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RESEARCH ARTICLE

Tau depletion diminishes vascular amyloid-related deficits in a mouse model of cerebral amyloid angiopathy

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Abstract

INTRODUCTION: Tau is essential for amyloid beta (Aβ)–induced synaptic and cognitive deficits in Alzheimer's disease (AD), making its downregulation a therapeutic target. Cerebral amyloid angiopathy (CAA), a major vascular contributor to cognitive decline, affects over 90% of patients with AD. This study explores the impact of tau downregulation on CAA pathogenesis.

METHODS: We crossed the Familial Danish Dementia mouse model (Tg-FDD), which develops vascular amyloid, with tau-null (mTau$^{-/-}$) mice to generate a CAA model lacking endogenous tau (Tg-FDD/mTau$^{-/-}$). Behavioral, electrophysiological, histological, and transcriptomic analyses were performed.

RESULTS: Tau depletion ameliorated motor and synaptic impairments, reduced vascular amyloid deposition, and prevented vascular damage. Tau ablation also mitigated astrocytic reactivity and neuroinflammation associated with vascular amyloid accumulation.

CONCLUSION: These findings provide the first in vivo evidence of the beneficial effects of tau downregulation in a CAA mouse model, supporting tau reduction as a potential therapeutic strategy for patients with parenchymal and vascular amyloid deposition.

KEYWORDS
cerebral amyloid angiopathy, neuroinflammation, tau, vascular amyloid

Highlights

- Tau ablation improves motor function and synaptic impair, reduces cerebrovascular amyloid deposits, and prevents vascular damage in a mouse model of cerebral amyloid angiopathy (CAA).

- Tau reduction decreases astrocytic reactivity, alters neuroinflammatory gene expression, and enhances oligodendrocyte function, suggesting a protective role against neuroinflammation in CAA.
- These findings highlight tau reduction as a potential therapeutic strategy to mitigate CAA-induced pathogenesis, with implications for treating patients with both parenchymal and vascular amyloid deposition.

1 | BACKGROUND

Cerebral amyloid angiopathy is typified by the cerebrovascular deposition of amyloid beta (Aβ) and has a close molecular relationship with Alzheimer's disease (AD) but remains clinically distinct. Vascular amyloid accumulation is found in an estimated 85% to 95% of individuals with AD,[1,2] positioning cerebral amyloid angiopathy (CAA) as one of the strongest vascular contributors to age-related cognitive decline. The mechanisms responsible for CAA pathogenesis and its downstream effects on the brain are complex and incompletely understood. Although CAA is highly associated with the accumulation of Aβ,[2] other types of amyloids have been shown to be associated with the vasculature.[3] For example, a main neuropathological hallmark of Familial British Dementia and Familial Danish Dementia (FDD) is that CAA is composed of British amyloid (ABri) and Danish amyloid (ADan), respectively.[4–6] In addition, some mutations in the *PrP* gene may result in the deposition of prion (APrP) amyloid in cerebral vessels.[7] These observations suggest that CAA is a general term for a heterogeneous group of biochemically and genetically diverse central nervous system (CNS) disorders characterized by the dynamic accumulation of different amyloid species in the vasculature. In many cases, vascular amyloidosis is accompanied by significant tau pathology.[7–9] It was recently shown that tau pathology correlates with memory impairment in patients with CAA.[10] Moreover, CAA interacts with neuritic plaques, and pathological tau species accumulate alongside amyloid in the vasculature, further accelerating neuronal damage and cognitive decline.[11,12] These findings support a unifying pathological mechanism by which vascular accumulation of amyloidogenic peptides triggers a complex pathological cascade leading to tau accumulation and neurodegeneration. In the context of parenchymal Aβ-amyloid accumulation, previous studies have shown that endogenous wild-type tau may cause synaptic damage and cognitive deficits in mouse models of AD.[13,14] In this context, tau ablation has been employed as a strategy to prevent neurodysfunction and neurodegeneration. For example, tau ablation has been shown to attenuate motor abnormalities in a Huntington's disease (HD) mouse model[15] and memory impairment in a mouse model of Parkinson's disease,[16] and to prevent deficits in spatial learning and memory following repeated mild frontal impact in wild-type mice.[17] Moreover, tau depletion prevents progressive blood–brain barrier (BBB) damage in a mouse model of tauopathy[18] and mitigates high dietary salt-induced cognitive impairment, despite persistent cerebral hypoperfusion, and neurovascular dysfunction in mice.[19] Based on this evidence, in our current study we crossed a Tau null mouse (mTau$^{-/-}$) with a mouse model for Familial Danish Dementia (Tg-FDD) to investigate the impact of the total removal of tau on CAA pathogenesis. The Tg-FDD model used in this study is characterized by the exclusive presence of CAA, consisting of the ≈4 kDa ADan amyloid, primarily in leptomeningeal cerebellar vessels, large and medium-sized parenchymal, and penetrating vessels of the brain.[5] At a late stage of CAA pathology, perivascular tau immunoreactive deposits and major glial activation have also been observed in this model.[20,21] Our results provide novel insights into how the reduction of tau prevents the behavioral, vascular, and synaptic impairment, and neuroinflammation induced by CAA-associated amyloid.

2 | METHODS

2.1 | Transgenic mouse model

Twenty-two-month-old mTau$^{-/-}$ (JAX stock # #007251), Tg-FDD/mTau$^{-/-}$, Tg-FDD, and wild-type male and female mice were used for our experiments, including cellular, biochemical, and immunofluorescence (IF) analyses. The Tg-FDD mice express an FDD-associated human mutant *BRI2* transgene that leads to the vascular accumulation of the ADan amyloid.[22] To ensure consistency in genetic background, the experimental groups were derived from breeding pairs in which a Tg-FDD mouse was crossed with either an mTau$^{-/-}$ or a wild-type mouse. Mice were housed at the Indiana University School of Medicine (IUSM) animal care facility and were maintained according to United States Department of Agriculture (USDA) standards (12 h light/dark cycle, food and water ad libitum), per the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, Bethesda, MD). Animals were deeply anesthetized and euthanized according to the IUSM Institutional Animal Care and Use Committee–approved procedures. After sacrifice, brains tissue was collected and stored at −80°C or formalin-fixed as described previously.[23,24]

2.2 | Grip strength test

Wild-type (17 male and 11 female), Tg-FDD (17 male and 16 female), Tg-FDD/mTau$^{-/-}$ (10 male and 5 female), and mTau$^{-/-}$ (8 male and

9 female) littermates were used. The grip strength of the forelimbs (front two paws) and all limbs (four paws) was evaluated using the Grip Strength Meter (Bioseb, BIO-GS3) as described previously.[24] Briefly, mice were held by the tail and lowered toward the apparatus and allowed to grab the metal grid using two or four paws. The mice were pulled backward horizontally, and the force applied to the grid just before they lost their grip was recorded as the peak tension, converted to grams by the transducer. Peak force was measured twice in succession for each mouse for the front two paws and all four paws. The mean value of both trials was used for analysis. Mice were given a minimum break of 5 min between trials.

