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REVIEW

ApoE-calypse tau: ApoE–tau synergy in Alzheimer's disease

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Alzheimer's disease (AD), the most common cause of dementia, is characterized by the accumulation of amyloid-β (Aβ) in senile plaques and abnormally hyperphosphorylated tau proteins in neurofibrillary tangles. While much of the research has focused on Aβ, tau-mediated neurodegeneration is more closely associated with synaptic loss and cognitive decline in AD, emphasizing the need for a deeper understanding of tau pathology. In this context, the interaction between tau and *APOE*, particularly the main genetic risk factor for AD *APOE* ε4, remains underexplored. *APOE* encodes apolipoprotein E (apoE), a protein important in lipid metabolism. In addition to promoting Aβ deposition, emerging evidence suggests that *APOE* ε4 exacerbates tau-mediated neurodegeneration and tau-related pathology. This review consolidates current knowledge on the interplay between apoE and tau, highlighting its potential as a key factor in disease progression. Targeting the apoE–tau axis may offer promising therapeutic strategies to address the molecular mechanisms driving AD and primary tauopathies.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder marked by progressive memory loss and cognitive decline that exceeds normal aging. AD is the leading cause of dementia, contributing to ∼60–80% of cases, and affects over 50 million people globally. The likelihood of developing AD rises with age, impacting up to 33.4% of those over 85 (Alzheimer's Association, 2024). The disease also presents a significant economic burden, which has grown considerably in recent years (Wong, 2020).

AD can be classified into early-onset autosomal dominant AD (ADAD), early-onset non-ADAD, and late-onset AD (LOAD). ADAD is a rare hereditary form of AD linked to mutations in the *APP*, *PSEN1*, or *PSEN2* genes, typically affecting individuals under 60. LOAD, accounting for more than 95% of cases, is influenced by both environmental and genetic factors, including *TREM2* (Guerreiro et al., 2013; Jonsson et al., 2013), *SORL1* (Pottier et al., 2012), *PLD3*, and *CLU* (Karch and Goate, 2015), with the *APOE* gene being the most influential genetic risk factor (Corder et al., 1993; Belloy et al., 2023).

AD pathophysiological changes occur years before symptoms appear (Perrin et al., 2009; Jack et al., 2010). The disease is characterized by two main pathological hallmarks that develop at different timepoints throughout AD (Musiek and Holtzman, 2012): extracellular neuritic amyloid plaques (senile plaques [SPs]) primarily composed of amyloid-β (Aβ) and intracellular neurofibrillary tangles (NFTs) comprised of hyperphosphorylated tau (p-tau) (Musiek and Holtzman, 2012). NFT accumulation correlates with neuronal loss (Gómez-Isla et al., 1997), suggesting that tau pathology is closely linked to memory and cognitive decline (Gallardo and Holtzman, 2019; La Joie et al., 2020). The specific distribution of these hallmarks, particularly tau, is unique to humans (Ferrer, 2023), and the distribution of tau helps in assessing the severity of AD using the Braak staging system (Braak and Braak, 1991).

SPs and NFTs are considered central to AD progression, as reviewed recently (Knopman et al., 2021; Ferrer, 2023). While amyloid pathology appears to initiate AD, followed by tau pathology and neurodegeneration, the exact sequence and mechanisms remain unclear. Nonetheless, most treatments have targeted amyloid pathology reviewed in Karran and De Strooper (2022). Recent anti-amyloid antibodies have shown modest success in slowing cognitive decline in very mild dementia caused by AD (Cummings et al., 2024), likely because the treatment is administered too late. Even in trials targeting mild cognitive decline to prevent AD (Huang et al., 2020), or trials with ADAD patients that are treated sooner (Levin et al., 2022), the treatment is started too late. This is due to the fact that mild and very mild dementia due to AD are already a relatively advanced pathological state, as the clinical manifestations are already driven by tau pathology and other factors such as inflammation (Self and Holtzman, 2023). Therefore, further understanding the impact of tau and other important variables, such as the main genetic risk factor *APOE*, on AD progression is of great importance.

The ε4 allele of *APOE* increases the risk of LOAD (Corder et al., 1993), likely due to its very strong effect in influencing the onset

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of amyloid deposition in the brain, with the effect of *APOE* being both isoform (ε4>ε3>ε2)- and dose-dependent (Holtzman et al., 2000; Fagan et al., 2002; DeMattos, 2004; Raulin et al., 2022). Given that amyloid appears to drive tau pathology, impacting disease progression and leading to cognitive decline, *APOE* could influence tau pathology through an amyloid-mediated pathway (Therriault et al., 2021; Ferrari-Souza et al., 2023). Nonetheless, evidence suggests apolipoprotein E (apoE) could influence tau pathology through various mechanisms, aside from its effects on amyloid pathology, despite direct molecule-to-molecule interactions between tau and apoE not being well documented. This review aims to explore the relationship between tau and apoE, potentially offering new insights into AD pathogenesis.

Tau

Tau is a microtubule-associated protein predominantly found in neuronal axons and oligodendrocytes, comprising 352–441 amino acids with a molecular weight of ∼45–65 kDa due to different tau isoforms and posttranslational modifications. It participates in the preservation of the structural integrity and proper functioning of the microtubule cytoskeleton, which is essential for neuronal morphology, synaptic plasticity, and axonal transport of organelles (Robbins et al., 2021), and its functions extend to neuroplasticity and neuropathology (Sotiropoulos et al., 2017). Tau is an intrinsically disordered protein known for its high solubility that comprises four functional domains: the acidic N-terminal or projection domain, which presents three potential isoform configurations—exon 2 (1N), exons 2 and 3 (2N), or lack of inserted exons (0N); the proline-rich domain, situated in the central region of the protein and containing a binding site for SH3 proteins, which remains conserved across all isoforms; alongside the C-terminal region (C); and lastly, the basic repeat domain, which encompasses three to four pseudo-repeats (3R or 4R), each ∼30 amino acids long (Mandelkow and Mandelkow, 2012). These repeats are crucial for facilitating microtubule binding and are referred to as the microtubule-binding domain (Naseri et al., 2019) (Fig. 1).

In humans, tau is encoded by the *MAPT* gene on chromosome 17 (Grundke-Iqbal et al., 1989), and six distinct isoforms (Goedert et al., 1989) are formed through alternative splicing of exons 2, 3, and 10, which can occur in different combinations. The expression of these isoforms varies across brain regions and stages of development. For example, 3R isoforms predominate during fetal development (Goedert et al., 1989), while both 3R and 4R isoforms are expressed in the adult brain, albeit in differing ratios depending on the brain region (Waheed et al., 2023), ranging between 3 and 5% expression in the case of the 2N3R isoform, and up to 23–30% expression for the 1N3R isoform (Buchholz and Zempel, 2024). Different tauopathies can be distinguished through their distinct isoform composition. In AD, all the different tau 3R and 4R isoforms contribute to the aggregates forming paired helical filaments and straight filaments, as opposed to other tauopathies that are characterized by tangles containing specific isoforms (Buée and Delacourte, 1999). For example, Pick's disease is characterized by narrow, single protofilament fibrils composed mainly of 3R tau (Falcon et al., 2018), whereas corticobasal degeneration and progressive supranuclear palsy present unique fibril architectures composed of 4R tau (Goedert et al., 2017). There are few studies regarding the contribution of specific tau isoforms to AD pathology, although the available evidence points toward an important contribution of 1N4R and 2N4R isoforms to AD pathology (Buchholz and Zempel, 2024). It is essential for future studies to decipher the role of different tau isoforms to further understand the mechanism underlying AD pathology.

Other tau forms exist, such as the so-called "Big tau", which is double the size of regular tau due to the insertion of an extra exon 4a, and has been suggested to be protective in AD (Fischer, 2023). Intriguingly, a preprint has recently suggested that Big tau expression in AD patients is higher in the cerebellum, the brain region spared from tau pathology, indicating that it could possibly confer resistance to tau pathology (Chung et al., 2024, *Preprint*).

The functions of tau are regulated by posttranslational modifications, including acetylation, glycosylation, and phosphorylation (Mandelkow and Mandelkow, 2012). 85 potential phosphorylation sites have been identified (Drepper et al., 2020), some of which, such as Ser202, Thr205, Thr231, and Ser422, are more prominent in AD (Arakhamia et al., 2020; Wegmann et al., 2021). A disruption of normal levels of tau phosphorylation can result in tau dysfunction, which has been implicated in various neurodegenerative diseases including AD, Pick's disease, and other primary tauopathies (Kovacs, 2017). Traditionally, physiological tau was believed to be the low-phosphorylated form, whereas p-tau was thought to be associated with pathology. However, studies indicate that phosphorylation alone, at least at certain sites, does not distinguish between health and disease, as p-tau is also found in the brain during early development and in hibernating animals without indicating pathology (Stieler et al., 2011). In fact, a recent study has suggested a crucial role of tau217 phosphorylation in early development, with plasma p-tau217 levels exceeding even those found in AD patients (Gonzalez-Ortiz et al., 2025).

Different posttranslational modifications could drive differences in tau aggregates across tauopathies (Arakhamia et al., 2020), which appear to differ in size. Cryo-electron microscopy studies have shown that tau filaments in AD appear to be substantially bigger and more complex than filaments in other tauopathies (Fitzpatrick et al., 2017), such as Pick's disease (Falcon et al., 2018) or progressive supranuclear palsy (Shi et al., 2021b). In the following section, we will focus on the characteristics of tau specifically in AD.

Tau in AD

In AD, abnormal phosphorylation of tau protein reduces its affinity for microtubules, likely leading to tau mislocalization and intracellular aggregation (Martin et al., 2011). This abnormal tau undergoes further posttranslational modifications, such as truncations and acetylation, which promote its aggregation into paired helical filaments and straight filaments, forming NFTs (Sinsky et al., 2021). Interestingly, a recent study has suggested that soluble tau oligomers, rather than NFTs, may be some of the primary toxic species, disrupting tau's normal role in stabilizing the microtubule cytoskeleton, impairing axonal transport, and

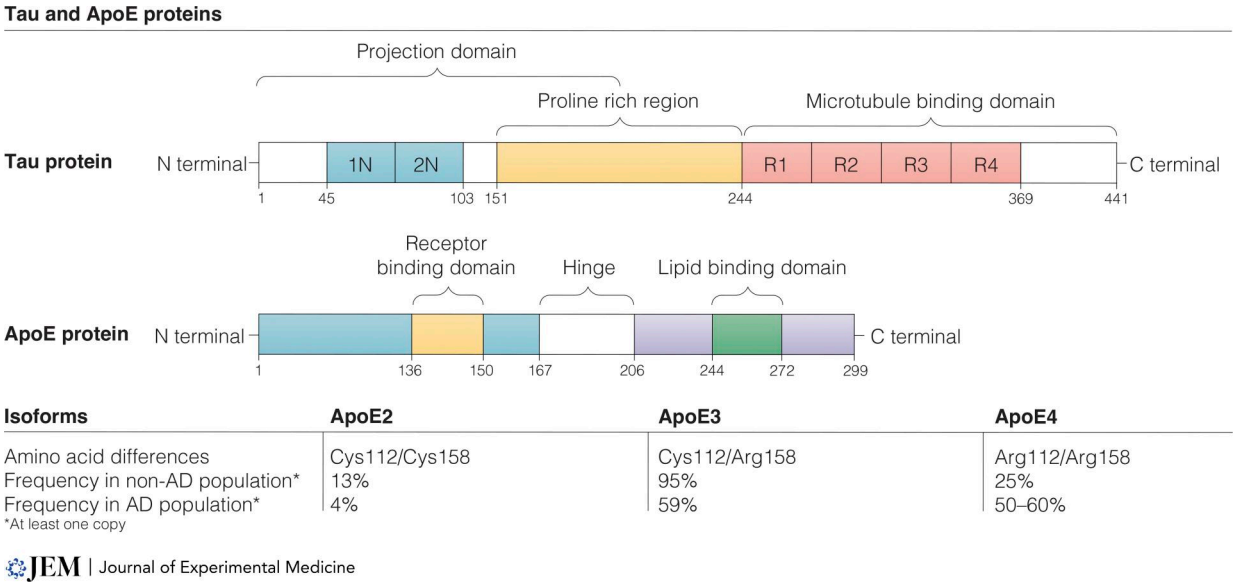

Figure 1. **Domains of tau and apoE proteins, and apoE isoform distribution.** Tau presents two domains that vary across isoforms: the projection domain (1N/2N) and the microtubule-binding region (MTBR), which can encompass either 3 or 4 repeats (3R/4R). These two domains are connected by the proline-rich region. ApoE presents three distinct regions: the N-terminal region (containing the receptor-binding domain), the C-terminal region (containing the lipid-binding domain), and a hinge region. The different apoE isoforms arise from amino acid substitutions at positions 112 and 158, where the *APOE* ε2 isoform (Cys112/Cys158) is the least frequent and the *APOE* ε3 isoform (Cys112/Arg158) is the most frequent. Within the AD population, the frequency of the risk gene, *APOE* ε4 (Arg112/Arg158), greatly increases.

compromising synaptic function (Zwang et al., 2024). Aggregated tau also accumulates as neuropil threads in brain areas without cell bodies (Braak and Braak, 1988) and can spread through the brain via axonal projections and synaptic circuits, propagating pathology through mechanisms such as synaptic transmission, exosomes, or tunneling nanotubes (Takeda et al., 2015; Pickett et al., 2017; Vogel et al., 2020).

