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

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*From the Contents*



## Abstract

Alzheimer's disease is the most prevalent neurodegenerative disease affecting older adults. Primary features of Alzheimer's disease include extracellular aggregation of amyloid-β plaques and the accumulation of neurofibrillary tangles, formed by tau protein, in the cells. While there are amyloid-β-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-β 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-β (Aβ) 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 0N3R, 1N3R, 2N3R, 0N4R, 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 0N, 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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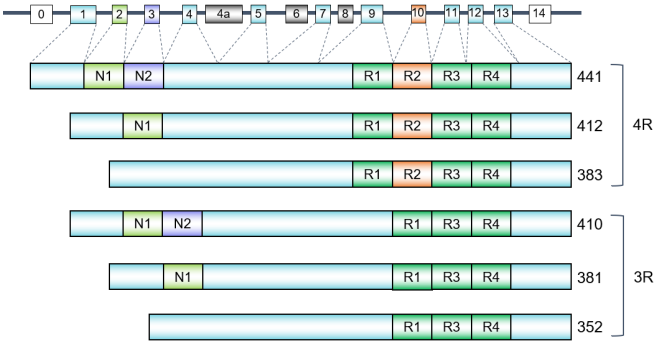


**Figure 1** | **Tau splicing and isoforms.**
Human MAPT gene is localized on chromosome 17q21.31 and consists of 16 exons. Exons 0 and 1 encode the 5′ untranslated sequences of MAPT mRNA. Exons 2, 3, and 10 are subjected to alternative splicing in the central nervous system. Exons 4a, 6, and 8 are present 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).

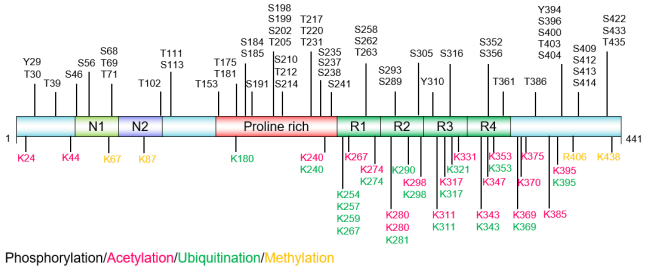


**Figure 2** | **Tau post-translational modifications (PTMs).**
Tau PTMs from Alzheimer's disease patients mapped on the longest isoform of tau (tau441). Phosphorylation is the major PTM of tau protein, with 55 phosphorylation sites distributed heterogeneously in the tau sequence. The proline rich domain (amino acids 151–243) contains multiple Thr-Pro or Ser-Pro motifs that are targets of proline-directed protein kinases, such as GSK-3β, 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. Methylations are seen only on the N- and C-terminals of tau sequence. Created with Microsoft Office PowerPoint. CDK5: cyclin-dependent kinase 5; GSK-3β: glycogen synthase kinase-3β; 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-3β (GSK-3β), 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-3β, 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-3β and CDK5 have gained significant interest. Numerous studies have shown colocalization of GSK-3β, CDK5, and pathological tau in AD brains. GSK-3β 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-3β activity or using GSK-3β 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-3β and PP2A. For instance, our studies have shown that GSK-3β 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-3β 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 P38γ can protect against Aβ-induced cell death, neuronal circuit aberrations, and memory deficits in early AD (Ittner et al., 2016); moreover, P38γ-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

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, pseudo-acetylation 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 $Tau_{1–314}$, $Tau_{1–368}$, and $Tau_{1–421}$, 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; Naserkhaki 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 Aβ plaques. However, activating the disease-associated microglia phenotype reduces Aβ-associated pathological tau seeding and propagation (Gratuze 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; Gratuze et al., 2021).

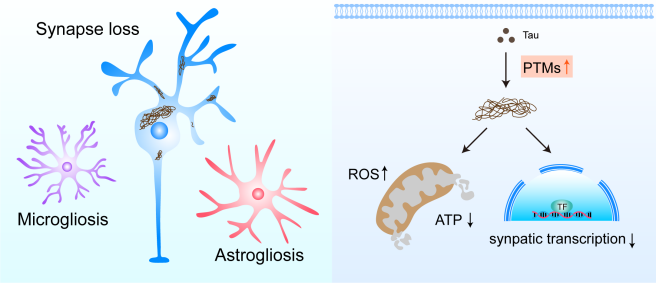


**Figure 3** | **Tau toxicity in Alzheimer's disease.**
Abnormal post-translational modifications promote tau accumulation, which results in mitochondria damage, synaptic impairments, gliosis, neuroinflammation, and eventually neurodegeneration. Created with Adobe Illustrator. ATP: Adenosine triphosphate; 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 $NAD^+$, 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; Prikas 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 $Ca^{2+}$/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 Aβ-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 κB signaling, could exacerbate tau spread and toxicity in an Aβ-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 complemental 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 Aβ 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 reprograming 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

Aβ (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/Aβ 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 Aβ 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 Aβ 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 Aβ cascade hypothesis; however, therapeutic outcomes have been unsatisfactory in clinical trials. Studies have demonstrated that tau mediates Aβ-induced toxicity and correlates better with clinical cognitive impairments than Aβ burden (Rapoport et al., 2002; Vossel et al., 2010; Brier et al., 2016). Thus, targeting tau could be an effective strategy, compared to Aβ 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 Sigurdsson, 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-3β is the most widely explored tau phosphorylation-targeted kinase. Treatment of double transgenic [tau and Aβ precursor protein (APP)] AD mice with tideglusib, an irreversible GSK-3β inhibitor, reduces the phosphorylation of tau protein, the burden of Aβ plaque, neuronal death, and memory deficits (Serenó et al., 2009). A phase II clinical trial showed that tideglusib 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 Ib 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 (Selnick 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 Aβ 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 Aβ clearance and treating patients with mild cognitive impairment due to AD. Aducanumab demonstrated promising efficacy in clearing Aβ (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 Aβ monoclonal antibody. Lecanemab is a humanized IgG1 monoclonal antibody with high Aβ 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 DC8E8 antibody, spanning six amino acids (HXPGGG) 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 Aβ 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 Fcγ 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 Aβ 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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## References

Ahmad W (2018) Dihydrolipoamide dehydrogenase suppression induces human tau phosphorylation by increasing whole body glucose levels in a C. elegans model of Alzheimer's disease. Exp Brain Res 236:2857-2866.

Ahmad WD, Shabbiri KD, Ahmad I (2020) Prediction of human tau 3D structure, and interplay between O-β-GlcNAc and phosphorylation modifications in Alzheimer's disease: C. elegans as a suitable model to study these interactions in vivo. Biochem Biophys Res Commun 528:466-472.

Albert M, Mairet-Coello G, Danis C, Lieger S, Caillierez R, Carrier S, Skrobala E, Landrieu I, Michel A, Schmitt M, Citron M, Downey P, Courade JP, Buée L, Colin M (2019) Prevention of tau seeding and propagation by immunotherapy with a central tau epitope antibody. Brain 142:1736-1750.

Alipour M, Tebianian M, Tofigh N, Taheri RS, Mousavi SA, Naseri A, Ahmadi A, Munawar N, Shahpasand K (2022) Active immunotherapy against pathogenic Cis pT231-tau suppresses neurodegeneration in traumatic brain injury mouse models. Neuropeptides 96:102285.

Alpaugh M, Masnata M, de Rus Jacquet A, Lepinay E, Denis HL, Saint-Pierre M, Davies P, Planel E, Cicchetti F (2022) Passive immunization against phosphorylated tau improves features of Huntington's disease pathology. Mol Ther 30:1500-1522.

Arakhamia T, Lee CE, Carlomagno Y, Duong DM, Kundinger SR, Wang K, Williams D, DeTure M, Dickson DW, Cook CN, Seyfried NT, Petrucelli L, Fitzpatrick AWP (2020) Posttranslational modifications mediate the structural diversity of tauopathy strains. Cell 180:633-644.e12.

Asai H, Ikezu S, Tsunoda S, Medalla M, Luebke J, Haydar T, Wolozin B, Butovsky O, Kügler S, Ikezu T (2015) Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nat Neurosci 18:1584-1593.