2.3 | Electrophysiology

Hippocampal slices from wild-type (three male and one female), Tg-FDD (three male and one female), Tg-FDD/mTau$^{-/-}$ (two male and two female), and mTau$^{-/-}$ (two male and two female) littermates were used. Slices of 300 µm in thickness were cut at 0.1 mm s^{-1} with a Leica VT1200 Vibratome in ice-cold oxygenated external solution containing a sucrose-based artificial cerebrospinal fluid (aCSF; 194 mM sucrose, 30 mM NaCl, 26 mM $NaHCO_3$, 10 mM glucose, 4.5 mM KCl, 0.5 mM NaH_2PO_4, and 1 mM $MgCl_2$; pH 7.4) bubbled with 95% O_2/5% CO_2. Before cutting, mice were anesthetized with isoflurane and perfused transcardially with 10 mL of cold aCSF solution. The brains were quickly removed and blocked. After cutting, slices were transferred to an incubation chamber containing oxygenated aCSF solution at 33°C for 1 h. Slices were then kept at room temperature until recording. Recordings were done at 30°C–32°C in a submersion chamber perfused (1–2 mL min^{-1}) with aCSF solution comprising 124 mM NaCl, 4.5 mM KCl, 1.2 mM NaH_2PO_4, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 26 mM $NaHCO_3$, and 10 mM glucose, continuously bubbled with 95% O_2/5% CO_2 at a pH of 7.4 and 310 mOsm. CA1 hippocampal neurons were recorded in the presence of 2.3-dioxo-6-nitro-7-sulfamoyl-benzo[f]quinoxaline (NBQX,10 µM) and DL-2-amino-5-phosphonovaleric acid (D-APV.50 µM) and recorded at a −60 mV holding potential.

2.4 | Brain sections immunofluorescence and thioflavin-S staining

Brain paraffin sections from wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice were deparaffinized in xylene, rehydrated in ethanol (EtOH), and washed with deionized water. Then the sections were heated in a low-pH antigen retrieval solution (eBioscience) for 4 min each. Sections were blocked with phosphate-buffered saline (PBS) 5% goat serum (Invitrogen, Cat 50197Z) and 0.01% Triton X-100 for 1 h at room temperature, and then incubated overnight at 4°C with the following antibodies: anti-alpha smooth muscle actin antibody (αSMA) (ab5694, Abcam), anti-Fibrinogen (4H9) (ma5-15906, Invitrogen), anti-IBA1 (019-19741, Wako Chemicals), anti-Glial Fibrillary Acidic Protein (GFAP) (G3893, Sigma), anti-CSF3R (BS-2574R, Bioss), and anti-C3AR1 (HM1123, Hycult Biotech). The next day, sections were quickly washed three times in PBS and incubated with secondary antibodies (1:500) for 1 h at room temperature. In the case of C3AR1 and IBA1 stainings, samples were incubated with ice-cold 50% methanol in PBS after deparaffinization for 15 min, and then incubated with 0.3% TritonX-100 in PBS for 10 min. Samples were blocked with an Animal-free blocker (SP-5035-100, Vector Laboratories). Specifically, for the C3AR1 staining, a tertiary antibody recognizing the secondary antibody was used to increase the signal. To stain vascular amyloid, 0.5% thioflavin-S dissolved in 100% EtOH was incubated for 15 min at room temperature, followed by four washes with PBS (5 min. each) and mounted with Vectashield mounting media (H-1000-10, Vector Laboratories).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using online journal sources. Previous studies show tau ablation alleviates neuropathology in Alzheimer's, Huntington's, and Parkinson's disease and some tauopathies. However, tau reduction effects on cerebral amyloid angiopathy (CAA) pathology have not been yet explored.
2. **Interpretation**: In this study, crossing Tau-null mice with a Familial Danish Dementia (Tg-FDD) model indicated tau removal's impact on CAA pathology, mitigating vascular amyloid deposition, vascular damage, and neuroinflammation.
3. **Future directions**: The findings suggest that total tau loss triggers a protective response that mitigates CAA pathology. The NanoString results could serve as a basis for further multi-omic studies to identify the cell types contributing to the beneficial effects of total tau ablation. This approach appears promising as a therapeutic strategy for neurodegenerative diseases; however, further research is essential to clarify the mechanisms through which tau ablation influences CAA.

2.5 | Microscopy and image analysis

Pictures were acquired using a 60X oil objective of a Nikon A1-R laser scanning confocal microscope coupled with Nikon AR software v.5.21.03.1 Post-processing and immune-intensity quantification were conducted using ImageJ (National Institutes of Health, v1.53c). For thioflavin-S and fibrinogen quantifications, a region of interest (ROI) was traced surrounding the vasculature, delimitated by αSMA. Defined ROIs were applied to the thioflavin-S or fibrinogen channels, and the percentage of immunoreactivity intensity in the area within the ROI was quantified. For the morphological analysis of microglia and astrocytes, three-dimensional (3D) visualization of glial cells was

carried out on Z-stack (0.5 µm intervals) images (512 × 512 pixels) of brain sections. Image analysis was performed using IMARIS 9.8 3D image analysis software (Oxford Instruments, Concord, MA). An average of four microglia or three astrocytes were analyzed per image. Microglia and astrocyte ramification was quantified on blend images using automatic filament tracing to determine the number of branches and Sholl intersections (largest diameter 6.0 µm and seed points 0.3 µm). Glial cells with incomplete soma were removed manually from the analysis. Cells that were merged incorrectly by the software were separated manually. Seed points were corrected manually if the auto trace algorithm placed them in incorrect spots. CSF3F and C3AR1 immunoreactivity within microglia was quantified as described previously.[25]

2.6 | NanoString gene expression analysis

Total messenger RNA (mRNA) was purified from wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice cortices and multiplexed using the nCounter analysis system (NanoString Technologies, Seattle, WA, USA). The nCounter Neuroinflammation Profiling Panel that includes 770 genes covering the core pathways defining glial cell homeostasis and activation, was performed as described previously.[26] Briefly, 100 ng total RNA per sample ($n = 5$–6, per condition) was hybridized with probes for 16 h at 65°C following the manufacturer's protocol. Counts for target genes were normalized to the best fitting housekeeping genes as determined by the nSolver software (v4.0) to account for variation in RNA content. The background signal was calculated as the mean value of the negative hybridization control probes. The expression data were excluded when they had lower-than- average background signals from the negative controls, and probes with <100 reads for six or more samples were removed from the analysis. Significant genes for undirected differential expression were identified using the Shapiro–Wilk test for normality, followed by an unpaired *t*-test. Downstream analyses and visualizations of gene expression datasets were performed using the nSolver software and GraphPad Prism.

2.7 | Immunoblot analysis

Western blot was performed as described previously, with some modifications.[20] Briefly, brain samples were homogenized in ice-cold 1X Tris-buffered-saline buffer (TBS) containing protease and phosphatase inhibitors, followed by sonication and centrifugation (15,000 × *g*, 15 min, 4°C). Protein concentration was measured via Bicinchoninic acid (BCA) assay (Bio-Rad). Samples were run on a 4%–12% Sodium dodecyl sulfate polyacrylamide (SDS-PAGE) gel, transferred to nitrocellulose, and blocked with EveryBlot buffer (12010020, Bio-Rad). Membranes were incubated overnight with the ITM2B/BRI2 antibody (1:1000, SC-374362, Santa Cruz) in 5% BSA TBS-Tween. Bands were detected via chemiluminescence (SuperSignal West Pico, ThermoFisher) and quantified using ImageJ (National Institutes of Health)

2.8 | Statistics and reproducibility

Sample sizes were determined based on previous publications. Sex was included as a biological variable when the sample size provided sufficient statistical power to detect potential differences. The experimental analyses and data collection protocols were performed blind unless otherwise stated. All data were analyzed for normality and outliers, followed by the appropriate statistical comparisons using GraphPad Prism, as detailed in each figure legend. Data are presented as the median ± standard error of the mean (SEM) unless otherwise stated. *, **, and *** denote $p < .05$, $p < .01$, and $p < .001$, respectively.

