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Review article

Molecular and environmental drivers of tau post-translational modifications and tau pathology

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ABSTRACT

Tau is an intrinsically disordered protein that functions to support cytoskeletal stability by binding microtubules in neuronal axons. While tau is involved in healthy neuronal function, it can become pathogenic by forming protein aggregates leading to neurologic diseases collectively known as tauopathies, which include Alzheimer's disease, frontotemporal dementia, and chronic traumatic encephalopathy. Post-translational modifications, including phosphorylation, glycosylation, acetylation, methylation, ubiquitination, and protein truncation are molecular drivers that promote tau aggregation and subsequent disease development. There is a growing, but incomplete, understanding of the complex crosstalk that occurs among distinct modifications and how they orchestrate tau pathogenesis in concert. The drivers of tau post-translational modifications are not fully understood, but environmental factors, such as traumatic brain injuries, microbial infections, alcohol abuse, chronic stress, and heavy metal pollutants, increase risk of tau pathology formation. In this article we review the current literature describing the molecular changes that increase tau aggregation propensity, the environmental factors that promote those changes, and the multifactorial crosstalk that modulates tau pathogenesis. Our goal is to outline the biological pathways and molecular factors that drive tau pathogenesis in order to identify potential points of behavioral and/or therapeutic intervention for tauopathies.

1. Introduction

Tau is a microtubule-associated protein that is primarily found within the axonal region of neurons (Barbier et al., 2019; Binder et al., 1985). In the Central Nervous System (CNS), alternative splicing of exons 2, 3, and 10 yields 6 distinct low molecular weight isoforms of approximately 35–50 kDA. These isoforms are referred to by the number of N-terminal inserts (0 N, 1 N, or 2 N) and C-terminal microtubule-binding repeat domains (3 R or 4 R). The longest low molecular weight isoform of tau includes exons 2, 3, and 10 (2N4R) while the shortest isoform excludes all three exons (0N3R). The 2N4R isoform contains 441 amino acids that comprise multiple functional domains that include an N-terminal domain, proline rich domain, microtubule binding domain, and C-terminal domain (Fig. 1**A**). Under physiologic conditions tau binds microtubules, providing structural support and facilitating their dynamic instability (Barbier et al., 2019; Didonna, 2020). In addition to the six CNS-enriched low molecular weight isoforms, a high molecular weight species known as "big tau" is preferentially expressed in the peripheral nervous system (PNS). This isoform ranges from 95 to 110 kDA due to the inclusion of exon 4 A (Fischer and Baas, 2020). The longer isoform of big tau is well suited to maintain axonal stability and resist mechanical stress incurred by the incredibly long axons of the PNS (Fischer and Baas, 2026).

In healthy neurons tau is found in its monomeric form as an intrinsically disordered protein; however, in disease tau adopts a cross-beta sheet structure, promoting its self-aggregation and assembly of pathogenic paired-helical filaments (PHFs). Tau aggregates are neurotoxic and have been implicated in numerous neurodegenerative diseases. There are approximately 25 neurodegenerative diseases, collectively known as tauopathies, that are defined by the presence of tau aggregates. The most common tauopathy is Alzheimer's disease (AD), which affects approximately 6 million Americans. However, tauopathies comprise a family of disorders that can be caused by specific familial mutations (e.g., frontotemporal dementia with parkinsonism−17 (FTDP−17)), environmental factors (e.g., chronic traumatic encephalopathy (CTE)), or unknown/mixed etiology (e.g., cortical basal degeneration (CBD)) in addition to AD. Many factors such as post-translational modifications (PTMs) and proteolytic cleavage contribute

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to tau aggregation and promote the formation of neurofibrillary tangle pathology.

Numerous PTMs, including phosphorylation, O-glycosylation, acetylation, methylation, and ubiquitination, regulate both the normal and pathologic functions of tau (Fig. 1**B**)[1]. Tau stabilizes microtubules by suppressing the intrinsic dissociation of tubulin dimers from the microtubule ends. This stabilization occurs through transient, 'kiss-and-hop' interactions among multiple microtubule polymers, with each interaction lasting only about 40 ms, which maintains structural stability without impeding axonal transport (Janning et al., 2014). It has long been recognized that tau phosphorylation slows microtubule polymerization by lowering the affinity of tau for microtubules (Biernat et al., 1993; Drechsel et al., 1992; Lindwall and Cole, 1984). In line with the "kiss-and-hop" model, phosphorylation may disrupt the dynamic equilibrium of tau with microtubules, reducing the "on" time and/or increasing the "off" time, ultimately disturbing these microtubule kinetics (Janning et al., 2014). In many tauopathies tau becomes hyperphosphorylated, decreasing its binding affinity for microtubules, elevating the levels of unbound tau, and increasing its aggregation propensity (Gao et al., 2018). In addition, proteolytic cleavage of tau contributes to altered microtubule interactions as well as aggregation by creating peptide products that are prone to form the aberrant cross-beta sheet structure and self-associate into fibrils (Conze et al., 2022).

Beyond the cell-autonomous effects on tau aggregation, PTMs serve as a critical determinant of its transcellular propagation and templated aggregation. It is now well established that tau aggregates can escape from a diseased neuron, enter an adjacent or synaptically connected neuron, and convert monomeric tau to an oligomeric seed through templated conformational change (Holmes and Diamond, 2014). Prior work has shown that therapeutic antibodies may target tau in the extracellular space, preventing its internalization and propagation by neighboring neurons and promoting its uptake and clearance by resident microglia (Funk et al., 2015); however, specific PTMs can impact each step of this process, ultimately affecting the ability of these aggregates to seed pathology.

Preclincial studies demonstrate that PTMs actively modulate the secretion, internalization, and conformational change of the seeding process, though the precise effects are complex. For example, cultured cells secrete tau through a sulfated proteoglycan-dependent mechanism that preferentially favors pseudo-phosphorylated tau, in which specific Ser/Thr residues are mutated to Asp to mimic phosphorylation (Katsinelos et al., 2018). Similarly, when distinct tau species were isolated from TgP301S transgenic tau mice, their seeding potency directly correlated with the abundance of large phosphorylated (Ser202/Thr205/Ser396/Ser404) and nitrated (nY29) tau species, whereas small oligomers (<10-mers) were less seed-competent (Jackson et al., 2016). In contrast, Dickson et al. used AD-relevant PTM-mimetics, including both pseudo-phosphorylation mutants and pseudo-acetylation mutants, in which specific Lys residues were mutated to Gln. Unexpectedly, the PTM-mimetic proteins showed reduced tau propagation compared to the wildtype protein, potentially due to impaired binding to tau uptake receptor LRP1 (Dickson et al., 2025).

These PTM-driven variations may stem from structural "strains," as the precise nature of these oligomeric seeds vary among distinct tauopathies (Vaquer-Alicea et al., 2021). Aggregates that accumulate in seeded cells remain structurally similar to the original seed, indicating templated conformational changes (Kaufman et al., 2016; Sanders et al., 2014; Tarutani et al., 2021). Cryo-EM and biochemical data indicate that these unique filament structures are defined, in part, by the composite PTM profile with disease-specific PTMs consistently localizing within and around the filament core (Arakhamia et al., 2020; Tarutani et al., 2023). Translating these insights to medicine, clinical data increasingly support the trans-cellular propagation hypothesis as several tau-directed immunotherapies specifically targeting these seed-competent or PTM-defined proteoforms have recently shown promising efficacy in human clinical trials (Courade et al., 2025).

Environmental factors including traumatic brain injuries (TBIs), microbial infections, chronic alcohol abuse, substance abuse, chronic stress, and pollutant exposure) promote tau alterations via PTMs and cleavage. These modifications increase the risk of pathogenic aggregate formation, ultimately driving the pathogenesis of Alzheimer's disease (AD) and other tauopathies. Here we review the current literature on the most significant PTMs that influence tau function and discuss the environmental risk factors that impact those modifications, promoting tau pathogenesis.