Tau accumulation correlates with cognitive decline in AD (Giannakopoulos et al., 2003), impairing tau's role in maintaining synaptic functions and neuronal projections, which may underlie memory deficits in AD (Selkoe, 2002) and affect long-term potentiation (LTP) and synaptic plasticity (Shentu et al., 2018). Tau knockout (KO) mice exhibit some memory and synaptic plasticity deficits, while tau knockdown mice show minimal effects (Biundo et al., 2018). Contradictory findings indicate that tau deletion in a *Drosophila* model did not affect phenotype (Burnouf et al., 2016), and tau ablation in mice protected against age-related cognitive decline (Jara et al., 2020), whereas tau reduction with antisense oligonucleotides (ASOs) was seen to be highly protective (DeVos et al., 2017) and is currently being tested in human trials (Mummery et al., 2023). The discrepancies observed between mouse and *Drosophila* studies may be due to differences between murine and *Drosophila* tau, which are homologous yet not identical. It would be of interest to observe the effect of tau ablation in these animal models expressing human tau. Within murine models, the strains used both consist in tau KO; however, the strain used in Biundo et al. (2018) also involved the inclusion of GFP in the original *Mapt* gene, which could influence the effect of the KO and therefore account for the differences observed. It is also important to note that mice appear to splice tau differently to humans, even when human *MAPT* is incorporated (Saito et al., 2019). These discrepancies highlight the need for further research on tau's normal role in development and the adult brain.

Aside from losing its physiological function in AD, tau also gains toxic functions, contributing to neurodegeneration through a plethora of mechanisms (Liang et al., 2022), such as inducing oxidative stress (Kandimalla et al., 2018), inhibiting mitochondrial transport (Briston and Hicks, 2018), and inducing the innate immune response (Mancuso et al., 2019; Shi et al., 2019). AD-associated tau oligomers reduce LTP in mouse hippocampal slices (Fá et al., 2016), and reducing tau phosphorylation can restore LTP and attenuate synapse loss in PS19 mice expressing human mutant P301S tau (Seo et al., 2017). A study using pseudo-p-tau showed that hyperphosphorylation impairs synaptic function by increasing tau dendritic localization, decreasing alpha-amino-3-hydroxy-5-methyl-4-isooxazole-propionic acid (AMPA) receptor presence, and reducing AMPA and N-methyl-D-aspartate (NMDA) receptor expression, without significant spine loss (Hoover et al., 2010). The presence of oligomeric tau presynaptically reduced excitatory postsynaptic potentials and increased short-term depression (Hill et al., 2019), whereas the presence of oligomeric tau postsynaptically impaired LTP induction (Ondrejcak et al., 2018; Hill et al., 2019). The presynaptic presence of oligomeric tau may be due to its binding to synaptic vesicles, which is mediated by the transmembrane protein synaptogyrin-3, potentially leading to vesicle clustering at presynaptic terminals (McInnes et al., 2018). As such, a reduction in synaptogyrin-3 levels rescued tau-induced pre- and postsynaptic loss and ameliorated working memory and LTP impairments (Largo-Barrientos et al., 2021). Nonetheless, it is important to note that many of these studies use extremely

high concentrations of tau that would not be found *in vivo*, which could impact the results and should be taken into consideration.

Aβ can also drive tau pathology in AD. Although tau and Aβ are two independent hallmarks that have been isolated in the respective tau and amyloid hypotheses developed, various studies have demonstrated links between these elements. Aβ can accelerate the rate of tau hyperphosphorylation by enhancing the activity of GSK-3β and CDK-5, which phosphorylate tau at different sites (Zempel et al., 2010). The presence of amyloid pathology has also been shown to accelerate tau pathology and neurodegeneration *in vivo* (Lewis et al., 2001). Aβ also affects the aggregation of tau by potentiating tau cleavage, leading to self-aggregation and the appearance of toxic tau oligomers that damage neurons and can act as tau seeds to propagate the pathology (Zhang et al., 2021b). Tau can in turn mediate the toxicity of Aβ by interacting with the Fyn kinase, the phosphorylation of which is crucial to Aβ-induced synaptic toxicity (Nygaard, 2018). Synergistic effects of Aβ and tau have also been described in damaging effects on mitochondria and glial cells, thus demonstrating that these proteins act together to drive AD pathology on a plethora of levels.

Given the links between tau pathology and the cognitive decline observed in AD, it is crucial to enhance our understanding of the factors underlying and driving tau pathology. In this regard, further information on the role the main genetic risk factor, *APOE*, plays in tau pathology could be essential to enhance our understanding of AD and potentially direct new therapeutic interventions in the future.

ApoE

ApoE is a glycoprotein composed of 299 amino acids and a molecular mass of ∼34 kDa, encoded by the *APOE* gene. It is ubiquitously present in the body, with significant production in the brain and liver (Liu et al., 2013). In the central nervous system (CNS), apoE is primarily produced by astrocytes under physiological conditions (Boyles et al., 1985). Its transcription and secretion are regulated by liver X receptor (LXR) and retinoid X receptor (Liang et al., 2004; Hong and Tontonoz, 2014), whereas apoE production is influenced by lipids, hormones, and transcription factors (Kockx et al., 2018). It can also be produced by other cells in the CNS such as microglia, oligodendrocytes, choroidal epithelial cells, and cells surrounding the brain vasculature (Martens et al., 2022).

ApoE consists of three regions: (1) the N-terminal region (residues 1–167) containing the receptor-binding domain, (2) the C-terminal region (residues 206–299) containing the lipid-binding domain, and (3) a flexible hinge region (residues 168–205) (Chen et al., 2021). Human apoE exists predominantly in three isoforms, resulting from single amino acid substitutions at positions 112 and 158 (Martens et al., 2022) (see Fig. 1):

- ApoE2 (cysteine at both positions), which protects against AD relative to apoE3.
- ApoE3 (cysteine at 112 and arginine at 158), the most common isoform.
- ApoE4 (arginine at both positions), the AD risk–associated variant relative to apoE3.

These substitutions cause significant structural differences, such as disulfide-linked dimer formation in apoE2 and, to a lesser extent, apoE3, which is absent in apoE4 (Elliott et al., 2010), and a possible salt bridge that appears exclusively in apoE4 linking the N- and C-terminal domains, which are otherwise separated (Yu et al., 2014). As the structure of physiological forms of apoE that are present in lipoprotein particles is not completely understood at high resolution, structural differences between physiological forms of the different apoE isoforms need to be better determined to understand their implications (Strickland et al., 2024).

Physiological function of apoE

ApoE is synthesized *de novo* in the brain, given that plasma apoE does not cross the blood–brain barrier (BBB) (Liu et al., 2012; Chernick et al., 2019). ApoE is a component of high-density-like lipoproteins in the CNS, offering them stability and guiding their transport and function (Feingold, 2022), thus playing a key role in lipid transport and cholesterol metabolism. In the brain, its main function appears to be in glial cells where it plays a role in lipid export (Nugent et al., 2020), although apoE also assists in lipid clearance (Mahley, 2016) and cell membrane repair after injury (Tensaouti et al., 2020). Despite performing crucial functions in the brain, a case study of an $APOE^{-/-}$ individual that was cognitively normal indicates that *APOE* may not be required for adequate brain functioning (Mak et al., 2014).

For proper functioning, apoE must be glycosylated, secreted, and lipidated. Its glycosylation varies between cerebrospinal fluid (CSF) and plasma (Flowers et al., 2020), and includes O-linked glycosylation and sialylation (Kockx et al., 2007), which modulate its lipid receptor affinity and metabolic functions (Kacperczyk et al., 2021). ApoE lipidation is regulated predominantly by ATP-binding cassette transporter A1 (ABCA1) and also ATP-binding cassette subfamily G member 1, which control cholesterol efflux to apoE (Vance and Hayashi, 2010). ApoE follows a "double-belt" model when binding discoidal lipids, as two apoE proteins wrap around the lipids in an anti-parallel formation (Strickland et al., 2024). ApoE isoforms vary in lipidation and lipid-binding preferences; however, it is not yet fully understood how apoE isoforms influence lipidation, and further studies on the subject are required.

To perform its functions, apoE interacts with members of the low-density lipoprotein receptor (LDLR) family (Holtzman et al., 2012), of which LDLR itself appears to be the main apoE receptor (Fryer et al., 2005a). To bind to receptors, apoE undergoes a conformational change upon lipoprotein binding, which separates the N- and C-terminal regions and exposes the receptor-binding domain (Chen et al., 2011). ApoE dimerization could play a role in its binding to receptors (Dyer et al., 1991), either as homodimers or as heterodimers (Martens et al., 2022). ApoE isoforms exhibit different receptor affinities; apoE4 has a higher affinity for LDLR-related protein 1 (LRP1) than apoE3 (Cooper et al., 2021), while apoE2 has markedly reduced binding affinity for LDLR (Zhao et al., 2018a). These variations in affinity could potentially underlie the differential effects of apoE isoforms on AD pathology.

Role of apoE as a pathological factor in AD

Since its discovery as the primary genetic risk factor for AD, numerous studies have explored the influence of *APOE* on different aspects of the pathology. Carrying one copy of *APOE* ε4 leads to a ∼4-fold risk of developing AD, whereas two copies increase the risk 12-fold relative to *APOE* ε3 homozygotes (Strittmatter et al., 1993; Holtzman et al., 2012; Yamazaki et al., 2019). Despite being present in around 25% of the European American population, over 50% of AD cases carry an *APOE* ε4 allele (Alzheimer's Association, 2024). This significant association has inspired a recently proposed categorization of AD into familial AD, *APOE* ε4–related LOAD, and *APOE* ε4–unrelated LOAD (Frisoni et al., 2022; Fortea et al., 2024). However, this model is highly controversial given the different impact of *APOE* ε4 across ancestry (Belloy et al., 2023), as the allele increases the risk of AD more in East Asian populations compared with European and African American backgrounds (Vance et al., 2024). Therefore, the model has not yet been universally adopted as clear distinctions cannot be made at this time.

A strong link exists between *APOE* ε4 and amyloid pathology, with studies showing that it increases amyloid plaque load (Tiraboschi et al., 2004), Aβ oligomers (Hashimoto et al., 2012), amyloid seeding (Liu et al., 2017), amyloid deposition (Holtzman et al., 2000), and also alters the Aβ40:Aβ42 ratio (Fryer et al., 2005b) and reduces Aβ clearance (Castellano et al., 2011). Changes in Aβ concentration and clearance, which can be detected before amyloid deposition, vary according to *APOE* isoforms in mice: the expression of *APOE* ε4 results in the highest levels of soluble Aβ in the brain interstitial fluid and the lowest clearance rate, whereas *APOE* ε2 shows the opposite tendency (Castellano et al., 2011).

APOE ε4 exacerbates various properties that may influence AD risk in addition to its effects on amyloid deposition, including BBB breakdown (Montagne et al., 2020) and neuroinflammation (Cudaback et al., 2011; Parhizkar and Holtzman, 2022). ApoE may influence microglial responses via receptors like TREM2 (triggering receptor expressed on myeloid cells 2) (Gratuze et al., 2018), which has been implicated in various AD-related functions including Aβ and tau seeding and spreading (Leyns et al., 2019; Parhizkar et al., 2019).

Lipid dysregulation in AD may also be tied to altered apoE functions, with apoE4 being less efficient at transporting cholesterol (Zhao et al., 2017), although conflicting studies exist (Tcw et al., 2022). Mutations in transporters responsible for apoE lipidation, like ABCA1, have been linked to increased risk of AD (Nordestgaard et al., 2015), and ABCA1 deficiency in *APOE* ε4 mice increased Aβ aggregation (Fitz et al., 2012).

Some studies suggest that apoE dysfunction affects synaptic maintenance and neuronal repair (Perdigão et al., 2020); *APOE* ε4 has been associated with reduced density of synapses (Dumanis et al., 2009) and dendritic spines (Jain et al., 2013), decreased presence of pre- and postsynaptic proteins (Lin et al., 2018), decreased LTP (Trommer et al., 2004), an altered synaptic proteome and exacerbated synaptic loss (Hesse et al., 2019), and poor learning and memory (Rodriguez et al., 2013). It should be noted, however, that in humans, the presence of apoE4 is not associated with impaired cognition in the absence of AD pathology (Knight et al., 2014).

