Mechanisms linking cerebrovascular dysfunction and tauopathy: Adding a layer of epiregulatory complexity

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Intracellular accumulation of hyperphosphorylated misfolded tau proteins are found in many neurodegenerative tauopathies, including Alzheimer's disease (AD). Tau pathology can impact cerebrovascular physiology and function through multiple mechanisms. *In vitro* and *in vivo* studies have shown that alterations in the blood–brain barrier (BBB) integrity and function can result in synaptic abnormalities and neuronal damage. In the present review, we will summarize how tau proteostasis dysregulation contributes to vascular dysfunction and, conversely, we will examine the factors and pathways leading to tau pathological alterations triggered by cerebrovascular dysfunction. Finally, we will highlight the role epigenetic and epitranscriptomic factors play in regulating the integrity of the cerebrovascular system and the progression of tauopathy including a few observartions on potential therapeutic interventions.

KEYWORDS
cerebrovascular, epigenetics, epitranscriptomics, neuroinflammation, tauopathy, therapeutic

Tauopathies are a group of heterogeneous neurodegenerative diseases characterized by the deposition of abnormal tau protein in the brain. Based on the isoforms of tau present in pathologic aggregates, the different brain regions and cellular types affected, several neuropathologic phenotypes have been differentiated. Primary tauopathies refer to neurodegenerative diseases where tau is the predominant aggregated protein found in the brain at autopsy. Neurodegenerative diseases characterized by tau accumulation where other proteins or pathogenic events are the driving force are considered secondary tauopathies (Chung et al., 2021). In tauopathies, tau protein becomes aberrantly aggregated forming various inclusions, which impairs tau physiological functions. Neuronal tau can accumulate in the form of neurofibrillary tangles, neuropil threads or Pick bodies. Tau also accumulates in astrocytes, mostly in primary tauopathies in the form of tufted astrocytes, astrocytic plaques and globular astrocytic inclusions. In oligodendrocytes, tau aggregates are found in the form of coiled bodies or globular oligodendroglial inclusions (Chung et al., 2021).

Tau protein is genetically encoded by the microtubule associated protein tau gene (*MAPT*) located on chromosome 17q21.31 and is comprised of 16 exons (Andreadis, 2005). In the central nervous system, alternative splicing of exons 2, 3 and 10 results in six different tau isoforms that range from 352 to 441 residues in length (Liu & Gong, 2008; Wei & Andreadis, 1998; Zhou et al., 2008). The six tau isoforms differ based on the presence or absence of 29- or 58-amino-acid inserts in the N-terminus domain and by the presence of either 3 microtubule-binding repeat (3R) or 4 microtubule-binding repeat (4R) sequences of 31 or 32 amino acids in the C-terminus (Goedert et al., 1989; Kosik et al., 1989).

Based on the ratio of the 3R to 4R tau isoforms present in the pathologic tau inclusions found in glia and neurons of the different affected brain areas (Gotz et al., 2019), tauopathy can be classified as

3R (Pick's disease [PiD]), 4R (progressive supranuclear palsy [PSP], corticobasal degeneration [CBD], argyrophilic grain disease [AGD], globular glial tauopathy [GGT] and ageing-related tau astrogliopathy [ARTAG]), or mixed 3R and 4R tauopathies (chronic traumatic encephalopathy [CTE], primary age-related tauopathy [PART] and Alzheimer's disease [AD]). Biochemical analysis of sarkosyl (sodium lauroyl sarcosinate) insoluble fractions shows different patterns of tau phosphorylation depending on the tauopathic brain samples examined (Kovacs, 2017; Lee et al., 2001; Sergeant et al., 2005; Spillantini & Goedert, 2013). Two or three major phospho-tau bands (60, 64 and 68 kDa) are observed by western blot. Accordingly, 3R tauopathy shows 60 and 64 kDa bands, 4R tauopathy shows 64 and 68 kDa bands and mixed 3R and 4R tauopathy shows 60, 64 and 68 kDa bands. Besides an abnormal ratio of hyperphosphorylated tau isoforms, other aberrant post-translational modifications such as acetylation, truncation and *O*-GlcNAcylation have been described to play a role in tauopathy (Wang & Mandelkow, 2016). In addition, recent cryo-electron microscopy evaluation of fibrillary tau aggregates from tauopathic brains has suggested a new structure-based classification (Shi et al., 2021).

1.1 | Genetic architecture of tauopathies

Mutations in the tau gene can cause hereditary forms of frontotemporal dementia (FTD: Ghetti et al., 2015; Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998). Corticobasal degeneration and progressive supranuclear palsy share a similar genetic basis with a higher frequency of the *MAPT* H1 haplotype (and the specific H1c sub-haplotype). However, the frequency of *MAPT* H1/H1 genotype tends to be higher in argyrophilic grain disease (Togo et al., 2002) and also in globular glial tauopathy (Ahmed et al., 2013). Studies reporting on apolipoprotein E alleles (*APOE*) have shown lower rate of *APOE* e4 carrier state in argyrophilic grain disease than in AD. Moreover, the incidence of APOE e2 allele is higher in argyrophilic grain disease (Tolnay & Probst, 2008) and the *APOE* e4 carrier state is low in primary age-related tauopathy (Janocko et al., 2012; Santa-Maria et al., 2012). In globular glial tauopathy, mainly e3 alleles are observed (Kovacs et al., 2008).

Currently, we still do not have a clear understanding of the aetiology of most of the tauopathies. However, we find shared features such as extensive neuronal loss and glial dysfunction, suggesting that there may be shared underlying biological mechanisms across the different disorders. Advancements in sequencing technologies have provided an opportunity to uncover novel insights into the molecular bases of tauopathies (Miyoshi et al., 2021). Genome-wide association studies (GWASs) have allowed the identification of disease-associated genetic risk variants, revealing new genes of interest with potential roles in the disease process. In this regard, genome-wide association studies have identified new susceptibility genes for progressive supranuclear palsy, such as *MAPT*, myelin basic protein gene (*MOBP*), syntaxin 6 gene (*STX6*), *EIF2AK3*, *SEMA4D*, dead-box helicase 27 gene (*DDX27)*, specificity protein 1 transcription factor gene (*SP1*), runt-related transcription factor 2 gene (*RUNX2*), dual specificity protein phosphatase 10 gene (*DUSP10*), WD repeat domain containing 63 gene (*WDR63*), microRNA 4423 gene (*MIR4423*), *SLCO1A2*, ArfGAP with SH3 domain, ankyrin repeat and PH domain 1 gene (*ASAP1*), *AMHR2*, centrosomal protein 57 gene (*CEP57*) and *RPS6KL1* (Chen et al., 2018; Hoglinger et al., 2011). Interestingly, it has been shown that corticobasal degeneration and progressive supranuclear palsy share the genetic risk factor at chromosome 3p22 *MOBP* (Kouri et al., 2015). Further genome-wide association studies for corticobasal degeneration identified kinesin family member 13B *(KIF13B)*, *SOS1*, *PRKAG2* and thrombospondin type laminin G domain and EAR repeats gene (*TSPEAR*) (Kouri et al., 2015).

