TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy

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Variants in the gene encoding the triggering receptor expressed on myeloid cells 2 (TREM2) were recently found to increase the risk for developing Alzheimer’s disease (AD). In the brain, TREM2 is predominately expressed on microglia, and its association with AD adds to increasing evidence implicating a role for the innate immune system in AD initiation and progression. Thus far, studies have found TREM2 is protective in the response to amyloid pathology while variants leading to a loss of TREM2 function impair microglial signaling and are deleterious. However, the potential role of TREM2 in the context of tau pathology has not yet been characterized. In this study, we crossed Trem2+/+ (T2+/+) and Trem2−/− (T2−/−) mice to the PS19 human tau transgenic line (PS) to investigate whether loss of TREM2 function affected tau pathology, the microglial response to tau pathology, or neurodegeneration. Strikingly, by 9 mo of age, T2−/− PS mice exhibited significantly less brain atrophy as quantified by ventricular enlargement and preserved cortical volume in the entorhinal and piriform regions compared with T2+/+ PS mice. However, no TREM2-dependent differences were observed for phosphorylated tau staining or insoluble tau levels. Rather, T2−/− PS mice exhibited significantly reduced microgliosis in the hippocampus and piriform cortex compared with T2+/+ PS mice. Gene expression analyses and immunostaining revealed microglial activation was significantly attenuated in T2−/− PS mice, and there were lower levels of inflammatory cytokines and astroglialsis. These unexpected findings suggest that impairing microglial TREM2 signaling reduces neuroinflammation and is protective against neurodegeneration in the setting of pure tauopathy.

TREM2 | Alzheimer’s disease | neurodegeneration | neuroinflammation | tau

Alzheimer’s disease (AD) is the most prevalent form of dementia and is thought to be caused by accumulation of two different proteins in the brain. Amyloid-β (Aβ) aggregates form extracellular plaques, while hyperphosphorylated tau (p-tau) is present in intracellular neurofibrillary tangles (1). Microgliosis, or activation of the innate immune cells in the brain, is an additional pathological signature routinely found in regions affected by abundant plaques and tangles (2, 3). Chronic microgliosis has long been hypothesized to influence accumulation of Aβ and tau, contribute to neuronal damage, and ultimately exacerbate neurodegeneration (4, 5). However, studies over the past two decades have reported both beneficial and detrimental effects of microglia in AD (4, 5). Thus, the role of microglia and inflammation in disease onset and progression remains poorly understood.

The discovery that rare coding variants in the triggering receptor expressed on myeloid cells 2 (TREM2) are associated with a twofold to fourfold increased risk for developing sporadic, late-onset AD further implicates the role of microglia in AD (6, 7). TREM2 is specifically expressed in microglia in the brain and has been shown to impact a multitude of functions including activation, inflammation, phagocytosis, proliferation, and survival (8). Although the exact molecular effects of AD-associated risk variants in TREM2 are still being investigated, the most common position 47 arginine-to-histidine (R47H) variant appears to reduce binding to anionic phospholipids, including binding to apolipoproteins such as ApoE, and reduce lipid-induced TREM2 activity (9–14). The exact physiological ligand(s) of TREM2 are currently unknown, but it is this thought that decreased ligand binding results in a loss of microglial functions, which consequently increases risk for the development of AD (8).

AD pathology is characterized first by the appearance of Aβ plaques followed by the spread of neurofibrillary tau tangles from the transentorhinal region, to the hippocampus, and into the neocortex (15). Several studies have investigated the effects of TREM2 on plaque deposition and associated pathologies (14, 16–20). One consistent observation has been that reduction or loss of TREM2 function reduces the number of plaque-associated microglia. However, the effects of TREM2 deficiency on overall plaque load have been variable (8). Interestingly, two recent reports found that, despite no difference in the number of plaques, alterations in plaque composition and morphology corresponded

Significance

Alzheimer’s disease (AD) is the most common cause of dementia and is a major public health problem for which there is currently no disease-modifying treatment. There is an urgent need for greater understanding of the molecular mechanisms underlying neurodegeneration in patients to create better therapeutic options. Recently, genetic studies uncovered novel AD risk variants in the microglial receptor, triggering receptor expressed on myeloid cells 2 (TREM2). Previous studies suggested that loss of TREM2 function worsens amyloid-β (Aβ) plaque-related toxicity. In contrast, we observe TREM2 deficiency mitigates neuroinflammation and protects against brain atrophy in the context of tau pathology. These findings indicate dual roles for TREM2 and microglia in the context of amyloid versus tau pathology, which are important to consider for potential treatments targeting TREM2.