As mentioned previously, apoE glycosylation is essential for its correct functioning, with plasma apoE glycosylation potentially being linked to amyloidosis (Lawler et al., 2023). Changes in apoE glycosylation have been associated with increased Aβ levels (Chua et al., 2010), and apoE glycosylation and dimerization appear to be altered in the CSF of AD patients (Lennol et al., 2022), which could represent apoE dysfunction.

These findings highlight the multifaceted role of apoE in AD pathology, particularly the isoform-specific effects of apoE4. The role of apoE may also be influenced by epigenetic factors, in particular dietary habits, by altering *APOE* DNA methylation (Tulloch et al., 2018; Lozupone et al., 2023). Recent reviews have detailed the pathological roles of *APOE* in AD (Tzioras et al., 2019; Fernández-Calle et al., 2022; Martens et al., 2022; Parhizkar and Holtzman, 2022). This review specifically examines the impact of *APOE* on tau pathology, including tau spreading, seeding, and clearance, as well as direct interactions between apoE and tau, and effects mediated by microglia.

APOE and tau: A review of current knowledge

Given the direct binding between apoE and Aβ, much research has focused on elucidating the interactions between these proteins. Nonetheless, numerous studies have established links between *APOE* and tau pathology, with *APOE* ε4 being associated with an exacerbation of tau pathology in AD in humans (Nicoll et al., 2011). An *APOE* ε4–mediated exacerbation of tau pathology has also been reported in mouse studies (Brecht et al., 2004; Harris et al., 2004), although these studies were performed using the mouse model developed by the Huang laboratory, which presents a set of *APOE* neuronal phenotypes that have not been reported in other models. The influence of *APOE* ε4 extends beyond AD and appears to be more frequent in other tauopathies, such as chronic traumatic encephalopathy (Atherton et al., 2022) and frontotemporal dementia (FTD) (Mishra et al., 2017), in which it is linked to increased atrophy (Agosta et al., 2009) and more severe behavioral deficits (Engelborghs et al., 2006). Despite this, the extent of the contribution of *APOE* ε4 to tau pathology in these diseases varies and is less consistently established compared with AD.

Interestingly, *APOE* ε4 is associated with decreased vulnerability to primary age-related tauopathy (PART), an Aβ-independent tauopathy with milder cognitive effects (Crary et al., 2014; Bell et al., 2019). The decreased risk of PART conflicts with the increased levels of NFTs in *APOE* ε4 AD patients (Zhao et al., 2018a), suggesting that the influence of *APOE* ε4 on tau pathology is diminished in the absence of amyloid pathology. However, this decreased vulnerability may also simply reflect an underrepresentation of *APOE* ε4 carriers in this demographic, given their drastically enhanced odds of developing AD.

The protective role of *APOE* ε2 in primary tauopathies is also less clear, as emerging evidence suggests it may not confer the same well-documented protective effects seen in AD. Indeed, *APOE* ε2 has been linked to an increased risk of certain tauopathies outside of AD (Zhao et al., 2018b; Robinson et al., 2020). It is unclear whether this is truly an effect of *APOE* ε2 on

increasing risk for these diseases, or whether it simply reflects the fact that *APOE* ε2–positive individuals are less likely to develop AD pathology and are thus more susceptible to other less common brain diseases. This divergence in the effects of *APOE* ε2 further highlights the complexity of *APOE*–tau interactions. The complex association between *APOE* and tau pathology is reviewed in the following sections, starting with the effects of *APOE* on tau pathology on a macroscopic level, before describing the effects on a cellular level.

Associations between tau and APOE *in the CNS*

APOE *directs tau spreading in the human brain.* In AD, intraneuronal lesions caused by misfolded and hyperphosphorylated tau protein are key to the pathology. Traditionally, the distribution and spreading of tau lesions throughout the brain were believed to follow a well-defined pattern, known as Braak stages (Braak and Braak, 1991). In Braak stages I and II, the earliest stages of the pathology, NFTs are confined to the entorhinal and transentorhinal cortex. Tau then spreads to limbic regions, including the hippocampus, in Braak stages III and IV, before spreading throughout the neocortex in stages V and VI (Braak et al., 2006). Nonetheless, despite the supposed uniform propagation of tau, different examples of tau patterns have emerged that do not fit the pre-established Braak stages, such as the limbic-predominant phenotype and a medial temporal lobe–sparing phenotype (Ferreira et al., 2020). The differences in tau spreading could affect AD progression and may be associated with other variables, such as *APOE*. In fact, studies have shown that the spread of tau is directed by *APOE*, and alterations in its expression levels may lead to earlier and more severe tau accumulation (Montal et al., 2022). The *APOE ε4* genotype leads to a more severe and Braak stage–like medial and temporal spread of tau (Baek et al., 2020; Sanchez et al., 2021), whereas *APOE* ε4 noncarriers more frequently present a non-Braak pattern, with increased spread in the neocortex (Mattson and Arumugam, 2018; Whitwell et al., 2018) (Fig. 2).

A study by Vogel et al. (2021) described four spatiotemporal subtypes of AD: limbic-predominant, medial temporal lobe–sparing, posterior occipitotemporal, and temporoparietal. Individuals with the limbic subtype were more likely to carry the *APOE* ε4 allele and exhibited relatively better performance in global cognition but worse memory scores, despite having a lower tau tangle burden compared with other subtypes. In contrast, *APOE* ε4 noncarriers can exhibit the medial temporal lobe–sparing subtype, associated with a higher neocortical tau burden, suggesting that *APOE* may play a role in guiding tau spreading throughout the brain of AD patients. Other studies have shown that *APOE* ε4 carriers present increased medial temporal neurodegeneration, with increased vulnerability to atrophy (Donix et al., 2010), and enhanced tau pathology in the entorhinal cortex and hippocampus, independent of Aβ (Therriault et al., 2020; Singh et al., 2023). Sex may also be important in the association between tau and *APOE* ε4, with stronger interactions being described in women (Ramanan et al., 2019; Wang et al., 2021); however, an opposite effect of *APOE* ε4 dosage on brain region–specific tau deposition exclusively in men has been reported (Yan et al., 2021).

It is worth noting that the precise mechanism through which *APOE* influences tau spreading in the brain is unclear. Some studies suggest it could be mediated by the amyloid burden and through microglial and astrocytic responses affecting neuroinflammation, which could facilitate the spread of tau throughout certain brain areas, such as the entorhinal cortex. Other studies suggest that carrying the *APOE* ε4 gene increases the vulnerability of the medial temporal lobes to hypometabolism (Lehmann et al., 2014) and atrophy (Donix et al., 2010), which could lead to an increase in tau spreading. It is therefore plausible that *APOE* ε4 enhances the vulnerability of specific brain areas to tau pathology, which can then spread to other areas in the presence of Aβ.

The study of tau aggregates spreading throughout the brain *in vivo* using positron emission tomography (PET) and the tau-PET tracer ^{18}F-AV-1451 (^{18}F-flortaucipir) has high diagnostic potential, as it allows one to observe pathology progression *in vivo*. The topography of tau-PET binding correlates with cognitive deficits (Ossenkoppele et al., 2016; Aschenbrenner et al., 2018), including memory loss (Young et al., 2023), and predicts the rate of atrophy (La Joie et al., 2020). Studies implementing this tau tracer have shown conflicting results, with some showing associations between medial temporal tau and *APOE* ε4 (Weigand et al., 2021), whereas others show no association (Salvadó et al., 2021). It is worth noting that the field of tau imaging is relatively young, as such it is still imperfect. For example, off-target binding to monoamine oxidase-B in the basal ganglia can complicate interpretation of results with some tau tracers (Leuzy et al., 2019), which is likely responsible for some of the discrepancies observed. Nevertheless, novel imaging techniques and the refinement of tau-PET tracers will help in the diagnosis of AD. Studying large cohorts of individuals with AD pathology at various stages of clinical disease and healthy individuals while controlling for factors such as *APOE* will contribute to our knowledge of variables that guide tau propagation and assist in predicting AD progression.

Associations between tau and apoE in the CSF. In recent years, the field of biomarkers in the diagnosis of AD has sparked a lot of interest, given the difficulties in achieving an early AD diagnosis. In this regard, CSF biomarkers present a potential advantage over blood biomarkers due to the proximity to the brain parenchyma, allowing easier detection of certain brain-derived proteins (Blennow et al., 2010). Both Aβ and tau are found in the CSF, and alterations in their levels contribute to the diagnosis of AD (Blennow and Zetterberg, 2018).

Both total tau (T-tau) and forms of p-tau can be detected in the CSF. T-tau levels correlate with the intensity of neurodegeneration in the brain (Blennow and Hampel, 2003), which appears to be increased in AD (Olsson et al., 2016), and higher levels are indicative of stronger disease progression (Buchhave et al., 2012). T-tau levels increase following acute brain damage (Zetterberg et al., 2006), and this lack of specificity limits its diagnostic utility in distinguishing AD from other disorders. P-tau levels, in contrast, are associated with tau phosphorylation, and certain p-tau forms are more characteristic of AD (Wallin et al., 2010), as they remain unaltered following acute brain damage or in individuals lacking NFTs (Skillbäck et al.,

2014). Although p-tau forms are also present in other tauopathies, they are usually present with distinct patterns. As such, the measurement of CSF p-tau levels is included in the diagnostic evaluation procedure of AD (Self and Holtzman, 2023). In particular, levels of p-tau 181 and p-tau 217 are especially good markers of amyloid deposition in the brain, while the levels of MTBR-243 are a very good marker for tau tangle burden (Barthélemy et al., 2020; Horie et al., 2022, 2023).

The concordance between tau CSF and PET studies assessing tau is low (Gordon et al., 2016) and may depend on factors such as disease state (Wolters et al., 2020). This discrepancy is likely because these techniques reflect distinct pathological processes, as CSF biomarkers measure soluble forms of tau, whereas PET imaging detects aggregated, misfolded tau; and also due to the timing of these changes, as CSF p-tau becomes elevated before tau-PET binding occurs (Groot et al., 2023). In this regard, T-tau and p-tau in the CSF represent neurodegeneration and tau phosphorylation, respectively, at several sites related to amyloid deposition and correlate with early markers of AD, whereas ^{18}F-flortaucipir tags tau misfolding, with PET scans correlating more closely with cerebral atrophy and cognitive deficits (Ossenkoppele et al., 2021).

Other AD-related proteins can be detected in the CSF, including apoE. ApoE alterations have been described in the CSF, affecting the glycosylation and dimerization of the protein (Lennol et al., 2022), and an imbalance of isoforms in heterozygous subjects has been reported (Minta et al., 2020). Studies quantifying CSF apoE levels have produced inconclusive findings, with *APOE* ε4 carriers presenting the lowest in some studies (Riddell et al., 2008), and the highest in others (Darreh-Shori et al., 2011). These discrepancies could be due to the experimental approach, as lower apoE levels were detected in the CSF of human *APOE*–targeted replacement mice, whereas higher levels were found in the CSF of *APOE* ε4 AD patients. The simplified mouse model may therefore not recapitulate all aspects of AD pathology, and apoE4 could be subjected to degradation that does not occur during AD due to complex factors that are not accounted for in mice. It is of utmost importance to determine which mechanisms differ between human patients and the mouse models used to further comprehend why discrepancies occur and how these differences could be impacting AD.

Associations have been found between apoE and levels of T-tau and p-tau (Martínez-Morillo et al., 2014), particularly in *APOE* ε4 carriers (Deming et al., 2017; Wattmo et al., 2020), who present higher tau CSF levels (Toledo et al., 2015; Dincer et al., 2022) (Fig. 2). These associations are likely modulated by amyloid pathology (Jack et al., 2017), as *APOE* ε4 carriers present higher levels of T-tau and p-tau even before tau pathology has been developed (Lim et al., 2023), which is very likely caused by elevations in tau species due to amyloid deposition (Maia et al., 2013; Barthélemy et al., 2020). In *APOE* ε4 carriers, tau levels seem to correlate with cognitive decline, whereas p-tau181 and p-tau217 correlate with amyloid pathology (Koch et al., 2017). Interestingly, the protective effect of *APOE* ε2 on AD pathology is not reflected in tau CSF levels, although most *APOE* ε2 carriers have no elevation of p-tau in CSF due to a delayed amyloid deposition (Grothe et al., 2017).