FTD genome-wide association studies found Ras-related protein Rab-38 gene (*RAB38*,) *CTSC*, major histocompatibility complex, class II, DR alpha gene *(HLA-DRA)/HLA-DRB5*, butyrophilin like 2 gene (*BTNL2)*, *MAPT*, *C9orf72/MOB3B*, transmembrane protein 106B gene (*TMEM106B)* and translocase of outer mitochondrial membrane 40 gene (*TOMM40)/APOE* (Ferrari et al., 2014). Recently, genome-wide association studies for primary age-related tauopathy revealed a novel significant association with a single nucleotide polymorphism on chromosome 4 (rs56405341) in a locus containing chromosome 4 open reading frame 33 gene (*C4orf33),* sodium channel and clathrin linker 1 gene (*SCLT1*) and Jade Family PHD Finger 1 (*JADE1*) (Farrell et al., 2022), and genetic meta-analysis of diagnosed AD has identified new risk loci and has implicated amyloid beta, tau, immunity and lipid processing (Kunkle et al., 2019). However, many of the genome-wide association studies variants reside in non-coding regions, making it difficult to interpret their functional roles. Therefore, new studies have attempted to rapidly translate genome-wide association study findings and multi-omics data to genotype-informed therapeutic discovery in AD and related tauopathies through an integrated, network-based artificial intelligence framework (Fang et al., 2022; Nicholls et al., 2020).

1.2 | Epidemiology and clinical symptoms of tauopathies

Tauopathies have varied symptoms, complicated manifestations and considerable overlap among the clinicopathological features exists. Most forms of tauopathies present with a variety of behavioural, movement, language and memory deficits (Kovacs, 2017; Zhang et al., 2022), each with distinct epidemiology and clinical phenotypes. Most of primary tauopathies present clinical features of FTD. FTD represents a heterogeneous group of disorders, some of which are tauopathies. It typically affects individuals between 45 and 65 years of age. The prevalence of frontotemporal dementia varies in different reports, ranging from 3% to 26% in early-onset dementia patients below 65 years of age (Bang et al., 2015). FTD presents with changes in behaviour, personality and language. Patients may show disinhibition, apathy, repetitive behaviours and impaired social interactions. Some subtypes of frontotemporal dementia, such as the semantic variant primary progressive aphasia (svPPA), are characterized by language deficits due to tau accumulation (Bang et al., 2015). Pick's disease is a rare form of FTD that typically affects individuals aged 40–65. Pick's disease presents most often with clinical phenotypes of frontotemporal dementia (Kovacs et al., 2013; Piguet et al., 2011) or, rarely, with an AD-like amnestic syndrome

(Kovacs et al., 2013). Pick's disease presents with personality changes, social disinhibition, emotional blunting and poor insight into one's condition. Language abnormalities are also common, such as non-fluent speech and word-finding difficulties. Progressive supranuclear palsy is a rare tauopathy, typically diagnosed in individuals over the age of 40. The prevalence of progressive supranuclear palsy is 5.8–6.5 per 100,000 (Ling, 2016). It is more common in males than females. Progressive supranuclear palsy is characterized by difficulties with balance and gait, leading to falls. Patients often experience stiffness, rigidity and gaze abnormalities, including vertical gaze palsy. Cognitive impairments, including changes in behaviour and language can also occur. Corticobasal degeneration is another rare tauopathy that typically affects individuals aged 50–70. It affects both men and women equally, but due to challenges of *in vivo* diagnosis of corticobasal degeneration the precise incidence and prevalence of corticobasal degeneration are unknown. Corticobasal degeneration is characterized by progressive asymmetric limb rigidity, apraxia (difficulty performing purposeful movements) and cortical sensory deficits. Corticobasal degeneration-type pathology may present with Richardson syndrome, posterior cortical atrophy syndrome, dementia with features similar to AD (Kouri et al., 2011) or rarely, cerebellar ataxia (Kouri et al., 2013). Argyrophilic grain disease-like pathology can be found between 5% and 43% in autopsy cohorts, clearly increasing with age (Ferrer et al., 2008). A few studies on argyrophilic grain disease report progressive cognitive decline, urinary incontinence, memory disturbances and personality changes often with aggression and ill temper (Tolnay & Probst, 2008). The prevalence of primary age-related tauopathy in different autopsy series varies between 3% and 20% (Crary et al., 2014; Jellinger et al., 2015). Symptoms in persons with primary age-related tauopathy usually range from normal to amnestic cognitive changes. Disorientation, depression and paranoid ideas may be also observed (Jellinger & Attems, 2007). There are descriptions of the association of progressive supranuclear palsy with corticospinal tract degeneration or Parkinsonism with motor neuron disease (Fu et al., 2010; Josephs et al., 2006); these syndromes are now included in the neuropathological group of globular glial tauopathys (Ahmed et al., 2013). Globular glial tauopathy is a very rare tauopathy and the most frequent clinical presentation of globular glial tauopathys is behavioural variant of FTD and, less frequently, progressive aphasia or even corticobasal syndrome or other movement disorders (Ahmed et al., 2013; Burrell et al., 2016). AD is the most common tauopathy. It primarily affects the elderly population and its prevalence increases with age. AD is characterized by progressive cognitive decline, memory impairment, language difficulties, disorientation and impaired judgement. As the disease advances, patients may experience behavioural changes, mood swings and difficulty performing daily tasks. Altogether, tauopathies manifest with varying clinical features and symptoms but share a common underlying mechanism of abnormal tau aggregation.

1.3 | Symptomatic treatments for tauopathies

Currently, approved therapeutic agents for Alzheimer's dementia such as acetylcholinesterase inhibitors and memantine have been used off-label to treat cognitive and behavioural symptoms in tauopathies, but the outcome has not been consistent. Therapeutic agents for the symptomatic treatment of Parkinson's disease (levodopa or dopamine agonists) are used for motor symptoms in tauopathies. For behavioural or psychopathological symptoms, treatment with antidepressants-especially selective serotonin reuptake inhibitors (SSRIs) have proved to be helpful (Karakaya et al., 2012). Antipsychotics are often not well tolerated because of their adverse effects (increased risk of cerebrovascular events), which are pronounced in tauopathies. In addition to pharmacologic options, physical, occupational or speech therapy can be applied to improve functional abilities (Islam et al., 2022). Each pharmacologic or nonpharmacologic intervention should be fitted to the specific symptoms of the individual patient. Therefore, accurate diagnosis is crucial for proper management of tauopathy patients.

