



# Targeting tau in Alzheimer's disease: from mechanisms to clinical therapy

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## From the Contents

Introduction	1489
Search Strategy	1489
Transcriptions, Domains, and Structures of Tau	1489
Tau Toxicity in Alzheimer's Disease	1492
Plasma Tau in Alzheimer's Disease Diagnosis	1493
Tau-Based Therapeutic Strategies	1493
Conclusions and Future Perspectives	1494

## Abstract

Alzheimer's disease is the most prevalent neurodegenerative disease affecting older adults. Primary features of Alzheimer's disease include extracellular aggregation of amyloid- $\beta$  plaques and the accumulation of neurofibrillary tangles, formed by tau protein, in the cells. While there are amyloid- $\beta$ -targeting therapies for the treatment of Alzheimer's disease, these therapies are costly and exhibit potential negative side effects. Mounting evidence suggests significant involvement of tau protein in Alzheimer's disease-related neurodegeneration. As an important microtubule-associated protein, tau plays an important role in maintaining the stability of neuronal microtubules and promoting axonal growth. In fact, clinical studies have shown that abnormal phosphorylation of tau protein occurs before accumulation of amyloid- $\beta$  in the brain. Various therapeutic strategies targeting tau protein have begun to emerge, and are considered possible methods to prevent and treat Alzheimer's disease. Specifically, abnormalities in post-translational modifications of the tau protein, including aberrant phosphorylation, ubiquitination, small ubiquitin-like modifier (SUMO)ylation, acetylation, and truncation, contribute to its microtubule dissociation, misfolding, and subcellular missorting. This causes mitochondrial damage, synaptic impairments, gliosis, and neuroinflammation, eventually leading to neurodegeneration and cognitive deficits. This review summarizes the recent findings on the underlying mechanisms of tau protein in the onset and progression of Alzheimer's disease and discusses tau-targeted treatment of Alzheimer's disease.

**Key Words:** acetylation; Alzheimer's disease; cognitive deficits; gliosis; mitochondria damage; neuroinflammation; phosphorylation; synaptic impairments; tau; tau immunotherapy

## Introduction

Tau, a microtubule-associated protein, maintains microtubule stability in neurons and promotes axonal growth. Under physiological conditions, hypophosphorylated tau is localized in the axons of neurons. Neurofibrillary tangles (NFTs) made of accumulated tau protein and senile plaques made of extracellular amyloid- $\beta$  ( $A\beta$ ) are the hallmark of Alzheimer's disease (AD; Wang and Liu, 2008). Significant advancement in understanding the role of tau toxicity in the pathogenesis of AD has been made in the past few decades. Studies have shown that post-translational modifications (PTMs), such as phosphorylation, acetylation, ubiquitination, small ubiquitin-like modifier (SUMO)ylation, and truncation of tau protein participate in its stability, misfolding, accumulation, and degradation (Wang and Liu, 2008). Accumulation of tau protein in cells leads to cognitive deficits, such as mitochondrial dysfunction, the impairment of synaptic plasticity, gliosis, and neuroinflammation via multiple pathways (Wang and Liu, 2008). In this review, we summarize the role of tau protein in these processes. Moreover, we provide an overview of tau toxicity in synaptic plasticity, memory, and learning in AD. Finally, we discuss the application potential of tau protein as a therapeutic target for ameliorating AD-related cognitive deficits and other related tauopathies.

## Search Strategy

The articles used in this narrative review were found via PubMed until June 2020. Only papers published in English were considered. The key words/terms were Alzheimer, tau, phosphorylation, acetylation, SUMOylation, ubiquitination, truncation, tau post-translational modifications, microglia, astrocyte, neuroinflammation, mitochondria damage, synaptic impairments, cognitive deficits, and tau immunotherapy. All studies were cited due to their relevance to the review.

## Transcriptions, Domains, and Structures of Tau

The microtubule-associated protein tau (MAPT) gene encodes for tau protein is located on chromosome 17 (17q21-q22) in humans (Wang and Liu, 2008).

In the adult human brain, six isoforms of tau protein, namely ON3R, 1N3R, 2N3R, ON4R, 1N4R, and 2N4R, are generated by selective splicing of exons 2, 3, and 10 (Neve et al., 1986). The alternative splicing of exons 2 and 3 leads to differences in the N-terminal inserts of these tau isoforms, known as ON, 1N, and 2N, while the alternative splicing of exon 10 results in tau protein containing three or four microtubule-binding repeat domains (MBDs; 3R or 4R; Figure 1). The 3R to 4R tau ratio in the healthy adult brain is nearly 1:1, whereas in primary tauopathies, the alternative splicing of exon 10 leads to 3R tau or 4R tau dominant pathological lesions in different tauopathies (Delacourte et al., 1998; Sergeant et al., 1999).

Tau protein is intrinsically disordered, and its higher-order structure is still unknown. The N- and C-terminal amino acid residues of tau are mainly acidic and neutral, respectively. The four domains of tau protein are the N-terminal projection, the proline-rich domain, the C-terminal assembly, and the MBDs. Several studies have shown that the N-terminal projection domain of tau extends from the microtubule and links it to the plasma membrane of neurons (Derisbourg et al., 2015; Gauthier-Kemper et al., 2018). The proline-rich domain contains multiple Ser/Thr phosphorylation motifs that bind Src homology 3 domains of proteins, such as tyrosine kinase Fyn (Lee et al., 1998). The binding affinity between the tau protein and microtubules is determined by MBD, which is encoded by exons 9–12 and contains four repeats (R1–4) (Kar et al., 2003; Cao and Mao, 2009). Due to R2, an additional repeat domain, the 4R isoform demonstrates higher affinity and efficiency in assembling microtubules compared to the 3R isoform (Goedert and Jakes, 1990). When tau aggregates into paired helical filaments (PHFs), the MBD forms the core region of the PHF, and the C-terminal and the long N-terminal domains project around the core region. Despite the use of modern techniques, imaging of the structure of PHF has proven challenging. Recently, with the rapid development of artificial intelligence technologies, such as alpha-Fold, the prediction model of tau protein 3D structure has injected new life into the analysis of tau higher-order structure (Sathish Kumar and Kannan, 2021). A study showed that the 3D structure of tau protein predicted by ab initio modeling can generate various PTMs, bringing new insights into the understanding of tau structure and related tau pathology (Ahmad et al., 2020).

