADvac1 have been completed. In a phase I trial (NCT01850238), AADvac1 was shown to be safe and well tolerated in AD patients [239]. A follow-up phase I study (NCT02031198, FUN-DAMANT) showed a similar safety profile, and higher

IgG titers were significantly associated with reduced hippocampal atrophy and cognitive decline [241]. The results from a phase II trial (NCT02579252, ADAMANT) showed that AADvac1 was safe and well tolerated and induced a strong IgG response [240]. The vaccine did not alter cognition or brain atrophy rates but was associated with a 58% attenuation of plasma NfL increases. However, larger stratified studies are still needed to evaluate the clinical effectiveness of this vaccine. An open-label phase I pilot trial (NCT03174886) was conducted in patients with nonfluent, agrammatic variant progressive aphasia (naPPA). The results have not yet been reported. A phase Ib study (ISRCTN13033912) revealed that ACI-35 was safe and well tolerated but had a weak immune response in patients with mild to moderate AD. The second-generation vaccine ACI-35.030 has improved immunogenicity and produces antibodies that specifically bind p-tau and recognize PHF in the brains of AD patients. A phase Ib/IIa trial (NCT04445831) is ongoing to test the safety and immunogenicity of ACI-35.030 in early AD. Interim results showed that all groups generated specific and potent antibody responses against p-tau and PHF and that there were no clinically relevant safety concerns [243]. Passive immunity is the administration of tau antibodies to target extracellular or intracellular tau to block its prion-like seeding [244, 245]. Multiple clinical trials have attempted to use tau antibodies to treat tauopathies [246, 247]. A phase I study (NCT05344989) of APNmAb005 (an anti-tau IgG antibody) is expected to be completed in July 2024. Three phase I trials of Bepranemab (UCB0107) (an IgG4 antibody that binds to aa 235–250 of tau) (NCT03464227, NCT03605082, and NCT04185415) showed that UCB0107 was safe and that the level of UCB0107 in CSF increased in a dose-dependent manner. A phase II trial of UCB0107 (NCT04867616) is ongoing. In addition, many tau antibodies, such as BIIB076, E2814, gosuranemab, and JNJ-63733657, are undergoing clinical trials. However, many trials have been terminated due to safety concerns.

Challenges and future opportunities of tau treatment

Currently, treatments for tau are in their infancy. Although many drug candidates targeting tau have been discovered and developed, few are clinically useful. Tau treatment faces several challenges. (1) The BBB limits the entry of drugs. More strategies need to be developed to pass through the BBB. (2) The mechanism of tauopathy remains unclear. Many issues need to be further addressed in the future. What initiates tauopathy? What is the relationship between A β pathology and tau pathology? Is tau the cause or a byproduct of tauopathy? Which form of tau exerts toxic effects? What is the relationship between different tau strains and clinical manifestations?

To develop new therapeutic strategies, we need to further explore the cellular and molecular pathways involved in the pathophysiology of tauopathies. (3) Animal or cellular models of tau pathology do not fully mimic human disease progression, and the results observed in vitro are difficult to replicate in clinical trials. We need to further develop novel tauopathy models, such as 3D organoids [248] and human iPSC tauopathy models [249]. (4) The timing of clinical intervention remains questionable. In clinical trials, clinical intervention may be too late to reverse disease progression. The development of new biomarkers is needed to facilitate early diagnosis. Furthermore, it may be more important to develop biomarkers in blood than in CSF. (5) Some clinical trials had a small number of participants or had a short observation period. In the future, larger clinical trials are needed, recruiting a larger number of patients, observing for a longer period, and designing more innovative and efficient clinical trials. In addition, further clinical trials of combination therapies including tau and A β are needed.

Conclusions

Here we have discussed the clinical and neuropathological features of different tauopathies. Tau plays an important role in these neurodegenerative diseases. Converging lines of evidence support that tau acts as a prion-like protein. Various post-translational modifications affect its aggregation. However, the effects of some post-translational modifications, such as tau phosphorylation and acetylation, on aggregation are controversial and deserve further investigation. The spread of tau is mediated by tau exocytosis and endocytosis, in which microglia play a mysterious role. Tau has several conformational states, including monomers, oligomers, and fibrils. Among them, oligomers are considered to be the most toxic. The pathogenic mechanisms of these different conformational states of tau also deserve more in-depth studies. CSF-, blood- and PET-based tau biomarkers are useful for the diagnosis of AD. Multiple approaches targeting tau have been explored for the treatment of AD and other tauopathies. Although animal experiments and preclinical studies have achieved encouraging results, the clinical data are not optimistic. Therefore, more in-depth basic research on tauopathy is necessary to determine the exact role of tau in neurodegenerative disease and to identify new therapeutic targets.

Abbreviations

AD	Alzheimer's disease
PSP	Progressive supranuclear palsy
FTDP-17	Frontotemporal dementia with parkinsonism-17
CBD	Corticobasal degeneration
CTE	Chronic traumatic encephalopathy
AGD	Argyrophilic grain disease
NFTs	Neurofibrillary tangles

PHFs	Paired helical filaments
DLB	Dementia with Lewy bodies
A β	Amyloid- β
PD	Parkinson's disease
MSA	Multiple system atrophy
PTMs	Post-translational modifications
PP	Protein phosphatase
SUMO1	Small ubiquitin-like modifier 1
AEP	Asparaginyl endopeptidase
DOPEGAL	3,4-Dihydroxyphenylacetaldehyde
PFF	Preformed fibril
T2DM	Type 2 diabetes mellitus
IAPP	Islet amyloid polypeptide
HSPG	Heparan sulfate proteoglycan
RAGE	Advanced glycation end products
ASO	Antisense oligonucleotide
MB	Methylene blue

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Declarations

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