1.4 | Disease-modifying therapeutic avenues targeting tau and vascular dysfunction

Tau toxicity plays a critical role in the pathogenesis of tauopathies. Different isoforms are affected in different tauopathy leading to aggregates with distinct structures, which accumulate in different cell types. Therapies that modulate tau levels or function have the potential to lead to clinically meaningful benefits in slowing or reversing disease progression (VandeVrede et al., 2020). Current therapeutic avenues include: small-molecule inhibitors that target post-translational modifications such as acetylation, phosphorylation and ubiquitination; genetically targeted therapies, such as antisense oligonucleotides and certain small molecules that can target tau synthesis; aggregation inhibitors for targeting tau aggregation; misfolded protein targeted protein degraders such as proteolysis targeting chimeras (PROTAC) and clearance enhancers; immunotherapies targeting extracellular tau; and neuroprotective agents including anti-inflammatory and neuroimmune modulatory agents. All these therapeutic avenues could limit the downstream impacts of tau pathology.

Currently, a small percentage of clinical trials for AD and related tauopathies is focusing on targeting cerebrovascular dysfunction. Few of the therapeutic avenues targeting vascular dysfunction include the following:- endothelin B (ET_B) receptor agonist, that augments activity of neuronal progenitor cells, neurovascular repair and neuroregeneration and combining with an angiotensin II receptor antagonists, along with several clinical trials are targeting neuroinflammation, which is known to trigger and exacerbate cerebrovascular dysfunction.

In this review, we explore the emerging data linking tauopathy and cerebrovascular dysfunction or vice versa, and we seek to highlight the role epiregulatory mechanisms play in modulating the progression of tauopathy and the integrity of the cerebrovascular system. Finally, we will comment on potential-related therapeutic interventions for these devastating neurodegenerative disorders.

2 | NEUROINFLAMMATION, A LINK BETWEEN TAU PATHOLOGY AND CEREBROVASCULAR DYSFUNCTION

In a healthy brain, the microtubule associated protein tau plays a role in a range of biological processes including microtubule dynamics, axonal transport, myelination, glucose metabolism, iron homeostasis, neurogenesis, motor function, learning and memory, neuronal excitability and DNA protection (Kent et al., 2020). In the brain, neurons have the highest expression level of tau while oligodendrocytes and astrocytes express tau at lower levels. In addition, microglia do not express tau.

On the other hand, diverse cell types and associated structures play a role in cerebrovascular function at different levels of the vascular network (Iadecola et al., 2023; Schaeffer & Iadecola, 2021). The neurovascular complex (NVC) is composed of brain endothelial cells, pericytes or vascular smooth muscle cells, glia and neurons, with diverse functions at different levels of the cerebrovascular tree (Schaeffer & Iadecola, 2021). The NVC comprises heterogeneous vascular modules regulated by factors intrinsic and extrinsic to the brain through segment-specific mechanisms. Throughout the brain, the NVC implements coordinated vascular responses to central and peripheral signals to maintain homeostasis (Schaeffer & Iadecola, 2021). The NVC controls blood–brain barrier (BBB) permeability and cerebral blood flow and maintains the chemical composition of the neuronal 'milieu', which is required for proper functioning of neuronal circuits (Zlokovic, 2011). NVC cells do not interact just with their immediate neighbours but reach out beyond their limited confines acting as a signalling source that regulates the homeostasis of neurons and glia in a very dynamic and specialized manner throughout the entire brain in the normal state (Schaeffer & Iadecola, 2021).

The mechanisms underlying cellular dysfunction and death in tauopathies are intricate (Gotz et al., 2019). Aberrant tau protein accumulation results in proteotoxic stress, enhanced oxidative stress and neuroinflammation, and ultimately results in neuronal cell death (Figure 1) (Dugger & Dickson, 2017). In tauopathies, tau accumulation appears jointly with neuroinflammation (Bevan-Jones et al., 2020; Malpetti et al., 2020; Pascoal et al., 2021). During neuroinflammation,