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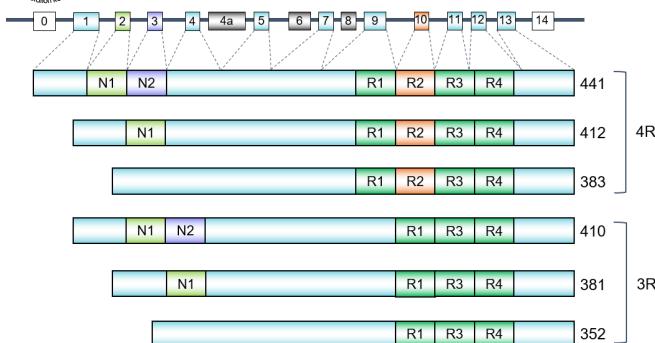
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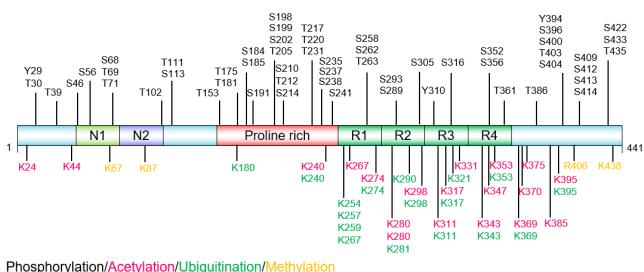
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**Figure 1 | Tau splicing and isoforms.**

**Figure 1 | Tau Splicing and Isoforms.**  
Human MAPT gene is localized on chromosome 17q21.31 and consists of 16 exons. Exons 0 and 1 encode the 5' untranslated sequences of MAPT mRNA. Exons 2, 3, and 10 are subjected to alternative splicing in the central nervous system. Exons 4a, 6, and 8 are present only in large tau in peripheral tissues. Exons 9–12 each contain a highly homologous microtubule-binding domain. Exon 14 is part of the 3' untranslated region of MAPT mRNA. Created with Microsoft Office PowerPoint. MAPT: Microtubule-associated protein tau; N1–2: the N-terminal insert 1–2 with 29-amino-acid sequence of tau protein; R1–4: the C-terminal repeat domain 1–4 of tau protein.

In humans, the tau protein undergoes 95 types of PTMs, including ubiquitination, phosphorylation, nitration, truncation, acetylation, methylation, O-GlcNAcylation, glycation, glycosylation, SUMOylation, and isomerization. Some PTMs, such as phosphorylation, acetylation, and glycosylation, occur under both physiological and pathological conditions. However, some of these PTM sites show critical pathological significance and thus, have attracted much attention (**Figure 2**). Specifically, a recent study that analyzed the PTM profile of tau found that these PTMs occur in a processive fashion, reflecting AD progression (Wesseling et al., 2020).



**Figure 2 | Tau post-translational modifications (PTMs).**

**Figure 2 | Tau post-translational modifications (PTMs).**  
Tau PTMs from Alzheimer's disease patients mapped on the longest isoform of tau (tau441). Phosphorylation is the major PTM of tau protein, with 55 phosphorylation sites distributed heterogeneously in the tau sequence. The proline rich domain (amino acids 151–243) contains multiple Thr-Pro or Ser-Pro motifs that are targets of proline-directed protein kinases, such as GSK-3 $\beta$ , CDK5, JNK, and MAPK. The C-terminal is frequently phosphorylated by proline-directed protein kinases and non-proline-directed protein kinases, including PKA and dual specificity tyrosine-phosphorylation-regulated kinase 1A. Acetylation and ubiquitination are confined mostly in the microtubule-binding repeat domain. Tau has 19 lysine residues in the microtubule-binding repeat domain, of which a large amount is subjected to both acetylation and ubiquitination. Methylation is seen only on the N- and C-terminals of tau sequence. Created with Microsoft Office PowerPoint. CDK5: cyclin-dependent kinase 5; GSK-3 $\beta$ : glycogen synthase kinase-3 $\beta$ ; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; N1–2: the N-terminal insert 1–2 with 29-amino-acid sequence of tau protein; PKA: protein kinase A; PTM: post-translational modification; R1–4: the C-terminal repeat domain 1–4 of tau protein.

## Tau phosphorylation

One of the most extensively studied PTMs of tau protein in AD and other related tauopathies is phosphorylation. In physiological conditions, phosphorylation regulates the affinity of tau to microtubules, thus controlling their stabilization and assembly (Xie et al., 1998). Studies have shown that tau phosphorylation is developmentally regulated. The levels of tau phosphorylation are significantly higher during the embryonic and early developmental stages (nearly eight phosphates/molecule) compared to tau phosphorylation in adults (approximately two phosphates per molecule). Moreover, the phosphorylation level of tau is high in the aged brain (approximately eight phosphates/molecule) (Kanemaru et al., 1992; Köpke et al., 1993).

The longest tau isoform (2N4R) has approximately 80 potential serine and threonine phosphorylation sites. One study identified nearly 40 of these phosphorylation sites in AD (**Figure 2**; Wang et al., 2014). Multiple protein kinases regulate these phosphorylation site clusters in the flanking region related to diseases. Tau protein kinases are divided into three groups based

on the recognized motif in the tau sequence: proline-directed protein kinases, tyrosine protein kinases, and non-proline-directed protein kinases. Proline-directed protein kinases consist of the glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), cyclin-dependent kinase 5 (CDK5), CDK2, p38 mitogen-activated protein kinase, and c-Jun N-terminal kinase families. These proline-directed protein kinases phosphorylate the tau protein at Ser or Thr and proline residues (Ser/Thr-Pro). Non-proline-directed protein kinases consist of Ca $^{2+}$ /calmodulin-dependent protein kinase II, cyclic adenosine monophosphate-dependent protein kinase A (PKA), protein kinase B, protein kinase N, casein kinase 1/2, tau-tubulin kinase 1/2, dual specificity tyrosine-phosphorylation-regulated kinase 1A, phosphorylase kinases, and microtubule affinity-regulating kinases. Tyrosine protein kinases, including the proline-rich tyrosine kinase 2 (Brody et al., 2022), Fyn lymphocyte-specific protein, and spleen tyrosine kinases belonging to the Src family and the Abelson (ABL) family members (ABL2 and ABL1) can all phosphorylate tau. Studies have shown an increase in GSK-3 $\beta$ , CDK5, tyrosine-phosphorylation-regulated kinase 1A, casein kinase 1/2, p38, and Fyn expression levels in AD brains (Shirazi and Wood, 1993; Wang et al., 2014; Rosenberger et al., 2016). Of these, GSK-3 $\beta$  and CDK5 have gained significant interest. Numerous studies have shown colocalization of GSK-3 $\beta$ , CDK5, and pathological tau in AD brains. GSK-3 $\beta$  and CDK5 can phosphorylate tau at several sites associated with AD, including Ser202, Thr212, Ser214, Ser404, Ser217, Thr205, Thr231, Ser235, Thr231, and Ser396 (Takahashi et al., 2000; Ferrer et al., 2002; Wegmann et al., 2021). Studies have also shown that inhibition of CDK5 reduces tau phosphorylation and related neurodegeneration in transgenic mice (Sundaram et al., 2013; Seo et al., 2017). Moreover, downregulating GSK-3 $\beta$  activity or using GSK-3 $\beta$  inhibitors showed similar beneficial effects (Zhang et al., 2014a; Shi et al., 2019; Zhou et al., 2022).