3 | RESULTS

3.1 | Tau depletion recovers motor strength in the Tg-FDD mouse model

Reducing endogenous tau alleviates behavioral abnormalities including memory and motor deficits in AD, Parkinson's disease, and Huntington's disease mice models,[13–16] and prevents spatial learning deficits in wild-type mice after mild frontal impacts.[17] To evaluate if reducing tau levels could produce beneficial effects in the context of CAA pathogenesis, we subjected 22-month-old Tg-FDD and Tg-FDD/mTau$^{-/-}$ mice to two-paw and four-paw grip strength tests, measuring the strength of the front two paws and all four paws, respectively. In the two-paw grip strength test, Tg-FDD mice showed significantly reduced grip strength compared to wild-type litermates, deficit that was not observed in Tg-FDD/mTau$^{-/-}$ mice (Figure 1A), suggesting a beneficial effect of endogenous tau ablation in a mouse model of CAA. The improvement in grip strength due to tau depletion was observed in male and female mice (Figure 1A). The same trend was observed when testing four-paw grip strength for male and female mice, suggesting that motor strength recovery induced by tau depletion was sex independent (Figure 1B). Of interest, impairment in inhibitory synapses has been previously associated with vascular amyloid deposit in the Tg-FDD model.[23] Therefore, we examined the status of γ-aminobutyric acid (GABA) transmission by measuring spontaneous inhibitory postsynaptic current (sIPSC) recordings in CA1 pyramidal neurons in the Tg-FDD and Tg-FDD/mTau$^{-/-}$ mice (Figure S1A). As reported previously, Tg-FDD mice displayed a significant decrease in the sIPSCs amplitude that was not recovered in the Tg-FDD/mTau$^{-/-}$ mice (Figure S1B). However, when we measured the sIPSC frequency, we found an inhibitory synaptic impairment in Tg-FDD that was partially recovered in the Tg-FDD/mTau$^{-/-}$ mice (Figure S1C). These findings suggest that tau downregulation prevents the alterations in presynaptic functions observed in the Tg-FDD model but does not influence the alterations in postsynaptic function observed in this model of CAA.

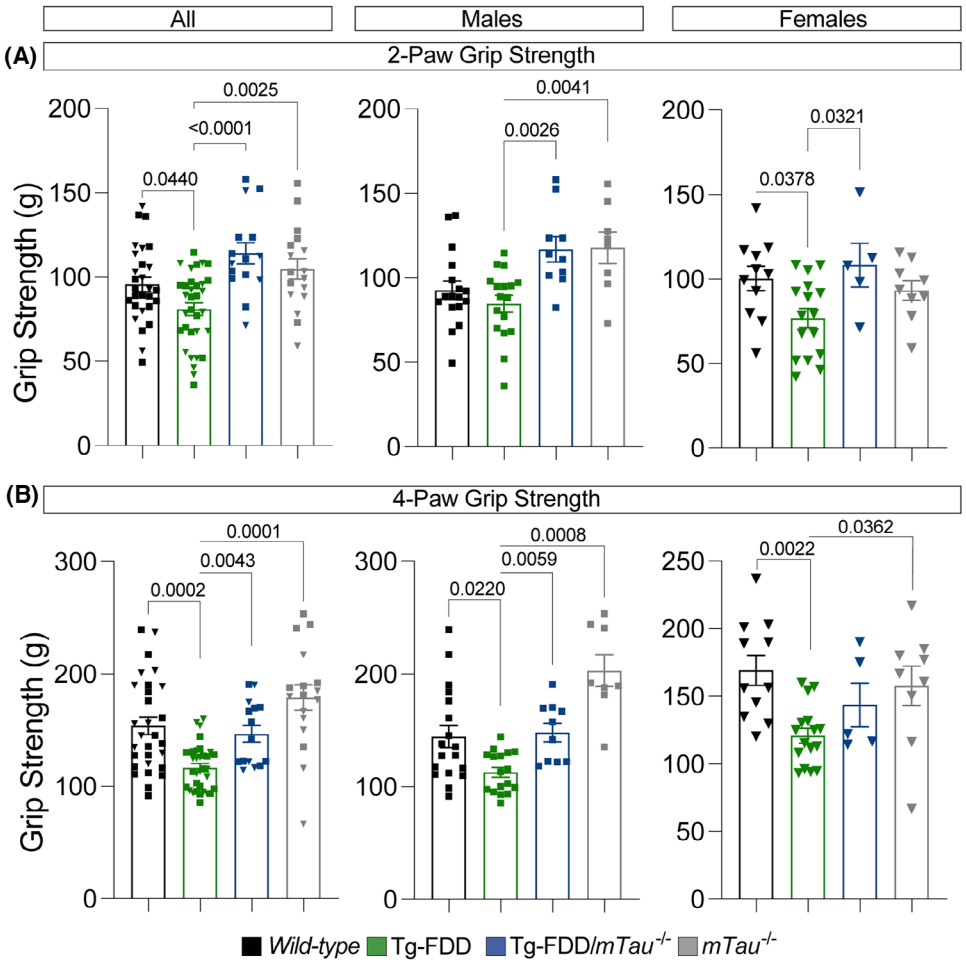

FIGURE 1 Reducing endogenous tau ameliorates motor impairment in a mouse model of CAA. Tg-FDD mice present lower grip strength compared to wild-type mice, whereas Tg-FDD/mTau$^{-/-}$ mice present recovery of motor function in the (A) 2-paw Grip Strength and in the (B) 4-paw Grip Strength. Data are shown as mean ± SEM *(females, inverted triangles; males, squares)*. Selected pairwise comparisons were assessed using one-way ANOVA followed by Sidak's multiple comparison test. Wild-type $n = 29$, Tg-FDD $n = 33$, Tg-FDD/mTau$^{-/-}$ $n = 15$, mTau$^{-/-}$ $n = 17$. ANOVA: analysis of variance; CAA, Cerebral amyloid angiopathy; SEM, Standard error of the mean.

3.2 | Reduction of endogenous tau protects against vascular amyloid deposition in the Tg-FDD mouse model and prevents vascular damage

Tau suppression does not have an effect on parenchymal amyloid deposition in the hAPP-J20 mouse model despite having a beneficial effect on behavioral improvement.[13,27] To determine whether tau ablation affects vascular amyloid accumulation, we performed thioflavin-S staining in the cerebral cortex of the Tg-FDD and Tg-FDD/mTau$^{-/-}$ mice (Figure 2A). The Tg-FDD/mTau$^{-/-}$ mice showed a marked reduction in thioflavin-S signal in vasculature compared to Tg-FDD mice, indicating that tau depletion reduces vascular amyloidosis in a sex-independent manner (Figure 2B). The decrease on vascular amyloid deposition was not due to an effect of tau ablation over the BRI2 transgenic protein levels (Figure S2A, B). It has been well established that cerebrovascular damage leads to extravasation and deposition of the plasma protein fibrinogen.[28] Therefore, to assess vascular damage, we evaluated the accumulation of fibrinogen in wild-type, Tg-FDD, and Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice (Figure 3A). We first evaluated the increase of fibrinogen immunoreactivity in Tg-FDD mice compared to wild-type, suggesting cerebrovascular damage in this model of CAA (Figure S2C). Of interest, when analyzed by sex, this effect was present only in male mice (Figure S2C), suggesting that vascular damage from amyloid deposition is sex dependent. When we evaluated in the context of tau depletion, downregulation of murine tau in male mice prevented fibrinogen deposition (Figure 3B), suggesting that endogenous tau downregulation may be protective in the context of vascular damage.