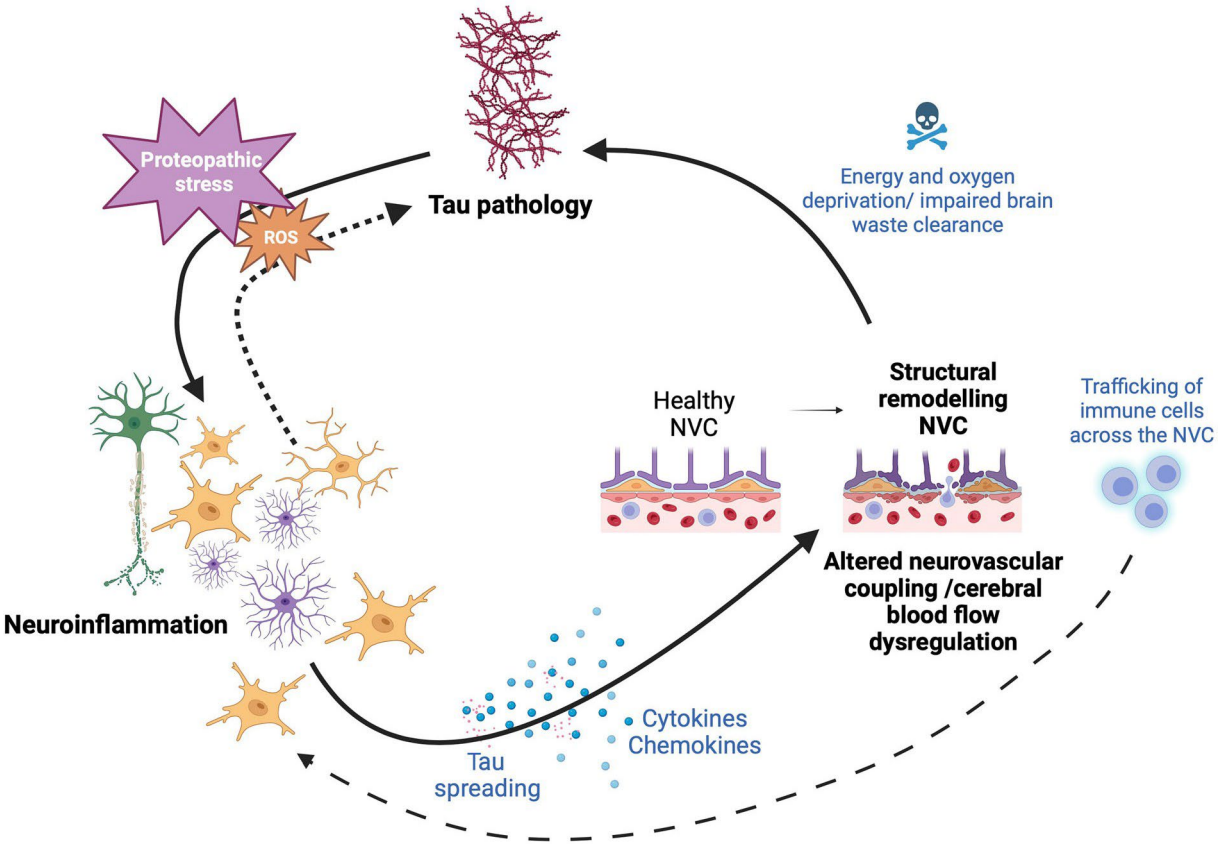

FIGURE 1 Mechanisms linking cerebrovascular dysfunction and tau pathology in tauopathies. Aberrant tau protein accumulation results in proteotoxic stress, enhanced oxidative stress and neuroinflammation. The presence of tau within glial cells induces the secretion of several pro inflammatory cytokines and chemokines, initiating a high inflammatory state, which promote structural changes and remodelling of cerebral vasculature. Structural remodelling of the brain vasculature contributes to the disease process in tauopathies leading to disruption of the neurovascular complex (NVC) and the BBB, resulting in cerebral blood flow dysregulation. Tau pathology-induced activation of glial cells also stimulates the trafficking of immune cells across the BBB which overtime is detrimental. In addition, tau pathological species, through astrocytic end-feet and interstitial fluids, may spread to endothelial cells and pericytes, inducing BBB disruption and permeability to blood-borne components. Figure created with BioRender.com.

reactive glial cells continuously secrete cytokines and chemokines, which further recruit and activate innate and adaptive immune cells (Farina et al., 2007; Streit et al., 2005), initiating a feed-forward detrimental inflammatory response, a feature of tauopathies, including AD (Aguilar-Pineda et al., 2021; Canepa & Fossati, 2020; Querfurth & LaFerla, 2010). The presence of aggregated or hyperphosphorylated tau around activated microglia with impaired phagocytic capacity has been observed in mice and humans with tau pathology (Canepa & Fossati, 2020; Perea et al., 2018). A link between tau accumulation and neuroinflammation is also supported by *in vitro* and *in vivo* studies demonstrating the pathological effect of tau modulating neuroinflammatory responses (Bellucci et al., 2004; Bolos et al., 2016; Brelstaff et al., 2018; Rexach et al., 2020; Stozicka et al., 2010; van Olst et al., 2020; Zilka et al., 2006). The effect of pathogenic tau is mostly mediated through the activation of glial cells. Tau pathology-induced activation of glial cells stimulates the trafficking of immune cells across the BBB (Figure 1), which overtime is detrimental (Blair et al., 2015; Chen et al., 2023; Majerova et al., 2019). Although correlative studies support an association of activated innate and adaptive immune cells with cognitive dysfunction, animal studies have suggested a clear cause–effect relationship between increased immune cell trafficking to the brain and cognitive decline (Iadecola, 2023). Furthermore, the recent discovery that central nervous system antigens accumulate in dural sinuses and are presented to circulating lymphocytes, a process disrupted during neuroinflammatory states and ageing, supports and alteration of the cross-talk between the central nervous system and systemic immunity in the disease process (Iadecola, 2023; Rustenhoven, 2021). In addition, tau pathological species, through astrocytic end-feet and interstitial fluids, may spread to endothelial cells and pericytes, inducing BBB disruption and permeability to blood-borne components, including peripheral blood monocyte-derived macrophages, immunoglubulins (IgGs and IgMs) and α2-macroglobulin (Figure 1) (Canepa & Fossati, 2020). Ultimately, the presence of tau within glial cells induces the secretion of several pro-inflammatory cytokines and chemokines, such as IL-1β, IL-6, IL-8, IL-10, IFNγ and MCP-1, initiating a high inflammatory state, which promote structural changes and remodelling of cerebral vasculature (Nelson et al., 2016). Structural remodelling of the brain vasculature contributes to the disease process in tauopathies leading to disruption of the NVC and the BBB, resulting in cerebral blood flow dysregulation (Figure 1) (Albrecht et al., 2020; Michalicova et al., 2020; Nelson et al., 2016).

3 | NEUROVASCULAR COUPLING DYSFUNCTION AND TAU PATHOLOGY

Neurovascular coupling is a pivotal mechanism in charge of matching the high energy demand of the brain with a supply of energy substrates from the blood. Signalling within the NVC is responsible for activity-dependent changes in cerebral blood flow (Stackhouse & Mishra, 2021).

Neurons interact with glia and blood vessels, and their communication at each of these interfaces influences how the NVC responds to neural activity to induce neurovascular coupling and mediate changes in cerebral blood flow (Attwell et al., 2010; Claassen et al., 2021; Kaplan et al., 2020; Stackhouse & Mishra, 2021). Neuronal activity can trigger local changes in cerebral blood flow directly by releasing vasoactive molecules onto arterioles to engage vascular smooth muscle cells or indirectly via signalling to astrocytes, which then release vasoactive molecules onto capillary pericytes (Biesecker et al., 2016; Mishra, 2017; Mishra et al., 2016). Normally, neuronal activity triggers neuronal nitric oxide synthase, which is bound to NMDA receptors in the post-synapse through the adaptor protein PSD95 (Brenman et al., 1996; Kornau et al., 1995). Activation of nitric oxide synthase produces nitric oxide (NO), which dilates blood vessels. The increase in cerebral blood flow in response to neural activity is also suggested to play a role in clearing the brain of waste by-products of normal function and metabolism, either via the blood itself or via perivascular mechanisms (Bacyinski et al., 2017; Iliff et al., 2012; Ramanathan et al., 2015). A decrease in cerebral blood flow or a loss of normal, robust neurovascular coupling could in theory starve neurons of necessary energy requirements while also creating a toxic environment due to lack of clearance (Chen et al., 2022; Kisler et al., 2017; Stackhouse & Mishra, 2021). In tauopathies, neuronal loss is accompanied by a loss of microvessels, endothelial cells and smooth muscle cells, indicating a close link between neuronal loss and cerebrovascular changes (Farkas & Luiten, 2001; Stackhouse & Mishra, 2021). Cerebrovascular dysfunction is an early event in individuals who develop cognitive impairment and progress to AD dementia (Iturria-Medina et al., 2016). In this regard, it has been described young mice overexpressing mutant human tau cannot amplify blood flow in their brains in response to neuronal activity (Park et al., 2020). The observed defect was caused by soluble tau in the post-synapse. In the tauopathy mouse model, tau protein displaced neuronal nitric oxide synthase, preventing synaptic activity from producing NO. Without NO, blood vessels did not expand (Park et al., 2020). Importantly, it has been observed in human tauopathy patients that changes in blood flow can occur over time during the disease progression (Korte et al., 2020; Sweeney et al., 2018; Visser, Verfaillie, et al., 2023). Given that it is currently unknown to what order of magnitude pharmacotherapeutic interventions may induce changes in cerebral blood flow, caution is warranted when using tau targeting radiotracer 18F-fortaucipir for investigating pathologic tau load differences between cognitively normal with subjective cognitive decline subjects and cognitively impaired tauopathy patients (Visser, Tuncel, et al., 2023). Dynamic scanning protocols, utilized for measuring relative cerebral blood flow, and fully quantitative data analysis methods are preferred when larger flow changes in the brain are expected (such as in later disease stages or pharmacotherapeutic interventions). Use of semiquantitative methods in such conditions carries the inherent risk that potential effective therapeutic interventions are discarded, especially when expected effect sizes are small (Visser, Tuncel, et al., 2023).