Protein kinases and phosphatases dynamically control tau phosphorylation levels. Five protein phosphatases, including phosphatase (PP)1, PP2A, PP2B, PP2C, and PP5, are highly expressed in the mammalian brain and can dephosphorylate tau. Moreover, nearly 70% of the phosphatase activity related to tau in the human brain is regulated by PP2A. Interestingly, an approximate 20% and 40% decrease in PP2A activity was observed in the gray and white matter in AD brains, respectively (Gong et al., 1993). However, the mechanism underlying PP2A inactivation in AD is not fully understood. Studies have shown several mechanisms involved in PP2A inactivation, including PTMs of the PP2A catalytic domain, lowered mRNA and protein expression of PP2A catalytic/regulatory subunits, and elevated levels of endogenous PP2A inhibitor, I1PP2A, I2PP2A, and cancerous inhibitor of PP2A (CIP2A) (Sontag et al., 2004; Liu et al., 2012, 2013). A study has shown that either okadaic acid or homocysteine-mediated PP2A inhibition could induce hyperphosphorylation of tau and memory deficits in animal models (Zhang et al., 2008). Moreover, silencing I2PP2A or inhibiting CIP2A expression could decrease hyperphosphorylation of tau and improve memory deficits (Liu et al., 2013; Zhang et al., 2014a; Shentu et al., 2018). In addition, CIP2A overexpression in primary neurons induces mislocalization of tau in the dendrites and synaptic degeneration, which may be the underlying mechanism of PP2A inhibition-induced defects in memory (Shentu et al., 2018). Furthermore, studies have shown an interaction between GSK-3 $\beta$  and PP2A. For instance, our studies have shown that GSK-3 $\beta$  regulates PP2A activity by increasing I2PP2A levels, promoting the phosphorylation of inhibitory Tyr307 residue, as well as the demethylation of the inhibitory Leu-309 residue of the PP2A catalytic subunit (Liu et al., 2008; Yao et al., 2011, 2012).

Although hyperphosphorylation of tau is a hallmark pathology of AD and other neurological diseases, the detailed phosphorylation sites of tau may act conversely in its physiological and pathological function. For instance, tau phosphorylation at Ser202 and Thr231 mediated by GSK-3 $\beta$  and CDK5 promotes tau aggregation, NFT formation, and synaptic impairments (Takahashi et al., 2000; Zhu et al., 2018). In a preclinical study, PNT001, a humanized monoclonal antibody that recognizes cis-Thr231 tau, markedly reduced NFT formation and tau seeding activity with improved synaptic and cognitive functions (Foster et al., 2023). In Huntington's disease models, 12 weeks of treatment of the monoclonal antibody CP13, which targets Ser202 of tau protein, improved motor and cognitive impairments, as well as general health (Alpaugh et al., 2022). In contrast, tau phosphorylation at Thr205 mediated by P38y can protect against A $\beta$ -induced cell death, neuronal circuit aberrations, and memory deficits in early AD (Ittner et al., 2016); moreover, P38y-mediated tau phosphorylation at Thr205 can reduce seizure susceptibility (Morey et al., 2022). These studies suggest that different tau phosphorylation sites play distinct roles in tau pathology and cognitive dysfunction. Thus, choosing suitable antigen epitopes when targeting tau phosphorylation may help improve the safety and effectiveness of targeted drugs.

## Tau acetylation

**Tau acetylation** A recent study has shown acetylation as a novel PTM of the tau protein (Caballero et al., 2021). The tau protein with > 20 lysine residues undergoes acetylation, primarily in the proline-rich domain and MDB. P300 acetyltransferase and cyclic adenosine monophosphate response element binding (CREB)-binding protein are identified as tau acetyltransferases. The mechanisms of acetylation in tau pathogenesis can be residue- and context-specific. Studies have shown that acetylation at Lys163, Lys281, Lys274, Lys280, Lys174, and Lys369 residues prevents tau degradation (Min et al., 2010; Caballero et al., 2021). Additionally, the acetylation on KXGS motifs (Lys259, Lys290, Lys321, and Lys353) inhibits phosphorylation and prevents aggregation of tau (Cook et al., 2014). Interestingly, tau also processes intrinsic enzymatic activity and catalyzes auto-acetylation at Lys280 residue via the

catalytic cysteine residues in MBD (Cohen et al., 2013). Mass spectrometry has shown an increase in the acetylation at Lys174 residue of tau in the brains of patients with AD (Min et al., 2015). Studies have also observed high acetylation levels at Lys274, Lys280, and Lys281 residues of tau in the brains of hAPP-J20 and PS19 mice (Cohen et al., 2013; Tracy et al., 2016). Recently, the monoclonal antibody Y01, which specially targets Lys280 of tau, showed significant therapeutic effects on tau accumulation, tau propagation, and cognitive deficits in a tau transgenic mice model (Song et al., 2023), elucidating the importance of choosing appropriate lysine residues when targeting tau. Additionally, sirtuin1 and histone deacetylase 6 can deacetylate tau protein. Histone deacetylase 6 aggregates with tau, deacetylating it at certain lysine residues (e.g., Lys311) in the brains of patients with AD, while the deletion of histone deacetylase 6 accelerates tau pathology and cognitive decline (Trzeciakiewicz et al., 2020); the inhibition of sirtuin1 expression demonstrates similar results (Min et al., 2010). A recent study has shown that acetylation at Lys263 and Lys270 residues of tau in mice (corresponding to tau Lys274 and Lys281 in humans) could lead to a critical pathological convergence from traumatic brain injury to AD. A decrease in the incidence of traumatic brain injury and AD was observed in patients receiving p300/CBP inhibitors, such as salsalate or diflunisal (Shin et al., 2021). Thus, targeting tau acetylation could be a novel therapeutic approach for treating tauopathies in humans.

### Tau ubiquitination

Ubiquitination is a three-step enzymatic reaction for transferring one or more ubiquitin subunits to lysine residues, and consists of ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin-ligating enzyme (E3). The longest 2N4R isoform has > 20 ubiquitylation sites in the proline-rich domain and MBD of the tau protein (Li et al., 2021). In most cases, ubiquitination promotes tau degradation via the ubiquitin-proteasomal system. One study found that CHIP-mediated Lys48-linked polyubiquitination is the most common type of tau ubiquitination and promotes tau proteasomal degradation (Petrucelli et al., 2004). Additionally, Lys63-linked polyubiquitination mediated by tumor necrosis factor receptor-associated factor 6 enhances proteasomal-targeted tau clearance (Puangmalai et al., 2022). Accumulation of non-aggregated, ubiquitin-negative, hyperphosphorylated tau was observed in CHIP knockout mice (Sahara et al., 2005). However, a separate study found that hyper-ubiquitination increases tau aggregation (Kim et al., 2021). Furthermore, multiple studies have revealed high levels of ubiquitination in PHFs of tau in AD brains (Morishima-Kawashima et al., 1993; Cripps et al., 2006; Arakhamia et al., 2020). These findings suggest significant involvement of ubiquitination in tau pathology. Recent studies have demonstrated that deubiquitinases, such as X-linked ubiquitin-specific peptidase 10 (USP10), USP11, and USP13, increase the aggregation of tau, enhance vulnerability to tauopathy, and delay tau degradation by deubiquitinating tau (Liu et al., 2019; Wei et al., 2022; Yan et al., 2022). Additionally, ubiquitination also inhibits tau-mediated microtubule assembly (Munari et al., 2020). Therefore, targeting ubiquitination could aid in managing patients with AD and related tauopathies. However, the roles, sites, and types of ubiquitination mediated by different E3 ligases and deubiquitinases in tau pathology and AD require further investigation.