The effect of *APOE* on tau CSF levels may be mediated by factors such as ancestry (Morris et al., 2019; Xu et al., 2024) or sex. Female *APOE* ε4 carriers reportedly have higher T-tau and p-tau levels (Altmann et al., 2014) and accelerated rates of longitudinal CSF p-tau accumulation (Buckley et al., 2019), leading to a stronger association between *APOE* and tau in women (Hohman et al., 2018). The influence of sex may be dependent on disease state, as the differences that are exacerbated in early stages of the pathology in *APOE* ε4 carriers diminish in the latter stages (Babapour Mofrad et al., 2020). Intriguingly, other factors, such as sleep deprivation, can alter the CSF levels of tau (Holth et al., 2019). Therefore, different factors should be considered when assessing associations between CSF levels of apoE and tau.

The development of plasma biomarkers, which are more accessible than the CSF, is promising, and may serve to screen for potential neurological damage or injuries, such as neurofilament light chain (Mattsson et al., 2019). In addition, plasma p-tau 217 is an excellent indicator of amyloid deposition (Barthélemy et al., 2024). A recent study correlating *APOE* ε4 with proteins involved in oxidative stress and mitochondrial function in the CSF demonstrated the same correlation when assessing plasma samples, thus showing the potential of using plasma samples (Dammer et al., 2024). Future studies should take place across different AD stages to determine which biomarkers are most useful at different time points, and when possible in the environment of primary care in order to account for the diverse populations and the possible interference of medical comorbidities (Ossenkoppele et al., 2022). For more information regarding recent advances in AD diagnostics, see Self and Holtzman (2023).

Transcriptomic links between* APOE *and tau. RNA sequencing (RNA-seq) allows the study of the transcriptomic profiles of different cell types in human AD brains, which could enhance our understanding of the different roles particular cells are playing in the disease. Studies have shown there are diverse microglial phenotypes in AD, with distinct profiles associated with Aβ and tau pathologies (Gerrits et al., 2021). Tau pathology has also been correlated with upregulated *APOE* expression in microglia, but not in astrocytes (Smith et al., 2022), which has been supported by a study identifying cell subtype–specific genetic variants that only affect microglial expression of *APOE* (Fujita et al., 2024). Regarding microglia, a *TREM2-APOE* pathway has also been shown to regulate microglial activation in neurodegenerative diseases (Krasemann et al., 2017). Astrocytic transcriptional changes have also been assessed (Sadick et al., 2022), and studies show that *APOE* follows an opposite trend and appears to be downregulated in astrocytes in AD (Grubman et al., 2019; Mathys et al., 2019).

Despite the promise surrounding RNA-seq, the approach presents certain limitations, such as the difficulty in performing high-throughput RNA profiling due to high costs and technical variability (Zhang et al., 2014; Stark et al., 2019), the loss of microglial signatures upon extraction (Thrupp et al., 2020), or the enrichment of certain cell types (Oh et al., 2022). Additional studies have also shown that the cellular isolation technique can lead to important biases when assessing microglial activation

(Kang et al., 2018a; Haimon et al., 2018). Furthermore, RNA-seq alone is unable to determine whether transcriptomic changes occur near SPs and NFTs, or whether they occur diffusely throughout the brain. As such, spatial transcriptomic methods have been developed (Zeng et al., 2023). Das et al. assessed transcriptomic changes in areas surrounding NFTs obtained *via* laser capture microdissection and showed that *APOE* ε4/ε4 was linked to the upregulation of proinflammatory, phagocytosis, cell death, protein translation, extracellular matrix, and cholesterol metabolism–associated genes, and the downregulation of neurotransmission and synaptic pathway–associated genes (Das et al., 2024) (Fig. 2). Single-nucleus RNA-seq offers an alternative approach and allows for the characterization of transcriptomic profiles of individual cells from postmortem human brain tissue (Hodge et al., 2019), and has been used to analyze the transcriptomic cellular heterogeneity in AD brains (Del-Aguila et al., 2019; Lau et al., 2020; Leng et al., 2021; Mathys et al., 2023; Sun et al., 2023). Nonetheless, the postmortem interval may be of crucial importance, as a recent study showed a postmortem interval of around 3 h significantly diminished the number of differentially expressed genes between WT and PS19 mice expressing human tau with the P301S mutation (Olney et al., 2025).

When assessing the field of RNA-seq in AD, it is also important to note that the results of studies in humans tend to vary significantly to those found in AD mouse models, given the heterogeneity of certain cell types across species (Zhou et al., 2020). Notwithstanding, various studies in murine models have described intriguing links between *APOE* and tau on a transcriptional level. A study in adeno-associated virus (AAV)–mediated P301L mice, a mouse model of tau pathology, showed that *APOE* upregulation leads to the activation of a microglial *APOE*-driven network that contributes to AD pathology (Kang et al., 2018a). In PS19 tau transgenic mice expressing human *APOE* ε4, a unique innate and adaptive immune response was found in mice with tauopathy, but not with amyloid deposition (Chen et al., 2023). Another study in THY-Tau22 mice, a different mouse model of tau pathology, found that, although tau pathology did not affect microglial gene expression to the same extent as Aβ, *APOE* was still upregulated (Sierksma et al., 2020). Importantly, some of the research models used (THY-Tau22 mice and AAV-mediated P301L) show little neurodegeneration, which could explain the discrepancy in the results observed.

Further studies are required to determine a common transcriptomic and proteomic background in AD. Furthermore, direct comparisons between transcriptomic and proteomic alterations across different *APOE* genotypes are necessary, as many studies assess individuals of a specific genotype to reduce variability, thus making the comparison difficult. Performing these studies in the brains of patients from different time points of AD could shed some light on the progression of the pathology.

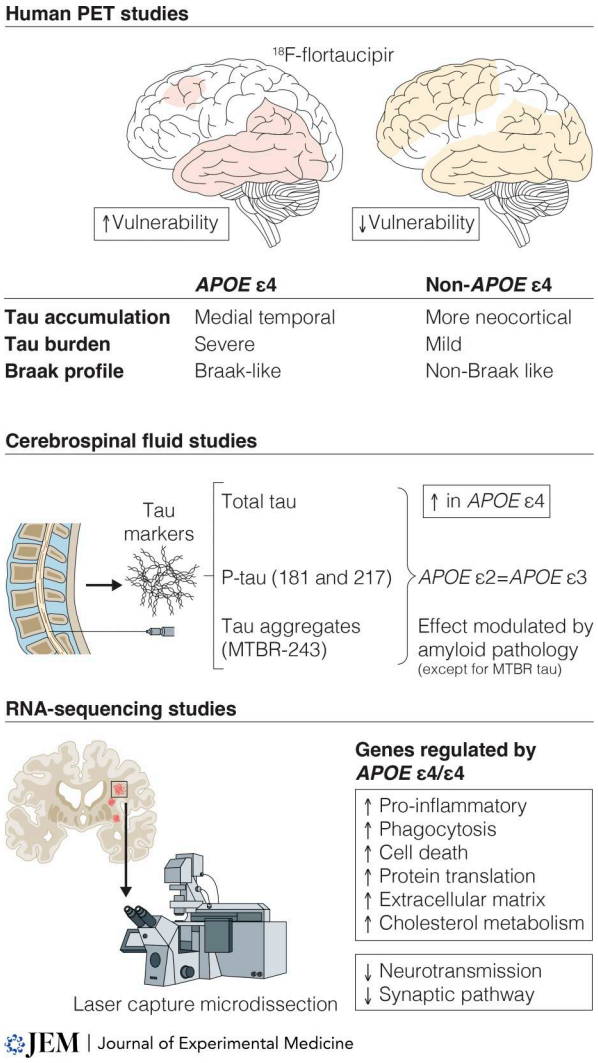

Figure 2. ***APOE* and tau in AD: Key findings from human studies.** A series of studies in humans have demonstrated that *APOE* ε4 is linked to exacerbated tau pathology. In PET studies, *APOE* ε4 has been linked to a more severe and Braak-like medial temporal accumulation of tau, whereas non-*APOE* ε4 individuals tend to present a more neocortical and mild tau burden. In the CSF, studies have shown that the levels of all tau markers (T-tau, p-tau, and tau aggregates) tend to increase in *APOE* ε4 individuals, an effect that appears to be modulated by sex and amyloid pathology (except for MTBR tau). Within the CSF, the tau biomarker levels do not appear to differ significantly between *APOE* ε2 and *APOE* ε3 individuals, despite the protective role of *APOE* ε2. RNA-seq studies have found that *APOE* ε4 appears to upregulate a series of genes, including genes associated with phagocytosis, cell death, and proinflammatory genes, whereas it downregulates neurotransmission and synaptic pathway genes.

Effects of APOE *on tau pathology at a cellular level*

Animal models to study AD. Various different mouse models have been developed to study AD, expressing different mutations that lead to amyloid and/or tau pathology. These models present an important level of heterogeneity, which is essential to take into consideration when interpreting the results obtained across studies. One of the most common models is the 5xFAD mouse model, which expresses human *APP* and *PSEN1* transgenes, two crucial genes that can cause ADAD when they present mutations. In this model, five total mutations are present: the Swedish, Florida, and London mutations in *APP*, and the M146L and L286V mutations in *PSEN1*, leading to the rapid development of severe amyloid pathology (Oakley et al., 2006). It is important to note that the 5xFAD model also presents

artifactual intraneuronal Aβ accumulation that is not present in AD or in most other models.

Other models that will be mentioned frequently in the subsequent sections focus on tau pathology, usually in the absence of amyloid pathology. It should be noted that although the following models express human mutant tau, endogenous mouse tau is also produced, leading to tau pathology in brain areas that are less relevant in AD (Sanchez-Varo et al., 2022). One such example is PS19 mice, which overexpress 1N4R human tau with the P301S mutation approximately fivefold under the control of the PrP promoter (Yoshiyama et al., 2007). The P301S mutation in humans causes early-onset FTD, and appears to lower the threshold for the protein to enter an aggregate-prone conformation. PS19 mice develop NFTs, LTP/LTD deficits, and cognitive impairment at 6 months, followed by neuronal loss at 9 months of age. Other variants of P301S mutant tau mice exist, such as the Thy1-driven P301S (Thy1-hTau.P301S) mice expressing P301S under the murine Thy1 promoter (Allen et al., 2002), or the THY-Tau22 model, which displays cognitive impairment at 10 months without motor deficits (Schindowski et al., 2006). Nonetheless, the tau pathology present in PS19 mice is more robust, given that the expression levels of human mutant tau are higher under the PrP promoter. The use of different promoters also influences the regions in which tau pathology occurs: in PS19 mice, the pathology mainly affects the hippocampus and spreads to the neocortex (Yoshiyama et al., 2007), whereas in Thy1-driven P301S, the pathology appears mostly in the spinal cord (Xu et al., 2014).

Other tau models incorporate the P301L mutation, which also causes FTD and mainly affects the hippocampus and neocortex (Mirra et al., 1999). PS19 mice show NFTs earlier than P301L mice, and synaptic loss is present from an early age. It is worth noting, however, that the median life expectancy of these animals is significantly lower and that amyloid pathology is absent in both models, thus only partially recapitulating AD-like pathology. It has been reported that the P301S mutation may cause the inability of microtubule assembly, whereas the P301L mutation could interfere with the rate of paired helical filament formation *in vitro* (Myers and McGonigle, 2019), although both leucine and serine substitutions at P301 have been shown to destabilize the local structure of tau and facilitate aggregation (Mirbaha et al., 2018). Importantly, both models lack tau ubiquitination and acetylation, which are relevant for late-stage AD, thus limiting their use (Wenger et al., 2023).

The background of these models is also of relevance, as earlier PS19 mice expressing the P301S mutation were originally bred on a mixed background and have now been backcrossed with C57BL/6J to generate a congenic line. Both lines exhibit tau inclusions and neuronal loss, although neuronal loss is observed later in the congenic model (Maruyama et al., 2013). Therefore, the specific mutations and promoters used, and the background of the specific strain of mice are of great importance and can contribute significantly to the results observed in studies. As mentioned, many models inducing tauopathy lack amyloid pathology, and thus, extrapolating these results to human AD is complex, and the relevance of the conclusions could be limited. Although double tau-amyloid models exist that likely recapitulate more aspects of AD, such as the 3xTg-AD model combining *MAPT*, *APP*, and *PS1* mutations, in this review, we will focus mainly on pure tauopathy models.

Potential mechanisms underlying* APOE *influence on tau pathology. Aside from the effects that *APOE* has on tau throughout the CNS, various early studies already demonstrated direct physical interactions between these proteins. ApoE has been detected in the damaged neurons of neurodegenerative disease patients (Farrer et al., 1995), and has been suggested to interact directly with tau (Strittmatter et al., 1994; Fleming et al., 1996) and to colocalize in NFTs (Namba et al., 1991), also in the form of apoE fragments (Huang et al., 2001; Rohn et al., 2012).