3.3 | Tau depletion ameliorates astrocytic reactivity in Tg-FDD male mice

Our previous findings demonstrated that in the Tg-FDD model of CAA, robust astrogliosis independent of microglial immune activation is a primary response to vascular amyloid deposition.[29] Therefore, to investigate whether endogenous tau reduction affects glial

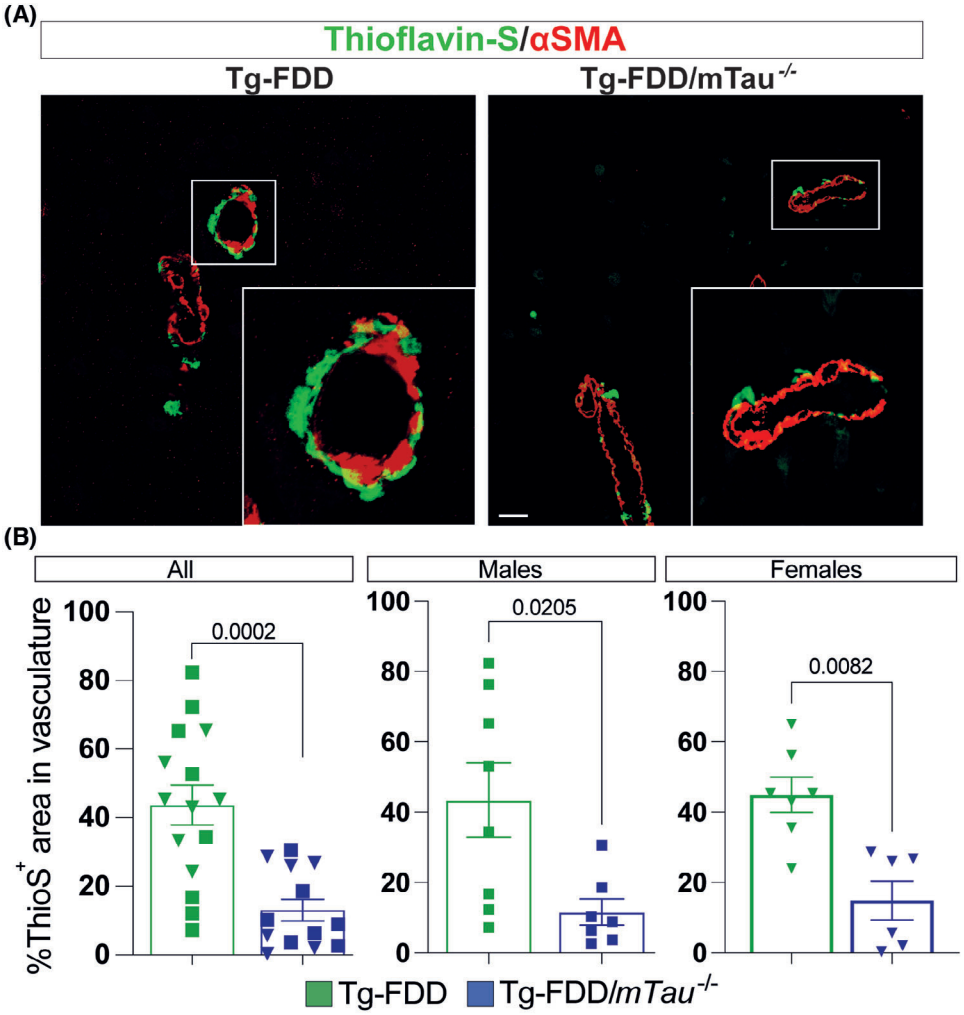

FIGURE 2 Total ablation of tau decreases vascular amyloid in the Tg-FDD mice. (A) Immunofluorescence against alpha smooth muscle actin (αSMA-red) and thioflavin-S staining (green) showing vascular amyloid deposition in the brain cortex of Tg-FDD and Tg-FDD/mTau$^{-/-}$ mice. *Scale bar: 20 μm.* (B) Quantification of percentage of thioflavin-S surrounding area in the perivasculature. Data are shown as mean ± SEM *(females, inverted triangles; males, squares)*. Shapiro–Wilk Normality Test and Mann–Whitney test were performed. Tg-FDD $n = 15$, Tg-FDD/mTau$^{-/-}$ $n = 13$.

reactivity, we stained brain cortex tissue from wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice using the astrocyte marker GFAP and the microglial marker IBA1. Astrocyte morphology analysis (Figure 4A) revealed an increased number of astrocytic branches in Tg-FDD mice compared to wild-type, an effect that was suppressed in Tg-FDD/mTau$^{-/-}$ mice (Figure 4B). A similar trend was observed using Scholl intersection analysis, reflecting the complexity of astrocyte branching (Figure 4C). When analyzed by sex, we only observed astrocytic reactivity in male Tg-FDD mice (Figure 4A–C) that showed a trend to decrease when tau was depleted (Figure 4A–C). Considering the central role of astrocytes in the neurovascular unit, the sex-dependent astrogliosis observed in the Tg-FDD could be due to the fact that only male mice present major cerebrovascular impairment measured by fibrinogen accumulation in this model of CAA (Figure 3). Notably, we observed that astrocytes are significantly less reactive in male and female mTau$^{-/-}$ mice in comparison to Tg-FDD. This observation supports our previous study in cell culture, where we observed how mTau$^{-/-}$ astrocytes are less reactive, adopting a neuroprotective profile.[26] We previously reported that no major microglia reactivity is observed in relation to vascular amyloid deposition in the Tg-FDD mice.[29] In concordance with our previous findings, we did not observed changes in microglia reactivity through morphology analyses when comparing all the conditions (Figure 4D–F).

3.4 | Tau ablation improves inflammatory profile and oligodendrocyte function associated with CAA

We used a NanoString Neuroinflammation panel to analyze the expression of 770 genes, allowing for a comprehensive assessment of 23 neuroinflammatory pathways. This analysis was performed on total mRNA extracts from the brain cortex of male wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice. Because vascular damage and astrocytic reactivity alterations were observed exclusively in male