### Tau SUMOylation

During SUMOylation, SUMO proteins are covalently attached to specific lysine residues of target proteins. SUMOylation at the Lys340 residue of tau protein is primarily observed in AD brains and has been shown to inhibit the degradation of tau by competing with ubiquitination for tau modification (Luo et al., 2014). Three SUMOs are expressed in the mammalian brain. SUMO1 preferentially SUMOylates the tau protein when compared to SUMOs 2 and 3. Immunohistochemistry results have shown the colocalization of SUMO1 and pathological tau in progressive supranuclear palsy (Takamura et al., 2022). High SUMO1 expression levels promote tau phosphorylation at multiple AD-associated sites, like Thr205, Ser214, Ser262, Ser396, Thr231, and Ser404 (Luo et al., 2014). Additionally, tau SUMOylation can be induced after hyperphosphorylation, followed by treatment with okadaic acid or colchicine (Dorval and Fraser, 2006), suggesting an interplay between tau SUMOylation and phosphorylation.

Multiple correlations exist between various tau PTMs, such as SUMOylation, acetylation, ubiquitination, and phosphorylation. Several lysine residues of the tau protein undergo acetylation, SUMOylation, and ubiquitination. Therefore, the addition of one chemical group to a given residue will compete with the addition of another group, thereby indicating a multilayered and dynamic characteristic of tau biology. One study found that removing ubiquitin allows for enzymatic acetylation of tau at Lys281 and 274 residues (Yan et al., 2022). High levels of SUMOylation inhibit ubiquitination and degradation of tau (Luo et al., 2014). Another study has shown the involvement of SUMOylation in tau phosphorylation, and that a mimic mutation at the K430R site (SUMOylation site) attenuates hyperphosphorylation of tau (Luo et al., 2014). Acetylation at different sites regulate the phosphorylation of tau in different ways. For instance, acetylation at K280 increases phosphorylation of tau at Ser199/202, Thr231, Ser202/Thr205, and Ser422 (Kim et al., 2022). However, pseudoacetylation of Lys163, Lys280, Lys281, and Lys369 significantly decreases the phosphorylation of tau in humans (Gorsky et al., 2017). Moreover, after traumatic brain injury, increased acetylation was not associated with phosphorylation level of tau (Shin et al., 2021). A recent study has shown that deubiquitination of tau by ubiquitin-specific protease 11 promotes aggregation and hyperphosphorylation of tau at Ser199 and Ser202/Thr205 residues (Wei et al., 2022). Conversely, tau hyperphosphorylation inhibits its

degradation, which is closely correlated with SUMOylation, acetylation, and ubiquitination of tau.

### Tau truncation

Tau truncation has been observed in AD and other tauopathies, which plays a crucial role in tau aggregation and neurodegeneration (Kang et al., 2020a). Truncated tau proteins, such as Tau<sub>1-314</sub>, Tau<sub>1-368</sub>, and Tau<sub>1-421</sub>, show enhanced aggregation, mislocalization in dendrites, and propagation. Mass spectrometry results have shown cleavage of tau at Asp13 and Asp421 by caspases 6 and 3 *in vitro*. Additionally, colocalization of caspase3-truncated tau and NFTs has been observed in AD brains (Wai et al., 2009; Lee and Shea, 2012). One study found that caspase 2-mediated truncation of tau at Asp314 residue promotes missorting of tau to dendritic spines and could cause reversible memory deficits (Zhao et al., 2016). Calpain-mediated cleavage of tau generates a 17-kDa tau fragment, which is neurotoxic and mediates Aβ-induced neurodegeneration (Park and Ferreira, 2005). Moreover, the role of asparaginyl endopeptidase, a lysosomal cysteine protease, in tau truncation has been widely studied. Asparaginyl endopeptidase is primarily found in lysosomes and cleaves tau at N255 and N368 residues, with N368 tau fragments being found in both AD brains and tauopathy mice models (Zhang et al., 2014b). N368 tau fragments impair microtubule assembly and axon elongation, while also promoting tau hyperphosphorylation and propagation, since tau devoid of the C terminus is prone to aggregation (Zhang et al., 2014b; Wang et al., 2017; Kang et al., 2020b). An *in vivo* study demonstrated that attenuating asparaginyl endopeptidase activity generates a therapeutic effect on tau pathology and cognitive deficits (Zhang et al., 2017); however, its potential as a therapeutic drug for AD and other tauopathies is unclear.

### Other PTMs of the tau protein

Tau undergoes several other PTMs, such as methylation, O-GlcNAcylation, O-linked β-N-acetylglucosaminylation, glycation, glycosylation, nitration, and isomerization. The presence of mono- or di-methylated tau protein has been observed in the normal human brain. However, only mono-methylated tau protein was identified in immunopurified PHF samples from AD brains (Kontaxi et al., 2017). Studies have shown that methylation facilitates interaction between tau proteins, thus suppressing tau aggregation and increasing microtubule dynamics (Funk et al., 2014; Shams et al., 2022). Tau undergoes O-linked N-acetylglucosamine (O-GlcNAc) modification, a reversible modification wherein the serine and threonine residues glycosylate with O-GlcNAc. Studies have shown a correlation between increased O-GlcNAcylation and reduced phosphorylation of tau protein. O-GlcNAc moieties are removed from proteins by an enzyme called O-GlcNAcase. *In vivo* studies have revealed that inhibiting O-GlcNAcase can reduce tau protein expression and ameliorate brain atrophy (Selnick et al., 2019; Wang et al., 2020e). Furthermore, tau protein has been shown to undergo N- and O-glycosylation. For instance, tau has been shown to undergo N-glycosylation in AD brains in humans, which facilitates hyperphosphorylation of tau and stabilizes PHF (Losev et al., 2021). Conversely, O-glycosylation occupies the Ser or Thr residue of Ser-Pro or Thr-Pro motifs and thus protects against tau phosphorylation and tau accumulation. During O-glycosylation, the enzyme O-GlcNAc transferases can add an N-acetylglucosamine to the Ser or Thr residue, which is believed to block tau phosphorylation. In *Caenorhabditis elegans* models expressing human tau, reduced O-linked β-N-acetylglucosaminylation levels linked with impaired glucose metabolism promotes tau hyperphosphorylation (Ahmad, 2018; Ahmad et al., 2020). Additionally, a correlation was observed between high O-glycosylation and reduced phosphorylation of tau in AD (Liu et al., 2004, 2009). A study has identified four nitration sites, including Tyr18, Tyr29, Tyr197, and Tyr394, in tau proteins, of which, tau nitration at Tyr29, Tyr18, and Tyr394 was observed in AD brains, while nitration at Tyr197 was observed in normal human brains (Reynolds et al., 2006). The nitration of tau at these sites alters tau-microtubule binding affinity, thereby facilitating tau aggregation (Reynolds et al., 2005). In addition, Tau undergoes another type of PTM called isomerization, which facilitates the rearrangement of proline residues. Pin1, a peptidyl-prolyl cis/trans isomerase, specifically isomerizes phosphorylated-Thr-Pro bonds and thus leads to cis to trans tau conformation (Wang et al., 2020a). Studies have shown the existence of cis tau in patients with AD and brain injury, which drives tau hyperphosphorylation and neurodegeneration, whereas trans tau is more accessible to dephosphorylation (Lu et al., 1999; Kondo et al., 2015; Naserkhani et al., 2019).