When assessing the impact apoE has on tau at a cellular level, it is important to reiterate that apoE is a secreted protein, whereas tau is present within the cytoplasm of neurons and axonal regions. Although some studies have reported that tau is also present in the extracellular space (Yamada et al., 2011), the direct interaction between the proteins in the extracellular space has yet to be definitively reported and remains controversial. Further studies using more sensitive methods, such as nuclear magnetic resonance spectroscopy, surface plasmon resonance, and/or size-exclusion chromatography coupled with multi-angle light scattering would be essential to confirm the direct physical interaction between tau and apoE. An indirect interaction may also take place through apoE receptors such as LRP1, which has been shown to bind tau and is present in both neurons and glial cells (Rauch et al., 2020).

Astrocytes can take up tau that is released from neurons (Narasimhan et al., 2017; Perea et al., 2019), which may be neuroprotective (Kovacs, 2020), an effect that could be influenced by *APOE* (Steele et al., 2022) (Fig. 3). As apoE is responsible for interacting with lipids released from neurons, it may also interact with extracellular pathophysiological forms of tau. Soluble oligomeric tau may be highly toxic (Maté de Gérando et al., 2021); therefore, excessive levels could result in damage to astrocytes (Sidoryk-Wegrzynowicz et al., 2017), which can cause a switch to a neurotoxic phenotype (Ezerskiy et al., 2022; Eltom et al., 2024), ultimately leading to damage to surrounding neurons (Wang and Ye, 2021). Intriguingly, a recent study from Eisenbaum and colleagues showed that astrocytic tau internalization is *APOE* isoform–specific, where *APOE* ε4 astrocytes appear to have the lowest rate of tau uptake (Eisenbaum et al., 2024). Although a reduced rate of tau internalization may be seen as beneficial for the reasons mentioned previously, the enhanced presence of tau in the extracellular space could facilitate its propagation or reuptake by neurons, as the rate of tau internalization is concentration-dependent (Evans et al., 2018). Furthermore, Eisenbaum et al. also demonstrated that *APOE* ε4 astrocytes presented the lowest rate of tau clearance due to an impairment in the endosomal–exosomal pathway, the mechanism through which astrocytes appear to clear tau (Chiarini et al., 2017), leading to an increased accumulation of tau within the cell. Moreover, these astrocytes presented lower resilience to neurodegenerative conditions and impacted mitochondrial homeostasis due to the lack of a compensatory response observed in *APOE* ε2 and *APOE* ε3 astrocytes. In this manner, the *APOE* ε4 genotype would be associated with both a

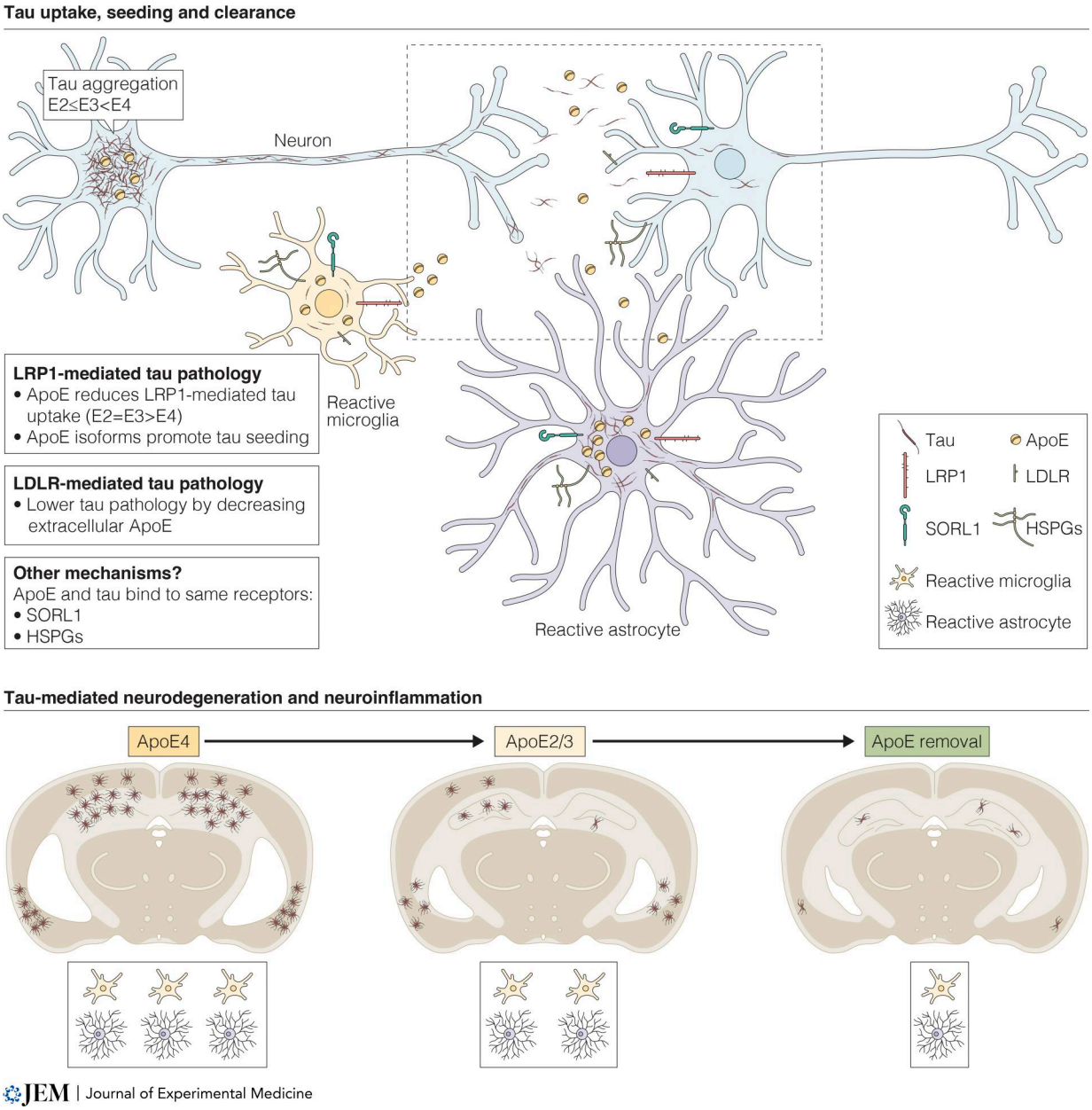

Figure 3. **Effects of *APOE* on tau propagation and tau-mediated neurodegeneration.** Despite the lack of definitive evidence suggesting direct interactions between apoE and tau, a series of studies have shown that *APOE* can modulate tau pathology. Tau aggregation varies across *APOE* genotypes, with ε4 cases presenting the highest levels and ε2 the lowest. Tau propagation and subsequent seeding could be mediated through apoE receptors capable of internalizing tau, such as LRP1, HSPGs, and SORL1. LDLR overexpression has also been seen to protect against tau-mediated neurodegeneration by reducing extracellular apoE levels. With regard to tau-mediated neurodegeneration and neuroinflammation, both appear to be exacerbated in *APOE* ε4 brains compared with *APOE* ε2 or *APOE* ε3, whereas *APOE* removal results in a decrease in both.

toxic accumulation of tau within astrocytes, exacerbating the pathology due to their increased sensitivity, and the accumulation of tau in the extracellular space due to a decreased rate of uptake and clearance through astrocytes.

Effects of* APOE *on the cell-to-cell propagation of tau. As mentioned, tau pathology propagates throughout cells in the CNS. For tau spreading to occur, tau species must be released from neurons to then enter recipient cells and induce tau aggregation (Kanmert et al., 2015). This cell-to-cell propagation can occur with tau monomers, oligomers, and aggregates (Zhang et al., 2021a) and occurs in a prion-like manner (Jucker and Walker, 2013). Different mechanisms leading to tau spreading exist, as tau oligomers can be internalized through the endolysosomal pathway (Wu et al., 2013), although tau can also spread following interaction with specialized receptors, such as heparan sulfate proteoglycans (HSPGs) or LRP1, which are also expressed in astrocytes and microglia. Astrocytes can internalize fibrillar and monomeric tau, whereas microglia phagocytose secreted tau, which can then be spread via exosomes to neurons (Asai et al., 2015), although this microglial function can be

abolished in the presence of amyloid pathology as demonstrated in studies using 5xFAD mice (Gratuze et al., 2021). The glial uptake of tau could therefore also significantly contribute to the propagation of tau.

APOE could play a role in the seeding and propagation of tau (Fig. 3), potentially through neuron communication pathways (Wegmann et al., 2019; Franzmeier et al., 2020), as human *APOE* has been seen to lead to an exacerbated response to tau pathology in PS19 mice (Williams et al., 2022). Interestingly, some studies have shown that *APOE* ε3 is associated with a more intense prion-like propagation of tau (Williams et al., 2022), whereas others have shown more Aβ-associated tau spread in *APOE* ε4 mice in the presence of sleep deprivation (Wang et al., 2023), supporting an *APOE*-dependent propagation of tau pathology, as observed in patients (Sabbagh et al., 2013; Zhao et al., 2018b; Therriault et al., 2021). Nonetheless, other studies failed to detect any influence of *APOE* on tau propagation (Koller et al., 2020; Davies et al., 2023). It is plausible that microglia might regulate this process, where apoE isoforms could play a crucial role (Shi et al., 2019; van der Kant et al., 2020; Chen et al., 2024), or that Aβ pathology is required for tau propagation to be exacerbated (Pooler et al., 2015). Furthermore, an indirect effect on tau propagation could be mediated by a loss-of-function alteration in apoE leading to cholesterol dysregulation, which is a key feature in AD (Tuck et al., 2022). Therefore, no clear consensus regarding the effect of the *APOE* genotype on tau spreading has been accomplished (Tzioras et al., 2019). These incongruences highlight the need for further studies regarding the interactions between tau and apoE, while taking into consideration crucial variables such as apoE lipidation and receptor binding, Aβ pathology, and microglial reactivity, among others.

Potential roles of apoE receptors in tau pathology. The effects of apoE internalization by certain cells through LDLR and other apoE receptors may be damaging, as suggested in a recent study (Guo et al., 2025). Lipidated apoE2 was seen to present significantly less binding to LDLR compared with lipidated apoE3 and apoE4, thus resulting in a reduced lipid burden. Furthermore, the internalization of apoE resulted in the redistribution of cell surface LDLR, which suppressed lipoprotein uptake, thus impacting lipid homeostasis and ultimately leading to enhanced lipid burden and consequent inflammatory responses, particularly in apoE4-treated cells (Guo et al., 2025). Finally, apoE also leads to the lysosomal deposition of lipofuscin, which is linked to vulnerability in the AD brain. PS19 mice expressing *APOE* ε4 accumulated even more lipofuscin in their neurons. Similarly, in induced pluripotent stem cell (iPSC)–derived neurons, adding tau seeds alongside apoE lipoprotein particles revealed that higher lipofuscin formation correlated with increased tau fibril internalization, with cells accumulating more fibrils under conditions promoting lipofuscin (Guo et al., 2025).

As mentioned previously, apoE receptors could mediate an indirect interaction between apoE and tau and could play a key part in apoE-mediated tau internalization and seeding, such as LRP1 (Rauch et al., 2020) (Fig. 3). LRP1 influences tau internalization in an apoE-dependent manner, with apoE4 presenting the highest receptor affinity and, intriguingly, the lowest levels of tau seeding, an effect that was absent in cells lacking LRP1 (Cooper et al., 2021). As such, LRP1 has been proposed as a potential regulator of tau spreading.

LDLR overexpression has been seen to protect against tau pathology and tau-associated neurodegeneration, likely by reducing the levels of extracellular apoE in PS19 mice (Shi et al., 2021a). Other apoE receptors could also be involved in the uptake of tau, such as HSPGs (Holmes and Diamond, 2014), which have been shown to internalize monomeric and oligomeric tau, but not tau fibrils (Rauch et al., 2018), and could be important for tau uptake and neuron-to-neuron transmission (Holmes et al., 2013). SORL1 is another candidate, as it has recently been shown to facilitate the internalization of monomeric and high molecular weight tau species, and to mediate tau seeding, therefore potentially playing an important role in modulating tau trafficking (Cooper et al., 2024). LRP1 has also been shown to be a receptor for monomeric and aggregated tau (Rauch et al., 2020; Chen et al., 2024). Other lesser known LDLR family members, such as LRP3 (Cuchillo-Ibañez et al., 2021), could also contribute to this process, although they have not been shown to internalize tau to date. Further studies are required to understand the importance of apoE receptors in the propagation of tau pathology.