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to increased neuritic dystrophy and p-tau accumulation around plaques in Trem2-deficient mouse models and in human R47H variant carriers (19, 20). Therefore, TREM2 deficiency attenuates tau-mediated neurodegeneration in this region compared with T2+/+PS mice. The reduced brain atrophy and preservation of hippocampal volume in T2−/−PS mice (Fig. 1A and D) indicates that TREM2 deficiency does not result in obvious changes to p-tau accumulation or tau solubility despite the attenuated neurodegenerative phenotype.

Fig. 1. TREM2 deficiency attenuates neurodegeneration in PS19 mice. (A) Representative images of Nissl staining from T2+/+PS and T2−/−PS mice. (Scale bars, 2.5 mm.) Quantification of the average volume of the (B) ventricles and (C) entorhinal cortex (E18) volume in T2−/−PS mice (Fig. 1A and C). While no significant differences in hippocampal volume were observed (Fig. 1A and D), levels of the synaptic protein, PSD-95, were significantly lower in T2−/−PS mice compared with T2+/+PS mice (Fig. 1E and F), indicating more synaptic degeneration in this region compared with T2−/−PS mice. The reduced brain atrophy and preservation of PSD-95 in T2−/−PS mice suggests that loss of TREM2 function is neuroprotective in the setting of tauopathy.

**TREM2 Deficiency Does Not Alter Phosphorylated or Insoluble Tau Levels.** To investigate whether the preservation of brain volume in T2−/−PS mice was due to a reduction in overall tau deposition, we performed a sequential biochemical extraction of hippocampal brain tissue. Samples were first extracted in a high-salt RAB buffer, the subsequent pellet was resuspended in a detergent radioimmunoprecipitation assay (RIPA) buffer, and the final pellet was solubilized in 70% formic acid (FA). RAB and RIPA fractions contain more soluble tau species while the 70% FA fraction contains insoluble, tau aggregates. The concentration of tau in each fraction was measured using an htau-specific ELISA. We observed no significant differences in tau levels in any fraction between T2+/+PS and T2−/−PS mice (Fig. 2E). These data indicate that TREM2 deficiency does not result in obvious changes to p-tau accumulation or tau solubility despite the attenuated neurodegenerative phenotype.
with a more activated phenotype, whereas microglia in T2−/−PS mice appeared ramified (Fig. 3I). Costaining with the proliferative cell marker, KI-67 (19), did not reveal differences between T2+/+PS and T2−/−PS mice (Fig. S4). There were very few proliferative microglia in either group (on average, approximately two microglia from two sections per mouse for both genotypes). Therefore, microglial proliferation does not appear to account for the decrease in the total number of microglia observed in T2−/−PS mice. The amount of reactive gliosis in human AD patient brains has been reported to more closely correlate with the degree of neurofibrillary tangle pathology as opposed to amyloid plaque burden (26, 27). Indeed, we observed that microgliosis, as measured by Iba1 staining in T2−/−PS mice, was significantly lower in T2−/−PS mice, indicating less microglial activation. While Cst7 is a microglia-specific gene (32), Apoe is expressed by both astrocytes and microglia in the brain (33). Increased expression of Apoe in microglia has been recently reported in several neurodegenerative disease models as an indicator of microglial activation in response to amassing pathologies and subsequent cell damage (28–31). Therefore, we investigated whether accrual of tau pathology in the piriform cortex altered accumulation of ApoE specifically in microglia. Communostaining revealed ApoE-positive puncta colocalized within Iba1-positive microglial cell bodies (Fig. 4B). Furthermore, the percentage of microglia displaying this phenotype was significantly lower in T2−/−PS mice (Fig. 4C). These data indicate an overall reduction in microglial activation in the absence of TREM2.