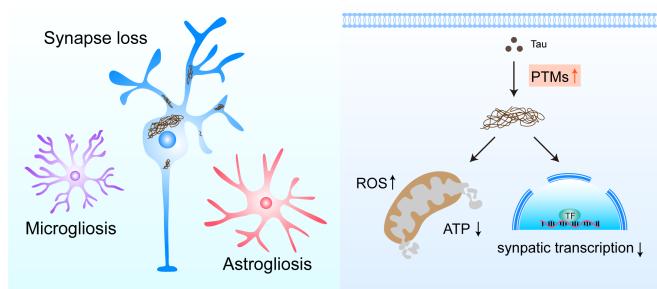
### Tau propagation

The distribution of pathological tau in the brain of patients with AD is highly predictable and follows spatiotemporal patterns. First, tau accumulates in the entorhinal cortex region, followed by accumulation in the hippocampus, and eventually spreads throughout the neocortex (Peng et al., 2020). Mounting evidence has shown that structural and functional defects in hippocampal plasticity contribute to learning and memory deficits in patients with AD. However, it is still unclear if tau dysfunction in the hippocampus occurs independently or is a secondary consequence of anatomical propagation of tau from the entorhinal cortex region. Various studies have shown that a donor cell secretes pathological tau seeds that are absorbed by a recipient cell. This could induce the propagation and misfolding of normal endogenous tau (Peng et al., 2020). Various factors, such as mutations, PTMs, tau clearance mediated by glial cells, neuronal activity, genes (e.g., APOE4, TREM2, and BIN1), aging, and interactions between tau and other pathological proteins affect tau propagation (Asai et al., 2015; Wegmann et al., 2019; Wang et al., 2020d; Polanco et al., 2021; Xu et al., 2021). Studies have shown that low-density lipoprotein receptor-related protein 1 and presynaptic scaffolding

protein Bassoon interact with tau seed, which exacerbates the transmission and toxicity of tau (Rauch et al., 2020; Martinez et al., 2022). Microglia are also implicated in tau propagation, but their role remains controversial. A study has shown that the depletion of microglia prevents entorhinal cortex-to-hippocampus propagation of tau protein (Asai et al., 2015). Furthermore, triggering receptors expressed on myeloid cell 2 (TREM2) knockout and microglial ablation significantly increase the seeding and propagation of tau around A<sub>B</sub> plaques. However, activating the disease-associated microglia phenotype reduces A<sub>B</sub>-associated pathological tau seeding and propagation (Gratze et al., 2021). Differences in these results may be due to the dual role of microglia activation in amyloid pathologies. Despite extensive progress in enhancing our understanding of tau propagation, additional studies are required to unravel the mechanism underlying pathological formation and the molecular nature of tau seeds. This would aid in designing tau-targeted therapeutic strategies.

## Tau Toxicity in Alzheimer's Disease

Abnormal PTMs impair the affinity of tau-microtubule binding, thus increasing free tau protein in the cytoplasm. Accumulated free tau protein promotes the formation of tau aggregates, which causes mitochondrial damage, impairs synaptic plasticity, and glial cell-mediated neuroinflammation (Figure 3). The implications and mechanism of tau toxicity in these pathological conditions are critically involved in eliciting/aggravating neurodegeneration and cognitive deficits in AD (Wang et al., 2020c; Gratze et al., 2021).



**Figure 3 | Tau toxicity in Alzheimer's disease.**

Abnormal post-translational modifications promote tau accumulation, which results in mitochondria damage, synaptic impairments, gliosis, neuroinflammation, and eventually neurodegeneration. Created with Adobe Illustrator. ATP: Adenosine triphosphate; PTM: post-translational modification; ROS: reactive oxygen species; TF: transcriptional factor.

### Mitochondrial damage

Mitochondria provide energy via oxidative phosphorylation to support neuronal activity and maintain the normal functioning of neurons (McElroy et al., 2023; Trigo et al., 2023; Wen et al., 2023). A study has shown that neurotoxic tau protein could disrupt the structural and functional integrity of mitochondria, including impaired mitochondrial biogenesis, abnormal mitochondrial fusion, fission, trafficking, and distribution, impaired mitochondrial biogenesis, and damaged mitophagy (Wang et al., 2020c). Mounting evidence has demonstrated that tau accumulation promotes abnormal mitochondrial elongation and alters the expression of mitochondrial fission proteins, such as a decrease in dynamin-like protein 1 (DLP1) expression level (DuBoff et al., 2012) or an increase in optic atrophy 1 and mitofusin (Mfn) expression level (DuBoff et al., 2012; Li et al., 2016). One study revealed that DLP1 abnormally interacts with hyperphosphorylated tau in AD neurons (Manczak and Reddy, 2012), which may partly explain low DLP1 expression in mitochondria. Studies have also shown a significant decrease in the expression level of all large dynamin-related GTPases, such as DLP1, optic atrophy 1, Mfn1, and Mfn2, in the AD brain (Wang et al., 2009; Manczak and Reddy, 2012). Different tau isoforms exert varied disrupting effects on mitochondrial distribution. A recent study demonstrated that overexpression of 1N3R-tau in astrocytes of the dentate gyrus can significantly decrease mitochondrial distribution in distal processes, whereas the 1N4R isoform of tau promotes mitochondria redistribution toward the soma (Richetin et al., 2020). Interestingly, our unpublished data have shown that P301S tau induces mitochondrial fission, whereas full-length human tau, 2N4R, induces mitochondrial fusion (Li et al., 2016).

In addition, accumulated tau impairs mitophagy by disrupting the parkin-dependent degradation of damaged mitochondria. Overexpression of wildtype and mutant tau in primary hippocampal neurons or neuroblastoma cells reduces translocation of parkin in the mitochondria due to abnormal interactions between parkin and tau projection domain, thus sequestering it in the cytosol (Hu et al., 2016; Cummins et al., 2019). Activation of mitophagy by supplementing NAD<sup>+</sup>, urolithin A, melatonin, and actinonin can attenuate the hyperphosphorylation of AD-associated tau in human neuronal cells and reverse memory deficits *in vivo* (Fang et al., 2019).