2. Molecular factors contributing to tau pathogenesis

PTMs play an important role in altering the function of tau and its interactions with other cellular components. Common PTMs that contribute to regulating tau's interactome include lysine acetylation, methylation, and ubiquitination as well as serine/threonine O-glycosylation and phosphorylation and less commonly, tyrosine phosphorylation. These PTMs, in concert with proteolytic cleavage, contribute to the regulation of tau both independently and in dynamic crosstalk amongst one another. Although necessary for modulating homeostatic function of tau, PTMs can also contribute to tau misfolding, self-aggregation, and ultimately, neuronal dysfunction and degeneration (Fig. 2).

2.1. Phosphorylation

Tau phosphorylation is the most well-studied PTM involved in altering tau's interactions with microtubules as well as promoting pathogenesis and has been extensively reviewed by others (Buée et al., 2000; Gómez-Ramos et al., 2004; Lindwall and Cole, 1984; Wegmann et al., 2021). Tau can be highly phosphorylated with over 80 potential phosphorylation sites located throughout the protein. While

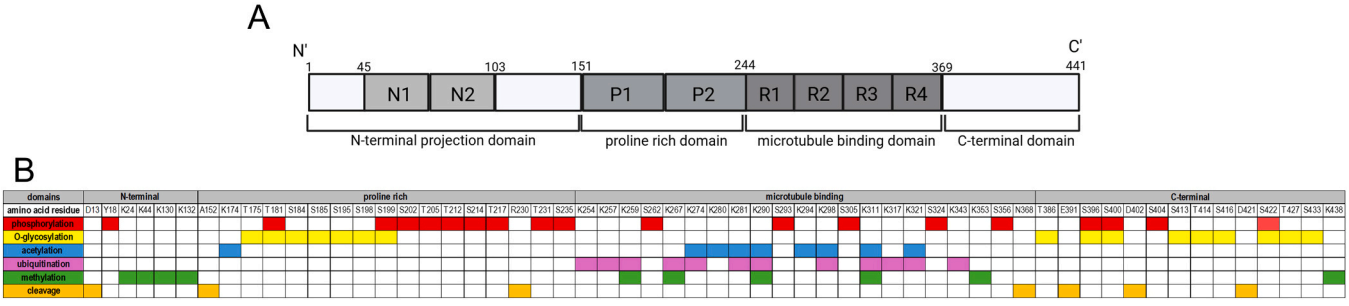

Fig. 1. Summary of tau PTMs. A) Tau protein isoforms are determined by the number of N-terminal inclusions (0 N, 1 N, or 2 N) and the number of microtubule binding repeats (3 R or 4 R). Distinct regions impact its homeostatic and pathologic protein functions. B) Tau PTMs include phosphorylation, O-glycosylation, acetylation, ubiquitination, methylation, and proteolytic cleavage, which span the length of tau protein. Specific sites of modification discussed in this review are identified.

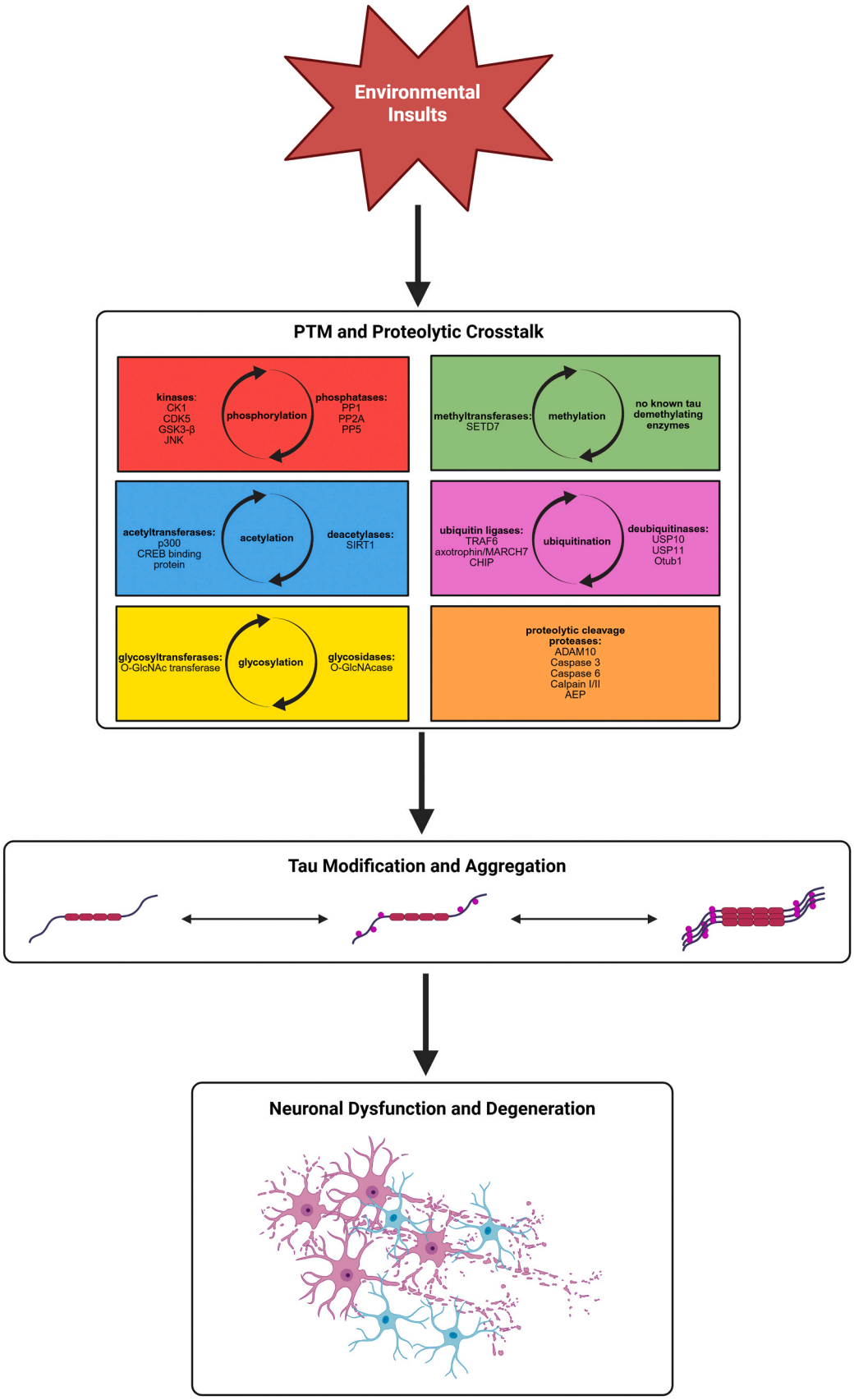

Fig. 2. PTM crosstalk modulates tau aggregation and neurodegeneration. Environmental factors reviewed here alter PTM levels individually and in concert through activation and inhibition of specific modifying enzymes. The compilation of tau modifications alters the aggregation propensity of the protein, potentially leading to neuronal dysfunction and degeneration.

post-mortem samples from healthy human brain tissue contain ~3 mol phosphate per mol tau, brain tissue samples from individuals with AD contain up to 9 mol phosphate per mol tau (Alonso et al., 1994). This correlates with an expansion in the number of phosphorylation sites. Tau from cognitively healthy human brains is phosphorylated on approximately 10 distinct amino acid residues, whereas tau from AD-affected brains are phosphorylated on approximately 45 different residues (Noble et al., 2013).

Kinases and phosphatases collectively contribute to the addition and removal of phosphate groups to proteins, respectively. The most well studied kinases involved in tau phosphorylation include casein kinase 1 (CK1), 5' adenosine monophosphate-activated protein kinase (AMPK), cyclin dependent kinase 5 (CDK5), and glycogen synthase kinase−3 (GSK−3), but many more may also contribute to some degree(Noble et al., 2013). There are fewer known tau phosphatases, which include protein phosphatase−1, −2A, and −5 (PP1, PP2A, and PP5) (Liu et al., 2005). Analysis of AD brains showed a decrease in the activity of PP2A by 50% and that of PP5 by 20% compared to control brains, which may contribute to tau hyperphosphorylation (Liu et al., 2005).