Asuni AA, Boutajangout A, Quartermain D, Sigurdsson EM (2007) Immunotherapy targeting pathological tau conformers in a tangle mouse model reduces brain pathology with associated functional improvements. J Neurosci 27:9115-9129.

Barthélemy NR, Li Y, Joseph-Mathurin N, Gordon BA, Hassenstab J, Benzinger TLS, Buckles V, Fagan AM, Perrin RJ, Goate AM, Morris JC, Karch CM, Xiong C, Allegri R, Mendez PC, Berman SB, Ikeuchi T, Mori H, Shimada H, Shoji M, et al. (2020) A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med 26:398-407.

Bittar A, Al-Lahham R, Bhatt N, Moore K, Montalbano M, Jerez C, Fung L, McAllen S, Ellsworth A, Kayed R (2022) Passive immunotherapy targeting tau oligomeric strains reverses tauopathy phenotypes in aged human-tau mice in a mouse model-specific manner. J Alzheimers Dis 90:1103-1122.

Briand LA, Lee BG, Lelay J, Kaestner KH, Blendy JA (2015) Serine 133 phosphorylation is not required for hippocampal CREB-mediated transcription and behavior. Learn Mem 22:109-115.

Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, Owen C, Aldea P, Su Y, Hassenstab J, Cairns NJ, Holtzman DM, Fagan AM, Morris JC, Benzinger TL, Ances BM (2016) Tau and Aβ imaging, CSF measures, and cognition in Alzheimer's disease. Sci Transl Med 8:338ra366.

Brody AH, Nies SH, Guan F, Smith LM, Mukherjee B, Salazar SA, Lee S, Lam TKT, Strittmatter SM (2022) Alzheimer risk gene product Pyk2 suppresses tau phosphorylation and phenotypic effects of tauopathy. Mol Neurodegener 17:32.

Brunello CA, Merezhko M, Uronen RL, Huttunen HJ (2020) Mechanisms of secretion and spreading of pathological tau protein. Cell Mol Life Sci 77:1721-1744.

Caballero B, Bourdenx M, Luengo E, Diaz A, Sohn PD, Chen X, Wang C, Juste YR, Wegmann S, Patel B, Young ZT, Kuo SY, Rodriguez-Navarro JA, Shao H, Lopez MG, Karch CM, Goate AM, Gestwicki JE, Hyman BT, Gan L, et al. (2021) Acetylated tau inhibits chaperone-mediated autophagy and promotes tau pathology propagation in mice. Nat Commun 12:2238.

Cao B, Mao C (2009) Identification of microtubule-binding domains on microtubule-associated proteins by major coat phage display technique. Biomacromolecules 10:555-564.

Castillo-Carranza DL, Sengupta U, Guerrero-Muñoz MJ, Lasagna-Reeves CA, Gerson JE, Singh G, Estes DM, Barrett AD, Dineley KT, Jackson GR, Kayed R (2014) Passive immunization with Tau oligomer monoclonal antibody reverses tauopathy phenotypes without affecting hyperphosphorylated neurofibrillary tangles. J Neurosci 34:4260-4272.

Chai GS, Feng Q, Wang ZH, Hu Y, Sun DS, Li XG, Ke D, Li HL, Liu GP, Wang JZ (2017) Downregulating ANP32A rescues synapse and memory loss via chromatin remodeling in Alzheimer model. Mol Neurodegener 12:34.

Chai GS, Feng Q, Ma RH, Qian XH, Luo DJ, Wang ZH, Hu Y, Sun DS, Zhang JF, Li X, Li XG, Ke D, Wang JZ, Yang XF, Liu GP (2018) Inhibition of histone acetylation by ANP32A induces memory deficits. J Alzheimers Dis 63:1537-1546.

Chatterjee P, Vermunt L, Gordon BA, Pedrini S, Boonkamp L, Armstrong NJ, Xiong C, Singh AK, Li Y, Sohrabi HR, Taddei K, Molloy M, Benzinger TLS, Morris JC, Karch C, Berman S, Chhatwal J, Cruchaga C, Graff-Radford NR, Day GS, et al. (2022) Plasma glial fibrillary acidic protein in autosomal dominant Alzheimer's disease: Associations with Aβ-PET, neurodegeneration, and cognition. Alzheimers Dement doi: 10.1002/alz.12879.

Choi H, Kim HJ, Yang J, Chae S, Lee W, Chung S, Kim J, Choi H, Song H, Lee CK, Jun JH, Lee YJ, Lee K, Kim S, Sim HR, Choi YI, Ryu KH, Park JC, Lee D, Han SH, et al. (2020) Acetylation changes tau interactome to degrade tau in Alzheimer's disease animal and organoid models. Aging Cell 19:e13081.

Cohen TJ, Friedmann D, Hwang AW, Marmorstein R, Lee VM (2013) The microtubule-associated tau protein has intrinsic acetyltransferase activity. Nat Struct Mol Biol 20:756-762.

Collin L, Bohrmann B, Göpfert U, Oroszlan-Szovik K, Ozmen L, Grüninger F (2014) Neuronal uptake of tau/pS422 antibody and reduced progression of tau pathology in a mouse model of Alzheimer's disease. Brain 137:2834-2846.

Congdon EE, Sigurdsson EM (2018) Tau-targeting therapies for Alzheimer disease. Nat Rev Neurol 14:399-415.

Congdon EE, Gu J, Sait HB, Sigurdsson EM (2013) Antibody uptake into neurons occurs primarily via clathrin-dependent Fcγ receptor endocytosis and is a prerequisite for acute tau protein clearance. J Biol Chem 288:35452-35465.

Cook C, Carlomagno Y, Gendron TF, Dunmore J, Scheffel K, Stetler C, Davis M, Dickson D, Jarpe M, DeTure M, Petrucelli L (2014) Acetylation of the KXGS motifs in tau is a critical determinant in modulation of tau aggregation and clearance. Hum Mol Genet 23:104-116.

Cripps D, Thomas SN, Jeng Y, Yang F, Davies P, Yang AJ (2006) Alzheimer disease-specific conformation of hyperphosphorylated paired helical filament-Tau is polyubiquitinated through Lys-48, Lys-11, and Lys-6 ubiquitin conjugation. J Biol Chem 281:10825-10838.

Cummins N, Tweedie A, Zuryn S, Bertran-Gonzalez J, Götz J (2019) Disease-associated tau impairs mitophagy by inhibiting Parkin translocation to mitochondria. EMBO J 38:e99360.

Dai CL, Hu W, Tung YC, Liu F, Gong CX, Iqbal K (2018) Tau passive immunization blocks seeding and spread of Alzheimer hyperphosphorylated Tau-induced pathology in 3×Tg-AD mice. Alzheimers Res Ther 10:13.

Dam T, Boxer AL, Golbe LI, Höglinger GU, Morris HR, Litvan I, Lang AE, Corvol JC, Aiba I, Grundman M, Yang L, Tidemann-Miller B, Kupferman J, Harper K, Kamisoglu K, Wald MJ, Graham DL, Gedney L, O'Gorman J, Haeberlein SB (2021) Safety and efficacy of anti-tau monoclonal antibody gosuranemab in progressive supranuclear palsy: a phase 2, randomized, placebo-controlled trial. Nat Med 27:1451-1457.

Delacourte A, Sergeant N, Wattez A, Gauvreau D, Robitaille Y (1998) Vulnerable neuronal subsets in Alzheimer's and Pick's disease are distinguished by their tau isoform distribution and phosphorylation. Ann Neurol 43:193-204.

Derisbourg M, Leghay C, Chiappetta G, Fernandez-Gomez FJ, Laurent C, Demeyer D, Carrier S, Buée-Scherrer V, Blum D, Vinh J, Sergeant N, Verdier Y, Buée L, Hamdane M (2015) Role of the Tau N-terminal region in microtubule stabilization revealed by new endogenous truncated forms. Sci Rep 5:9659.

Dorval V, Fraser PE (2006) Small ubiquitin-like modifier (SUMO) modification of natively unfolded proteins tau and alpha-synuclein. J Biol Chem 281:9919-9924.