Since a significant proportion of patients with neurodegenerative conditions show vascular diseases (Albrecht et al., 2020; Azarpazhooh et al., 2018; Crary et al., 2014; Nelson et al., 2016), a recent study investigated the genomic data of 14,669 individuals of diverse ethnic backgrounds to identify genetic associations that might constitute the link between neurodegenerative pathologies and vascular disease (Lee et al., 2022). The top hit was a gene called formin-like protein 2 (*FMNL2*), a member of a protein family implicated in cytoskeletal rearrangements and Tau-dependent amyloid toxicity in neuronal synapses (Faix & Grosse, 2006; Qu et al., 2017). *FMNL2* expression increases with both vascular disease and amyloid or Tau toxicity in humans and in AD models of zebrafish and mouse (Cosacak et al., 2019; Lee et al., 2022). Based on transient knockdowns in zebrafish brain with amyloid toxicity, *FMNL2* was suggested to be required for astroglial cells to retract their endfeet upon pathology to allow better clearance of toxic protein aggregates through blood–brain barrier plasticity, gliovascular niche interactions and recruitment of microglia (Lee et al., 2022). The study also found elevated FMNL2 levels in human autopsies as a response to primary age-related tauopathy (Lee et al., 2022). Therefore, in humans, genetic variations could impinge on the function of critical components of clearance mechanism at the blood–brain interface and exacerbate the disease pathology through impaired clearance.

4 | ALTERED EPIREGULATORY MECHANISMS IN TAUOPATHIES

To develop novel and better therapeutic strategies for tauopathy, a deeper characterization of molecular mechanisms behind the disease process is needed. For this reason, several laboratories have recently turned their focus on investigating the epigenetic and epitranscriptomic alterations affecting neurodegenerative disorders including tauopathies (Dermentzaki & Lotti, 2020; Zimmer-Bensch & Zempel, 2021).

Dynamic epigenetic and epitranscriptomic changes alter gene expression without affecting the DNA or RNA sequence, respectively (Berger et al., 2009; Giallongo et al., 2022). Epigenetic mechanisms include DNA methylation, histone modification, chromatin remodelling and non-coding RNA action, resulting in genomic instability and altered gene expression. Specifically, methyl groups are added to DNA mostly on cytosines, but also on adenines via DNA methyltransferases (DNMTs) (Greenberg, 2020), with DNMT1 and DNMT3A being the major DNMTs in the brain (Bayraktar & Kreutz, 2018). The addition of methyl groups affects gene expression by modulating (1), the transcriptional control when occurring at enhancer and promoter sites, (2) the alternative promoter usage and (3), the alternative splicing (Zimmer-Bensch & Zempel, 2021). Interestingly, histone modifications predispose for the set-up of DNA methylation signatures and vice versa (Hashimshony et al., 2003). DNMTs by modulating the expression of genes coding for enzymes of histone modifying complexes can shape histone modifications. Moreover, certain non-coding RNAs have been described to target DNMTs and histone modifying complexes to specific genomic locations (Marchese et al., 2017).

Epitranscriptomics refers to post-transcriptional modifications on coding and non-coding RNAs that modulate their physiological functions. RNA modifications are an additional layer of gene regulation offering a rapid fine-tuning of gene expression in response to specific environmental cues. In cooperation with a diverse and versatile set of effector proteins, RNA modifications such as N^1-methyladenosine (m^1A), pseudouridine (Ψ), 5-methylcytidine (m^5C) and N^6-methyladenosine (m^6A) can mediate and control diverse fundamental cellular functions, such as pre-mRNA splicing, nuclear export, stability and translation (Dermentzaki & Lotti, 2020).

4.1 | Epigenetic alterations in tauopathies

Epigenetic modifications are of great importance to human health and its alterations play a causative role in various neurodegenerative disorders (Berson et al., 2018). Altered DNA methylation signatures at CpG and non-CpG sites have been found in tauopathy post-mortem brain tissues (Lord & Cruchaga, 2014; Monti et al., 2020; Pellegrini et al., 2021). Cell type-specific differential methylation profiles have been observed for genes such as the microtubule associated protein 2 gene (*MAP2*), S100 calcium binding protein B gene (*S100B*), guanine nucleotide exchange factor DBS gene (*MCF2L*), ankyrin 1gene (*ANK1*), *STK32C* and leucine rich repeat containing 8 VRAC subunit B gene (*LRRC8B*) associated with AD progression (Gasparoni et al., 2018). Abnormal methylation levels in the promoter regions of genes involved in tau hyperphosphorylation have also been found in post-mortem human brain tissues of tauopathy patients and in tauopathy models of the disease, supporting a role of epigenetic alterations in the molecular mechanisms of disease progression (Zimmer-Bensch & Zempel, 2021) (Table 1). In addition, histone modifications such as acetylation, methylation, ubiquitination, phosphorylation and lactylation are implicated in multiple pathways involved in tauopathy and vascular dysregulation progression, including inflammatory response, neuronal plasticity, cognition and cell death (Park et al., 2022). Importantly, a recent study revealed lysine lactylation (Kla) as a new type of histone mark (Zhang et al., 2019). A genome-wide analysis showed that H4K12la is enriched at the promoters of glycolytic genes (*PKM2*, lactate dehydrogenase A [*LDHA*] and hypoxia inducible factor 1 subunit alpha [*HIF1A*]) and activates transcription, thereby increasing glycolytic activity. This positive feedback loop triggers microglial-mediated neuroinflammation, which plays a role in triggering cerebrovascular dysfunction in the disease process (Pan et al., 2022). Furthermore, genome-wide alteration of histone modifications and chromatin accessibility in tauopathy brains have been described for histone marks such as H3K9ac (associated with transcription activation and chromatin opening; Klein et al., 2019), H4K16ac (an active mark localized to both enhancers and promoters related to ageing and DNA damage; Nativio et al., 2018), H3K27ac (a transcription activation mark; Marzi et al., 2018), H3K4me3 (a permissive histone mark abundant around transcription start sites;

TABLE 1 Role of epigenetic regulation in tau pathology, inflammation and vascular pathology.