Phosphorylation normally regulates the physiologic function of tau in microtubule binding and stabilization; however, in diseased states tau can become hyperphosphorylated. The term "hyperphosphorylation" refers to both the collective elevation of phosphorylation levels spanning the protein as well as phosphorylation of certain amino acid residues that dramatically impact its structure and function. Most phosphorylation sites are within tau's proline rich and C-terminal domains; however, other phosphorylation sites have been identified within the N-terminal and microtubule binding domains, leading to differential regulation. For example, phosphorylation of T231 and S235 (p-T231 and p-S235, respectively), located within the proline rich region, as well as S262, in the microtubule binding domain, inhibit tau-microtubule interactions (Sengupta et al., 1998). Phosphorylation at these specific sites along with elevated phosphorylation levels across the span of the protein are thought to be a major driver of tau aggregation.

Traditionally, antibodies that recognize specific phosphorylated sites have been used by clinicians and researchers to identify tau aggregates in postmortem brain samples for definitive diagnosis and staging of disease. Gold standard antibodies include AT8 and AT100, which recognize the dual phosphorylation sites p-S202/p-T205 and p-T212/p-S214, respectively. These sites appear to be involved in destabilizing tau-microtubule interactions leading to tau aggregation (Noble et al., 2013). More recent work has identified p-T181 in the cerebrospinal fluid (CSF) as an additional disease-associated site of hyperphosphorylation that is now being used clinically to diagnose AD (Lifke et al., 2019). In a major breakthrough for the field, p-T181 and p-T217 were detected in the blood of patients with AD (Karikari et al., 2020; Palmqvist et al., 2024). Although not yet used for routine screening for AD, these diagnostic markers are increasingly being used in clinical research settings. Although there is some data to indicate that p-T217 may be able to distinguish AD from other tauopathies, such as primary age-related tauopathy (PART) (Yu et al., 2023), there is little research investigating blood-based biomarkers across the range of tauopathies (Iqbal et al., 2005). Identifying additional disease-specific modification sites will be of great importance in the development of new biomarkers that facilitate early detection of AD and other tauopathies.

2.2. O-glycosylation

O-GlcNAcylation is a specific form of intracellular O-glycosylation that is defined by the addition of β-D-N-acetylglucosamine (GlcNAc) to serine and threonine residues via an O-linkage (Wani et al., 2017). This modification is dynamically regulated by O-GlcNAc transferases (OGT), which are responsible for the addition of GlcNAc, and O-GlcNAcases (OGA), which remove GlcNAc from these residues (Wani et al., 2017). O-GlcNAcylation has garnered increasing interest because it competes for the same serine and threonine residues targeted by kinases for phosphorylation (Liu et al., 2004).

Recent mapping of the 2N3R and 2N4R isoforms identified several O-GlcNAcylation sites, including T175, T181, S400, S413, T414, S416, S422, T427, and S433 (Alhadidy et al., 2025). Although many O-GlcNAcylation sites were shared between 2N3R and 2N4R isoforms, some isoform-specific modifications were found. GlcNAc modifications specific to 2N4R included S184, S185, S195, S198, S199 while modifications specific to 2N3R included T386 and S396 (Alhadidy et al., 2025). Functionally, GlcNAc-modified 2N3R and 2N4R isoforms showed lower aggregation propensity compared to their unmodified counterparts, highlighting the presumably protective role of this modification (Alhadidy et al., 2025).

Modulating tau O-GlcNAcylation levels may be leveraged to alter tau phosphorylation, and ultimately pathogenesis. In a mouse model in which food was withheld, mice showed lower levels of brain glucose uptake, decreased tau O-GlcNAcylation, and increased tau phosphorylation, mimicking results seen in human AD patients (Liu et al., 2004). As a potential therapeutic, rTg4510 mice that overexpress human tau containing a P301L mutation were treated with an OGA inhibitor (MK−8719), which successfully increased levels of O-GlcNAc in the brain and reduced pathologic tau aggregation and brain atrophy (Wang et al., 2020). Collectively, these data suggest that O-GlcNAcylation of tau protects against neurodegeneration by blocking aggregation-promoting phosphorylation. Further exploration of strategies to exploit O-GlcNAc modifications on tau may provide new targets to reduce or prevent tau phosphorylation and subsequent aggregation.

2.3. Acetylation

In addition to phosphorylation, tau is post-translationally modified through acetylation of lysine residues, primarily within the microtubule binding domain (Ye et al., 2022). Lysine acetylation shifts the net charge of this residue from positive to neutral, ultimately impacting interactions between proteins as well as downstream signaling pathways (Alquezar et al., 2021). Acetyltransferases and deacetylases are responsible for the addition and removal of acetyl groups to protein lysine residues, respectively. Although less well studied than phosphorylation, several enzymes have been found to acetylate and deacetylate tau, including p300 and CREB binding protein (CBP), which were originally described as histone acetyltransferases, and SIRT1 deacetylase (Min et al., 2010). Additionally, there is evidence to suggest that tau harbors intrinsic auto-acetylation activity coupled with auto-proteolytic activity (Cohen et al., 2016, 2013).

In general, acetylation increases tau pathogenicity directly by reducing protein turnover and increasing self-aggregation, as well as indirectly through crosstalk with other PTMs (Min et al., 2010); however, data indicate that this depends on many factors, such as the specific amino acid residue and protein isoform (Chakraborty et al., 2023). Individuals with early (Braak stages 1–2) to moderate (Braak stages 3–4) tau pathology showed increased tau acetylation relative to healthy controls (Braak stage 0) (Min et al., 2010). More specifically, acetylation at K280 (ac-K280) was increased in AD and CTE patients, likely promoting tau aggregate formation and leading to neuronal death and cognitive dysfunction (Lucke-Wold et al., 2017; Min et al., 2015). Tau aggregation is driven by amyloidogenic motifs ^{275}VQIINK^{280} and ^{306}VQIVYK^{311}, referred to as PHF6* and PHF6, which are localized within the microtubule binding domain (Nizynski et al., 2017). Notably, acetylation of K280 and K311, which conclude each of these motifs, stabilized the tau fibril structure, thus promoting aggregation (Li et al., 2023). Acetylation of K174 was also shown to enhance neurotoxicity by promoting tau aggregation and reducing tubulin polymerization *in vitro* (Rane et al., 2019). Additionally a recent study using PS19 mice, which harbor the FTDP−17-associated P301S tau mutation, showed that ac-K174 promoted tau accumulation and impaired spatial working memory (Min et al., 2015).

While most studies indicate that lysine acetylation promotes tau

aggregation, acetylation of specific residues may prevent aggregation in certain tauopathies. Pick's disease is unique in that its aggregates are composed of 3 R tau, rather than exclusively 4 R tau as in CBD and PSP or a mixture of 3 R and 4 R tau as in AD. The structure that tau adopts is also distinct to the disease, thus altering the impact of lysine acetylation (Falcon et al., 2018). Using a cofactor-free *in vitro* acetylation reaction with recombinant 3 R and 4R tau followed by high resolution mass spectrometry, Chakraborty et al. found three acetylated lysine residues (ac-K290, ac-K294, and ac-K298) located within the second microtubule repeat domain and thus, excluded from the 3R isoforms (Chakraborty et al., 2023). Introducing acetyl-lysine mimics at K294 and K298 delayed fibrillization of 4R tau, but introducing an acetyl-lysine mimic in 3R tau accelerated fibrillization (Chakraborty et al., 2023). These data provide evidence that lysine acetylation within the second repeat domain of 4R tau may be protective against aggregate formation, thus selectively favoring accumulation of 3R tau (Chakraborty et al., 2023). This was further investigated using a cellular model of seeded aggregation in which HEK293 cells expressed 0N4R tau with the P301L mutation. Smith et al. tested the impact of various acetyl-mimetic or acetyl-null mutations within the core fibril domain on templated aggregation by either AD or PSP patient samples. Their results showed that these acetyl mutants did not significantly impact the templated aggregation of tau (Smith et al., 2025). However, whether other genetic alterations or tau constructs beyond the 0N4R isoform with the P301L mutation respond to acetylation differently is not yet known, and the molecular and cellular components that drive these differences in site-specific modifications remain to be tested.