### Impairment of synaptic plasticity

Alteration in the strength or efficacy of synaptic transmission based on preexisting synaptic activity is called synaptic plasticity and is extensively

accepted as the cellular basis of learning and memory. The molecular mechanisms behind impairments in synaptic plasticity induced by tau can be classified into two categories. First, synaptic abnormalities are induced by direct mislocalization of tau. Studies have shown localization of neurotoxic tau in the dendrites, dendritic spines, neuronal membranes, and nuclear speckle, which obstructs the formation of new synapses and impairs the stability of preexisting synapses (Hoover et al., 2010; Ittner et al., 2010; Merezhko et al., 2018; Lester et al., 2021; Priks et al., 2022). Recently, with the development of new biochemical technologies, such as the engineered ascorbic acid peroxidase approach with quantitative affinity purification mass spectrometry, high-throughput proteomics, ultra-high magnification microscopic imaging, and proximity ligation assays, tau interactome at subcellular and amino acid levels in human neurons have been conducted. These tau interactomes have revealed interactions between tau and presynaptic vesicle proteins during activity-dependent tau secretion, as well as the tau-binding sites to the cytosolic domains of integral synaptic vesicle proteins (Largo-Barrientos et al., 2021; Tracy et al., 2022). These advancements provide authentic illustrations of the properties of synaptic tau mislocalization. Second, tau overexpression may suppress the transcription of synapse-regulating genes by altering multiple synapsis-associated transcriptional factors. Ours and others' studies have shown the involvement of mammalian signal transducer and activator of transcription (STAT) in regulating tau-induced defects in synaptic plasticity (Li et al., 2019; Zhang et al., 2021). A different study found that tau accumulation in cells activates JAK2-dependent STAT1 in animal models and patients with AD. While STAT1 directly binds to the GAS element of GluN1, GluN2A, and GluN2B promoters to suppress N-methyl-D-aspartate receptors expression (Li et al., 2019), STAT3 positively regulates N-methyl-D-aspartate receptor transcription. Additionally, studies have shown STAT3 inactivation in tau-accumulating neurons in AD and frontotemporal dementia (Hong et al., 2020; Wan et al., 2021). Mechanically, tau directly acetylates STAT1, enhancing its binding to STAT3 in the cytoplasm, thus sequestering and inhibiting the translocation of STAT3 from the cytoplasm to the nucleus and eventually reducing STAT3 transcription (Wan et al., 2021). Finally, tau activates STAT1 and inhibits STAT3 to reduce the transcription and expression of N-methyl-D-aspartate receptor proteins (Li et al., 2019; Wan et al., 2021). The involvement of transcription factor CREB in regulating learning and memory has been widely studied. When Ser133 residue of the kinase-inducible domain of CREB is phosphorylated by PKA, ERK, and Ca<sup>2+</sup>/calmodulin-dependent protein kinase II, CBP, a transcriptional coactivator, is then recruited to CREB to activate it (Briand et al., 2015). Overexpression of human wild-type, full-length tau significantly dephosphorylates CREB at Ser133 residue by activating phosphatase calcineurin and suppressing calcium/calmodulin-dependent protein kinase IV expression (Yin et al., 2016). Moreover, tau inhibits PKA activity by increasing nuclear proteasome-dependent PKA regulatory subunit 2α levels, thereby dephosphorylating CREB (Ye et al., 2020). Histone acetylation, an epigenetic mechanism, has received widespread attention in AD. Inhibition of histone 3, acetylated at K19 and K14, and histone 4, acetylated at K5 and K12, by increasing the expression of acidic nuclear phosphoprotein 32 family member A, which is a key component of inhibitor of acetyltransferases, leads to synapse-related proteins decrease (Chai et al., 2017, 2018).

### Gliosis and neuroinflammation

Reactive gliosis and neuroinflammation are closely associated with tau accumulation and neuronal degeneration in AD and other tauopathies. The prolonged activation of glial cells, primarily astrocytes and microglia, induces the production and secretion of pro-inflammatory chemokines, cytokines, and reactive oxygen species. This creates a pro-inflammatory microenvironment in glial cells and neurons. Recently, conditional genetic manipulation and genome-wide association studies have identified multiple immune-related genes (TREM2, CD33, ATP-binding cassette transporter (ABCA) 7, CX3CR1, CR1, and BIN1) as risk factors for tau pathology and AD, thereby supporting a critical involvement of glial cells and neuroinflammation in tauopathies (Zhong et al., 2017; Pimenova et al., 2018; Brunello et al., 2020; Wang et al., 2020b, 2022; Griciuc and Tanzi, 2021; Haass, 2021; Jin et al., 2021; Lee et al., 2021; Wang and Ye, 2021; Zhao et al., 2022; Zhu et al., 2022; Jain et al., 2023; Ochoa et al., 2023; Udeochu et al., 2023).

In the early stage of tau pathology, intracellular accumulation of tau protein causes neuronal oxidative stress, which results in the production and release of cytokines, inflammatory chemokines, and reactive oxygen species, thus provoking adjacent glial cell responses and mild inflammation. Furthermore, persistent excessive accumulation of pathological tau promotes neuronal death and production of cell debris, leading to intense glial cell activation and neuroinflammation. Additionally, pathological tau can be released into the extracellular space in free form or encapsulated by extracellular vesicles or exosomes (Brunello et al., 2020). Extracellular tau can enter glial cells through phagocytosis or receptor mediated endocytosis, thereby activating various inflammatory pathways in glial cells. For example, a recent study demonstrated that pathological tau protein in microglia can activate the inner immune pathway cyclic GMP-AMP synthase-stimulator of interaction genes, thus promoting nuclear translation of nuclear factor κB and inflammatory gene transcription (Jin et al., 2021). The type I interaction signal is also a downstream of cyclic GMP-AMP synthase-stimulator in the interaction genes pathway, which responds to tau accumulation and mediates tau-dependent microglial inflammation (Udeochu et al., 2023). In primary astrocytes, recombinant filamentous human tau can enter the cell by directly binding to integrin αV/β1 receptor, resulting in nuclear factor κB activation, neurotoxic astrocyte-like cell phenotype, and the release of inflammatory factors (Wang



and Ye, 2021). Moreover, pathogenic tau can drive neuroinflammation through elevated double-stranded RNA in astrocytes (Ochoa et al., 2023).

In the brain, microglia are the resident innate immune cells that play a central role in tau-related neuroinflammation. In patients with AD and tau transgenic mice, reactive microglia hierarchically associate with pathological tau. Mounting evidence has demonstrated that TREM2 expressed on the surface of microglia is a risk factor in the preclinical stages of AD. In the cerebrospinal fluid, a positive correlation was observed between TREM2 and total tau, as well as phosphorylated tau (Zhong et al., 2017). Studies have shown that loss-of-function mutation (especially R47H) or deletion of TREM2 could increase the accumulation and spreading of tau protein and brain atrophy in amyloid pathology (Haass, 2021; Lee et al., 2021; Zhu et al., 2022). While a recent study reported that chronic TREM2 activation exacerbates the seeding and spreading of A $\beta$ -related tau (Jain et al., 2023), several earlier studies have presented the beneficial effects of TREM2 agonist antibodies in private amyloid pathology (Wang et al., 2020b; Zhao et al., 2022). A possible explanation may be that the activation of TREM2 downstream signaling, such as nuclear factor  $\kappa$ B signaling, could exacerbate tau spread and toxicity in an A $\beta$ -independent manner (Wang et al., 2022). Other AD risk factors are enriched by or are uniquely expressed in microglia, such as ATP-binding cassette transporter family, complement, CD33, HLA-family, MEF2C, and MS4A family, have been identified by genome-wide association studies (Pimenova et al., 2018; Griciuc and Tanzi, 2021).