Epiregulatory mechanism	Pathological process	Outcome	References
DNA methylation	Altered DNA methylation signatures at CpG and non-CpG sites	Tauopathy pathogenesis	(Lord & Cruchaga, 2014; Monti et al., 2020; Pellegrini et al., 2021)
DNA methylation	Altered cell type specific methylation profiles in the promoter regions of genes such as MAP2, S100B, MCF2L, ANK1, STK32C and LRRC8B	Tauopathy pathogenesis	(Gasparoni et al., 2018; Zimmer-Bensch & Zempel, 2021)
Histone methylation	Histone mark H3K9m2 associated with transcriptional repression	Tauopathy pathogenesis	(Marzi et al., 2018)
Histone acetylation	Histone mark H4K16ac localized to regulatory DNA elements such as enhancers and promoters	Ageing, DNA damage and tauopathy	(Klein et al., 2019)
Histone acetylation	Histone marks H2K9ac and H3K27ac associated with transcription activation and chromatin opening	Tauopathy pathogenesis and cerebrovascular dysfunction	(Klein et al., 2019)
Histone methylation	Histone mark H3K4me3 at transcription start sites	Tauopathy pathogenesis	(Cao et al., 2020)
Histone lactylation	Histone mark H4K12la enriched at promoters of glycolytic genes such as PKM2, Ldha and Hif-1alpha	Tauopathy pathogenesis	(Pan et al., 2022)
MicroRNAs	Dysregulation of microRNAs such as miR-34a, miR-132/212, miR-219-5p, miR-15, miR-146a-5p, miR-369, or miR125b	Tauopathy pathogenesis	(Millan, 2017)
MicroRNAs	Dysregulation of pro-inflammatory, anti-inflammatory and immunomodulatory microRNAs	Neuroinflammation and tauopathy pathogenesis	(Gaudet et al., 2018)
Noncoding RNAs	MicroRNAs, long noncoding RNAs, circular RNAs and YRNAs dysregulation	Vascular pathogy	(Jae & Dimmeler, 2020)
MicroRNAs	Dysregulation of microRNAs such as miR-21, miR-181a, miR-124, miR-107 and miR-132 critical in blood–brain barrier maintenance and vascular integrity	Blood–brain barrier disruption and tauopathy pathogenesis	(Atif & Hicks, 2019; El Fatimy et al., 2018; Li et al., 2019; Salta & De Strooper, 2017; Sun et al., 2022; Wu et al., 2019; Xu et al., 2017)

Cao et al., 2020) and H3K9me2 (a mark associated with transcriptional repression; Zheng et al., 2019), indicating that tau leads to large-scale changes in histone modifications and chromatin rearrangements triggering changes in the expression of several genes like serum/glucocorticoid regulated kinase 1 (*SGK1;* involved in cellular stress responses), early growth response protein 1 (EGR1) (involved in immune responses and apoptosis), SELE (selectin E; an endothelial adhesion molecule), CLEC7A (a pattern recognition receptor expressed by myeloid phagocytes) and cystatin F (*CST7*; with a role in immune regulation), among multiple others genes playing a role in tau pathology and cerebrovascular dysfunction (Table 1). Given the link between tau pathology and cerebrovascular dysfunction, it is also important to highlight the role non-coding RNAs play in the onset and progression of cerebrovascular dysfunction and tau pathology through the regulation of multiple pathways. Several non-coding RNAs have been shown to regulate cerebrovascular homeostasis in healthy conditions and the disease processes (Jae & Dimmeler, 2020; Zurek et al., 2021). On the other hand, dysregulation of noncoding RNAs is also associated with the pathogenesis of tauopathies, of which microRNAs (miRNAs) are the most broadly studied. Many miRNAs have been found to be involved in numerous aspects of tau regulation and pathology. Some miRNAs such as miR-34a, miR-132/212 and miR-219-5p can bind to MAPT mRNA and regulate tau synthesis, but most of the tau-associated miRNAs are shown to regulate kinases and phosphatases that act on tau such as MiR-15, miR146a-5p, miR-369, or miR-125b (Millan, 2017). In addition to miRNAs regulating tau proteostasis, miRNAs play important roles in regulating neuroinflammation. Key pro-inflammatory (*miR-155*, *miR-27b*, miR-132, *miR-326*), anti-inflammatory (*miR-124*, *miR-146a*, *miR-21*, *miR-223*) and mixed immunomodulatory (*let-7* family) miRNAs regulate neuroinflammation in various pathologies, including tauopathies (Gaudet et al., 2018; Walgrave et al., 2023) (Table 1).

Several miRNAs have been associated with BBB disruption (Sun et al., 2022); miR-21 loss in tauopathy promotes endothelial apoptosis, decreases junctional proteins expression and derepresses angiogenic factors critical to BBB maintenance (Atif & Hicks, 2019).

The decline of miR-181a is also correlated with proteotoxic accumulation-induced pericyte apoptosis and BBB breakdown in AD mice (Wu et al., 2019). MiR-124 is down-regulated in AD targets and suppresses complement C1q like 3 gene *(C1QL3)* to up-regulate expression of Zonula occludens-1 (ZO-1; a tight junction protein) to enhance BBB integrity (Li et al., 2019). In addition, miR-107 which direct targets and down-regulates endophilin-1 and regulates BBB permeability and the expression of ZO-1, occludin and claudin-5 is also found down-regulated in AD (Table 1).

Interestingly, a study has shown that neurons secrete miR-132-containing exosomes to regulate brain vascular integrity (Xu et al., 2017) and loss of miR-132 expression is found in human tauopathies (El Fatimy et al., 2018; Salta & De Strooper, 2017).