In addition to the direct role of lysine acetylation in promoting tau misfolding and aggregation, tau acetylation can indirectly promote protein accumulation through altered degradation. Tau can be degraded through both the ubiquitin-proteosome system (UPS) and autophagic systems (Dennissen et al., 2012; Lee et al., 2013). Autophagic pathways include bulk degradation by macroautophagy and selective degradation by chaperone-mediated autophagy (CMA) and endosomal microautophagy. Both CMA and endosomal microautophagy are mediated by heat shock cognate 70 (HSC70) interacting with a protein's KFERQ-like motif. In CMA, KFERQ-containing proteins are translocated across the lysosome membrane (Dice, 1990), while in endosomal microautophagy proteins are engulfed by invaginated lysosomal membrane (Sahu et al., 2011). Tau contains two KFERQ-like motifs (^{336}QVEVK^{340} and ^{347}KDRVQ^{351}) that target it to CMA and/or microautophagy degradation (Wang et al., 2009). When unmodified, tau can be degraded by CMA; however, introduction of tau acetylation mimetics (K174Q and K274Q mutations) inhibited the CMA process, and tau was instead degraded by macroautophagy and microautophagy (Caballero et al., 2021). This inhibitory effect of ac-tau on CMA caused it to be redirected through the endosomal pathway and released extracellularly, promoting its pathogenic spread through the brain and further disease progression (Caballero et al., 2021). Collectively, these studies show that tau acetylation contributes to pathogenesis through multiple distinct but complementary mechanisms.

2.4. Ubiquitination

Ubiquitin is a small, 76 amino acid protein that is covalently added to lysine residues through a series of enzymatic reactions. The enzymes involved in the ubiquitination process include a ubiquitin activating enzyme (E1), ubiquitin conjugating enzyme (E2), and ubiquitin protein ligase (E3) (Hershko and Ciechanover, 1998). Deubiquitinases, including USP10, USP11, and Otub1, remove ubiquitins from lysine residues of tau and other proteins (Wang et al., 2017; Yan et al., 2022). Lysine residues can be mono-ubiquitinated or poly-ubiquitinated, resulting in diverse ubiquitin chains that drive distinct biological functions. Ubiquitination is well known to promote protein degradation via both the proteasomal and autophagic systems, but it can also impact tau function in other ways (Lee et al., 2013). Tau ubiquitin ligases include TNF receptor-associated factor 6 (TRAF6), axotrophin/MARCH7, and the HSC70-interacting protein (CHIP) complex (Babu et al., 2005; Flach et al., 2014). CHIP is the most well-studied tau ubiquitinase, targeting tau for proteasomal degradation (Petrucelli et al., 2004). CHIP was found to ubiquitinate at least 12 lysine residues of a recombinant peptide fragment comprising the four repeat domain (4RD amino acid residues 244–372, referred to as K18) (Parolini et al., 2023), many of which were also found to be modified in AD patients (Wesseling et al., 2020); however, the sites of ubiquitination can differ between the monomeric and fibrillized forms of tau. More specifically, increased ubiquitination was found in insoluble tau from post-mortem AD samples compared to control samples on amino acid residues K254, K257, K259, K267, K274, K281, K290, K298, K311, K317, K321 and K343, all of which fall within the microtubule binding domain (Wesseling et al., 2020).

To compare the functional effect of ubiquitination on tau aggregation, Parolini et al. compared the 4RD recombinant peptide, which forms fibrils only when induced, versus a shorter peptide fragment comprising the fibril core (amino acid residues 297–391), which forms fibrils more structurally similar to the pathologic fibrils found in AD. Their results showed that fibrillized tau had lower levels of ubiquitination, specifically at amino acid residues that would likely be inaccessible when in a cross-β structure. Furthermore, this ubiquitination did not limit the ability of tau to seed further aggregation *in vitro* (Parolini et al., 2023). In fact proteomic analysis of tau PTMs indicated that while acetylation and ubiquitination were both observed in tau aggregates, ubiquitination was unique to seed-competent tau, whereas acetylation was observed in both seed-competent and -incompetent tau forms (Wesseling et al., 2020). Altered ubiquitination of tau plays a critical role in the formation and reduced clearance of tau aggregates contributing to tau pathogenesis alongside other PTMs.

2.5. Methylation

In addition to acetylation and ubiquitination, lysine residues can also become methylated through the addition of mono-, di-, and tri-methyl groups by methyltransferases. As of now, the only known tau methyltransferase is SETD7 (Bichmann et al., 2021), and no demethylating enzymes have been identified for tau; however many methylating and demethylating enzymes are known to modify histone proteins (Husmann and Gozani, 2019). In general, less is known about the impact of methylation on tau's homeostatic or pathogenic functions compared with other PTMs described above. Mass spectrometry analysis of tau isolated from cognitively healthy human brains found 11 methylated lysine residues (Funk et al., 2014). In comparison, only 7 of the 11 potential methylation sites were found to be methylated on paired helical filament (PHF) tau isolated from AD brain; however, it is important to note that these analyses were done independently (Thomas et al., 2012). A more direct comparison between cognitively healthy and AD conditions was achieved by analyzing tau from cognitively normal middle aged individuals, cognitively normal elderly individuals, and those with AD (Huseby et al., 2019). Huseby et al. showed that methylation stoichiometries were highest in the cognitively normal middle aged group (~1 mol methyl group per mol tau), and lowest in the AD group, which was not statistically different from a zero methylation stoichiometry (Huseby et al., 2019). Although this trend agrees with prior hypotheses that tau methylation depresses aggregation and its loss during aging and disease facilitates pathogenesis, even at the highest levels of methylation (the cognitively normal middle aged group), total methylation stoichiometry was less than what was previously found to significantly lower tau aggregation propensity (Funk et al., 2014). Altogether, these data support methylation as a physiological PTM of tau but may indicate that its impact on pathogenesis is due to site-specific modifications rather than bulk methylation stoichiometry.

Unlike tau phosphorylation, which primarily occurs on the regions flanking the microtubule binding domains, tau methylation is enriched within the microtubule binding domains at sites that include K259,

K290, K311, and K353 (Funk et al., 2014). Each of these residues were found to be methylated in cognitively normal but not AD-affected samples (Funk et al., 2014; Thomas et al., 2012). Notably, K311 lies within the "PHF6" motif that mediates tau aggregation propensity (Li and Lee, 2006), and K259, K290, and K353 each lie within "KXGS" motifs that regulate microtubule binding (Yoshida and Goedert, 2012), each of which can also be acetylated and ubiquitinated as described above. Within the cognitively normal middle aged and elderly cohorts, mono-methylation of K259 and mono- or di-methylation of K267 were the most consistent methyl-lysine modifications. Another study extracted detergent-soluble tau from human brains with AD (Braak stages III-IV) and control (Braak stages 0-I) and identified novel sites of methylation by mass spectrometry (Bichmann et al., 2021). This analysis identified K130, K132, and K438 as consistent sites of mono-methylation in both AD and control groups (Bichmann et al., 2021). Using an antibody raised against these methylation sites, Bichmann et al. found increased levels of methylation at K130 and K132 in both soluble and insoluble fractions in brain tissue from individuals with more advanced disease (Braak stages V-VI) compared with either stages (0-II or III-IV) (Bichmann et al., 2021). These results were supported by experimental data using rTg4510 transgenic mice, which showed an increase in K130 and K132 methylation as tau pathology progressed (Bichmann et al., 2021). Interestingly, tau with methylated K130 and K132 residues were found to be predominantly nuclear and may point to methylation regulating subcellular localization (Bichmann et al., 2021). Together, these data support the hypothesis that tau methylation regulates its pathogenesis via direct and indirect mechanisms.

2.6. Proteolytic cleavage of tau

Alongside biochemical modifications to the amino acid side chains, tau can be proteolytically cleaved resulting in peptide fragments of various lengths, which are thought to contribute to disease progression by increasing tau aggregation (Friedrich et al., 2021; Mondragón-Rodríguez et al., 2008). The amyloid core of the tau aggregate is a 12 kDa fragment that comprises the microtubule binding domain ending at E391 (Kolarova et al., 2012; Novak et al., 1993). This has been modeled in cell culture and cell-free systems by genetically deleting parts of the protein and assessing pathogenic functions such as aggregation, hyperphosphorylation, and templated seeding. Results showed that the I151-E391 peptide, which comprises the proline-rich and the microtubule repeat domains, was the most pathologically active (Gu et al., 2020). ADAM10 is capable of cleaving tau after A152 to generate the peptide fragment studied *in vitro*, and calpain I/II can cleave after R230 to form the *in vivo* amyloid core, but no protease has been identified that can cleave at the E391 locus (Gu et al., 2020). A variety of other proteases have been found to cleave tau including asparagine endopeptidases (AEP) and caspases, among many others (Quinn et al., 2018).