APOE-mediated exacerbation of tau-linked neurodegeneration. Shi and colleagues studied the impact of human *APOE* and *APOE* KO in the PS19 tau mouse model (Shi et al., 2017). They found that *APOE* knock-in (KI) leads to significant amounts of brain atrophy in an *APOE*-dependent manner (ε4 > ε2/ε3 > εKO), with significant atrophy in the hippocampus, amygdala, and piriform and entorhinal cortex, as well as ventricular enlargement, whereas *APOE* KO largely protected against these effects (Fig. 3). These results were supported by *in vitro* data with high levels of neuronal cell death in P301S tau–expressing neurons cocultured with *APOE* ε4 KI glial cells. Neuronal loss was also observed in neuronal cultures treated with apoE directly, with an exacerbated effect in apoE4-treated cells, suggesting a direct role of apoE in mediating neurotoxicity. ApoE thus appears to affect tau pathology, particularly tau-related neurodegeneration, independently of Aβ. Intriguingly, these results suggest that in the context of tau pathology, *APOE* ε2 appears to act in the same manner as *APOE* ε3, rather than presenting a protective effect, which may indicate that the influence of apoE on tau is complex and may be modulated by characteristics such as lipid preference. In fact, a conflicting study by Zhao et al. showed that *APOE* ε2 is associated with increased tau pathology in progressive supranuclear palsy, another tauopathy (Zhao et al., 2018b). The same study demonstrated enhanced tau pathology in an AAV-mediated P301L model (Cook et al., 2015) expressing *APOE* ε2, with increased accumulation of p-tau, thioflavin S–positive tau aggregates, and tau-related astrogliosis, whereas *APOE* ε4 showed no effect on tau pathology (Zhao et al., 2018b). Nonetheless, it is important to note that neurodegeneration was not present in this AAV model. The discrepancies in the effects of *APOE* ε2 and *APOE* ε4 on tau pathology could be accounted for by the approaches used, as they differ significantly in various aspects, including the levels of tau expression, the tau mutation used, the age of the animals, and the lack of neurodegeneration in the AAV approach of Zhao et al. (2018b). It is therefore

plausible that both the detrimental effects of *APOE* ε4 and the protective effects of *APOE* ε2 are triggered by neurodegeneration or some aspect of tau pathology that is not present in every model, thus highlighting the need for further consensus and understanding of the models used.

APOE ε4 has also been seen to exacerbate tau pathology in AD iPSC–derived organoids, with enhanced levels of p-tau (Lin et al., 2018), an effect that can be attenuated by converting *APOE* ε4 to *APOE* ε3 (Zhao et al., 2020). iPSC-derived neurons expressing *APOE* ε4 had decreased neurite branching, higher levels of p-tau, enhanced sensitivity to calcium dysregulation, and more cell death compared with cells corrected to *APOE* ε3, and these effects appear to be independent of Aβ pathology (Wadhwani et al., 2019).

As mentioned, *APOE* ε2 has been largely seen as protective against AD; however, the studies presented here show that it appears to act in a similar fashion to *APOE* ε3 in animal models with tau pathology, as it does not exert a protective effect in the context of tauopathy. As such, the role apoE plays in propagating tau pathology likely occurs through common mechanisms between apoE2 and apoE3, such as their shared lipid preference or dimerization capacity, rather than specific gains of function that may be present in other aspects. The influence of apoE on tau propagation may also be influenced by apoE receptors; however, apoE2 and apoE3 appear to lead to similar levels of LRP1-mediated tau internalization (Cooper et al., 2021). Therefore, further knowledge regarding the protective effect of *APOE* ε2 in AD is required, which may be associated mostly with Aβ pathology.

Effects of cell type–specific* APOE *removal. The impact of astrocyte-derived apoE removal has been studied in the PS19 model, and an attenuation in the brain atrophy described previously (Shi et al., 2017) in *APOE* ε4 mice was observed, as well as significantly reduced p-tau levels, particularly in female mice (Wang et al., 2021) (Fig. 3). Removal of astrocytic *APOE* ε4 also protected against a reduction in the transcriptional levels of neuronal populations, and leads to an increased proportion of homeostatic astrocytes and microglia-dependent phagocytosis of synapses, but only when *APOE* ε4 was removed (Wang et al., 2021). No comparable effects were observed in these studies when removing *APOE* ε3, thus highlighting the specific impact of this deleterious isoform on AD pathology.

Neuronal *APOE* ε4 removal reduced NFTs, p-tau levels, tau propagation, and gliosis, while also preventing tau-induced neurodegeneration and neuronal hyperexcitability (Koutsodendris et al., 2023). Transcriptomic changes following neuronal *APOE* ε4 removal showed reduced disease-associated neuronal, astrocytic, and microglial profiles, consistent with findings that link neuronal *APOE* to exacerbated tau pathology and neurodegeneration (Zalocusky et al., 2021). Interestingly, these protective effects of neuronal *APOE* removal were observed across all genotypes, suggesting that neuronal apoE may generally play a harmful role in tauopathies. It is worth noting, however, that other studies have shown that neuron-specific overexpression of *APOE* ε4 is not sufficient to affect tau pathology (Koller et al., 2020). This discrepancy could be due to the model used, as the studies performed by Koutsodendris et al. and Zalocusky et al. used the Huang *APOE* ε4 model, which, as mentioned previously, presents a neuronal *APOE* phenotype that has not been replicated in other *APOE* knock-in or conditional KO models. As the apoE that may be expressed by neurons could be a compensatory mechanism that ultimately proves to be harmful to neurons, further studies are required to confirm whether apoE is secreted from neurons, and what role this species plays in AD. Furthermore, it is important to note that no single-cell RNA-seq studies have provided definitive evidence of *APOE* expression in neurons of AD patients, and the effects may be due to the research model used or other factors. Therefore, although the role of neuronal apoE could be an exciting field of research, further information is required.

An important aspect to be studied is the characteristics of apoE produced by astrocytes (and other cell types) under the stress conditions induced by AD. As the levels of apoE production increase, potentially to cope with the increase in lipids in the extracellular space due to neuronal death, this apoE may be functionally or structurally different to apoE produced under physiological conditions, such as through poor glycosylation. ApoE produced from reactive astrocytes may present gain-of-function effects, in which it participates in the clearance of different proteins. Although this process may be beneficial at first, the long-term consequences may exacerbate AD through the propagation of the pathology, and could explain why certain phenomena, such as the presence of tau in astrocytes or the presence of intraneuronal apoE, occur in AD.

The role of microglia in APOE *and tau interplay*

Recent research indicates that *APOE* affects AD progression partly by modulating the immune response through its influence on microglial reactivity (Fig. 4). This immunomodulatory role of *APOE* is likely linked to its indirect interactions with TREM2, a receptor primarily expressed by microglia in the CNS.

Microglia, the innate immune cells of the CNS, are crucial for maintaining brain homeostasis by monitoring and responding to threats and cellular damage (Kreutzberg, 1996; Colonna and Butovsky, 2017). In AD, microgliosis manifests and leads to changes in microglial morphology and function (Butovsky and Weiner, 2018). Key microglial states, such as disease-associated microglia (DAM) (Keren-Shaul et al., 2017; Krasemann et al., 2017) and lipid droplet–accumulating microglia (LDAM) (Haney et al., 2024), have been identified, with DAM showing increased proinflammatory and phagocytosis-related genes, and LDAM exhibiting elevated lipid processing genes.

To elucidate the role of microglia in tau propagation, pathology, and consequent neurodegeneration, studies involving microglial ablation have been conducted using AD models presenting Aβ and tau pathologies (Table 1). In a model combining 5xFAD mice for amyloid pathology and PS19 mice for tau pathology (5xFAD/P301S), microglial depletion reduced tau propagation following the injection of pre-aggregated tau (Lodder et al., 2021). Additionally, in the amyloid model of humanized APP mutant knock-in mice expressing P301L in the medial entorhinal cortex, p-tau propagation decreased, while plaque burden increased when microglia were depleted (Clayton et al.,

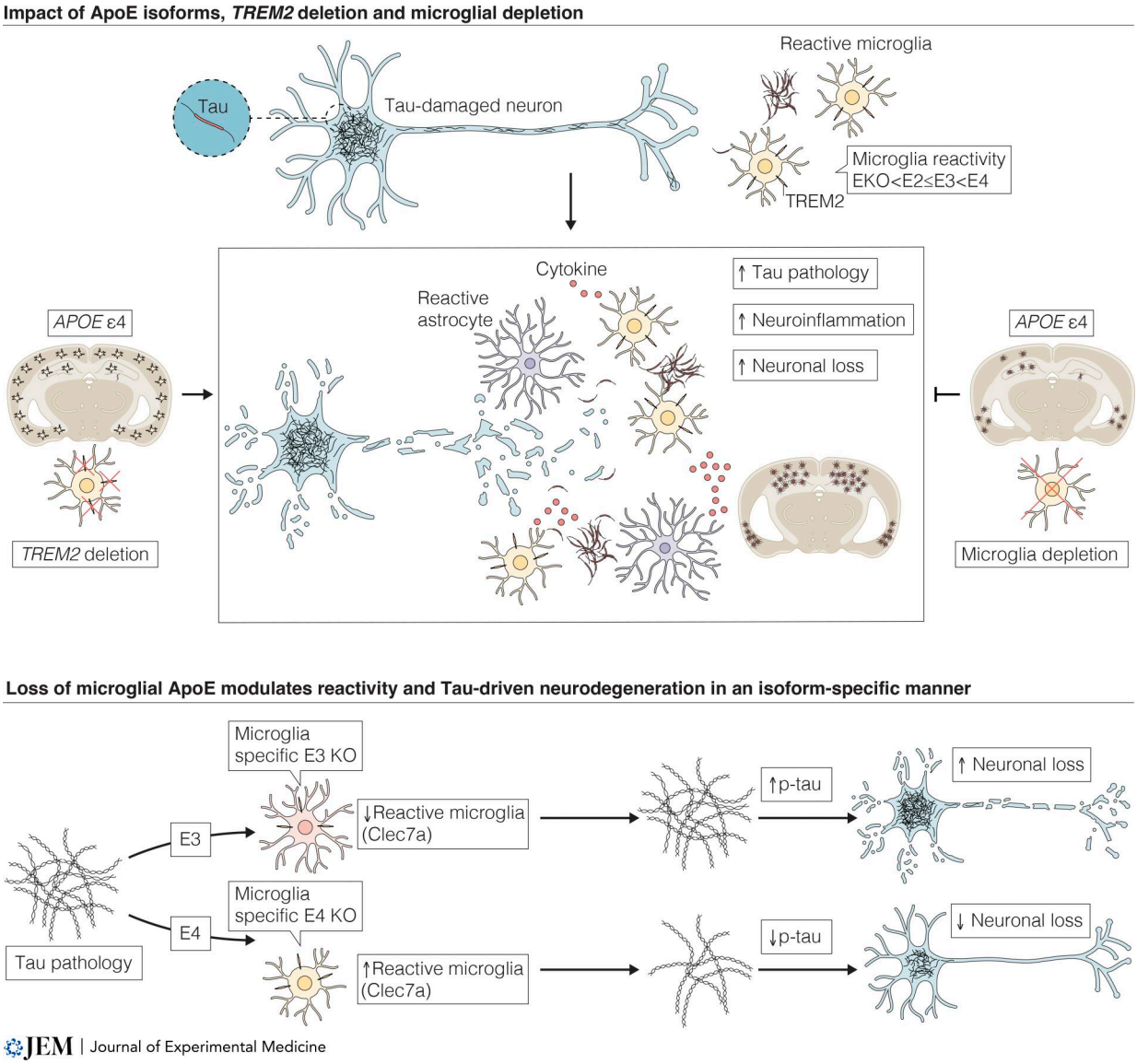

Figure 4. **Microglial contributions to the effects of *APOE* on tau-linked pathologies.** *APOE* ε4 is linked with harmful microglial states that exacerbate tau pathology. Tau-induced microglial reactivity is modulated by the *APOE* genotype, with ε4 conferring the highest microglial reactivity and ε2 the lowest, whereas microglia in an *APOE* KO context present even lower reactivity. *APOE* ε4 is linked to higher tau pathology, neuronal loss, and neuroinflammation, an effect that is exacerbated following depletion of TREM2, a crucial regulator of the microglial response. On the other hand, microglial depletion has an opposite effect and dampens the influence of *APOE* ε4 on tau pathology. In the context of tau pathology, the loss of microglial *APOE* has opposing effects according to the specific isoform. Loss of microglial apoE3 leads to a reduced number of reactive microglia, resulting in enhanced levels of p-tau and subsequent neuronal loss. In contrast, removal of microglial apoE4 enhances the level of reactive microglia, reducing the levels of p-tau and neuronal loss, thus demonstrating the negative influence of apoE4 on tau pathology. https://BioRender.com/u31n304.