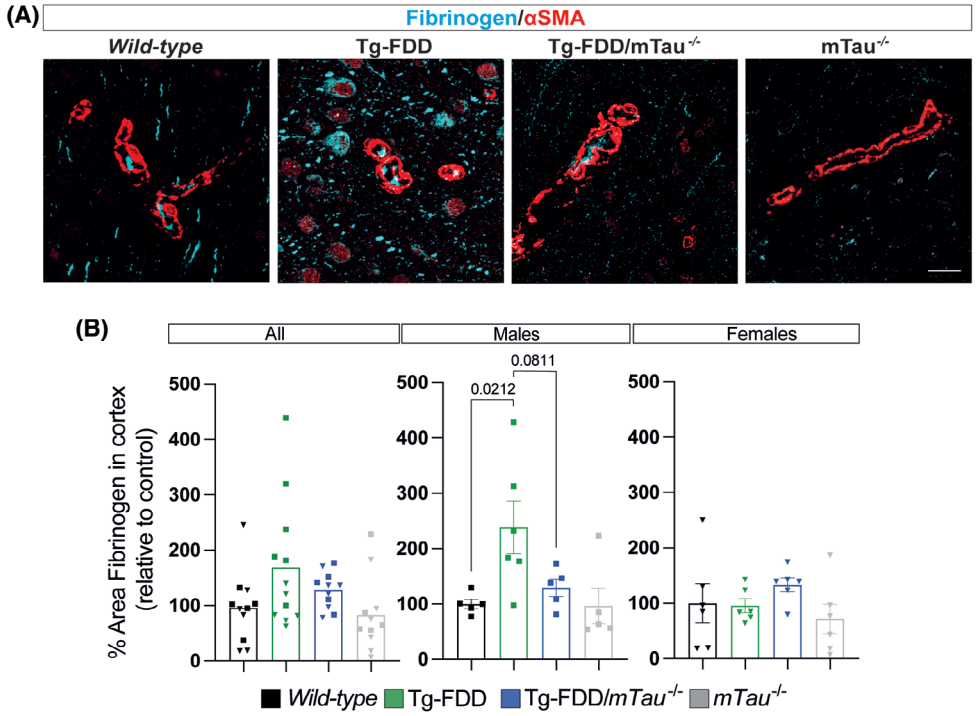

FIGURE 3 Tau ablation reduces fibrinogen deposition in the Tg-FDD mice. (A) Immunofluorescence against fibrinogen (cyan) and αSMA (red) in the brain cortex of wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice. *Scale bar: 20 μm.* (B) Quantification of the percentage of positive area for fibrinogen in cortex. Data are shown as mean ± SEM (females, inverted triangles; males, squares), One-way ANOVA Tukey's multiple comparisons test. Wild-type $n = 11$, Tg-FDD $n = 12$, Tg-FDD/mTau$^{-/-}$ $n = 11$, mTau$^{-/-}$ $n = 12$).

mice, only male mice were included in the NanoString analysis. Nineteen genes were upregulated in Tg-FDD mice, compared to eight in wild-type mice (Figure 5A and Table S1**: NanoString DEGs -Differential Expressed genes-**), indicating a heightened inflammatory profile in Tg-FDD mice. This inflammatory response was reduced when tau levels were lowered, as shown by 13 upregulated genes in Tg-FDD versus 9 in Tg-FDD/mTau$^{-/-}$ mice (Figure 5B and Table S1**: NanoString DEGs)**. Next, we analyzed pathway annotation scores (Figure 5C), which consolidate information from multiple genes belonging to a specific pathway into a single score. When compared to wild-type mice, CAA alterations in the Tg-FDD mice led to overexpression of several genes classified as part of microglia function (green highlighted genes), oligodendrocyte function (red highlighted genes), and cytokine signaling (blue highlighted genes). *Ccr5* is classified as part of microglia function and cytokine signaling (dark cyan). These alterations were recovered to wild-type levels when tau was reduced (Figure 5C and Figure S3A–C). A complete list of the genes associated with microglia function (Figure S3D), oligodendrocyte function (Figure S3E), and cytokine signaling (Figure S3F) is provided in the heatmaps of Figure S3. We further evaluated the DEGs in wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice by plotting the normalized individual counts (Figure 5D). Our results showed that 12 genes were influenced by amyloid deposition in the Tg-FDD mice, an effect that was mitigated when tau levels were reduced, either trending toward an increase or decrease. Notably, network analysis revealed that the 11 genes that were impacted by CAA and tau depletion showed interactions (Figure 5E) with Gene Ontology (GO) terms related with "regulation of natural killer cell chemotaxis" (GO:2000501, biological process) and "chemokine activity" (GO:008009, molecular function). There were two clusters clearly identified: cytokine activity (from the annotations "microglia function" and "cytokine signaling") and myelination (from the annotation "oligodendrocyte function"). As shown in the volcano plots in Figure 5A and 5B, the neuroinflammatory profile of Tg-FDD mice is characterized by elevated expression of *Abcc3*, *C3ar1*, *Jag1*, *and Spp1* genes and decreased expression of *Csf3r*. Although *Abcc3*, *C3ar1*, *Spp1*, and *Csf3r* are highly expressed in microglia, *Jag1* is expressed in endothelial cells.[30] The colony-stimulating factor 3 receptor (CSF3r), also known as granulocyte colony-stimulating factor (G-CSF) is decreased in the cerebrospinal fluid of patients with AD.[31] Furthermore, CSF3r administration has shown neuroprotective effects in a rat model of Aβ-induced memory loss, and has been reported to enhance cognitive function in healthy adults older than 45 years of age following subcutaneous injection.[32,33] Considering this, we analyzed CSF3r levels in the brain cortex of wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice (Figure 6A). Consistent with the NanoString gene expression data, we observed a significant decrease in overall CSF3r immunoreactivity in Tg-FDD mice compared to wild-type mice in both males and females. This decrease was partially recovered when tau levels were reduced (Figure 6B). The same trend was observed when we analyzed CSF3r immunoreactivity specifically in microglia (Figure 6C, D). Of interest, protective effects of C3AR1 downregulation has been previously shown in the