Lysosomal protease legumain (LGMN) is the mammalian form of AEP that cleaves the C-terminal side of asparagine sites on proteins. This protease has been implicated as a driving factor of tau cleavage promoting aggregate formation. An increase in LGMN promotes cleavage of tau at N368 in both transgenic PS19 mice and AD brain samples relative to controls. *In vitro* studies showed that tau fragment 1–368 that is produced by LGMN cleavage was neurotoxic when expressed in neurons (Zhang et al., 2014).

Caspases, a group of cysteine-aspartic proteases, are well associated with inflammation and cell death pathways (Theofilas et al., 2024). In addition to these canonical functions, caspases can promote tau proteolysis. Caspase−3 cleaves tau at D421, producing a truncated form known as TauC3, which is increased in AD patient samples relative to healthy controls (Conze et al., 2022). Most research on tau PTMs has focused on their gain-of-function effects promoting aggregation, or to a lesser extent, their loss-of-function effect of lowering microtubule affinity and stability. In contrast, TauC3 exhibited toxic gain-of-function effects through increased microtubule affinity. In reference to the "kiss-and-hop" dynamic typical for tau-microtubule interactions, this increased "on" time impaired microtubule transport of mitochondria and APP-containing vesicles, resulting in dendritic atrophy of CA1 neurons in an organotypic hippocampal slice culture model (Conze et al., 2022).

Additionally, caspase−6 has been shown to drive the development of neurodegenerative diseases like AD depending on the site of proteolytic cleavage on tau (Foveau et al., 2016). Using post-mortem human brain tissue from individuals separated into three groups based on cognitive function (non-cognitively impaired (NCI), mild cognitively impaired (MCI), and AD), activated caspase−6 was shown to positively correlate with tau but not amyloid pathology in the anterior olfactory nucleus (Foveau et al., 2016). Specific caspase−6 cleavage sites include D13, D402, and D421 (Gamblin et al., 2003; Guo et al., 2004; Horowitz et al., 2004), and tau cleavage at D421 was shown to increase the rate and degree of tau filament assembly in vitro (Gamblin et al., 2003). On the contrary, LGMN was found to cleave endogenous mouse tau *in vitro* and *in vivo* at N368, however, LGMN cleavage of tau was not found to change between control and AD samples. A small portion of cleaved N368 tau was found in the insoluble extract of AD samples but was not statistically higher than insoluble extracts of control samples (Schlegel et al., 2019). Although several studies connect protease activity with tau truncation, aggregation, and pathology, the mechanisms that drive this activity are not well understood.

2.7. Post-translational modification crosstalk

While individual PTMs result in functional changes to tau, these modifications do not occur in isolation. Rather tau is regulated by numerous PTMs and proteolytic cleavages simultaneously that function coordinately to impact aggregation and pathogenesis. As noted above, there is competition for serine and threonine residues between phosphorylation and O-glycosylation while lysine residues are subject to competing PTMs, and the differential addition of acetyl, methyl, and ubiquitin groups have distinct impacts on tau function. Furthermore, the addition of one modification may affect the addition of a second modification. As an example, tau has intrinsic auto-acetylation capability at K280, which promotes auto-proteolysis at two hypothesized cleavage sites within the second and fourth microtubule binding domains (Cohen et al., 2016). Additionally residues K24 and K44 are subject to methylation, and considering their close proximity to putative caspase and calpain cleavage sites, it is possible that their modification may impact protease activity or site recognition (Funk et al., 2014). In AD brain tissue sections, phospho-dependent antibody staining at S202/T205, S396, and S422 colocalized with tau cleavage at D421 and conformation-dependent antibody Alz−50 in a manner that suggested that truncation and conformational changes occur following phosphorylation events (Mondragón-Rodríguez et al., 2008). A more direct association was found in AEP, an endopeptidase that was found to cleave both tau and the PP2A inhibitor I_2 (Basurto-Islas et al., 2013). Thus, AEP activity promotes tau pathogenesis two-fold: through protein truncation and inactivation of an important tau phosphatase (Basurto-Islas et al., 2013).

In addition to the direct impact of lysine acetylation on tau aggregation, it may also influence surrounding PTMs including neighboring phosphorylation sites and competing lysine modifications. Within each microtubule binding repeat region lies a KXGS motif, in which a lysine residue (K259, K290, K321, and K353) is adjacent to a serine residue (S262, S293, S324, and S356), phosphorylation of which regulates microtubule binding and self-assembly (Yoshida and Goedert, 2012). Ajit et al. showed that acetylation of K321 inhibited phosphorylation of adjacent S324 leading to decreased tau aggregation (Ajit et al., 2019). However, using a cell culture model of seeded aggregation, Smith et al. showed that phosphorylation at S305 is a critical determinant of templated aggregation by AD-specific tau seeds but not PSP-specific tau

seeds (Smith et al., 2023). More recently they showed that the inclusion of acetyl-mimetics in addition to the phospho-mimetic slightly increased the seeding responsiveness to PSP-tau seeds. These data indicate that while phosphorylation and acetylation occur together, phosphorylation is a stronger driver of strain specificity than acetylation, which is likely a secondary modifier of filament structure (Smith et al., 2025). Hierarchical clustering analysis of quantitative proteomics data suggest a cascade of PTM additions, starting with phosphorylation in the proline rich region, followed by acetylation and ubiquitination in the microtubule binding domain as the disease progresses (Wesseling et al., 2020). The dynamic relationships among PTMs, tau truncation, and tau pathology are likely to be complex and still largely unknown. Further research is necessary to understand the role of PTM crosstalk on tau truncation and pathogenesis.

3. Environmental factors that contribute to tau PTMs and pathogenesis

Although genetic mutations can contribute to the development of various tauopathies, they are generally considered to be rare (Langerscheidt et al., 2024). Rather, environmental factors, and their intersection with genetic modifiers, are increasingly recognized to drive the initiation of tau pathology (Chornenkyy et al., 2019). There are a variety of environmental factors that promote molecular changes to tau, such as the PTMs and proteolytic cleavage described above. These environmental risk factors include traumatic brain injuries, microbial infection, chronic alcohol abuse, broader substance abuse, chronic stress, and environmental pollutants. Evidence suggests that exposure to these environmental factors promote the development of tau pathology, leading to irreversible damage and neurodegeneration (Fig. 2). In this section, we discuss the interaction between environmental factors and molecular changes that drive tau aggregation.

3.1. Traumatic brain injuries

Traumatic Brain Injury (TBI) results from the rapid movement of the brain within the skull due to an external force. Common causes of TBIs include contact sports, motor vehicle collisions, and accidental falls. Epidemiologic data have established TBIs as a significant risk factor for the development of tauopathies (Hay et al., 2016). Consecutive TBIs lead to cellular changes, such as axonal damage and increased astrocyte reactivity, as well as cognitive impairments, including memory dysfunction (Prins et al., 2011).

The use of tau transgenic PS19 mice has revealed specific molecular and cellular changes that occur following various models of TBI. Using a model of controlled cortical impact, Edwards et al. showed that brain injury accelerated tau hyperphosphorylation and aggregation *in vivo* (Edwards et al., 2020). Additionally, spatial learning and long-term memory were compromised following the TBI. A progressive increase in tau hyperphosphorylation was found in both the cortex and hippocampus throughout the 6-month study period, establishing the long-term effects of TBIs on tauopathy progression (Edwards et al., 2020). Comparing a single brain injury versus repetitive brain injuries revealed differences in the morphology of tau aggregates. Tau oligomers isolated from wildtype mice that experienced a single mild TBI using a blast model differed from those isolated following repetitive mild TBI blasts. Tau oligomers isolated from repetitive TBI blasts induced neurotoxicity, impaired long-term potentiation, and decreased synaptic marker levels when applied to primary neurons and ex vivo brain slice cultures (Bittar et al., 2019). When injected into the brains of C57BL/6 J wildtype mice, tau oligomers from both single and repetitive mild TBI blasts promoted tau hyperphosphorylation and aggregation in the hippocampus of recipient mice, but only tau oligomers from repetitive TBI blasts induced cognitive and motor deficits. Specifically, phosphorylation at Y18, S202, and T205 was elevated in mice injected with tau oligomers from either single TBI or repetitive TBI mice (Puangmalai et al., 2024).