2021). On the other hand, in 5xFAD mice injected with AD brain–derived tau, microglial depletion strongly exacerbated Aβ-associated p-tau seeds, whereas plaque burden remained unchanged (Gratuze et al., 2021). Despite these variations, both models showed an increase in plaque-associated p-tau+ dystrophic neurites. Decreased DAM gene expression was linked to elevated tau seeding due to inefficient clearance, despite repopulated microglial clustering around Aβ plaques (Gratuze et al., 2021). Early microglial depletion in 5xFAD mice injected with AD brain–derived tau decreased cortical plaque-associated microglia, Aβ plaque burden, and cortical APP-positive dystrophic processes, as well as tau pathology (Delizannis et al., 2021).

TREM2, a cell surface receptor predominantly expressed in myeloid cells and involved in key immune pathways, is crucial in regulating the microglial response (Ulrich et al., 2017). Studies examining TREM2 deficiency in various Aβ mouse models, including those co-expressing tau or injected with tau aggregates, have demonstrated increased Aβ-associated tau propagation (Leyns et al., 2019; Gratuze et al., 2021), elevated levels of p-tau, enhanced neuritic dystrophy, and reduced microglial responses (Leyns et al., 2019; Gratuze et al., 2021; Lee et al., 2021). Similar

Table 1. **Summary of microglia and TREM2 effects on tau-linked pathologies in animal models**

Condition		Model	Age	Tau propagation and tau pathology	Neurodegeneration	Glial reactivity	Aβ	Reference
Microglial depletion	Aβ models	5xFAD × P301S + injection of recombinant tau seeds	7 mo	↓ AT8 area (CX, HC)	↓ Neurodegeneration (CX, HC)	Remaining microglia exhibit DAM phenotype	No difference	Lodder et al. (2021)
		$App^{NL\text{-}G\text{-}F}$+ AAV-P301L-tau injection	6 mo	↓ AT8 propagation ↑ AT8 plaque area	-	↓ MGnD+ total and plaque area (Clec7a)	↑ SP N ↑ SP areas ↑ SP size	Clayton et al. (2021)
		5xFAD + injection of AD brain–derived tau	9.5 mo	↑ AT8 seeding and propagation ↑ AT8 area (CX, HC)	-	No difference in microglial reactivity (CD68) No difference in astrocyte clustering around plaques ↑ GFAP RNA expression	No difference	Gratuze et al. (2021)
		5xFAD + injection of AD brain–derived tau	6 mo	↓ AT8 signal (CX)	-	-	↓ SP load ↓ SP size	Delizannis et al. (2021)
	Tau models	P301S	4 mo	↓ AT8 ↓ globular tau oligomers ↓ NFTs No difference in AT8 or T-tau (ELISA)	↓ Neurodegeneration	↓ Expression of proinflammatory cytokines	-	Mancuso et al. (2019)
		P301S × APOE4 KI or apoE KO	9 mo	↓ AT8 area (HC) ↓ HJ14.5 (pSer396) levels (CX)	↓ Neurodegeneration (entorhinal/piriform CX, HC)	Remaining microglia exhibit reactive state (CD68)	-	Shi et al. (2019)
		C57BL/6 + injection of AAV-GFP/tau	4.5 mo	↓ tau propagation (?) ↓ $AT8^+$ cells (EC and DG)	-	-	-	Asai et al. (2015)
		Tg4510	15 mo	No differences	No difference	Microglia exhibit DAM phenotype (e.g., apoE, CD68) No change in astrocyte reactivity (GFAP)	-	Bennett et al. (2018)

Table 1. **Summary of microglia and TREM2 effects on tau-linked pathologies in animal models (*Continued*)**

Condition		Model	Age	Tau propagation and tau pathology	Neurodegeneration	Glial reactivity	Aβ	Reference
TREM2 depletion or R47H expression	Aβ models	APPPS1-21 × TREM2 KO Or TREM2 R47H + injection of AD brain–derived tau	8.5 mo	↑ AT8 seeding and propagation ↑ AT8 area (CX) ↑ AT8 signal near plaques	-	↓ Microglial reactivity (Iba1)	↑ Aβ42 in and around SP (CX)	Leyns et al. (2019)
		5xFAD + injection of AD brain–derived tau	9 mo	↑ AT8 seeding and propagation ↑ AT8 area (CX, HC)	-	↓ Microglial reactivity (Iba1) ↓ Astrocytic reactivity (GFAP)	↑ SP coverage (CX, HC)	Gratuze et al. (2021)
	Tau models	P301S + TREM2 shRNA injection	7 mo	↑ AT8, AT100, and AT180	↑ Neurodegeneration (CX, HC)	↑ Expression of proinflammatory cytokines	-	Jiang et al. (2015)
		htau × TREM2 KO	6 mo	↑ AT8 (CX, HC) ↑ AT180, PHF-1 (CX)	-	-	-	Bemiller et al. (2017)
		P301S × TREM2 KO or TREM2 haploinsufficient mice	8–9 mo	↑ AT8 area (CX of haploinsufficient mice) ↑ MC1 area (HC of haploinsufficient mice) No difference in TREM2 KO mice	↓ Neurodegeneration (ventricle area)	↑ Microglial reactivity (based on morphology in haploinsufficient mice) TREM2 KO microglial morphology similar to WT	-	Sayed et al. (2018)
		THY-Tau22 × TREM2 KO	12 mo	↑ AT8 (HC) ↑ N° of AT100$^+$ and Gallyas$^+$ neurons	↓ Neurodegeneration (surface CA1) No difference in pyramidal nucleus layer thickness	↓ Microglial reactivity (e.g., CD68, IL-1β) No difference in astrocyte reactivity (GFAP)	-	Vautheny et al. (2021)
		AAV-P301L tau injection	5 mo	↑ tau spreading	-	↑ Microglial reactivity (e.g., CD68, Clec7a, CD9 in DG) ↑ Microglial reactivity in MEC (CD9)	-	Zhu et al. (2022)
		P301S x R47H	9 mo	↓ AT8 and PG5 area (HC) ↓ AT180 area (piriform CX)	↓ Neurodegeneration (HC, entorhinal, piriform CX, pyramidal and DG layer thickness, ventricle volume)	↓ Microglial reactivity (Iba1, CD68) ↓ DAM gene expression ↓ Proinflammatory cytokines	-	Gratuze et al. (2020)
		TREM2 KO + injection of AD brain–derived tau	9 mo	↓ AT8 area No difference in HC	-	↓ Microglial reactivity (Iba1) ↓ Neuroinflammatory response No change in astrocyte reactivity (GFAP)	-	Lee-Gosselin et al. (2023)
		P301S × TREM2 KO	9 mo	No difference	↓ Neurodegeneration (entorhinal, piriform CX, ventricle volume)	↓ Microglial reactivity (Iba1) ↓ Inflammatory markers Reduced astrocytic reactivity (GFAP)	-	Leyns et al. (2017)
		TREM2^{R47H}/TYROBP (*Drosophila melanogaster*)	7 d	No difference	No difference	↓ Inflammatory response	-	Sekiya et al. (2018)
TREM2 overexpression		P301S + lentiviral-mediated TREM2 overexpression	7 mo	↓ AT8 and AT180 (CX, HC)	↓ Neurodegeneration (CX, HC)	↓ Proinflammatory cytokines ↑ Anti-inflammatory markers	-	Jiang et al. (2016)

CX: cortex; HC: hippocampus; GFAP: Glial Fibrillary Acidic Protein; SP: senile plaque; EC: entorhinal cortex; DG: dentate gyrus.

findings were observed in mice carrying the TREM2 loss-of-function R47H mutation (Leyns et al., 2019), a well-known risk factor for AD (Guerreiro et al., 2013; Jonsson et al., 2013). Additionally, TREM2 deletion in the presence of Aβ was linked to increased neuronal loss (Lee et al., 2021). Taken together, these findings indicate that in the absence of TREM2, tau accumulation and propagation are increased, thereby accelerating brain atrophy.

In the absence of Aβ pathology, microglial depletion with a CSF1R inhibitor has been shown to strikingly protect against tau-mediated neurodegeneration in mice overexpressing P301S tau protein under the murine Thy-1 promoter (Mancuso et al., 2019) and in PS19 mice expressing human *APOE* ε4 (Shi et al., 2019; Chen et al., 2023). Similar protective effects have been shown on tau propagation and neurotoxicity in AAV-GFP/tau-injected mice (Asai et al., 2015). Microglial depletion in 12-month-old Tg4510 mice, a tauopathy mouse model, resulted in only mild microglial depletion and had no impact on tau burden, cortical atrophy, or astrocytic activation despite exacerbating some DAM gene expression (Bennett et al., 2018).

TREM2 ablation or the presence of the R47H mutation has been reported to reduce microgliosis (Fig. 4). The impact of TREM2 on tau pathology is inconsistent across studies: some report exacerbation (Jiang et al., 2015; Bemiller et al., 2017; Sayed et al., 2018; Vautheny et al., 2021; Zhu et al., 2022), others report reduction (Gratuze et al., 2020; Lee-Gosselin et al., 2023), whereas some observe no effect (Lee et al., 2021; Leyns et al., 2017; Sekiya et al., 2018) in TREM2 KO or haploinsufficient mice, or those carrying the R47H mutation. Not surprisingly, the effects of TREM2 loss of function on tau-mediated neurodegeneration and astrogliosis are similarly mixed (Jiang et al., 2015, 2016; Leyns et al., 2017; Sayed et al., 2018; Sekiya et al., 2018; Gratuze et al., 2020; Vautheny et al., 2021; Lee-Gosselin et al., 2023). Additionally, synaptic and memory impairments were noted in TREM2-deficient animals (Jiang et al., 2015, 2016; Zhu et al., 2022); however, mice with the R47H mutation showed reduced synaptic loss (Gratuze et al., 2020). The conflicting results across studies likely arise from variations in experimental conditions, genetic backgrounds, mouse models, and methodologies. Some of these discrepancies could also be caused by side products of some of the TREM2 KO lines, such as an artifactual ∼350-fold overexpression of TREML1 due to the lack of UbC-neo cassette removal (Kang et al., 2018b). Therefore, differences in how TREM2 is removed, the specific models used, the variation in disease progression, and the timing of assessments can all contribute to the incongruent findings.

Recent studies propose that TREM2 and apoE are functionally connected, acting as key regulators of microglial responses to neurodegenerative challenges in AD. At the microglial level, *APOE* expression was reduced in TREM2-deficient mice (Leyns et al., 2017), and *in vitro* studies have identified apoE as a possible ligand of TREM2, hinting at a potential partnership and modulatory effect on TREM2 activity (Atagi et al., 2015; Bailey et al., 2015; Yeh et al., 2016; Jendresen et al., 2017). However, there is no direct evidence that apoE acts as a TREM2 ligand *in vivo*. ApoE appears to function downstream of TREM2 activation, modulating phagocytosis of apoptotic neurons, and regulating genes associated with neurodegeneration (Krasemann et al., 2017). The interaction between TREM2 and apoE appears to be equal across all *APOE* isoforms (Atagi et al., 2015; Bailey et al., 2015; Jendresen et al., 2017; Yeh et al., 2017), and apoE appears to regulate microglial reactivity in both TREM2-dependent and TREM2-independent manners (Keren-Shaul et al., 2017; Krasemann et al., 2017). However, in the context of tau-related neurodegeneration, TREM2-independent microglial reactivity seems to be sufficient to drive tau-linked pathologies when *APOE* ε4 is present (Gratuze et al., 2023). In PS19 mice carrying an *APOE* ε4 knock-in, neurodegeneration increased in the absence of TREM2, accompanied by elevated levels of phosphorylated and pathologically aggregated tau, despite a decrease in TREM2-dependent microgliosis. Interestingly, synaptic loss was predominantly influenced by the presence of *APOE* ε4 in PS19 mice and remained unaltered by TREM2 deficiency (Gratuze et al., 2023). These results were further supported by comparable observations in AD patients carrying the R47H and R62H TREM2 variants.

The complex relationship between *APOE* and microglial activity is a key factor in regulating neuroinflammation and tau pathology. LDAM, which are characterized by significant lipid accumulation (Marschallinger et al., 2020; Victor et al., 2022; Haney et al., 2024), are especially common in AD patients with *APOE* ε4 (Haney et al., 2024). Recent findings suggest that an LDAM-associated impairment in lipid metabolism is associated with increased neuronal p-tau accumulation and subsequent neurotoxicity (Haney et al., 2024).