We also assessed several inflammatory markers previously implicated in AD (5). Consistent with the reduction in reactive microglia in T2−/−PS mice, we observed a significant decrease in the expression of both IL-1 isoforms, IL-1β and IL-1α (Fig. 4D). IL-1 signaling has been shown to induce expression of other proinflammatory mediators such as TNF-α and IL-6 (5). Accordingly, TNF-α was significantly down-regulated in T2−/−PS mice; however, IL-6 transcript levels were unaltered (Fig. 4D). In addition to cytokines, complement proteins are reported to be increased in brain regions with AD pathology (5). We found the early subcomponent of the complement cascade, C1q, was significantly down-regulated.

**Nine-Month-Old T2−/−PS Mice Have Decreased Microglial Activation and Expression of Inflammatory Genes.** We further wanted to examine whether the loss of TREM2 influenced microglial homeostasis and expression of proinflammatory genes in T2−/−PS mice despite equivalent levels of tauopathy. Quantitative RT-PCR (qRT-PCR) was performed on cortical tissue from T2+/+PS and T2−/−PS mice to assess the expression of several genes that have been reported as homeostatic (Tmem119 and P2ry12) versus activated (Cst7, Spp1, and Apoe) microglia markers (28–31) (Fig. 4A). Only Apoe and Cst7 transcripts were significantly altered and were lower in T2−/−PS mice, indicating less microglial activation. While Cst7 is a microglia-specific gene (32), Apoe is expressed by both astrocytes and microglia in the brain (33). Increased expression of Apoe in microglia has been recently reported in several neurodegenerative disease models as an indicator of microglial activation in response to amassing pathologies and subsequent cell damage (28–31). Therefore, we investigated whether accrual of tau pathology in the piriform cortex altered accumulation of ApoE specifically in microglia. Communostaining revealed ApoE-positive puncta colocalized within Iba1-positive microglial cell bodies (Fig. 4B). Furthermore, the percentage of microglia displaying this phenotype was significantly lower in T2−/−PS mice (Fig. 4C). These data indicate an overall reduction in microglial activation in the absence of TREM2.

**Fig. 2.** No differences were observed in tau phosphorylation or solubility in 9-mo-old T2+/+PS and T2−/−PS mice. Quantification of the percent area covered by biotinylated AT8 staining in the (A) piriform cortex (P = 0.9499; T2+/+PS, n = 13; T2−/−PS, n = 21) and (B) hippocampus (P = 0.0652; T2+/+PS, n = 13; T2−/−PS, n = 20). Representative images of biotinylated AT8 p-tau staining in the (C) piriform cortex and (D) hippocampus from T2+/+PS and T2−/−PS mice. (Scale bars, 1 mm.) (E) Tau solubility in the hippocampus was quantified using a human-tau (htau) specific sandwich ELISA to measure (Left) RAB-soluble htau (P = 0.8562; T2+/+PS, n = 14; T2−/−PS, n = 17), (Center) RIPA-soluble htau (P = 0.1233; T2+/+PS, n = 14; T2−/−PS, n = 17), and (Right) FA-soluble htau levels (P = 0.9584; T2+/+PS, n = 14; T2−/−PS, n = 17). Data are presented as mean ± SEM. Significance was determined using an unpaired, two-tailed Student’s t test.