4.2 | Epitranscriptomic regulation in tauopathies

Epitranscriptomic regulation adds a layer of post-transcriptional control to brain function during development and adulthood. Thus, the identification of RNA-modifying enzymes has opened the possibility of investigating the role epitranscriptomic changes play in the disease process (Kumar & Mohapatra, 2021). The most prevalent RNA methylation modification in eukaryotes is N6-methyladenosine (m^6A), which has attracted much attention in the nervous system research in the last decade. M^6A RNA modification plays an important role in brain function; during brain development, m^6A RNA modification levels increase and exhibit tissue specificity (Meyer et al., 2012). However, the role m^6A RNA modification plays in the ageing brain, and neurodegenerative disorders is still under investigation (Table 2). The discovery that the levels of m^6A modified RNA in the AD brains differs from that of controls supported a possible role of m^6A RNA modification in the disease pathogenesis (Shafik et al., 2021). In this respect, it was shown levels of fat mass and obesity-associated protein (FTO), an epitranscriptomic eraser, is increased in AD brains and regulates phosphorylation levels of tau in a tuberous sclerosis 1 (TSC1)-mTOR-dependent manner (Li et al., 2018). On the other hand, a deficiency of the brain enriched RNA methyltransferase (NOP2/Sun RNA methyltransferase 2 [NSun2]) has been discovered in tauopathy brains. NSun2 dysregulation can lead to the build up of toxic hyperphosphorylated forms of tau and progressive atrophy and loss of function of neurons. Decreased levels of neuroprotective NSun2 promotes epitranscriptomic alterations in miR-125b and tau hyperphosphorylation (Kim et al., 2023). In addition, a recent investigation has shown m^6A methylated RNA and its protein partner heterogeneous nuclear ribonucleoprotein A2/B1 (HNRPA2B1) bind hyperphosphorylated tau and accumulate in neurofibrillary tangles as AD pathology worsens (Jiang et al., 2021). Recently, other studies have started to show an alteration in the levels of other epitranscriptomics regulators such as METTL3 with an effect on tau protein homeostasis in the brain (Lv et al., 2022; Tang et al., 2023) (Table 2).

Most of our current understanding on mechanism of cerebrovascular dysfunction comes from research studies that have started to unravel the cellular and molecular mechanisms causing brain damage from impaired blood flow (Vijayan & Reddy, 2016). Epitranscriptome research in human cerebrovascular pathology is still in its infancy, but the number of studies on RNA modifications and their effector proteins (writers, readers and erasers) in various forms of vascular remodelling has recently increased (Nossent, 2022), which open up new avenues for research in AD and related tauopathies. In this regard, a recent study has shown NSun2 deficiency protects endothelium from inflammation via mRNA methylation of Intercellular adhesion molecule 1 (ICAM-1). Methylation of ICAM-1 mRNA by NSun2 promotes enhanced translation of this molecule and results in increased adhesion of leukocytes to endothelial cells (Luo et al., 2016). This study supports a beneficial role for NSun2 down-regulation in vascular health, suggesting reduction of NSun2 levels observed in AD brains could occur as a consequence of inflammation in brain specific regions. Furthermore, future studies will uncover important roles of m^6A RNA modification in the pathophysiological mechanisms of AD and related tauopathies by regulating microglia's pro-inflammatory and anti-inflammatory responses in the brain (Li et al., 2021), thus serving as a potential link between tau pathology and vascular dysregulation (Table 2).

5 | THERAPEUTIC OPPORTUNITIES TO TARGET THE EPIGENOME AND THE EPITRANSCRIPTOME ALTERATIONS IN NEURODEGENERATIVE TAUOPATHIES

Epigenetic changes are observed in the brain of individuals with major neurodegenerative tauopathies, including AD (Coppede, 2021). Due to their reversibility, several epigenetic marks have been proposed as potential therapeutic targets to treat or delay progressive atrophy and loss of function of neurons in neurodegenerative diseases. DNMTs inhibitors or supplementation of methyl donor compounds such as B-group vitamins, folates or S-adenosylmethionine (SAM) required for SAM production have been proposed as a therapeutic option to neurodegeneration. However, DNMT inhibitors are toxic to non-dividing cells like neurons. Thus, dietary supplementation of SAM represents a safer alternative that could restore methylation levels and ameliorate neuropathology (Coppede et al., 2022).

Histone modifications such as acetylation regulate the chromatin structure and the accessibility of gene regulatory regions. Histone acetylation results in a relaxed chromatin structure allowing transcription while histone deacetylation mediated by histone deacetylases (HDACs) results in chromatin compaction and transcriptional repression. Recently, several laboratories have tested HDAC inhibitors in animal models of neurodegenerative disorders. However, most of these compounds present very low selectivity and induce neurotoxicity (Shukla & Tekwani, 2020). Therefore, future studies are needed to determine which HDACs should be inhibited in different neurodegenerative disorders and to test new and more selective and safer HDACs inhibitors (Dietz & Casaccia, 2010).

TABLE 2 Role of epitranscriptomic regulation in tau pathology, inflammation and vascular pathology.

Materials	Epiregulatory mechanism	Pathological process	Outcome	References
Primary neurons/FTO knockdown	Levels of eraser FTO decrease	FTO regulated the phosphorylation of tau in a TSC1-mTOR-dependent manner.	Reduction in levels of hyperphosphorylated tau	(Li et al., 2018)
3xTg-AD	Levels of eraser FTO increased in the brain.	FTO regulated the phosphorylation of tau in a TSC1-mTOR-dependent manner.	Neurofibrillary tau tangle formation and cognitive deficits	(Li et al., 2018)
3xTg-AD/FTO conditional knockout mice	Levels of eraser FTO decreased in neurons.	FTO regulated the phosphorylation of tau in a TSC1-mTOR-dependent manner.	Reduction in cognitive deficits	(Li et al., 2018)
Human mutant tau transgenic *Drosophila melanogaster*; METTL3 knockdown	METTL3 levels are reduced.	Increase tau toxicity	METTL3 down-regulation promotes tau toxicity.	(Shafik et al., 2021)
Primary cortical neurons	Tau oligomerization promotes HNRPA2/B1 reader cytoplasmic translocation and binding to m^{6}A RNA.	Oligomeric tau-HNRPA2/B1-m^{6}A-RNA complex leads to tau proteostasis dysregulation, nuclear membrane disruption and neurodegeneration.	Oligomeric tau-HNRPA2/B1-m^{6}A-RNA complex regulates stress response and inhibits protein synthesis.	(Jiang et al., 2021)
Primary cortical neurons	Expression of HNRPA2/B1 is reduced.	Knockdown of HNRPA2/B1 reduces formation of complexes.	Knockdown of HNRPA2/B1 reduces the response to pathological tau.	(Jiang et al., 2021)
PS19 P301S tau mice	Oligomeric tau binds to HNRNPA2/B1 and m^{6}A-marked transcripts forming a complex.	Oligomeric tau/HNRNPA2/B1/m^{6}A-marked RNA complexes increased.	Oligomeric tau-HNRPA2B1-m^{6}A-RNA complex regulates stress response and inhibits protein synthesis.	(Jiang et al., 2021)
Human brain tissue	Oligomeric tau-HNRPA2/B1-m^{6}A-RNA complex regulates stress response and inhibits protein synthesis.	Tau oligomerization promotes HNRPA2B1 m^{6}A reader altered location within neurons.	Oligomeric tau-HNRPA2B1-m^{6}A-RNA complex regulates stress response and inhibits protein synthesis.	(Jiang et al., 2021)
Human brain tissue	m^{6}A progressively increases with disease severity in human AD brains.	m^{6}A accumulates parallel to phosphorylated tau deposition.	HNRPA2/B1 links oligomeric tau with cytoplasmic m^{6}A in human AD cases.	(Jiang et al., 2021)
Human brain tissue	NSun2 levels are decreased in AD hippocampal and prefontal cortex neurons.	Tau pathology	NSun2 down-regulation is associated with tau hyperphosphorylation in neurons.	(Kim et al., 2022)
iPSC-derived neurons/NSun2 knockdown	NSun2 levels are reduced.	Increase in levels of phosphorylated tau	NSun2 down-regulation promotes tau phosphorylation.	(Kim et al., 2022)
Human tau transgenic *Drosophila melanogaster*; NSun2 knockdown	NSun2 levels are reduced.	Increase tau toxicity	NSun2 down-regulation promotes tau toxicity.	(Kim et al., 2022)
NSun2 knockout mice	Expression of NSun2 absent in neurons	Increase in levels of phosphorylated tau	NSun2 regulates tau phosphorylation levels by regulating the levels and m^{6}A methylation of miR-125b.	(Kim et al., 2022)
iPSC-derived neurons and rat primary hippocampal neurons treated with amyloid beta oligomers	Expression of NSun2 was reduced.	Increase in levels of phosphorylated tau	Amyloid beta induced NSun2 down-regulation and tau hyperphosphorylation.	(Kim et al., 2022)