Drummond E, Pires G, MacMurray C, Askenazi M, Nayak S, Bourdon M, Safar J, Ueberheide B, Wisniewski T (2020) Phosphorylated tau interactome in the human Alzheimer's disease brain. Brain 143:2803-2817.

DuBoff B, Götz J, Feany MB (2012) Tau promotes neurodegeneration via DRP1 mislocalization in vivo. Neuron 75:618-632.

Ezerskiy LA, Schoch KM, Sato C, Beltcheva M, Horie K, Rigo F, Martynowicz R, Karch CM, Bateman RJ, Miller TM (2022) Astrocytic 4R tau expression drives astrocyte reactivity and dysfunction. JCI Insight 7:e152012.

Fang EF, Hou Y, Palikaras K, Adriaanse BA, Kerr JS, Yang B, Lautrup S, Hasan-Olive MM, Caponio D, Dan X, Rocktäschel P, Croteau DL, Akbari M, Greig NH, Fladby T, Nilsen H, Cader MZ, Mattson MP, Tavernarakis N, Bohr VA (2019) Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat Neurosci 22:401-412.

Feng Q, Luo Y, Zhang XN, Yang XF, Hong XY, Sun DS, Li XC, Hu Y, Li XG, Zhang JF, Li X, Yang Y, Wang Q, Liu GP, Wang JZ (2020) MAPT/Tau accumulation represses autophagy flux by disrupting IST1-regulated ESCRT-III complex formation: a vicious cycle in Alzheimer neurodegeneration. Autophagy 16:641-658.

Ferrer I, Barrachina M, Puig B (2002) Glycogen synthase kinase-3 is associated with neuronal and glial hyperphosphorylated tau deposits in Alzheimer's disease, Pick's disease, progressive supranuclear palsy and corticobasal degeneration. Acta Neuropathol 104:583-591.

Foster K, Manca M, McClure K, Koivula P, Trojanowski JQ, Havas D, Chancellor S, Goldstein L, Brunden KR, Kraus A, Ahlijanian MK (2023) Preclinical characterization and IND-enabling safety studies for PNT001, an antibody that recognizes cis-pT231 tau. Alzheimers Dement doi: 10.1002/alz.13028.

Funk KE, Thomas SN, Schafer KN, Cooper GL, Liao Z, Clark DJ, Yang AJ, Kuret J (2014) Lysine methylation is an endogenous post-translational modification of tau protein in human brain and a modulator of aggregation propensity. Biochem J 462:77-88.

Gauthier-Kemper A, Suárez Alonso M, Sündermann F, Niewidok B, Fernandez MP, Bakota L, Heinisch JJ, Brandt R (2018) Annexins A2 and A6 interact with the extreme N terminus of tau and thereby contribute to tau's axonal localization. J Biol Chem 293:8065-8076.

Goedert M, Jakes R (1990) Expression of separate isoforms of human tau protein: correlation with the tau pattern in brain and effects on tubulin polymerization. EMBO J 9:4225-4230.

Gong CX, Singh TJ, Grundke-Iqbal I, Iqbal K (1993) Phosphoprotein phosphatase activities in Alzheimer disease brain. J Neurochem 61:921-927.

Gorsky MK, Burnouf S, Sofola-Adesakin O, Dols J, Augustin H, Weigelt CM, Grönke S, Partridge L (2017) Pseudo-acetylation of multiple sites on human Tau proteins alters Tau phosphorylation and microtubule binding, and ameliorates amyloid beta toxicity. Sci Rep 7:9984.

Gratuze M, Chen Y, Parhizkar S, Jain N, Strickland MR, Serrano JR, Colonna M, Ulrich JD, Holtzman DM (2021) Activated microglia mitigate Aβ-associated tau seeding and spreading. J Exp Med 218:e20210542.

Griciuc A, Tanzi RE (2021) The role of innate immune genes in Alzheimer's disease. Curr Opin Neurol 34:228-236.

Haass C (2021) Loss of TREM2 facilitates tau accumulation, spreading, and brain atrophy, but only in the presence of amyloid pathology. Neuron 109:1243-1245.

Höglinger GU, Litvan I, Mendonca N, Wang D, Zheng H, Rendenbach-Mueller B, Lon HK, Jin Z, Fisseha N, Budur K, Gold M, Ryman D, Florian H (2021) Safety and efficacy of tilavonemab in progressive supranuclear palsy: a phase 2, randomised, placebo-controlled trial. Lancet Neurol 20:182-192.

Hong XY, Wan HL, Li T, Zhang BG, Li XG, Wang X, Li X, Liu Q, Chen CY, Yang Y, Wang Q, Li SP, Yu H, Wang JZ, Yang XF, Liu GP (2020) STAT3 ameliorates cognitive deficits by positively regulating the expression of NMDARs in a mouse model of FTDP-17. Signal Transduct Target Ther 5:295.

Hoover BR, Reed MN, Su J, Penrod RD, Kotilinek LA, Grant MK, Pitstick R, Carlson GA, Lanier LM, Yuan LL, Ashe KH, Liao D (2010) Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. Neuron 68:1067-1081.

Hu Y, Li XC, Wang ZH, Luo Y, Zhang X, Liu XP, Feng Q, Wang Q, Yue Z, Chen Z, Ye K, Wang JZ, Liu GP (2016) Tau accumulation impairs mitophagy via increasing mitochondrial membrane potential and reducing mitochondrial Parkin. Oncotarget 7:17356-17368.

Ittner A, Chua SW, Bertz J, Volkerling A, van der Hoven J, Gladbach A, Przybyla M, Bi M, van Hummel A, Stevens CH, Ippati S, Suh LS, Macmillan A, Sutherland G, Kril JJ, Silva AP, Mackay JP, Poljak A, Delerue F, Ke YD, et al. (2016) Site-specific phosphorylation of tau inhibits amyloid-β toxicity in Alzheimer's mice. Science 354:904-908.

Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J, Wölfing H, Chieng BC, Christie MJ, Napier IA, Eckert A, Staufenbiel M, Hardeman E, Götz J (2010) Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. Cell 142:387-397.

Iyaswamy A, Krishnamoorthi SK, Zhang H, Sreenivasmurthy SG, Zhu Z, Liu J, Su CF, Guan XJ, Wang ZY, Cheung KH, Song JX, Durairajan SSK, Li M (2021) Qingyangshen mitigates amyloid-β and Tau aggregate defects involving PPARα-TFEB activation in transgenic mice of Alzheimer's disease. Phytomedicine 91:153648.

Jain N, Lewis CA, Ulrich JD, Holtzman DM (2023) Chronic TREM2 activation exacerbates Aβ-associated tau seeding and spreading. J Exp Med 220:e20220654.

Jangampalli Adi P, Reddy PH (2021) Phosphorylated tau targeted small-molecule PROTACs for the treatment of Alzheimer's disease and tauopathies. Biochim Biophys Acta Mol Basis Dis 1867:166162.

Jin M, Shiwaku H, Tanaka H, Obita T, Ohuchi S, Yoshioka Y, Jin X, Kondo K, Fujita K, Homma H, Nakajima K, Mizuguchi M, Okazawa H (2021) Tau activates microglia via the PQBP1-cGAS-STING pathway to promote brain inflammation. Nat Commun 12:6565.

Kanemaru K, Takio K, Miura R, Titani K, Ihara Y (1992) Fetal-type phosphorylation of the tau in paired helical filaments. J Neurochem 58:1667-1675.

Kang SS, Ahn EH, Ye K (2020a) Delta-secretase cleavage of Tau mediates its pathology and propagation in Alzheimer's disease. Exp Mol Med 52:1275-1287.

Kang SS, Liu X, Ahn EH, Xiang J, Manfredsson FP, Yang X, Luo HR, Liles LC, Weinshenker D, Ye K (2020b) Norepinephrine metabolite DOPEGAL activates AEP and pathological Tau aggregation in locus coeruleus. J Clin Invest 130:422-437.

Kar S, Fan J, Smith MJ, Goedert M, Amos LA (2003) Repeat motifs of tau bind to the insides of microtubules in the absence of taxol. EMBO J 22:70-77.

Karlawish J, Grill JD (2021) The approval of Aduhelm risks eroding public trust in Alzheimer research and the FDA. Nat Rev Neurol 17:523-524.