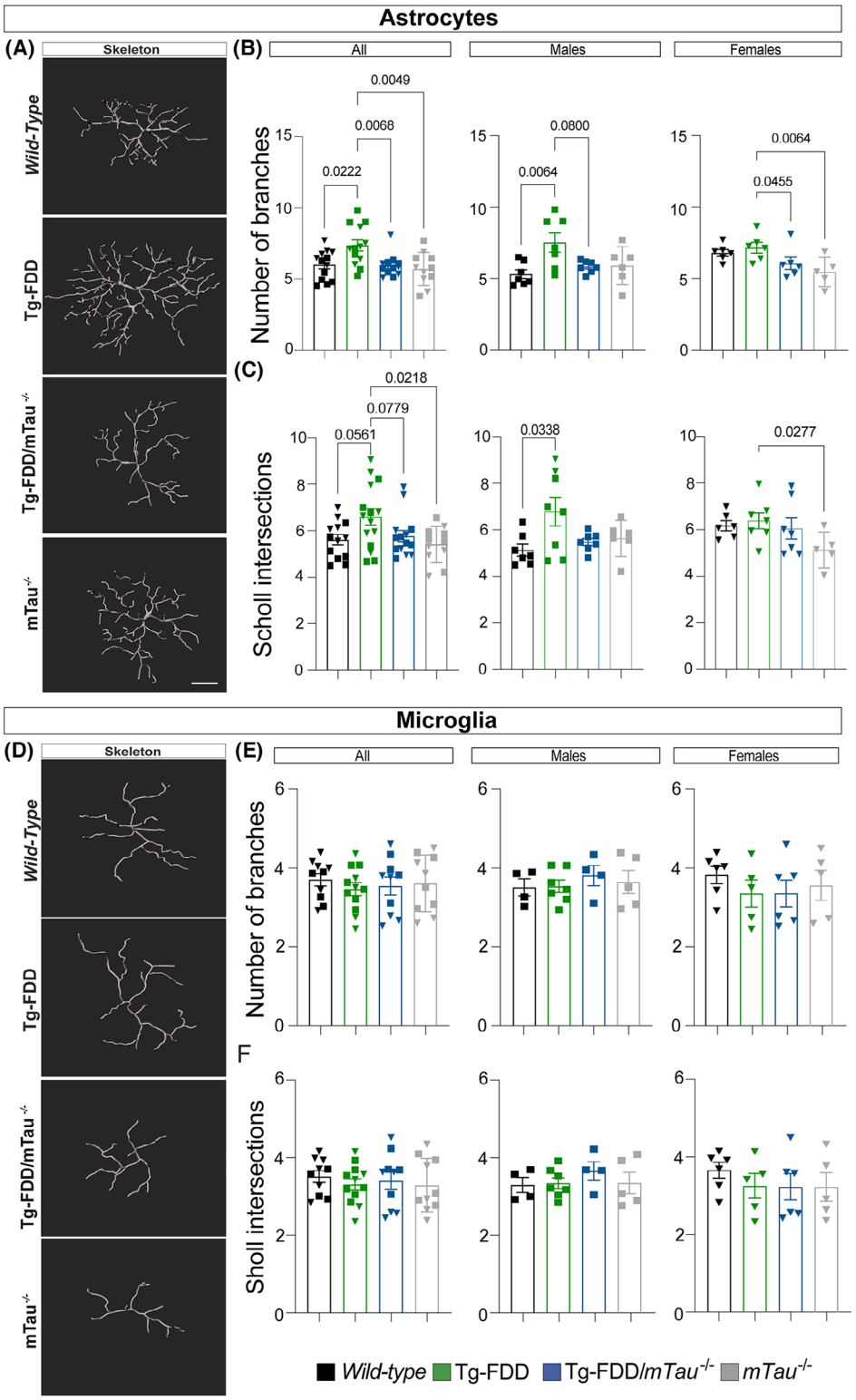

FIGURE 4 Tau ablation affects astrocytic but not microglia's morphology. (A) Representative Imaris 3D reconstructions from astrocytes stained with GFAP. Individual astrocytes were selected, isolated, and skeletonized for analysis from brain cortex of wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice. (B–C) Quantification of the average of astrocytic number of branches (B) and Scholl intersections (C). Data are shown as mean ± SEM, one-way Kruskal–Wallis test followed by Dunn's multiple comparisons test. $n = 11–13$ animals per condition; an average of 40 astrocytes per animal were analyzed. (D) Representative Imaris 3D reconstructions from microglia stained with IBA1. Individual microglia were selected, isolated, and skeletonized for analysis from brain cortex of wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice. (E–F) Quantification of the average of microglial number of branches (E) and Scholl intersections (F). Data are shown as mean ± SEM, One-way Kruskal–Wallis test followed by Dunn's multiple comparisons test. $n = 10–12$ animals per condition; an average of 50 microglia per animal were analyzed (females, inverted triangles; males, squares).

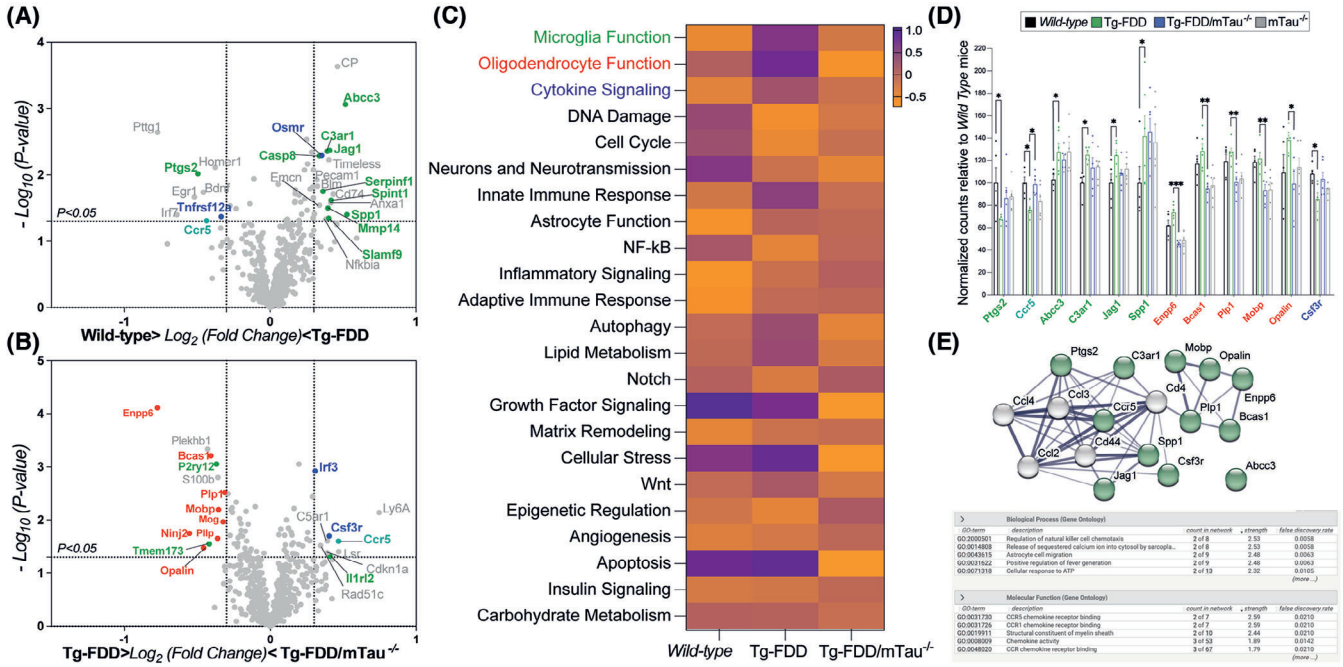

FIGURE 5 Tau deletion affects the neuroinflammatory and oligodendrocyte response associated with vascular amyloid deposition in Tg-FDD male mice. Total mRNA was isolated from the brain cortex of wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice to perform the NanoString neuroinflammation panel. (A) Volcano plot of the DEGs between Tg-FDD and wild-type mice. (B) Volcano plot of the DEGs between Tg-FDD and Tg-FDD/mTau$^{-/-}$ mice. Discontinued lines parallel to *y* indicates a fold change over 1.2 ($\log_2(FC) = \pm 0.3$) and discontinued lines parallel to *x* indicates *p* value of .05 ($-\log_{10}$ (*p*-value) = 1.3). Transcripts in green, red, and blue denote the genes up- or downregulated with the largest $\log_2$ fold change belonging to the microglia function, oligodendrocyte function, and cytokine signaling, respectively. One gene in dark cyan was classified as both microglia function and cytokine signaling. (C) Heatmap showing changes between wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice NanoString annotations. (D) Normalized counts of DEGs related to microglia function, cytokine signaling, and oligodendrocyte function that were consistently altered by CAA or tau depletion. Significance was determined by one-way ANOVA, n.s. followed by Tukey's multiple comparisons. *p*-value > .05. $n = 5–6$. (E) Network String analysis of the annotated genes highlighted in (D). FC: Fold Change.

context of tau pathology,[34] microglia reactivity and vascular damage.[35] To further evaluate C3AR1 levels in the context of vascular damage, we performed immunofluorescence analysis in the brain cortex of wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice. Overall, we observed a trend toward increased C3AR1 levels in the cortex of Tg-FDD mice compared to wild-type mice, an effect noted only in males mice (Figure S4A, S4B). However, analysis of C3AR1 immunoreactivity specifically in microglial cells (Figure S4C) revealed that female Tg-FDD mice exhibited higher C3AR1 levels than female wild-type mice, an increase that was prevented with tau reduction (Figure S4D). These results suggest that although no major microgliosis is observed in the CAA model, microglia function is impaired in the context of vascular amyloid deposition, which can be reduced when endogenous tau is depleted.