Astrocytes, the most abundant type of cells in the brain, are critically involved in regulating neuronal homeostasis and neuroinflammation. It is believed that neurotoxic reactive astrocytes (also named A1 astrocytes), which highly upregulate many classical complement cascade genes (C1q, C3a, C3b, C3d), exhibit impaired phagocytosis and promote neuronal death. By contrast, A2 astrocytes are neuroprotective with high expression levels of neurotrophic factors (Liddelow et al., 2017). Reactive astrocytes surrounding NFTs and A $\beta$  plaques are neuropathological hallmarks of AD. Manipulating the expression of several astrocyte-related genes, such as complement C3, interleukin-3, chitinase-3-like protein 1, alpha 2-Na $^+$ /K $^+$  adenosine triphosphatase, and histone acetylase 7, exert beneficial effects on reprogramming microglia and limiting neuroinflammation (Litvinchuk et al., 2018; Lananna et al., 2020; McAlpine et al., 2021; Mann et al., 2022; Ye et al., 2022). Additionally, genetic tau overexpression or treatment of recombinant tau fibrils drives astrocyte reactivity and neuroinflammation (Wang and Ye, 2021; Ezerskiy et al., 2022). Moreover, the astrocyte marker glial fibrillary acidic protein may serve as a candidate blood-based biomarker for the diagnosis and prognosis of patients with AD (Chatterjee et al., 2022).

## Plasma Tau in Alzheimer's Disease Diagnosis

A $\beta$  (A), tau (T), and neurodegeneration (N), denoted as A/T/N, are the three major classes of biomarkers included in the classification system for unbiased AD diagnosis. Positron emission tomography scans for tau/A $\beta$  and magnetic resonance imaging for brain atrophy can provide accurate diagnostic evidence. However, positron emission tomography is invasive, expensive, and limited in its availability, presenting a challenge for AD diagnosis. Blood-based biomarkers are a less invasive and potentially cost-effective option for the diagnosis and classification of AD pathology. Plasma phospho-tau is a potential biomarker for early diagnosis and prediction of AD progression, as well as A $\beta$  pathology. Currently, three tau epitopes, (p-tau181, p-tau217, and p-tau231) have been identified as plasma biomarkers for predicting AD progression, early diagnosis, and differentiation from non-AD neurodegenerative diseases (Mielke et al., 2018; Palmqvist et al., 2020; Milà-Alomà et al., 2022). Moreover, a recent study demonstrated that p-tau181 and p-tau217 exhibit initial increases in aggregate A $\beta$  as early as two decades prior to the development of aggregated tau pathology (Barthélemy et al., 2020).

## Tau-Based Therapeutic Strategies

In the past decades, the primary therapeutic strategies for AD have been focused on the A $\beta$  cascade hypothesis; however, therapeutic outcomes have been unsatisfactory in clinical trials. Studies have demonstrated that tau mediates A $\beta$ -induced toxicity and correlates better with clinical cognitive impairments than A $\beta$  burden (Rapoport et al., 2002; Vossel et al., 2010; Brier et al., 2016). Thus, targeting tau could be an effective strategy, compared to A $\beta$  clearance, in patients with prominent clinical symptoms of AD. With the progress in our understanding of tau-dependent neurotoxicity and the promising effects of tau immunotherapies in several preclinical studies (Congdon and Sjögrensson, 2018), tau-based therapeutic strategies could shed new light on AD drug development. Tau-based therapies can be classified into the following several groups.

### Targeting PTMs of tau

PTMs, like phosphorylation, acetylation, and ubiquitination, of tau regulate the accumulation and mislocalization of tau. Therefore, modifying the enzymatic activity involved in these processes could be a promising strategy to mitigate AD pathology. GSK-3 $\beta$  is the most widely explored tau phosphorylation-targeted kinase. Treatment of double transgenic [tau and A $\beta$  precursor protein (APP)] AD mice with tidesglusib, an irreversible GSK-3 $\beta$  inhibitor, reduces the phosphorylation of tau protein, the burden of A $\beta$  plaque, neuronal death, and memory deficits (Serenó et al., 2009). A phase II clinical trial showed that tidesglusib was safe, but had no significant clinical benefits (Lovestone et al., 2015). Salsalate is a nonsteroidal, anti-

inflammatory, small-molecule drug that inhibits the acetylation of tau at Lys174 residue. In PS19 mice, the inhibition of p300 histone acetyltransferase with salsalate reduces acetylation of tau at Lys174 residue, preserves hippocampal volume, and improves memory (Min et al., 2010). These results indicate that modulating tau acetylation could be an effective strategy for treating tau pathology. In addition, a phase Ia clinical trial (NCT0327573) of salsalate is currently underway to determine if salsalate is safe and tolerable by patients with prodromal to mild AD. Inhibiting O-GlcNAcase is a novel therapeutic approach to block tau pathology in AD. MK-8719 is a small molecule selective inhibitor of O-GlcNAcase in humans (Selznick et al., 2019). In animal models, MK-8719 significantly reduces pathological tau associated with brain atrophy (Wang et al., 2020e). In 2016, the United States Food and Drug Administration (FDA) approved MK-8719 as an orphan drug for treating progressive supranuclear palsy.

### Promoting tau clearance

The autophagy-lysosome pathway and ubiquitin-proteasomal system are the primary methods for clearing misfolded or abnormally aggregated proteins. In the brains of AD patients and tauopathy mice models, impaired autophagic flux and failed fusion of autophagosomes and lysosomes have been seen in dystrophic neurites and cell bodies, as evidenced by enhanced accumulation of autophagic vacuoles (Nixon et al., 2005; Sanchez-Varo et al., 2012; Piras et al., 2016; Feng et al., 2020). Our results showed that accumulated tau repressed autophagosome-lysosome fusion through downregulation of IST1, which is a factor associated with the endosomal sorting complex required for transport-III (ESCRT-III); ESCRT-III is a positive modulator for the formation of the endosomal sorting complex required for transport, which is required for autophagosome-lysosome fusion, and overexpression of IST1 ameliorates autophagy deficits, resulting in attenuated tau accumulation and improved cognition (Feng et al., 2020). Transcription factor EB is a master regulator of lysosomal biogenesis and autophagy. Transcription factor EB activators, including curcumin analog C1, celastrol, and Qingyangshen, enhance the degradation of tau aggregates and improve synaptic plasticity as well as cognitive functions in several AD mice models (Song et al., 2020; Iyaswamy et al., 2021). Similar to the autophagy-lysosome pathway, alterations in the ubiquitin-proteasomal system are associated with tau degradation. One study observed an association between insoluble tau accumulation and decreased peptidase activity of 26S proteasomes in the brain (Myeku et al., 2016). A recent study suggests that C004019, a novel small-molecule PROteolysis Targeting Chimera (PROTAC) designed to simultaneously recruit tau and E3-ligase, and thus selectively enhance ubiquitination and proteolysis of tau proteins, can selectively and efficiently promote tau clearance (Wang et al., 2021). PROTAC is an emerging strategy for targeting undruggable proteins with several advantages, such as easy design, low cost, high selectivity, and specificity; hence, it has attracted widespread attention in the clearance of tau and other misfolded proteins. Several tau-targeting small PROTAC molecules have shown high selectivity for clearing tau and improved cognitive functions in multiple AD models (Jangampalli Adi and Reddy, 2021; Zheng et al., 2021). However, the effects of tau-targeting PROTACs for clinical AD or other neurodegenerative diseases are yet to be determined.