Kim JH, Lee J, Choi WH, Park S, Park SH, Lee JH, Lim SM, Mun JY, Cho HS, Han D, Suh YH, Lee MJ (2021) CHIP-mediated hyperubiquitylation of tau promotes its self-assembly into the insoluble tau filaments. Chem Sci 12:5599-5610.

Kim MS, Mun YS, Lee SE, Cho WY, Han SH, Kim DH, Yoon SY (2022) Tau acetylation at K280 regulates tau phosphorylation. Int J Neurosci doi: 10.1080/00207454.2022.2081165.

Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen CH, Yao Y, Lin YM, Driver JA, Sun Y, Wei S, Luo ML, Albayram O, Huang P, Rotenberg A, Ryo A, Goldstein LE, Pascual-Leone A, McKee AC, Meehan W, et al. (2015) Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. Nature 523:431-436.

Kontaxi C, Piccardo P, Gill AC (2017) Lysine-directed post-translational modifications of tau protein in Alzheimer's disease and related tauopathies. Front Mol Biosci 4:56.

Köpke E, Tung YC, Shaikh S, Alonso AC, Iqbal K, Grundke-Iqbal I (1993) Microtubule-associated protein tau. Abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease. J Biol Chem 268:24374-24384.

Lananna BV, McKee CA, King MW, Del-Aguila JL, Dimitry JM, Farias FHG, Nadarajah CJ, Xiong DD, Guo C, Cammack AJ, Elias JA, Zhang J, Cruchaga C, Musiek ES (2020) Chi3l1/YKL-40 is controlled by the astrocyte circadian clock and regulates neuroinflammation and Alzheimer's disease pathogenesis. Sci Transl Med 12:eaax3519.

Largo-Barrientos P, Apóstolo N, Creemers E, Callaerts-Vegh Z, Swerts J, Davies C, McInnes J, Wierda K, De Strooper B, Spires-Jones T, de Wit J, Uyterhoeven V, Verstreken P (2021) Lowering Synaptogyrin-3 expression rescues Tau-induced memory defects and synaptic loss in the presence of microglial activation. Neuron 109:767-777.e5.

Lee G, Newman ST, Gard DL, Band H, Panchamoorthy G (1998) Tau interacts with src-family non-receptor tyrosine kinases. J Cell Sci 111 ( Pt 21):3167-3177.

Lee S, Shea TB (2012) Caspase-mediated truncation of tau potentiates aggregation. Int J Alzheimers Dis 2012:731063.

Lee SH, Meilandt WJ, Xie L, Gandham VD, Ngu H, Barck KH, Rezzonico MG, Imperio J, Lalehzadeh G, Huntley MA, Stark KL, Foreman O, Carano RAD, Friedman BA, Sheng M, Easton A, Bohlen CJ, Hansen DV (2021) Trem2 restrains the enhancement of tau accumulation and neurodegeneration by β-amyloid pathology. Neuron 109:1283-1301.e6.

Lester E, Ooi FK, Bakkar N, Ayers J, Woerman AL, Wheeler J, Bowser R, Carlson GA, Prusiner SB, Parker R (2021) Tau aggregates are RNA-protein assemblies that mislocalize multiple nuclear speckle components. Neuron 109:1675-1691.e9.

Li L, Jiang Y, Wang JZ, Liu R, Wang X (2021) Tau ubiquitination in Alzheimer's disease. Front Neurol 12:786353.

Li L, Miao J, Chu D, Jin N, Tung YC, Dai CL, Hu W, Gong CX, Iqbal K, Liu F (2022) Tau antibody 77G7 targeting microtubule binding domain suppresses proteopathic tau to seed tau aggregation. CNS Neurosci Ther 28:2245-2259.

Li XC, Hu Y, Wang ZH, Luo Y, Zhang Y, Liu XP, Feng Q, Wang Q, Ye K, Liu GP, Wang JZ (2016) Human wild-type full-length tau accumulation disrupts mitochondrial dynamics and the functions via increasing mitofusins. Sci Rep 6:24756.

Li XG, Hong XY, Wang YL, Zhang SJ, Zhang JF, Li XC, Liu YC, Sun DS, Feng Q, Ye JW, Gao Y, Ke D, Wang Q, Li HL, Ye K, Liu GP, Wang JZ (2019) Tau accumulation triggers STAT1-dependent memory deficits by suppressing NMDA receptor expression. EMBO Rep 20:e47202.

Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung WS, Peterson TC, Wilton DK, Frouin A, Napier BA, Panicker N, Kumar M, Buckwalter MS, Rowitch DH, Dawson VL, Dawson TM, Stevens B, et al. (2017) Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541:481-487.

Litvinchuk A, Wan YW, Swartzlander DB, Chen F, Cole A, Propson NE, Wang Q, Zhang B, Liu Z, Zheng H (2018) Complement C3aR inactivation attenuates tau pathology and reverses an immune network deregulated in tauopathy models and Alzheimer's disease. Neuron 100:1337-1353.e5.

Liu F, Iqbal K, Grundke-Iqbal I, Hart GW, Gong CX (2004) O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease. Proc Natl Acad Sci U S A 101:10804-10809.

Liu F, Shi J, Tanimukai H, Gu J, Gu J, Grundke-Iqbal I, Iqbal K, Gong CX (2009) Reduced O-GlcNAcylation links lower brain glucose metabolism and tau pathology in Alzheimer's disease. Brain 132:1820-1832.

Liu GP, Zhang Y, Yao XQ, Zhang CE, Fang J, Wang Q, Wang JZ (2008) Activation of glycogen synthase kinase-3 inhibits protein phosphatase-2A and the underlying mechanisms. Neurobiol Aging 29:1348-1358.

Liu GP, Wei W, Zhou X, Zhang Y, Shi HH, Yin J, Yao XQ, Peng CX, Hu J, Wang Q, Li HL, Wang JZ (2012) I(2)(PP2A) regulates p53 and Akt correlatively and leads the neurons to abort apoptosis. Neurobiol Aging 33:254-264.

Liu GP, Wei W, Zhou X, Shi HR, Liu XH, Chai GS, Yao XQ, Zhang JY, Peng CX, Hu J, Li XC, Wang Q, Wang JZ (2013) Silencing PP2A inhibitor by lenti-shRNA interference ameliorates neuropathologies and memory deficits in tg2576 mice. Mol Ther 21:2247-2257.

Liu W, Zhao L, Blackman B, Parmar M, Wong MY, Woo T, Yu F, Chiuchiolo MJ, Sondhi D, Kaminsky SM, Crystal RG, Paul SM (2016) Vectored intracerebral immunization with the anti-tau monoclonal antibody PHF1 markedly reduces tau pathology in mutant tau transgenic mice. J Neurosci 36:12425-12435.

Liu X, Hebron ML, Mulki S, Wang C, Lekah E, Ferrante D, Shi W, Kurd-Misto B, Moussa C (2019) Ubiquitin specific protease 13 regulates tau accumulation and clearance in models of Alzheimer's disease. J Alzheimers Dis 72:425-441.

Losev Y, Frenkel-Pinter M, Abu-Hussien M, Viswanathan GK, Elyashiv-Revivo D, Geries R, Khalaila I, Gazit E, Segal D (2021) Differential effects of putative N-glycosylation sites in human Tau on Alzheimer's disease-related neurodegeneration. Cell Mol Life Sci 78:2231-2245.

Lovestone S, Boada M, Dubois B, Hüll M, Rinne JO, Huppertz HJ, Calero M, Andrés MV, Gómez-Carrillo B, León T, del Ser T (2015) A phase II trial of tideglusib in Alzheimer's disease. J Alzheimers Dis 45:75-88.

Lu PJ, Wulf G, Zhou XZ, Davies P, Lu KP (1999) The prolyl isomerase Pin1 restores the function of Alzheimer-associated phosphorylated tau protein. Nature 399:784-788.

Luo HB, Xia YY, Shu XJ, Liu ZC, Feng Y, Liu XH, Yu G, Yin G, Xiong YS, Zeng K, Jiang J, Ye K, Wang XC, Wang JZ (2014) SUMOylation at K340 inhibits tau degradation through deregulating its phosphorylation and ubiquitination. Proc Natl Acad Sci U S A 111:16586-16591.