Our NanoString data also showed that in the context of CAA, reducing tau levels appears to have a more pronounced impact on oligodendrocyte-related genes such as Enpp6, Bcas1, Plp1, Mobp, and Opalin. Although these genes tend to be more expressed in Tg-FDD mice than in wild-type, the differences shown in Figure 5D were not statistically significant. These genes have been associated as markers of oligodendrocytes at early stages of the development and differentiation,[36–39] suggesting that Tg-FDD mice may present oligodendrocytes in a poor state of maturation. Consistent with this notion, previous studies have shown that inhibition of oligodendrocyte differentiation in mice impairs cognitive function. Moreover, an increase in immature or abnormal oligodendrocytes has been observed in mouse models of AD,[40–42] highlighting the toxic effects of amyloid on oligodendrocytes precursor cells and oligodendrocytes in AD brains.[42,43]

4 | DISCUSSION

Experimental models of AD characterized by amyloid plaque accumulation, but lacking aggregated tau, have demonstrated that reducing endogenous wild-type tau levels provides beneficial effects.[13,14] These studies form the basis for supporting tau downregulation using antisense oligonucleotides (ASOs) as a therapeutic entry point for AD, which is currently in the early stages of clinical trials.[44] In our present study we provide the first in vivo evidence of the favorable effects of tau downregulation in a mouse model for CAA. Our data show that ablation of endogenous tau expression ammeliorates behavioral and synaptic impairment in Tg-FDD mice. Furthermore, our results demonstrated how the removal of tau decreases the accumulation of vascular

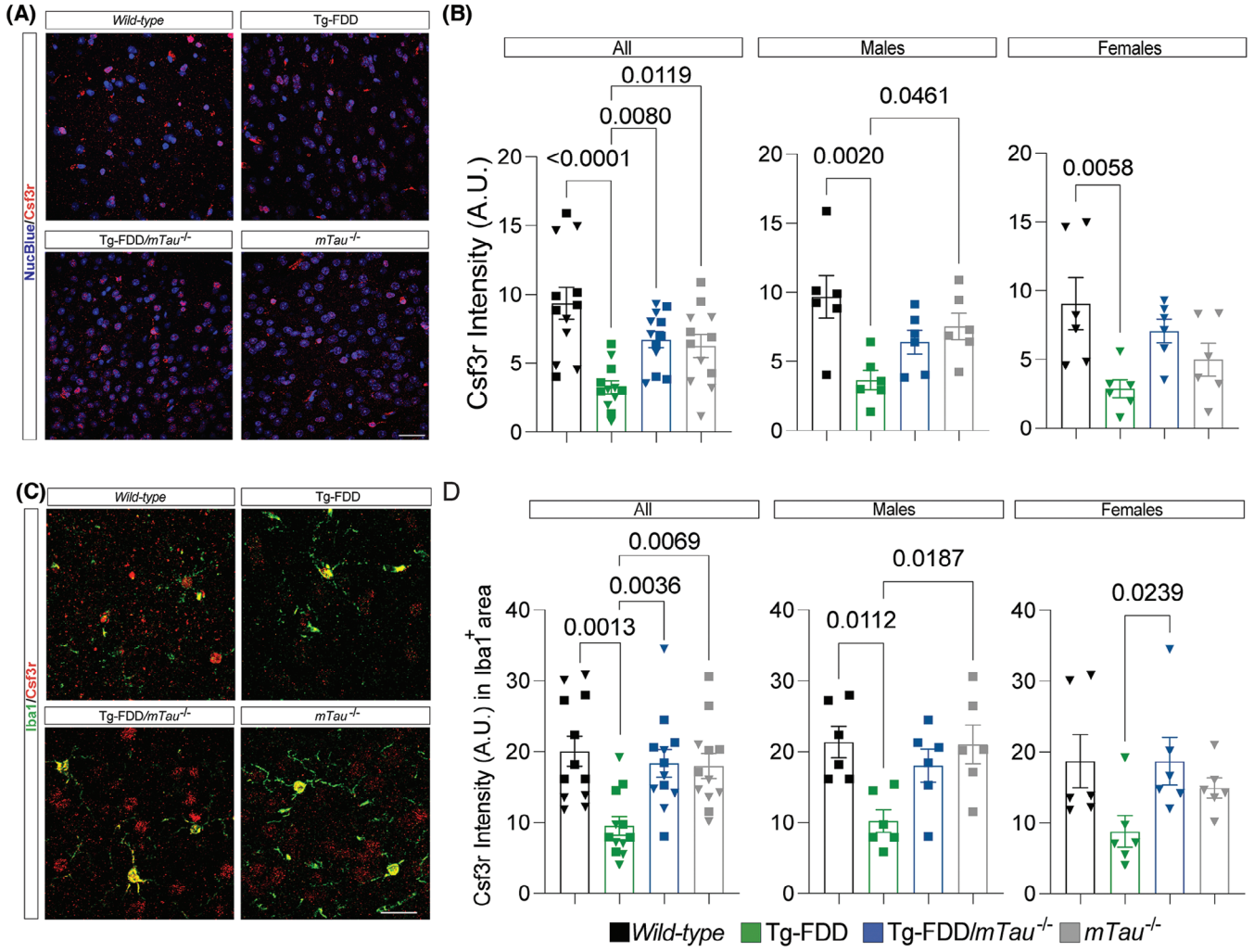

FIGURE 6 Ablation of endogenous tau **prevents** the reduction of microglial CSF3R levels in the cortex of Tg-FDD mice. (A) Immunofluorescence against CSF3R (red) and the nuclear staining NucBlue (blue) in the cortex of wild-type, Tg-FDD, Tg-FDD/mTau$^{-/-}$, and mTau$^{-/-}$ mice. *Scale bar: 30 μm*. (B) Quantification of CSF3R immunoreactivity. Data are shown as mean ± SEM, one-way ANOVA analysis of variance followed by Sidak's multiple comparison test. $n = 12$, per condition. (C) Immunofluorescence against CSF3R (red) and IBA1 (green) and NucBlue (blue). *Scale bar: 20 μm*. (D) Quantification of CSF3R immunoreactivity within the IBA1-positive area. Data are shown as mean + *SEM*, one-way Kruskal–Wallis test followed by Dunn's multiple comparisons test. $n = 12$, per condition (females, inverted triangles; males, squares).

amyloid, mitigates vascular impairment, and reduces astrocytic reactivity. Given that over 90% of AD patients develop CAA and that amyloid-related imaging abnormalities (ARIA), a major side effect of anti-amyloid immunotherapy, may result from anti-amyloid antibodies binding to vascular amyloid,[45] it is crucial to identify therapeutic targets that provide beneficial outcomes for both amyloid pathologies.

In many cases, vascular amyloidosis is accompanied by significant tau pathology.[7–9] It was recently shown that tau pathology correlates with memory impairment in CAA patients[10] and that CAA interacts with neuritic plaques to accelerate tau burden and cognitive decline.[11] Furthermore, the accumulation of perivascular tau aggregates is also linked to vascular cognitive impairment.[46,47] Previously we described the perivascular deposition of tau oligomers in the Tg-FDD mouse model characterized by the cerebrovascular accumulation of ADan peptides.[20] Given in vivo studies showing that genetic ablation of endogenous murine tau in an hAβPP mouse model prevent behavioral deficits without altering parenchymal Aβ plaque,[13] we evaluated the total removal of murine tau in the Tg-FDD model.

Complete knockout of tau expression throughout the brain recovered the decline in motor strength and inhibitory synapse dysfunction in the Tg-FDD model. The reduction of endogenous tau also decreases vascular amyloid accumulation. Of interest, the beneficial effects of decreasing endogenous tau levels in mouse models of AD do not alter the number of parenchymal Aβ plaques,[13] supporting the notion that tau is downstream of amyloid-related neurotoxicity.[48] Furthermore, there is general agreement that CAA reflects perivascular drainage impairment, triggering a self-reinforcing pathway in which exacerbated vascular amyloid accumulation activates vascular injury pathways. This process results in the impairment of vascular physiology, leading to further increases in amyloid accumulation.[49,50] In addition, it has been demonstrated that tau downregulation can rescue the cerebrovascular damage observed in a mouse model of tauopathy.[18] Therefore, it can

be suggested that in the context of CAA, tau ablation could improve the perivascular drainage of amyloid resulting in an overall decrease of vascular amyloid deposition. Alternatively, studies have suggested that a neuroinflammatory response associated with vascular amyloid could further enhance the accumulation of amyloid in the vasculature, leading to vascular damage and cognitive decline.[51] Therefore, based on our results, it is also possible to suggest that the depletion of tau could abrogate the neuroinflammatory response associate with early stages of vascular amyloid deposition, thereby breaking the amyloid deposition–inflammation cycle and its detrimental effects at the vascular level. Nevertheless, further studies are required to determine with exactitute whether the beneficial effects of tau ablation in the context of CAA are upstream or downstream of vascular amyloid deposition.