In a separate multimodal TBI study, investigators tested the effect of concussive injury, early-phase blast wave exposure, and controlled cortical impact on tau pathogenesis in wildtype mice. Results showed that brain injury promoted an increase in acetylation of endogenous mouse tau at K263 and K270 (corresponding with human tau sites K274 and K281) in the cerebral cortex and hippocampus but no increase in tau phosphorylation. Acetylation of K263 and K270 persisted in mice at 17 months following the injury (Shin et al., 2021). Researchers attributed the increase in tau acetylation following the TBI to S-nitrosylation of GAPDH, which promotes the acetyltransferase activity of p300/CBP and inhibits the deacetylase activity of Sirtuin1 (Sirt1). Sirt1 was also shown to have increased levels of S-nitrosylation further inhibiting its activity leading to a net increase in tau acetylation (Shin et al., 2021).

As noted above in relation to TBI crosstalk, AEP increases tau pathogenesis through peptidyl cleavage of both tau and the PP2A inhibitor I_2 (Basurto-Islas et al., 2013). In a controlled cortical impact model, TBI caused I_2 to be mislocalized to the cytoplasm, resulting in AEP activation. This effect was modeled in primary neurons through oxygen-glucose deprivation, which could be limited by treating cells with AENK, a pharmacologic inhibitor of AEP. In further support of this, when rats were given AENK immediately following a TBI, their memory deficits were alleviated and tau pathology was diminished (Liu et al., 2020). Together, these data support the hypothesis that TBIs can cause molecular changes to tau that promote the initiation and progression of degenerative pathology.

3.2. Microbial infection

Emerging epidemiologic data suggests that microbial infections correlate with long-term health consequences, such as AD development (Lotz et al., 2021). A recent study by Levine et al. examined medical records from the Finnish biobank, FinnGen, and from the UK biobank where they determined an association between viral infection and increased risk of neurodegenerative disease (Levine et al., 2023). Across both the FinnGen and UK biobanks, investigators found 22 associations between different viruses and neurodegenerative diseases. More specifically, researchers noted that influenza infection combined with pneumonia was associated with an increased risk of AD (Levine et al., 2023). This study relied on medical records prior to the COVID−19 outbreak and did not have access to patient tissue samples to examine tau biomarkers specifically.

A more recent study examined the pathologic connection between SARS-CoV−2 and AD pathology specifically by analyzing brain tissue samples from individuals who died and were not infected with SARS-CoV−2, died during acute infection, or died following recovery from infection in the 4–13 month range (Qi et al., 2024). Within the acute and recovered SARS-CoV−2 groups, results showed an increase in phosphorylation in both the hippocampus and medial entorhinal cortex relative to the non-infected group, specifically at amino acid residues T181, S199, S202, T205, and T217 (Qi et al., 2024). While this study did not show changes in beta-amyloid deposition or hippocampal neuron numbers (Qi et al., 2024), a plasma biomarker study showed that SARS-CoV−2 infection resulted in changes in beta-amyloid levels and phosphorylation on tau at T181 consistent with AD (Duff et al., 2025). Although full epidemiologic connections between SARS-CoV−2 and AD have not yet been made, changes at the molecular level suggest that SARS-CoV−2 may increase the risk of future AD.

To experimentally examine the impact of viral infection on tau pathogenesis, Sy et. al infected 3xTg-AD mice, which contain three mutations associated with AD, with a neuroadapted mouse coronavirus known as mouse hepatitis virus strain JHM (MHV-JHM) (Sy et al., 2011). Results showed increased tau hyperphosphorylation at amino acids S202 and T205 at both 2 and 4 weeks post-infection relative to the sham control. To model bacterial infection-related chronic inflammation, LPS was injected into 3xTg-AD mice twice weekly for 6 weeks.

Results showed elevated levels of phosphorylation at T212/S214 (AT100) and S396/S404 (PHF−1) following LPS injection relative to saline injected control mice. This hyperphosphorylation was attributed to increased activity of GSK3-β and CDK5/p25 because inhibition of GSK3-β by lithium treatment rescued tau pathology (Sy et al., 2011). Although MHV is a beta-coronavirus similar to SARS-CoV−2, they differ in host specificity, tissue tropism, and neurovirulence. To investigate the impact of SARS-CoV−2 more specifically on tau phosphorylation and aggregation, Di Primio et al. exposed SH-SY5Y neuroblastoma cells and transgenic mice expressing the human ACE2 receptor (K18-*hACE2* mice) to 3 different SARS-CoV−2 strains (Di Primio et al., 2023). The use of transgenic mice expressing the hACE2 receptor is necessary in this experimental paradigm as it facilitates the entry of SARS-CoV−2 into cells more effectively than the native mouse receptor (Liu et al., 2024). Data indicate that infection promotes phosphorylation at S262 and S396 as well as insoluble tau accumulation in SH-SY5Y neuroblastoma cells and K18-*hACE2* mice, though further confirmation of these results are necessary (Di Primio et al., 2023).

Although SARS-CoV−2 has reinvigorated broad interest in the microbial etiology hypothesis, HSV−1 was a primary pathogen of interest prior to the COVID−19 outbreak and had already been shown to promote biochemical changes associated with tau pathology. To investigate this, researchers developed a mouse model of viral reactivation using primary HSV−1 inoculation followed by cycles of thermal stress (De Chiara et al., 2019). Hippocampal tissue lysates from HSV−1 infected mice subjected to seven thermal stress cycles showed an increase in disease-associated tau phosphorylation (at T205, T212, and S214) relative to mock-infected controls (De Chiara et al., 2019). Additionally, using the TauC3 antibody, cleavage at D421 was found to be increased in HSV−1 infected hippocampal tissue, suggesting that HSV−1 infection drives molecular changes that increases the aggregation propensity of tau (De Chiara et al., 2019). Interestingly, this relationship may be bi-directional; recent data from Eimer et al. suggested that tau phosphorylated by GSK3β can bind the HSV−1 viral capsid and block infectivity; however, this potential antiviral defense mechanism needs further validation (Eimer et al., 2026).

In addition to viral infections, bacterial pathogens such as *P. gingivalis* have been associated with AD pathology (Dominy et al., 2019). Intravenous tail vein inoculation of Sprague-Dawley rats with *P. gingivalis* 3 times per week for 12 weeks showed an increase in tau hyperphosphorylation at T181 and T231. Further evidence showed that *P. gingivalis* infection induced tau hyperphosphorylation by promoting the expression of IL−1β and suppressing activity of PP2A (Tang et al., 2021). While many pathogens have been identified as potential drivers of AD progression, additional research is necessary to determine the molecular mechanisms and signaling pathways connecting microbial infection and tau pathogenesis.

3.3. Chronic alcohol abuse

Chronic alcohol consumption, considered to be prolonged, heavy drinking behavior sustained for months or years, is a widely established neurotoxic stressor and known risk factor for neurodegenerative disease, including AD and related tauopathies (Sullivan et al., 2010). Ethanol induces neuronal stress, especially in critical cognitive processing regions such as the hippocampus and frontal cortex, through neuroinflammation, oxidative stress, excitotoxicity, altered glial support, and disruptions to proteostasis (Chastain and Sarkar, 2014; Crews and Nixon, 2009; Das and Vasudevan, 2007; Luo, 2014; Marshall et al., 2020). Epidemiology strongly suggests a long-term detrimental correlation between frequent alcohol use in early and mid-life and increased risk for AD and related dementias (Langballe et al., 2015). Notably, the retrospective study by Schwarzinger et al. included over one million subjects and identified heavy alcohol use as the primary modifiable risk factor for dementia (Schwarzinger et al., 2018). Beyond its influences on cognition and brain shrinkage, ethanol metabolism is increasingly implicated in direct dysregulation of tau homeostasis, promoting pathologic phosphorylation, impaired clearance, and aggregation in both preclinical models and human studies (Coleman et al., 2021, 2017; Dani et al., 2018; Luo, 2014). Activation of kinases and suppression of phosphatases are key mechanisms by which alcohol promotes tau hyperphosphorylation. Chronic ethanol use upregulates expression of tau kinases GSK−3β and CDK5, particularly increasing phosphorylation at sites such as S199, S202, T205, T231, and S396 (Goggin et al., 2014; Pascual et al., 2012; Saito et al., 2010). Ji et al. demonstrated in an adolescent rat model that binge alcohol exposure caused disinhibition of GSK−3β via dephosphorylation at S9, leading to hippocampal degeneration; however, this article did not examine tau phosphorylation directly (Ji et al., 2018).