Manczak M, Reddy PH (2012) Abnormal interaction between the mitochondrial fission protein Drp1 and hyperphosphorylated tau in Alzheimer's disease neurons: implications for mitochondrial dysfunction and neuronal damage. Hum Mol Genet 21:2538-2547.

Mann CN, Devi SS, Kersting CT, Bleem AV, Karch CM, Holtzman DM, Gallardo G (2022) Astrocytic α2-Na(+)/K(+) ATPase inhibition suppresses astrocyte reactivity and reduces neurodegeneration in a tauopathy mouse model. Sci Transl Med 14:eabm4107.

Martinez P, Patel H, You Y, Jury N, Perkins A, Lee-Gosselin A, Taylor X, You Y, Viana Di Prisco G, Huang X, Dutta S, Wijeratne AB, Redding-Ochoa J, Shahid SS, Codocedo JF, Min S, Landreth GE, Mosley AL, Wu YC, McKinzie DL, et al. (2022) Bassoon contributes to tau-seed propagation and neurotoxicity. Nat Neurosci 25:1597-1607.

McAlpine CS, Park J, Griciuc A, Kim E, Choi SH, Iwamoto Y, Kiss MG, Christie KA, Vinegoni C, Poller WC, Mindur JE, Chan CT, He S, Janssen H, Wong LP, Downey J, Singh S, Anzai A, Kahles F, Jorfi M, et al. (2021) Astrocytic interleukin-3 programs microglia and limits Alzheimer's disease. Nature 595:701-706.

McElroy T, Zeidan RS, Rathor L, Han SM, Xiao R (2023) The role of mitochondria in the recovery of neurons after injury. Neural Regen Res 18:317-318.

McEwan WA, Falcon B, Vaysburd M, Clift D, Oblak AL, Ghetti B, Goedert M, James LC (2017) Cytosolic Fc receptor TRIM21 inhibits seeded tau aggregation. Proc Natl Acad Sci U S A 114:574-579.

Merezhko M, Brunello CA, Yan X, Vihinen H, Jokitalo E, Uronen RL, Huttunen HJ (2018) Secretion of Tau via an Unconventional Non-vesicular Mechanism. Cell Rep 25:2027-2035.e4.

Mielke MM, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, Airey DC, Knopman DS, Roberts RO, Machulda MM, Jack CR, Jr., Petersen RC, Dage JL (2018) Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. Alzheimers Dement 14:989-997.

Milà-Alomà M, Ashton NJ, Shekari M, Salvadó G, Ortiz-Romero P, Montoliu-Gaya L, Benedet AL, Karikari TK, Lantero-Rodriguez J, Vanmechelen E, Day TA, González-Escalante A, Sánchez-Benavides G, Minguillon C, Fauria K, Molinuevo JL, Dage JL, Zetterberg H, Gispert JD, Suárez-Calvet M, et al. (2022) Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease. Nat Med 28:1797-1801.

Min SW, Cho SH, Zhou Y, Schroeder S, Haroutunian V, Seeley WW, Huang EJ, Shen Y, Masliah E, Mukherjee C, Meyers D, Cole PA, Ott M, Gan L (2010) Acetylation of tau inhibits its degradation and contributes to tauopathy. Neuron 67:953-966.

Min SW, Chen X, Tracy TE, Li Y, Zhou Y, Wang C, Shirakawa K, Minami SS, Defensor E, Mok SA, Sohn PD, Schilling B, Cong X, Ellerby L, Gibson BW, Johnson J, Krogan N, Shamloo M, Gestwicki J, Masliah E, et al. (2015) Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits. Nat Med 21:1154-1162.

Morey N, Przybyla M, van der Hoven J, Ke YD, Delerue F, van Eersel J, Ittner LM (2022) Treatment of epilepsy using a targeted p38γ kinase gene therapy. Sci Adv 8:eadd2577.

Morishima-Kawashima M, Hasegawa M, Takio K, Suzuki M, Titani K, Ihara Y (1993) Ubiquitin is conjugated with amino-terminally processed tau in paired helical filaments. Neuron 10:1151-1160.

Munari F, Barracchia CG, Parolini F, Tira R, Bubacco L, Assfalg M, D'Onofrio M (2020) Semisynthetic modification of tau protein with di-ubiquitin chains for aggregation studies. Int J Mol Sci 21:4400.

Myeku N, Clelland CL, Emrani S, Kukushkin NV, Yu WH, Goldberg AL, Duff KE (2016) Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling. Nat Med 22:46-53.

Naserkhaki R, Zamanzadeh S, Baharvand H, Nabavi SM, Pakdaman H, Shahbazi S, Vosough M, Ghaedi G, Barzegar A, Mirtorabi D, Hedayatshodeh M, Ehsani E, Falahati M, Hajipour MJ, Shahpasand K (2019) cis pT231-Tau drives neurodegeneration in bipolar disorder. ACS Chem Neurosci 10:1214-1221.

Neve RL, Harris P, Kosik KS, Kurnit DM, Donlon TA (1986) Identification of cDNA clones for the human microtubule-associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein 2. Brain Res 387:271-280.

Nixon RA, Wegiel J, Kumar A, Yu WH, Peterhoff C, Cataldo A, Cuervo AM (2005) Extensive involvement of autophagy in Alzheimer disease: an immuno-electron microscopy study. J Neuropathol Exp Neurol 64:113-122.

Novak P, Schmidt R, Kontsekova E, Zilka N, Kovacech B, Skrabana R, Vince-Kazmerova Z, Katina S, Fialova L, Prcina M, Parrak V, Dal-Bianco P, Brunner M, Staffen W, Rainer M, Ondrus M, Ropele S, Smisek M, Sivak R, Winblad B, et al. (2017) Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Neurol 16:123-134.

Novak P, Kovacech B, Katina S, Schmidt R, Scheltens P, Kontsekova E, Ropele S, Fialova L, Kramberger M, Paulenka-Ivanovova N, Smisek M, Hanes J, Stevens E, Kovac A, Sutovsky S, Parrak V, Koson P, Prcina M, Galba J, Cente M, et al. (2021) ADAMANT: a placebo-controlled randomized phase 2 study of AADvac1, an active immunotherapy against pathological tau in Alzheimer's disease. Nat Aging 1:521-534.

Ochoa E, Ramirez P, Gonzalez E, De Mange J, Ray WJ, Bieniek KF, Frost B (2023) Pathogenic tau-induced transposable element-derived dsRNA drives neuroinflammation. Sci Adv 9:eabq5423.

Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, Su Y, Chen Y, Serrano GE, Leuzy A, Mattsson-Carlgren N, Strandberg O, Smith R, Villegas A, Sepulveda-Falla D, Chai X, Proctor NK, Beach TG, Blennow K, Dage JL, et al. (2020) Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA 324:772-781.

Park SY, Ferreira A (2005) The generation of a 17 kDa neurotoxic fragment: an alternative mechanism by which tau mediates beta-amyloid-induced neurodegeneration. J Neurosci 25:5365-5375.

Peng C, Trojanowski JQ, Lee VM (2020) Protein transmission in neurodegenerative disease. Nat Rev Neurol 16:199-212.

Petrucelli L, Dickson D, Kehoe K, Taylor J, Snyder H, Grover A, De Lucia M, McGowan E, Lewis J, Prihar G, Kim J, Dillmann WH, Browne SE, Hall A, Voellmy R, Tsuboi Y, Dawson TM, Wolozin B, Hardy J, Hutton M (2004) CHIP and Hsp70 regulate tau ubiquitination, degradation and aggregation. Hum Mol Genet 13:703-714.

Pimenova AA, Raj T, Goate AM (2018) Untangling genetic risk for Alzheimer's disease. Biol Psychiatry 83:300-310.

Piras A, Collin L, Grüninger F, Graff C, Rönnbäck A (2016) Autophagic and lysosomal defects in human tauopathies: analysis of post-mortem brain from patients with familial Alzheimer disease, corticobasal degeneration and progressive supranuclear palsy. Acta Neuropathol Commun 4:22.