### Tau immunotherapies

Active and passive A $\beta$  immunotherapies exhibit benefits in APP transgenic models. Recently, two monoclonal antibodies were approved by the FDA. In 2021, the FDA approved aducanumab, a monoclonal antibody developed for A $\beta$  clearance and treating patients with mild cognitive impairment due to AD. Aducanumab demonstrated promising efficacy in clearing A $\beta$  (Karlawish and Grill, 2021); however, data on its effect on slowing or halting disease progression in AD are not sufficient. Furthermore, amyloid-related imaging abnormalities and edema were observed in a few patients (Karlawish and Grill, 2021). Recently, the FDA also approved lecanemab, another A $\beta$  monoclonal antibody. Lecanemab is a humanized IgG1 monoclonal antibody with high A $\beta$  soluble protofibril binding affinity, and has been shown to slow cognitive decline in patients with mild and early AD (van Dyck et al., 2023). In an 18-month phase 3 trial, although adverse effects like brain edema and intracerebral hemorrhage were observed in approximately 13% of patients receiving lecanemab, patients treated with lecanemab showed markedly reduced brain amyloid levels and less cognitive decline (Teng et al., 2022). These successes offer critical guidance for the design of tau immunotherapies. Tau is an intrinsically unfolded protein and mainly accumulates in cells; therefore, identifying an appropriate epitope for the immunization of pathological tau is undoubtedly more challenging.

Recently, a phase II randomized clinical trial demonstrated that semorinemab, a monoclonal antibody, was well-tolerated, accepted, and safe among patients with prodromal to mild AD. However, it could not slow the clinical progression of AD. Semorinemab targets 6–23 residues in the N-terminal domain of tau (Teng et al., 2022), but this epitope may be not present in pathological tau primarily responsible for tau spread in prodromal to mild AD (Teng et al., 2022). AADvac1 is an active peptide vaccine created based on the epitopes of the DC2E8 antibody, spanning six amino acids (HXP $\beta$ GGG) of tau MBDs. In a phase I clinical trial, 30 patients with mild-to-moderate AD were treated with AADvac1, of which 29 developed an IgG response. In addition, no patients developed meningoencephalitis or vasogenic edema after administration (Novak et al., 2017). In a phase II clinical trial, AADvac1 was well tolerated by patients for over a 104-week study period. AADvac1 reduced cerebrospinal fluid p-tau-217, p-tau181, total tau, and plasma neurofilament light chain levels. Although AADvac1 did not show any significant benefit in patients, post hoc analyses suggest that AADvac1 treatment could slow cognitive and

functional decline in patients with AD having both amyloid and tau pathology (Novak et al., 2021). A larger phase IIb trial of AADvac1 is planned to recruit 400 participants with biomarker evidence of A $\beta$  and tau pathology. Several monoclonal antibodies against p-tau [Ser202 (Walls et al., 2014), pThr231 (Sankaranarayanan et al., 2015; Alipour et al., 2022), pSer396/404 (Asuni et al., 2007; Liu et al., 2016), p-Ser413 (Umeda et al., 2015), p-Ser422 (Collin et al., 2014; van Ameijde et al., 2018)], oligomeric tau (Castillo-Carranza et al., 2014; Bittar et al., 2022), fragmented tau (Dam et al., 2021), N-terminal tau (Dai et al., 2018), and total tau (Höglinger et al., 2021)] have been shown to be effective in tau transgenic models. Some of these antibodies (Dam et al., 2021; Höglinger et al., 2021) are currently in clinical trials.

The fact that pathological tau aggregates primarily intracellularly may raise concerns about application prospects of tau immunotherapies. However, several studies have confirmed that tau antibodies can enter cells and bind to pathological tau (Peng et al., 2020; Li et al., 2022). Tau antibodies can enter neurons through crystallizable fragment (Fc) receptor mediated endocytosis and bulk endocytosis. For example, 4E6G7, a monoclonal tau antibody, which recognizes the Ser396/404 region [CTDHGAEIVYK(pS) PVVSGDT(pS)PRHL], can enter neurons via clathrin-dependent Fc receptor endocytosis (Congdon et al., 2013). Moreover, the tau-antibody complex in the cytoplasm can recruit the tripartite motif protein 21, a newly identified cytosolic Fc receptor, thereby promoting the neutralization of the complex through proteasomal degradation (McEwan et al., 2017). Mounting evidence has shown that tau can be released into the extracellular space and plays a critical role in tau propagation, both in tauopathy animal models and human brains. Tau antibodies can effectively recognize these extracellular tau species and slow the spread of tau pathology. In animal models expressing tau by a prion protein virus promoter, or injected with exogenous tau, tau antibodies can effectively block the spread of tau pathology to anatomically connected regions (Albert et al., 2019; Li et al., 2022; Song et al., 2023). Of note, tau antibodies can block neuronal internalization of AD tau species by masking neuron surface proteoglycans (Weisová et al., 2019). Hence, tau immunotherapies could delay or block tau pathology through multiple paths (Weisová et al., 2019; Li et al., 2022). In conclusion, although the mechanisms of tau immunotherapy remain unclear, it is a rapidly developing avenue of research, with several clinical trials likely to start soon.

## Conclusions and Future Perspectives

To the best of our knowledge, tau is significantly involved in the pathogenesis of AD and other neurodegenerative diseases. Intensive research has revealed the critical involvement of tau hyperphosphorylation, acetylation, ubiquitination, truncation, propagation, tau-mediated mitochondrial damage, synaptic deficits, and neuroinflammation in an effort to better understand the processes behind AD pathogenesis. However, additional studies are required to determine the underlying mechanisms and the significance of these changes in patients with AD. Recent studies have shown that phosphorylation and acetylation of tau alter its interactomes, and that these interactions between tau and synaptic/mitochondrial processes are associated with neurodegeneration (Choi et al., 2020; Drummond et al., 2020; Tracy et al., 2022). Phosphorylated tau also serves as a significant cerebrospinal fluid marker in AD diagnosis and prediction, which is correlated with the onset of clinical symptoms long after the appearance of A $\beta$  pathology. Therefore, timely detection and elimination of neurotoxic tau at an early stage or before the onset of AD could be an effective strategy to maintain neuronal network activity and stop or delay AD progression. Recently, the development of PROTAC technology, which exhibits high specificity and designability, could aid in clearing pathological tau. Moreover, clinical trials on anti-tau vaccines and other passive/active immunotherapies are ongoing and have shown tremendous potential for treating AD in the future.

This review is subject to several limitations. First, the literature referenced in this review is sourced from only the PubMed database, meaning that incomplete retrieval of identified research was likely. Second, this incomplete retrieval of completed research studies, as well as reporting bias, may have inadvertently affected the rationality of the study.

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