Mechanisms by which ethanol promotes kinase and phosphatase dysregulation include ROS production and inflammatory signaling. Ethanol prolongs CDK5 activity by inducing oxidative stress and calcium dysregulation, which promote calpain-mediated cleavage of the CDK5 activator p35 into p25, forming a hyperactive complex (Lee et al., 2000; Mah et al., 2011; Samak et al., 2016). Additionally, evidence from Li et al. suggested that toxic metabolites of ethanol induce tau phosphorylation via ROS, a product of ethanol metabolism that promotes oxidative stress and activates p38, MAPK, and JNK (Li et al., 2022). Ethanol also exacerbates microglial activation and promotes secretion of proinflammatory cytokines including IL−1β, TNF, and IL−6, as well as ROS, contributing to a feed-forward loop that propagates pathologic kinase upregulation, PP2A suppression, and sustained aggregation (Chastain and Sarkar, 2014; Coleman et al., 2017; Marshall et al., 2020; Samak et al., 2016). Crews et al. demonstrated that alcohol caused elevated levels of Toll-like receptors (TLRs), which further sensitized the brain to immune gene induction and subsequent increases in HMGB1 and TLRs (Crews et al., 2013).

In addition to impacts on tau hyperphosphorylation, alcohol disrupts tau clearance mechanisms, particularly via the autophagic and UPS systems (Hamano et al., 2021; Luo, 2014) promoting accumulation of aggregation-prone tau species (Gendron et al., 2008). TLR4 mediates ethanol-induced disruptions to protein degradation by upregulating mTOR and decreasing expression of proteasome subunits in cerebral cortices, resulting in diminished clearance via autophagy and UPS, respectively (Liu et al., 2006; Pla et al., 2014). Importantly, these pathological changes are not entirely reversible with discontinued use; ethanol-induced dysregulation of immunoinflammatory and autophagic systems persist through prolonged abstinence. Tucker et al. detected long-term maladaptations in the cortical pro-inflammatory signature, concurrent with persistent downregulation of protective disease-associated-microglial (DAM) genes, including APOE, TREM2, LPL, and CTSD. Subsequently, persistently dysregulated lysosomal LAMP1 expression in the hippocampus and correlating tau accumulation indicated long-term dysfunction of the autophagic pathway (Tucker et al., 2022). Altogether these studies support the hypothesis that chronic heavy alcohol use sensitizes the CNS to tau aggregation by both promoting pathogenic tau hyperphosphorylation and inhibiting clearance mechanisms, potentially via mechanisms described above.

3.4. Broader substance abuse

Prevalent illicit drugs, including cocaine, methamphetamine, and opioids, have been implicated as potent environmental risk factors for tau pathology (Cao et al., 2013; Chen et al., 2019; Kovacs et al., 2015; Liu et al., 2003; Ramage et al., 2005; Xu et al., 2018), along with alcohol, through distinct yet converging mechanisms to induce similar dysregulating effects. While reports on the relationships between substance use disorders and neurodegeneration primarily center on cumulative neuronal loss and cognitive decline, emerging evidence suggests that they may specifically disrupt tau homeostasis (Walsh et al., 2024; Wang et al., 2022). Further, chronic substance abuse is broadly associated with blood-brain barrier (BBB) disruption, which facilitates the entry of

peripheral inflammatory mediators that may contribute to neurodegeneration and tau dysregulation (Pimentel et al., 2020; Sajja et al., 2016; Wei et al., 2021). Similar to alcohol, chronic exposure to psychoactive substances can alter expression of CDK5, p35, and p25, promoting tau phosphorylation (Bibb et al., 2001; Z. Chen et al., 2017; Chergui et al., 2004; Ferreras et al., 2017; Meyer et al., 2008). Stimulants, including cocaine and methamphetamine, induce excessive dopamine release and excitotoxicity, leading to tau phosphorylation and cytoskeletal instability through oxidative stress and mitochondrial dysfunction (Cole et al., 2021; Dietrich et al., 2005; Lazzeri et al., 2018; Li et al., 2018; Walker et al., 2014). Experimental studies in rodent models and neuronal culture suggest that methamphetamine upregulates GSK−3β and CDK5, leading to elevated tau phosphorylation at sites like T231, S396, S400, and S404 (Cantrelle et al., 2021; Xiao et al., 2018). Evidence also suggests that cocaine, through its effects on the mesolimbic dopamine system, indirectly activates GSK−3β signaling pathways (Miller et al., 2014, 2009).

Opioids, particularly heroin and fentanyl, alter autophagic pathways that impair the clearance of hyperphosphorylated tau (Cai et al., 2016; Karoussiotis et al., 2022). Additional evidence associates long-term opioid use with microglial reprogramming and altered activation states, inducing a chronic, low-grade inflammatory environment that further promotes tauopathy progression (Cahill and Taylor, 2017). Kovacs et al. presented evidence from postmortem brains of long-term opioid users indicating increased markers of tau phosphorylation and glial reactivity, particularly in cortical and limbic regions (Kovacs et al., 2015). Although opioid effects on tau are less well-characterized than those of alcohol and stimulants, it is likely that their established interaction with stress-responsive circuits (e.g. hypothalamic-pituitary-adrenal axis dysfunction) augments tau-related risks (Zhang et al., 2008). It is also important to note that the high prevalence of polysubstance use in opioid-dependent populations complicates understanding of distinct mechanistic consequences and emphasizes the need for more targeted studies (Compton et al., 2021). While evidence is more limited for heavy cannabis and nicotine use, preclinical studies suggest that chronic exposure can modulate tau kinases and indirectly affect proteostasis, especially in conjunction with other stressors (Oddo et al., 2005; Tyrakis et al., 2024). Nevertheless, across substance classes several themes surface: kinase activation, oxidative stress, impaired clearance pathways, and neuroinflammation. These processes not only promote tau misfolding and accumulation but may also act in concert with genetic susceptibility, other environmental factors, and polysubstance use, amplifying the complexity and progression of tau accumulation and subsequent aggregation. Understanding the molecular mechanisms linking substance abuse to tau pathology provides a promising avenue for development of targeted interventions, including mitigation of their neurotoxic effects and reduction of tau dysregulation and associated neurodegeneration.

3.5. Chronic stress

Stress plays a critical yet underappreciated role in the progression of tauopathy as a cogent mediator of brain structure and activity patterns. In particular, chronic stress is governed, in part, by mechanisms that are distinct from those driving acute stress responses (Herman et al., 2016; Sierra-Fonseca and Gosselink, 2018). Chronic psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, inducing a cascade of endocrine, inflammatory, and molecular changes, such as elevated glucocorticoid levels (predominantly cortisol in humans), advanced hippocampal atrophy, and dendritic remodeling (Herman et al., 2016; Wilson et al., 2006). Overactivation of the HPA axis is also known to occur in AD, encouraging a closer look at the potential mechanistic contributions of stress mediators in exploration of such pathologies (Swaab et al., 2005; Wilson et al., 2006).