Polanco JC, Hand GR, Briner A, Li C, Götz J (2021) Exosomes induce endolysosomal permeabilization as a gateway by which exosomal tau seeds escape into the cytosol. Acta Neuropathol 141:235-256.

Prikas E, Paric E, Asih PR, Stefanoska K, Stefen H, Fath T, Poljak A, Ittner A (2022) Tau target identification reveals NSF-dependent effects on AMPA receptor trafficking and memory formation. EMBO J 41:e10242.

Puangmalai N, Sengupta U, Bhatt N, Gaikwad S, Montalbano M, Bhuyan A, Garcia S, McAllen S, Sonawane M, Jerez C, Zhao Y, Kayed R (2022) Lysine 63-linked ubiquitination of tau oligomers contributes to the pathogenesis of Alzheimer's disease. J Biol Chem 298:101766.

Rapoport M, Dawson HN, Binder LI, Vitek MP, Ferreira A (2002) Tau is essential to beta -amyloid-induced neurotoxicity. Proc Natl Acad Sci U S A 99:6364-6369.

Rauch JN, Luna G, Guzman E, Audouard M, Challis C, Sibih YE, Leshuk C, Hernandez I, Wegmann S, Hyman BT, Gradinaru V, Kampmann M, Kosik KS (2020) LRP1 is a master regulator of tau uptake and spread. Nature 580:381-385.

Reynolds MR, Berry RW, Binder LI (2005) Site-specific nitration differentially influences tau assembly in vitro. Biochemistry 44:13997-14009.

Reynolds MR, Reyes JF, Fu Y, Bigio EH, Guillozet-Bongaarts AL, Berry RW, Binder LI (2006) Tau nitration occurs at tyrosine 29 in the fibrillar lesions of Alzheimer's disease and other tauopathies. J Neurosci 26:10636-10645.

Richetin K, Steullet P, Pachoud M, Perbet R, Parietti E, Maheswaran M, Eddarkaoui S, Bégard S, Pythoud C, Rey M, Caillierez R, K QD, Halliez S, Bezzi P, Buée L, Leuba G, Colin M, Toni N, Déglon N (2020) Tau accumulation in astrocytes of the dentate gyrus induces neuronal dysfunction and memory deficits in Alzheimer's disease. Nat Neurosci 23:1567-1579.

Rosenberger AF, Morrema TH, Gerritsen WH, van Haastert ES, Snkhchyan H, Hilhorst R, Rozemuller AJ, Scheltens P, van der Vies SM, Hoozemans JJ (2016) Increased occurrence of protein kinase CK2 in astrocytes in Alzheimer's disease pathology. J Neuroinflammation 13:4.

Sahara N, Murayama M, Mizoroki T, Urushitani M, Imai Y, Takahashi R, Murata S, Tanaka K, Takashima A (2005) In vivo evidence of CHIP up-regulation attenuating tau aggregation. J Neurochem 94:1254-1263.

Sanchez-Varo R, Trujillo-Estrada L, Sanchez-Mejias E, Torres M, Baglietto-Vargas D, Moreno-Gonzalez I, De Castro V, Jimenez S, Ruano D, Vizuete M, Davila JC, Garcia-Verdugo JM, Jimenez AJ, Vitorica J, Gutierrez A (2012) Abnormal accumulation of autophagic vesicles correlates with axonal and synaptic pathology in young Alzheimer's mice hippocampus. Acta Neuropathol 123:53-70.

Sankaranarayanan S, Barten DM, Vana L, Devidze N, Yang L, Cadelina G, Hoque N, DeCarr L, Keenan S, Lin A, Cao Y, Snyder B, Zhang B, Nitla M, Hirschfeld G, Barrezueta N, Polson C, Wes P, Rangan VS, Cacace A, et al. (2015) Passive immunization with phospho-tau antibodies reduces tau pathology and functional deficits in two distinct mouse tauopathy models. PLoS One 10:e0125614.

Sathish Kumar P, Kannan ND (2021) A system-level approach to investigate alloxan-induced toxicity in microtubule-binding protein to lead type 2 diabetes mellitus. Mol Divers 25:911-924.

Selnick HG, Hess JF, Tang C, Liu K, Schachter JB, Ballard JE, Marcus J, Klein DJ, Wang X, Pearson M, Savage MJ, Kaul R, Li TS, Vocadlo DJ, Zhou Y, Zhu Y, Mu C, Wang Y, Wei Z, Bai C, et al. (2019) Discovery of MK-8719, a potent O-GlcNAcase inhibitor as a potential treatment for tauopathies. J Med Chem 62:10062-10097.

Seo J, Kritskiy O, Watson LA, Barker SJ, Dey D, Raja WK, Lin YT, Ko T, Cho S, Penney J, Silva MC, Sheridan SD, Lucente D, Gusella JF, Dickerson BC, Haggarty SJ, Tsai LH (2017) Inhibition of p25/Cdk5 attenuates tauopathy in mouse and iPSC models of frontotemporal dementia. J Neurosci 37:9917-9924.

Serenó L, Coma M, Rodríguez M, Sánchez-Ferrer P, Sánchez MB, Gich I, Agulló JM, Pérez M, Avila J, Guardia-Laguarta C, Clarimón J, Lleó A, Gómez-Isla T (2009) A novel GSK-3beta inhibitor reduces Alzheimer's pathology and rescues neuronal loss in vivo. Neurobiol Dis 35:359-367.

Sergeant N, Wattez A, Delacourte A (1999) Neurofibrillary degeneration in progressive supranuclear palsy and corticobasal degeneration: tau pathologies with exclusively "exon 10" isoforms. J Neurochem 72:1243-1249.

Shams H, Matsunaga A, Ma Q, Mofrad MRK, Didonna A (2022) Methylation at a conserved lysine residue modulates tau assembly and cellular functions. Mol Cell Neurosci 120:103707.

Shentu YP, Huo Y, Feng XL, Gilbert J, Zhang Q, Liuyang ZY, Wang XL, Wang G, Zhou H, Wang XC, Wang JZ, Lu YM, Westermarck J, Man HY, Liu R (2018) CIP2A Causes Tau/APP phosphorylation, synaptopathy, and memory deficits in Alzheimer's disease. Cell Rep 24:713-723.

Shi XL, Wu JD, Liu P, Liu ZP (2019) Synthesis and evaluation of novel GSK-3β inhibitors as multifunctional agents against Alzheimer's disease. Eur J Med Chem 167:211-225.

Shin MK, Vázquez-Rosa E, Koh Y, Dhar M, Chaubey K, Cintrón-Pérez CJ, Barker S, Miller E, Franke K, Noterman MF, Seth D, Allen RS, Motz CT, Rao SR, Skelton LA, Pardue MT, Fliesler SJ, Wang C, Tracy TE, Gan L, et al. (2021) Reducing acetylated tau is neuroprotective in brain injury. Cell 184:2715-2732.e23.

Shirazi SK, Wood JG (1993) The protein tyrosine kinase, fyn, in Alzheimer's disease pathology. Neuroreport 4:435-437.

Song HL, Kim NY, Park J, Kim MI, Jeon YN, Lee SJ, Cho K, Shim YL, Lee KH, Mun YS, Song JA, Kim MS, Pack CG, Jung M, Jang H, Na DL, Hong M, Kim DH, Yoon SY (2023) Monoclonal antibody Y01 prevents tauopathy progression induced by lysine 280-acetylated tau in cell and mouse models. J Clin Invest 133:e156537.

Song JX, Malampati S, Zeng Y, Durairajan SSK, Yang CB, Tong BC, Iyaswamy A, Shang WB, Sreenivasmurthy SG, Zhu Z, Cheung KH, Lu JH, Tang C, Xu N, Li M (2020) A small molecule transcription factor EB activator ameliorates beta-amyloid precursor protein and Tau pathology in Alzheimer's disease models. Aging Cell 19:e13069.

Sontag E, Hladik C, Montgomery L, Luangpirom A, Mudrak I, Ogris E, White CL, 3rd (2004) Downregulation of protein phosphatase 2A carboxyl methylation and methyltransferase may contribute to Alzheimer disease pathogenesis. J Neuropathol Exp Neurol 63:1080-1091.