(Continues)

TABLE 2 (Continued)

Materials	Epiregulatory mechanism	Pathological process	Outcome	References
Tyrobp$^{-/-}$ mice	The mRNA levels of Mettl3, Mettl14 and Wtap, which encode methyltransferases, were significantly reduced in the hippocampus.	Increase in levels of total tau and phosphorylated tau	Learning and memory deficits	(Lv et al., 2022)
SH-SY5Y and HT22 cells treated by Aβ1–42	Expression of METTL3 was decreased.	The level of phosphorylated tau was significantly increased.	METTL3 enhanced autophagic phosphorylated tau clearance through the m^{6}A-IGF2BP1-dependent regulation of STUB1 mRNA.	(Tang et al., 2023)
APP/PS1 mice	Expression of METTL3 was decreased.	The level of phosphorylated tau was significantly increased.	Overexpression of METTL3 can ameliorate hippocampal damage and Aβ deposition and improve AD by enhancing phosphorylated tau autophagy.	(Tang et al., 2023)
Human umbilical vein endothelial cells and NSun2 knockout rats	NSun2 levels are reduced.	Regulation of ICAM-1 expression impacts on vascular inflammation	NSun2 deficiency protects endothelium from inflammation via mRNA methylation of ICAM-1.	(Luo et al., 2016)
Primary newborn rat microglia culture	Distinct m^{6}A epitranscriptome in microglia	Regulation of microglia pro-inflammatory response	Potential role of m^{6}A modification in regulating the inflammatory response in microglia	(Li et al., 2021)

Another field of research that should be explored further is the use of small molecules to target specific non-coding RNAs involved in the tauopathy disease onset and progression (Nguyen et al., 2021). Induced pluripotent stem cell-derived *in vitro* cellular and transgenic *in vivo* animal models provide useful tools for pre-clinical screening for drugs in various aspects of tau pathology (Avior et al., 2016; Bhattarai et al., 2017; Choi et al., 2016; Giong et al., 2021; Lee et al., 2006; Papadimitriou et al., 2018).

The field of epitranscriptome is still growing and is a great promise for therapy intervention. Identification of inhibitors or modulators targeting RNA modifications regulatory genes strongly support the idea that RNA modifications have potential as emerging therapeutic targets (Qiu et al., 2023). However, much effort is needed to characterize and the mechanisms of RNA modifications in human neurodegenerative diseases. Moreover, the challenge is now to investigate whether epitrancriptomics offers mechanisms that can be effectively targeted by low molecular weight bioavailable compounds that cross the BBB and are thus druggable (Berdasco & Esteller, 2022; Cayir, 2022).

6 | CHALLENGES, PERSPECTIVES AND FUTURE RESEARCH

A better understanding of the mechanisms that cause cerebrovascular dysfunction and tauopathy is of clinical importance allowing the development of new therapeutic strategies that can prevent and/or treat these devastating neurodegenerative disorders. Currently, there exists a need for a more detailed study and characterization of the neuroinflammation process in relation to BBB dynamics and their detrimental effects in cerebrovascular health and tau proteostasis. This could result in the discovery of potential novel therapeutic targets for the prevention of tauopathies. However, one challenge is developing therapeutic strategies that prevent neurotoxicity without compromising its neuroprotective role. Another challenge is the multiple disease mechanisms acting at the same time and need for drugs that are directed to multiple targets simultaneously, for which new technologies and approaches have started to emerge (Turgutalp et al., 2022; Wenzel & Klegeris, 2018; Zhou et al., 2019).

New avenues of research are starting in the neurodegeneration field. Scientists have tied short-chain fatty acids, churned out by some gut microbes, to cytokine production by innate immune cells which may stoke damaging glial responses in the brain mediating tau pathology and cerebrovascular alterations (Seo et al., 2023). These exciting results highlight the potential to harness the gut microbiota to prevent or slow the progression of AD and other tauopathies and raise awareness about the potential long-term effects of early life diet on brain health.

Moreover, we know that neurovascular coupling is pivotal to brain health, but whether neurovascular coupling dysfunction drive tau pathology or if tau pathology drives neurovascular coupling alterations needs further investigation. Thus, much more effort is needed to unravel cellular and molecular mechanisms contributing to the

onset of the disease and defining which mechanisms are consequences of the neurodegenerative process.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Christopoulos, et al. 2021; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Davies, Beuve, et al. 2021; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Davies, Boison, et al. 2021; Alexander, Kelly, et al. 2021).

AUTHOR CONTRIBUTIONS

Y. A. Kim, M. Mellen, C. Kizil and I. Santa-Maria contributed to the writing (original draft). Y. A. Kim, M. Mellen, C. Kizil and I. Santa-Maria contributed to the writing (review and editing). All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflict of interest.

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