APOE is upregulated in DAM (Keren-Shaul et al., 2017), and its impact on DAM activation has generated conflicting results. In PS19 mice, *APOE* ε4 led to an increase in neuroinflammation (Shi et al., 2017) and tau-mediated neurodegeneration (Shi et al., 2017; Shi et al., 2019). *APOE* ε4 reduced the expression of homeostatic microglial genes, whereas the absence of *APOE* prevented tau-induced neurodegeneration and the increase in DAM (Shi et al., 2017). Likewise, a transcriptional study in microglia lacking *APOE* revealed that *APOE* modulates Microglial Neurodegenerative phenotype (MGnD), as its deletion resulted in the reduction of microglial homeostatic factors, alongside the activation of an inflammatory transcriptional program (Krasemann et al., 2017). *APOE* also appears to regulate the transcriptional profile of MGnD, as *APOE* ε4 impedes the transition into the MGnD phenotype upon neurodegeneration in PS19 mice, whereas microglial *APOE* ε4 removal restored the MGnD phenotype linked with neuroprotection, thereby reducing tau hyperphosphorylation and ameliorating neuronal survival (Yin et al., 2023). Selective microglial deletion of *APOE* ε3 decreased the MGnD marker CLEC7A to levels comparable to *APOE* ε4 knock-in mice, suggesting that the microglial expression of *APOE* ε3 is crucial for triggering the MGnD response, and its absence accelerates neurodegeneration. Another study demonstrated that eliminating microglia or deleting *APOE* in PS19 mice provided marked protection against the worsening effect of *APOE* ε4 on tau-induced neurodegeneration (Shi et al., 2019). Interestingly, in contrast to Yin et al., they noted reduced levels of CD68+-reactive microglia, a marker for MGnD, in mice lacking *APOE* compared with those expressing *APOE* ε4. This

discrepancy may be because they explored the complete KO of *APOE*, whereas Yin et al. investigated the targeted removal of microglial *APOE* ε4. Intriguingly, the influence of *APOE* on tau pathology and immunoreactivity was abolished in the absence of microglia, indicating that microglia-mediated damage significantly contributes to the neurotoxic effects of pathological tau and is a strong driver of neurodegeneration in the presence of *APOE* ε4 in PS19 mice (Shi et al., 2019).

Taken together, *APOE* ε4 is associated with harmful microglial states that exacerbate tau accumulation and neurotoxicity, potentially leading to accelerated disease progression (Fig. 4). In contrast, the absence or selective removal of *APOE* from microglia, similar to microglia depletion, can abolish these effects, suggesting a crucial role of microglia in apoE-mediated neurodegeneration. Further research is needed to determine whether these findings are specific to *APOE* ε4.

Tau pathology treatment: apoE as a mediator

Therapies targeting Aβ pathology have been the focus of attention, and although the progress made has been substantial, there is a need for complementary therapeutic targets. The efficacy of anti-amyloid antibody treatments may be influenced by *APOE* ε4, as this allele has been linked to increased risks of amyloid-related imaging abnormalities (ARIA) during Aβ immunotherapy (Cummings et al., 2022; Filippi et al., 2022; Cummings et al., 2023). ARIA-E (edema) and ARIA-H (microhemorrhages) can occur in treated individuals, especially among *APOE* ε4 carriers. While severe symptomatic complications are rare—occurring in about 1% of treated patients—the high prevalence of ARIA in trials requires careful consideration. Notably, around 70% of patients participating in these trials present at least one copy of *APOE* ε4.

While tau pathology is a potential therapeutic target given its correlation to AD progression, no effective treatments are currently available (Imbimbo et al., 2022). Tau antibody approaches have failed to target toxic intracellular forms of tau, and to date only affect tau found in the extracellular space (Teng et al., 2022; Florian et al., 2023). ASOs successfully reversed tau pathology in PS19 mice (DeVos et al., 2017), and reduced aggregated tau as detected by tau-PET scans in humans (Mummery et al., 2023). While promising, these trials are in the experimental stages, and their long-term efficacy and safety remain to be determined.

ApoE is a focus for novel therapeutic approaches, particularly *APOE* ε4 (Vance et al., 2024) (Fig. 5). Removal of astrocytic (Wang et al., 2021), microglial (Butovsky and Weiner, 2018; Yin et al., 2023), and neuronal apoE4 (Koutsodendris et al., 2023) all protect against tau-mediated neuronal loss. Whether lowering apoE in the brain has any detrimental effects needs to be monitored, although the case study by Mak et al. (2014) indicates that humans may present normal brain function even in the absence of *APOE*. Strategies to reduce apoE4 levels, such as using ASOs (Litvinchuk et al., 2021) or LDLR overexpression (Shi et al., 2021a), show promise in preclinical models, mitigating tau pathology and neurodegeneration. An anti-apoE antibody binding to nonlipidated apoE that is bound to amyloid plaques reduces brain apoE and Aβ levels, as well as Aβ-mediated tau seeding and spreading (Liao et al., 2018; Xiong et al., 2021; Gratuze et al., 2022). Given the risks of depleting apoE, especially peripherally, novel approaches could be promising, like apoE mimetic antibodies that compete with apoE4 for receptor binding, such as HSPGs (Marino et al., 2023), small interfering RNAs (Zhang et al., 2021c), or ASOs (Litvinchuk et al., 2021). Structure-correcting molecules can restore the functionality of apoE4 to that of apoE3 or apoE2 (Chen et al., 2012), an effect replicated in iPSC-derived neurons (Wang et al., 2018). Interestingly, expressing *APOE* ε2 in APP/PS1/*APOE* ε4 mice can protect against further Aβ deposition and cognitive decline, without the necessity of removing *APOE* ε4 (Jackson et al., 2024).

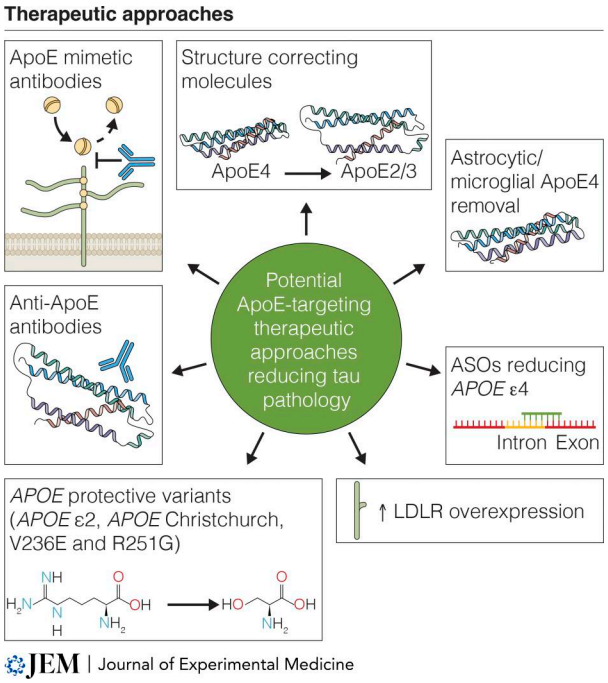

Figure 5. **Targeting the apoE–tau interplay for therapeutic interventions.** Given the evidence of the effects *APOE* has on tau pathology and tau-mediated neurodegeneration, a series of therapeutic approaches targeting tau through apoE have been proposed. Specific removal of astrocytic or microglial apoE has proven beneficial with regard to tau-mediated neuronal loss. The reduction of apoE levels through ASOs or LDLR overexpression has shown preclinical promise in reducing tau pathology. Anti-apoE antibodies targeting nonlipidated amyloid-bound apoE reduce Aβ-mediated tau seeding and spreading. To mitigate the risks of apoE depletion, apoE mimetic antibodies that compete particularly with apoE4 for binding at receptors are a potential approach. Finally, molecules correcting the structure of apoE4 to that of apoE2 or apoE3 have been shown to recover the functionality of apoE.

Augmenting glial lipid export function with an LXR agonist has recently been seen to attenuate tau pathology and neurodegeneration in the PS19 model expressing *APOE* ε4, by increasing lipid efflux and reducing astrocytic and microglial reactivity (Litvinchuk et al., 2024).

Recent findings could lead to additional therapeutic advances, such as the discovery of the Christchurch mutation in *APOE* ε3 (*APOEch*) (Arboleda-Velasquez et al., 2019), which replaces arginine with serine at position 136 within the receptor-binding domain and heparin sulfate–binding domain (Mahley et al., 1999). The homozygous presence of the *APOEch* mutation reduced tau pathology and protected against neurodegeneration

and cognitive decline in an individual with a *PSEN1* mutation despite high levels of brain amyloid.

In PS19 mice expressing *APOE* ε4 and human iPSCs, the Christchurch mutation protected against *APOE* ε4–driven tau pathology and lipid accumulation (Nelson et al., 2023). In one study, the Christchurch variant has also been seen to strongly bind tau and reduce its uptake into neurons and microglia in PS19 mice, thus reducing neurotoxicity (Chen et al., 2025). In the *PSEN1* carrier with the *APOE* ε3^{Ch} variant, there was reduced microgliosis (Sepulveda-Falla et al., 2022). Interestingly, in PS19 mice the variant protected against synaptic loss by suppressing the microglial and astrocytic response to tau-damaged neurons, whereas it enhanced the DAM microglial profile in 5xFAD mice, thus reducing plaque load (Tran et al., 2025). The variant therefore appears to have distinct modulatory effects on glial cells by enhancing DAM reactivity when faced with amyloid pathology, yet reducing neuroinflammation when in the context of tau pathology (Tran et al., 2025). Importantly, in a mouse model of amyloidosis, the *APOE* ε3^{Ch} variant reduced Aβ-induced tau seeding by enhancing the clustering of microglia around plaques and elevating microglial phagolysosomal activity (Chen et al., 2024). The phenotype seen in this model is similar to what was seen in the *PSEN1* carrier homozygous for the *APOE* ε3^{Ch} variant (Arboleda-Velasquez et al., 2019). Furthermore, recent studies have shown that *APOE* ε3^{Ch} shows impaired receptor binding, leading to reduced binding to HSPGs and decreased LDLR-dependent uptake of lipids and apoE similar to apoE2, which could be responsible for its protective effects in AD (Guo et al., 2025).

Heterozygous carriers of the mutation were recently shown to present delayed onset of AD pathology (Quiroz et al., 2024), although a conflicting study showed earlier AD onset and increased Aβ deposition in brain vessels, suggesting a potential deleterious effect (Hernandez et al., 2021). Other *APOE* variants like the V236E (or Jacksonville variant) in *APOE* ε3 and the R251G variant in *APOE* ε4 also protect against AD (Le Guen et al., 2022). For a detailed review of apoE-directed therapeutic approaches, see Serrano-Pozo et al. (2021).

Daily life habits can significantly impact AD development and progression, for example, through changes in gut microbiota (Seo et al., 2023) and sleep patterns. Sleep disturbances are common in AD and correlate with poor cognitive performance (Lucey et al., 2021) and tau pathology (Holth et al., 2017; Wang and Holtzman, 2020), as sleep deprivation increases interstitial fluid levels of Aβ and tau (Holth et al., 2019). Sleep deprivation affects microglial reactivity in a TREM2-dependent manner, which may also be influenced by apoE (as discussed above in the Microglia section) (Parhizkar et al., 2023). *APOE* ε4 may exacerbate AD progression associated with sleep deprivation by reducing Aβ clearance, increasing dystrophic neurites around plaques (Sadleir and Vassar, 2023), and decreasing microglial clustering (Wang et al., 2023). These findings highlight the complex interplay between *APOE*, tau, and AD progression influenced by various factors.

Conclusions

While also influenced by other factors such as Aβ and neuroinflammation, the development of tau pathology highly correlates with synaptic loss and cognitive deficits present in AD, pointing out its importance in the disease. The role of *APOE*, especially the risk-enhancing ε4 allele, has been well documented, but studies exploring interactions between tau and *APOE* are limited. These studies show important connections and emphasize the need for further research on their interactions in AD.

Current Aβ-targeted therapies are promising as they appear to mitigate AD symptoms; nonetheless, combinatory therapies are likely necessary to yield more positive results, highlighting the need to explore new targets like tau and apoE. Targeting the interplay between apoE and tau could be crucial for developing effective interventions. Furthermore, clarity regarding the characteristics of the apoE produced under physiological and pathological conditions would also be beneficial, as would clear conclusions regarding the differences derived from the source of apoE (e.g., neuronal vs. glial vs. other cells).

A clear consensus regarding the research models used is required. Mouse models are an invaluable tool in AD research, as they can model the progression of different aspects of pathology in a stable and reproducible manner. Nonetheless, many models incorporate Aβ or tau pathology alone, and do not control other important variables such as *APOE*. The inclusion of human *APOE* is crucial, given the differences between human and mouse apoE, and the functions they perform. Coherence in the models used would reduce the incongruences between studies and allow for more reproducible data. Importantly, the interpretation of *APOE* effects should always consider the limitations of experimental models, which may not fully replicate the complexity of human pathology.

In conclusion, apoE and tau appear to be two factors contributing to AD not only independently, but also through complex intrinsic relationships. Future studies are required to clarify how these proteins interact, directly, indirectly, or both. In a similar manner, other yet undiscovered protein interactions could be playing important roles in the multifaceted pathology that is AD, and therefore, a shift in the focus away from just the key candidates to other potential players could lead to new and important breakthroughs in the field.

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