Sundaram JR, Poore CP, Sulaimee NH, Pareek T, Asad AB, Rajkumar R, Cheong WF, Wenk MR, Dawe GS, Chuang KH, Pant HC, Kesavapany S (2013) Specific inhibition of p25/Cdk5 activity by the Cdk5 inhibitory peptide reduces neurodegeneration in vivo. J Neurosci 33:334-343.

Takahashi M, Iseki E, Kosaka K (2000) Cdk5 and munc-18/p67 co-localization in early stage neurofibrillary tangles-bearing neurons in Alzheimer type dementia brains. J Neurol Sci 172:63-69.

Takamura H, Nakayama Y, Ito H, Katayama T, Fraser PE, Matsuzaki S (2022) SUMO1 modification of tau in progressive supranuclear palsy. Mol Neurobiol 59:4419-4435.

Teng E, Manser PT, Pickthorn K, Brunstein F, Blendstrup M, Sanabria Bohorquez S, Wildsmith KR, Toth B, Dolton M, Ramakrishnan V, Bobbala A, Sikkes SAM, Ward M, Fuji RN, Kerchner GA (2022) Safety and efficacy of semorinemab in individuals with prodromal to mild Alzheimer disease: a randomized clinical trial. JAMA Neurol 79:758-767.

Tracy TE, Sohn PD, Minami SS, Wang C, Min SW, Li Y, Zhou Y, Le D, Lo I, Ponnusamy R, Cong X, Schilling B, Ellerby LM, Huganir RL, Gan L (2016) Acetylated tau obstructs KIBRA-mediated signaling in synaptic plasticity and promotes tauopathy-related memory loss. Neuron 90:245-260.

Tracy TE, Madero-Pérez J, Swaney DL, Chang TS, Moritz M, Konrad C, Ward ME, Stevenson E, Hüttenhain R, Kauwe G, Mercedes M, Sweetland-Martin L, Chen X, Mok SA, Wong MY, Telpoukhovskaia M, Min SW, Wang C, Sohn PD, Martin J, et al. (2022) Tau interactome maps synaptic and mitochondrial processes associated with neurodegeneration. Cell 185:712-728.e14.

Trigo D, Vitória JJ, da Cruz E Silva OAB (2023) Novel therapeutic strategies targeting mitochondria as a gateway in neurodegeneration. Neural Regen Res 18:991-995.

Trzeciakiewicz H, Ajit D, Tseng JH, Chen Y, Ajit A, Tabassum Z, Lobrovich R, Peterson C, Riddick NV, Itano MS, Tripathy A, Moy SS, Lee VMY, Trojanowski JQ, Irwin DJ, Cohen TJ (2020) An HDAC6-dependent surveillance mechanism suppresses tau-mediated neurodegeneration and cognitive decline. Nat Commun 11:5522.

Udeochu JC, Amin S, Huang Y, Fan L, Torres ERS, Carling GK, Liu B, McGurran H, Coronas-Samano G, Kauwe G, Mousa GA, Wong MY, Ye P, Nagiri RK, Lo I, Holtzman J, Corona C, Yarahmady A, Gill MT, Raju RM, et al. (2023) Tau activation of microglial cGAS-IFN reduces MEF2C-mediated cognitive resilience. Nat Neurosci 26:737-750.

Umeda T, Eguchi H, Kunori Y, Matsumoto Y, Taniguchi T, Mori H, Tomiyama T (2015) Passive immunotherapy of tauopathy targeting pSer413-tau: a pilot study in mice. Ann Clin Transl Neurol 2:241-255.

van Ameijde J, Crespo R, Janson R, Juraszek J, Siregar B, Verveen H, Sprengers I, Nahar T, Hoozemans JJ, Steinbacher S, Willems R, Delbroek L, Borgers M, Dockx K, Van Kolen K, Mercken M, Pascual G, Koudstaal W, Apetri A (2018) Enhancement of therapeutic potential of a naturally occurring human antibody targeting a phosphorylated Ser(422) containing epitope on pathological tau. Acta Neuropathol Commun 6:59.

van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T (2023) Lecanemab in early Alzheimer's disease. N Engl J Med 388:9-21.

Vossel KA, Zhang K, Brodbeck J, Daub AC, Sharma P, Finkbeiner S, Cui B, Mucke L (2010) Tau reduction prevents Abeta-induced defects in axonal transport. Science 330:198.

Wai MS, Liang Y, Shi C, Cho EY, Kung HF, Yew DT (2009) Co-localization of hyperphosphorylated tau and caspases in the brainstem of Alzheimer's disease patients. Biogerontology 10:457-469.

Walls KC, Ager RR, Vasilevko V, Cheng D, Medeiros R, LaFerla FM (2014) p-Tau immunotherapy reduces soluble and insoluble tau in aged 3xTg-AD mice. Neurosci Lett 575:96-100.

Wan HL, Hong XY, Zhao ZH, Li T, Zhang BG, Liu Q, Wang Q, Zhao S, Wang JZ, Shen XF, Liu GP (2021) STAT3 ameliorates cognitive deficits via regulation of NMDAR expression in an Alzheimer's disease animal model. Theranostics 11:5511-5524.

Wang C, Fan L, Khawaja RR, Liu B, Zhan L, Kodama L, Chin M, Li Y, Le D, Zhou Y, Condello C, Grinberg LT, Seeley WW, Miller BL, Mok SA, Gestwicki JE, Cuervo AM, Luo W, Gan L (2022) Microglial NF-κB drives tau spreading and toxicity in a mouse model of tauopathy. Nat Commun 13:1969.

Wang JZ, Liu F (2008) Microtubule-associated protein tau in development, degeneration and protection of neurons. Prog Neurobiol 85:148-175.

Wang JZ, Gao X, Wang ZH (2014) The physiology and pathology of microtubule-associated protein tau. Essays Biochem 56:111-123.

Wang L, Zhou Y, Chen D, Lee TH (2020a) Peptidyl-prolyl cis/trans isomerase Pin1 and Alzheimer's disease. Front Cell Dev Biol 8:355.

Wang P, Ye Y (2021) Filamentous recombinant human Tau activates primary astrocytes via an integrin receptor complex. Nat Commun 12:95.

Wang S, Mustafa M, Yuede CM, Salazar SV, Kong P, Long H, Ward M, Siddiqui O, Paul R, Gilfillan S, Ibrahim A, Rhinn H, Tassi I, Rosenthal A, Schwabe T, Colonna M (2020b) Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. J Exp Med 217:e20200785.

Wang W, Zhao F, Ma X, Perry G, Zhu X (2020c) Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. Mol Neurodegener 15:30.

Wang W, Zhou Q, Jiang T, Li S, Ye J, Zheng J, Wang X, Liu Y, Deng M, Ke D, Wang Q, Wang Y, Wang JZ (2021) A novel small-molecule PROTAC selectively promotes tau clearance to improve cognitive functions in Alzheimer-like models. Theranostics 11:5279-5295.

Wang X, Su B, Lee HG, Li X, Perry G, Smith MA, Zhu X (2009) Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. J Neurosci 29:9090-9103.

Wang X, Liu EJ, Liu Q, Li SH, Li T, Zhou QZ, Liu YC, Zhang H, Wang JZ (2020d) Tau acetylation in entorhinal cortex induces its chronic hippocampal propagation and cognitive deficits in mice. J Alzheimers Dis 77:241-255.

Wang X, Li W, Marcus J, Pearson M, Song L, Smith K, Terracina G, Lee J, Hong KK, Lu SX, Hyde L, Chen SC, Kinsley D, Melchor JP, Rubins DJ, Meng X, Hostetler E, Sur C, Zhang L, Schachter JB, et al. (2020e) MK-8719, a novel and selective O-GlcNAcase inhibitor that reduces the formation of pathological tau and ameliorates neurodegeneration in a mouse model of tauopathy. J Pharmacol Exp Ther 374:252-263.

Wang ZH, Liu P, Liu X, Manfredsson FP, Sandoval IM, Yu SP, Wang JZ, Ye K (2017) Delta-secretase phosphorylation by SRPK2 enhances its enzymatic activity, provoking pathogenesis in Alzheimer's disease. Mol Cell 67:812-825.e5.