Corticotropin-releasing hormone (CRH) plays a vital role in linking stress to tau pathology as an activator of the HPA axis released from the hypothalamus in direct response to stress, as well as being implicated in upregulation of tau kinases and promotion of neuroinflammation (Joshi et al., 2012; Sierra-Fonseca and Gosselink, 2018). Rissman et al. found that acute stress increased tau phosphorylation, particularly at T181, S199, S202, T205, T212, T231, S396, S404, and S422, an effect that was mediated by corticotropin-releasing factor (CRF) differentially signaling through its receptors (CRFR1 and CRFR2) (Rissman et al., 2007). While adaptive in short bursts, chronically elevated release of glucocorticoids induced by chronic CRH signaling can exert neurotoxic effects and influence tau kinase activity, neuroprotective signaling, and distribution of phosphorylated tau (Sotiropoulos et al., 2011). Glucocorticoids have been shown to upregulate both GSK−3β and CDK5, increasing phosphorylation at numerous sites, including S202, T231, and S396, all of which promote detachment of tau from microtubules and increase its propensity to aggregate (Dey et al., 2017; Sotiropoulos et al., 2011, 2008; Yi et al., 2017). CRH and activation of its receptors in tauopathy-vulnerable regions increases intracellular calcium and cAMP, further encouraging downstream activation of tau kinase signaling, including GSK−3β and MAPK/JNK (Futch et al., 2017; Rissman et al., 2007). Further, glucocorticoid and CRH receptor signaling induce suppression of neuroprotective signaling, including brain-derived neurotrophic factor (BDNF) which typically contributes to cytoskeletal stability and synaptic integrity, thus leaving neurons more vulnerable to tau-induced dysregulation (H. Chen et al., 2017; Hauger et al., 2009; Suri and Vaidya, 2013).

Moreover, chronic stress induces neuroinflammation with notable influence from CRH overactivity to further exacerbate tau pathology (Carroll et al., 2011; Lopes et al., 2016). Like the effects induced by chronic ethanol metabolism, stress-primed microglia adopt a proinflammatory phenotype and secrete cytokines, such as IL−1β, IL−6, and TNF, promoting tau phosphorylation and misfolding (Benita and Koss, 2024; De Pablos et al., 2014; Frank et al., 2021; Kiecolt-Glaser et al., 2003). Additionally, chronic stress significantly alters expression and distribution of phosphorylated tau in both the cortex and hippocampus of rodent models (Green et al., 2006; Yan et al., 2010). In addition to enhanced tau dysfunction and accumulation, chronic stress can impair tau clearance mechanisms, including the autophagic and UPS systems, by disrupting intracellular trafficking and lysosomal pH regulation (Ghavami et al., 2014; Lie and Nixon, 2019; Puangmalai et al., 2022; Silva et al., 2019; Vaz-Silva et al., 2018). Stress also alters astrocytic function, resulting in impaired metabolic support and glymphatic clearance of tau aggregates (Park et al., 2025; Tuan and Lee, 2019; Vasciaveo et al., 2023), which is active during slow-wave sleep. Because of this, sleep disruption, a common byproduct or symptom of chronic stress, contributes to tau dysregulation (Bah et al., 2019; Holth et al., 2019; Rothman et al., 2013). Acute sleep deprivation leads to increased interstitial fluid tau levels, which may increase the propensity for seed formation and subsequent tauopathy propagation (Harrison et al., 2020; Holth et al., 2019).

Effects of stress on tau pathology are particularly prominent when exposure occurs during critical development windows, such as in early life or adolescence (Catale et al., 2022; Desplats et al., 2020; Minné et al., 2023). Rodent models of early-life stress (e.g., maternal separation, social isolation) exhibit increased tau phosphorylation and neuroinflammatory markers in adulthood, even in the absence of subsequent upsets (Lumertz et al., 2022; Majcher-Maślanka et al., 2019; Steinmetz et al., 2015). These findings suggest that early stress provokes long-term vulnerability to tau aggregation and its regulatory pathways, priming the brain for future environmental challenges. Additionally, chronic stress often co-occurs with substance use disorders, either as a precursor, a consequence, or both, further compounding risk for tau-related neurodegeneration. The bidirectional relationship between stress and substance abuse often persists long-term in a neurobiological feedback loop, in which stress-induced tau dysregulation increases susceptibility to substance-induced damage, and vice versa (Juliano et al., 2025). Neuroimaging of individuals exposed to various types of chronic stress, including psychological trauma, familial caregiving, and

socioeconomic strain, also demonstrates hippocampal atrophy and heightened vulnerability to tau-driven neurodegeneration (Surget and Belzung, 2022; Woon et al., 2010). While the mechanisms and extent of these interactions remain unclear, they highlight the need for integrative models of tauopathy that account for synergistic and cumulative effects of environmental and lifestyle stressors.

3.6. Additional environmental risk factors of tau pathogenesis

Recent evidence suggests that exposure to pollutants and pesticides contribute to tau pathogenesis and increase risk of neurodegeneration (Chin-Chan et al., 2015). Heavy metal pollutants including methylmercury (MeHg), sodium arsenite, lead, and aluminum have been implicated in contributing to tau pathology formation (Bihaqi and Zawia, 2013; Fujimura et al., 2009; Shin et al., 1994). Young adult mice that were given 30 ppm MeHg via drinking water for 8 weeks displayed increased levels of tau phosphorylation at pathogenic sites T205, S404, and S422 (Fujimura et al., 2009). These biochemical changes were attributed to activation of tau kinases JNK, MKK4, and GSK3-β (Fujimura et al., 2009). In addition, sodium arsenite, a component found in pesticides and herbicides, is postulated to be an environmental risk factor for AD. Treating human neuroblastoma SH-SY5Y cells with sodium arsenite caused an increase in total tau levels and phosphorylation at S202 (Wisessaowapak et al., 2021). Together, correlative studies link pollutants and pesticides with tau pathology, and certain biochemical changes are seen in mouse and cell models that are consistent with tau pathogenesis; however, it is not yet known whether these are persistent changes with long-term impacts on neurologic health or biologically relevant changes.

4. Conclusion

In this review we have discussed the role of PTMs and proteolytic cleavage of tau in the development of tauopathies. Current research suggests phosphorylation, O-GlcNAcylation, acetylation, ubiquitination, methylation, and truncation all play a role in the regulation of tau and contribute to the formation of aggregates involved in tauopathies. Additionally, environmental factors like traumatic brain injuries, microbial infections, substance abuse, stress, and heavy metal pollutants promote cellular pathways that drive disease-associated PTMs and aggregation. While connections between environmental factors and molecular changes to tau have been established, the signaling pathways and mechanisms that connect environmental factors to these changes remain poorly defined. Further research is critical to outline the biological pathways and molecular factors that drive tau pathogenesis in order to identify potential points of behavioral and/or therapeutic intervention.

List of abbreviations

Abbreviation	Definition
4RD	Four repeat domain
AD	Alzheimer's disease
AEP	Asparagine endopeptidases
AMPK	5' adenosine monophosphate-activated protein kinase
CBD	Cortical basal degeneration
CBP	CREB binding protein
CDK5	Cyclin-dependent kinase 5
CHIP	HSC70-interacting protein
CK1	Casein kinase 1
CMA	Chaperone-mediated autophagy
CSF	Cerebrospinal fluid
CTE	Chronic traumatic encephalopathy
FTDP−17	Frontotemporal dementia with parkinsonism−17
GSK−3	Glycogen synthase kinase−3
OGA	O-GlcNAcases
OGT	O-GlcNAc transferases
hACE2	Human ACE2 receptor
HSC70	Heat shock cognate 70
LGMN	Lysosomal protease legumain
MCI	Mild cognitively impaired
MHV-JHM	Mouse hepatitis virus strain JHM
NCI	Non-cognitively impaired
PART	Primary age-related tauopathy
PHFs	Pathogenic paired-helical filaments
PP1, PP2A, and PP5	Protein phosphatase−1, −2A, and 5
PTMs	Post-translational modifications
TBI	Traumatic Brain Injury
TRAF6	TNF receptor-associated factor 6
UPS	Ubiquitin-proteosome system

Authors contributions

TMP is credited with conceptualization of the research, writing the original draft, and creating the figures. AET is credited with researching and writing portions of the manuscript. KEF is credited with conceptualization of the research and revising the manuscript. All authors approve of the submitted manuscript and are accountable for their contributions to the finished product.

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The authors declare that they have no competing interests.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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