Accumulation of fibrinogen in the brain parenchyma has been utilized widely to establish impairment of the BBB.[52] Throught this measurement, we observed how tau ablation limits the impairment of the BBB in the CAA model. It is intriguing that the accumulation of fibrinogen in the brain parenchyma and its subsequent decrease due to tau deletion were observed only in male Tg-FDD but not in female mice, suggesting a sex-dependent effect of vascular amyloid deposits on BBB integrity in this mouse model of CAA. Of interest, a previous study examining the role of sex in CAA among patients with AD concluded that sex influenced the presence and severity of CAA in AD. After correcting for age, Braak stage, and Thal amyloid phase, the authors observed that the overall CAA scores were higher in male than in female patients.[53] The results from this study suggest that factors contributing to sex differences in CAA may differ from those that contribute to sex differences in AD, which is known to have a higher prevalence in females.[54] In addition, studies have suggested that there are sex differences in BBB permeability, with females having lower permeability than males. For instance, studies in rats have reported a protective effect of female sex hormones on BBB permeability under normal and pathological conditions.[55,56] Human studies have also shown that females have lower BBB permeability than males. One study, conducted on more than 20,000 human subjects, found that females showed significantly lower CSF/serum albumin ratio compared with males, suggesting that females may have a less permeable BBB than males.[57] Overall, these studies support the notion that the detrimental effect of vascular amyloid accumulation on BBB permeability is more pronounced in males due to a higher baseline permeability in comparison to females. Still, further studies are necessary to mechanistically explain this sex difference and protective effect of tau deletion on BBB impairment due to vascular amyloid accumulation.

Concomitant with the effect of tau ablation on BBB permeability, we observed how tau depletion mitigates astrogliosis, microglial dysfunction, and synaptic impairment, three pathologies previously reported in the Tg-FDD model,[23,29] as well as oligodendrocyte dysfunction. In the majority of studies evaluating the beneficial effects of tau downregulation, the focus has been neuronal-centric.[58–60] Of interest, a recent study demonstrated how tau ablation suppresses inflammation-related gene expression changes in a hAPP-J20 mouse model.[61] In this study, the authors proposed that the effects of tau reduction on inflammation-related gene expression resulted indirectly from the modulation of neuronal activity.[61] This idea was based on previous research that suggested that tau reduction alters neuronal activity in ways that counteract hypersynchronous network activity,[62] a type of network dysfunction that is known to change microglia activity.[63] Alternatively, considering the evidence showing that tau is also expressed in astrocytes, microglia, and oligodendrocytes,[30,64] it is possible to suggest that the ablation of tau in these glial cells could contribute to the beneficial effect of global tau depletion observed in the Tg-FDD model for CAA. For instance, we demonstrated recently that downregulating tau in mouse primary astrocytes mitigates synaptic loss triggered by the exposure to Aβ.[26] Another study demonstrated that lowering tau levels in 4R tau-expressing iPSC-derived astrocytes improves neuronal survival.[65] In contrast, a recent study found that endogenous tau is essential for the formation of glial lipid droplets (LDs) and protection against neuronal toxic peroxidized lipids (LPOs) in *Drosophila*.[66] Even more, the authors showed how endogenous tau is required in rat astrocytes for LD formation and the breakdown of toxic LPOs.[66] Therefore, further studies are necessary to determine the physiological role of astrocytic tau in astrocyte function and the effects of manipulating endogenous tau levels in these glial cells.

In addition, oligodendrocyte dysfunction has been linked to the pathogenesis of AD.[67,68] Moreover, an increased occurrence of immature or abnormal oligodendrocytes has been observed in AD mouse models characterized by amyloid plaque accumulation.[42,41] This suggests that oligodendrocyte progenitors respond specifically to amyloid plaque deposition in both AD-related mouse models and human AD.[42,41] Of interest, we observed an increase in genes associated with immature oligodendrocytes in the Tg-FDD mouse model, suggesting a similar response of oligodendrocytes in the context of vascular amyloid accumulation.

Recent studies have found that tau is expressed in mature oligodendrocytes in the mouse brain, but not in oligodendrocyte progenitors or immature oligodendrocytes, with tau expression occurring after the peak of myelination.[69] Furthermore, the authors showed that tau knockout mice exhibit normal myelination and oligodendrocyte development, suggesting that tau does not have a function during oligodendrocyte development but rather in mature oligodendrocytes.[69] Considering the evidence suggesting a physiological role of tau in mature oligodendrocytes, it is possible to suggest that the beneficial effect of global tau depletion on oligodendrocyte function in our CAA model could be due in part to the downregulation of tau in oligodendrocytes. Overall, it is possible that the effect in astrogliosis, microglial function, and oligodendrocyte function due to tau depletion in the Tg-FDD model could be due not only to the beneficial effect on neuronal tau ablation, which could indirectly affect glial cells through changes in synaptic network activity, but to a direct effect on distinct pathways governed by tau in each of these cell types. Nevertheless, further in vivo studies are necessary to determine the mechanisms involved in the beneficial effects of tau depletion in AD, CAA, and related disorders at the single cell resolution.

Our study highlights the beneficial effects of reducing endogenous tau levels in a mouse model of cerebral amyloid angiopathy (or CAA). Tau depletion not only ammeliorates behavioral deficits

and synaptic impairment but also reduces vascular amyloid accumulation, neuroinflammation, and BBB dysfunction. Intriguingly, these improvements exhibit a sex-dependent pattern, with males demonstrating greater BBB recovery. Furthermore, tau ablation mitigates glial pathologies, including astrogliosis, microglial dysfunction, and oligodendrocyte abnormalities, suggesting both direct and indirect roles in improving vascular and neural function.

Considering the high prevalence of CAA among patients with AD and its interaction with amyloid-related therapies, tau-reduction interventions represent a promising therapeutic avenue. Nevertheless, future studies are essential to determine the effects of partial tau reduction in adulthood, its dose–response relationship, and to unravel the mechanisms underlying tau's role across cell types and its implications for the treatment of AD, CAA, and related dementias at the cellular and molecular levels.

AUTHOR CONTRIBUTIONS

C.L-R. designed the study and N.J.-G and C.L-R wrote the manuscript. R.V. provided Tg-FDD mice. Y.M., A.P., N.J.-G, K.V., and M.D.M. assisted in animal maintenance and breeding. H.P. and E.C.J performed behavioral testing and analysis. G.V. and B.K.A. performed electrophysiology, and E.C.-J. contributed to the analysis. N.J.-G. performed histology and analysis to access amyloid deposition. N.J.-G and K.V. performed histology and analysis to assess vascular damage. E.C.-J and J.M. performed histology and analysis to access microglia and astrocytic reactivity. N.J.-G. performed NanoString neuroinflammation nCounter and analysis. E.C.-J. and J.M. performed NanoString validations. C.L.-R., R.V., and N.J.-G. critically revised the manuscript and interpreted the data. All the authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest in this study. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

No human subject materials were utilized in this study

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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