Wegmann S, Biernat J, Mandelkow E (2021) A current view on Tau protein phosphorylation in Alzheimer's disease. Curr Opin Neurobiol 69:131-138.

Wegmann S, Bennett RE, Delorme L, Robbins AB, Hu M, McKenzie D, Kirk MJ, Schiantarelli J, Tunio N, Amaral AC, Fan Z, Nicholls S, Hudry E, Hyman BT (2019) Experimental evidence for the age dependence of tau protein spread in the brain. Sci Adv 5:eaaw6404.

Wei Z, Zeng K, Hu J, Li X, Huang F, Zhang B, Wang JZ, Liu R, Li HL, Wang X (2022) USP10 deubiquitinates Tau, mediating its aggregation. Cell Death Dis 13:726.

Weisová P, Cehlár O, Škrabana R, Žilková M, Filipčík P, Kováčech B, Prčina M, Wojčiaková Ľ, Fialová Ľ, Smolek T, Kontseková E, Žilka N, Novák M (2019) Therapeutic antibody targeting microtubule-binding domain prevents neuronal internalization of extracellular tau via masking neuron surface proteoglycans. Acta Neuropathol Commun 7:129.

Wen S, Zou ZR, Cheng S, Guo H, Hu HS, Zeng FZ, Mei XF (2023) Ginsenoside Rb1 improves energy metabolism after spinal cord injury. Neural Regen Res 18:1332-1338.

Wesseling H, Mair W, Kumar M, Schlaffner CN, Tang S, Beerepoot P, Fatou B, Guise AJ, Cheng L, Takeda S, Muntel J, Rotunno MS, Dujardin S, Davies P, Kosik KS, Miller BL, Berretta S, Hedreen JC, Grinberg LT, Seeley WW, et al. (2020) Tau PTM profiles identify patient heterogeneity and stages of Alzheimer's disease. Cell 183:1699-1713.e13.

Xie H, Litersky JM, Hartigan JA, Jope RS, Johnson GV (1998) The interrelationship between selective tau phosphorylation and microtubule association. Brain Res 798:173-183.

Xu Y, Du S, Marsh JA, Horie K, Sato C, Ballabio A, Karch CM, Holtzman DM, Zheng H (2021) TFEB regulates lysosomal exocytosis of tau and its loss of function exacerbates tau pathology and spreading. Mol Psychiatry 26:5925-5939.

Yan Y, Wang X, Chaput D, Shin MK, Koh Y, Gan L, Pieper AA, Woo JA, Kang DE (2022) X-linked ubiquitin-specific peptidase 11 increases tauopathy vulnerability in women. Cell 185:3913-3930.e19.

Yao XQ, Li XC, Zhang XX, Yin YY, Liu B, Luo DJ, Wang Q, Wang JZ, Liu GP (2012) Glycogen synthase kinase-3β regulates leucine-309 demethylation of protein phosphatase-2A via PPMT1 and PME-1. FEBS Lett 586:2522-2528.

Yao XQ, Zhang XX, Yin YY, Liu B, Luo DJ, Liu D, Chen NN, Ni ZF, Wang X, Wang Q, Wang JZ, Liu GP (2011) Glycogen synthase kinase-3β regulates Tyr307 phosphorylation of protein phosphatase-2A via protein tyrosine phosphatase 1B but not Src. Biochem J 437:335-344.

Ye J, Zhong S, Deng Y, Yao X, Liu Q, Wang JZ, Xiao S (2022) HDAC7 activates IKK/NF-κB signaling to regulate astrocyte-mediated inflammation. Mol Neurobiol 59:6141-6157.

Ye J, Yin Y, Liu H, Fang L, Tao X, Wei L, Zuo Y, Yin Y, Ke D, Wang JZ (2020) Tau inhibits PKA by nuclear proteasome-dependent PKAR2α elevation with suppressed CREB/GluA1 phosphorylation. Aging Cell 19:e13055.

Yin Y, Gao D, Wang Y, Wang ZH, Wang X, Ye J, Wu D, Fang L, Pi G, Yang Y, Wang XC, Lu C, Ye K, Wang JZ (2016) Tau accumulation induces synaptic impairment and memory deficit by calcineurin-mediated inactivation of nuclear CaMKIV/CREB signaling. Proc Natl Acad Sci U S A 113:E3773-3781.

Zhang CE, Tian Q, Wei W, Peng JH, Liu GP, Zhou XW, Wang Q, Wang DW, Wang JZ (2008) Homocysteine induces tau phosphorylation by inactivating protein phosphatase 2A in rat hippocampus. Neurobiol Aging 29:1654-1665.

Zhang Y, Ma RH, Li XC, Zhang JY, Shi HR, Wei W, Luo DJ, Wang Q, Wang JZ, Liu GP (2014a) Silencing I2PP2A rescues tau pathologies and memory deficits through rescuing PP2A and inhibiting GSK-3β signaling in human tau transgenic mice. Front Aging Neurosci 6:123.

Zhang Z, Li XG, Wang ZH, Song M, Yu SP, Kang SS, Liu X, Zhang Z, Xie M, Liu GP, Wang JZ, Ye K (2021) δ-Secretase-cleaved Tau stimulates Aβ production via upregulating STAT1-BACE1 signaling in Alzheimer's disease. Mol Psychiatry 26:586-603.

Zhang Z, Song M, Liu X, Kang SS, Kwon IS, Duong DM, Seyfried NT, Hu WT, Liu Z, Wang JZ, Cheng L, Sun YE, Yu SP, Levey AI, Ye K (2014b) Cleavage of tau by asparagine endopeptidase mediates the neurofibrillary pathology in Alzheimer's disease. Nat Med 20:1254-1262.

Zhang Z, Obianyo O, Dall E, Du Y, Fu H, Liu X, Kang SS, Song M, Yu SP, Cabrele C, Schubert M, Li X, Wang JZ, Brandstetter H, Ye K (2017) Inhibition of delta-secretase improves cognitive functions in mouse models of Alzheimer's disease. Nat Commun 8:14740.

Zhao P, Xu Y, Jiang L, Fan X, Li L, Li X, Arase H, Zhao Y, Cao W, Zheng H, Xu H, Tong Q, Zhang N, An Z (2022) A tetravalent TREM2 agonistic antibody reduced amyloid pathology in a mouse model of Alzheimer's disease. Sci Transl Med 14:eabq0095.

Zhao X, Kotilinek LA, Smith B, Hlynialuk C, Zahs K, Ramsden M, Cleary J, Ashe KH (2016) Caspase-2 cleavage of tau reversibly impairs memory. Nat Med 22:1268-1276.

Zheng J, Tian N, Liu F, Zhang Y, Su J, Gao Y, Deng M, Wei L, Ye J, Li H, Wang JZ (2021) A novel dephosphorylation targeting chimera selectively promoting tau removal in tauopathies. Signal Transduct Target Ther 6:269.

Zhong L, Chen XF, Wang T, Wang Z, Liao C, Wang Z, Huang R, Wang D, Li X, Wu L, Jia L, Zheng H, Painter M, Atagi Y, Liu CC, Zhang YW, Fryer JD, Xu H, Bu G (2017) Soluble TREM2 induces inflammatory responses and enhances microglial survival. J Exp Med 214:597-607.

Zhou Q, Li S, Li M, Ke D, Wang Q, Yang Y, Liu GP, Wang XC, Liu E, Wang JZ (2022) Human tau accumulation promotes glycogen synthase kinase-3β acetylation and thus upregulates the kinase: a vicious cycle in Alzheimer neurodegeneration. EBioMedicine 78:103970.

Zhu B, Liu Y, Hwang S, Archuleta K, Huang H, Campos A, Murad R, Piña-Crespo J, Xu H, Huang TY (2022) Trem2 deletion enhances tau dispersion and pathology through microglia exosomes. Mol Neurodegener 17:58.

Zhu H, Zhang W, Zhao Y, Shu X, Wang W, Wang D, Yang Y, He Z, Wang X, Ying Y (2018) GSK3β-mediated tau hyperphosphorylation triggers diabetic retinal neurodegeneration by disrupting synaptic and mitochondrial functions. Mol Neurodegener 13:62.

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