**Fig. 3.** TREM2 deficiency reduces microgliosis in PS19 mice. Quantification of the percent area covered by Iba1 staining in the (A) piriform cortex (P = 0.0242; T2+/+PS, n = 14; T2−/−PS, n = 21), hippocampus (P = 0.0266; T2+/+PS, n = 14; T2−/−PS, n = 21). Representative images of Iba1 staining in the (A) piriform cortex and (D) hippocampus from T2+/+PS and T2−/−PS mice. (Scale bars, 1 mm.) (E) Quantification of immunofluorescence staining for Iba1-positive cell bodies in the piriform cortex (P = 0.0478; T2+/+PS, n = 12; T2−/−PS, n = 20). (F) Representative images of Iba1 immunofluorescence staining in the piriform cortex. Microglia in T2−/−PS mice display a more amplified phenotype as opposed to in T2+/+PS mice where microglia appear quiescent. Images represent maximum-intensity projections of z stacks. (Scale bars, 50 μm.) Data are mean ± SEM. Significance was determined using an unpaired, two-tailed Student’s t test with *P < 0.05.
in T2−/−PS mice (Fig. 4D). Thus, there is a decrease in neuroinflammation in T2−/−PS mice despite tangle deposition and tau-induced damage.

Astroglosis Is Reduced in T2−/−PS Mice. Regions burdened by pathology in AD and other neurodegenerative conditions are also characterized by the presence of reactive astrocytes. Recent studies have further demonstrated that microglia can influence astrocyte reactivity in several disease models (34, 35). In our qRT-PCR analyses for inflammatory mediators, we found that the reactive astrocytic marker, glial fibrillary acidic protein (GFAP), was significantly reduced in the cortex of T2−/−PS mice (Fig. 5A). Immunostaining for GFAP confirmed significantly less astroglia in both the piriform cortex (Fig. 5B and D) and hippocampus (Fig. 5C and E) of T2−/−PS compared with T2+/+PS mice. The degree of GFAP staining in the hippocampus strongly correlated with the amount of p-tau pathology in both groups (Fig. S4A). Interestingly, however, the correlation between GFAP astrocyte and Iba1 microglia staining was diminished in T2−/−PS compared with T2+/+PS mice (Fig. S4B).

This supports the notion that microglia influence reactive astrocytes in tauopathy and that this occurs in a TREM2-dependent manner.

Discussion

Our study provides insights into how loss of TREM2 function impacts tau-associated pathologies and the neurodegeneration that ensues in the brain. Surprisingly, it indicates that TREM2 deficiency in the setting of pure tauopathy limits gliosis and neuroinflammation as well as protects against brain atrophy. T2−/−PS mice had significantly attenuated ventricular enlargement and thinning of the entorhinal and piriform cortex layers compared with T2+/+PS mice despite no significant differences in p-tau and insoluble tau accumulation. Further analysis revealed decreased microgliosis and astroglia in regions affected by tauopathy in T2−/−PS mice, which corresponded with reduced expression of several proinflammatory genes. These observations suggest that TREM2 facilitates a microglial response to tau pathology and or tau-mediated damage in the brain. Furthermore, our results support that microgliosis can contribute to the neurodegenerative process in tauopathy without altering tau aggregation.

The absence of TREM2 is associated with decreased microgliosis and astroglia in a variety of disease models, but the ultimate effects on the different pathologies and neuronal integrity differ. It has previously been shown that TREM2 mediates a microglial response to amyloidosis although not necessarily impacting total plaque load (20, 23). Reminiscent of these observations, we did not detect any obvious effects on tau deposition in T2−/−PS mice but did find decreased microgliosis in areas with abundant tauopathy. Altogether, these data suggest that lack of TREM2 function impairs microglial response to protein aggregation in AD but does not necessarily aggravate it. However, the consequences of TREM2-mediated microgliosis in the context of plaque and tangle pathologies diverge. Previous work illustrates that TREM2 helps sustain...
a microglial response around plaques that may function to contain toxic Aβ species and protect surrounding neurites (19, 20). Thus, TREM2 signaling may be beneficial in responding to amyloid pathology, while variants leading to a loss of TREM2 function are detrimental. In contrast, our study revealed lack of TREM2 during tauopathy was neuroprotective, reducing gliosis and neuroinflammation, which corresponded with preservation of brain volume. Furthermore, no effects on p-tau pathology were seen in this model, as opposed to observations of increased neuritic dystrophy and p-tau accumulation surrounding amyloid plaques in TREM2-deficient mice (19, 20). We hypothesize that the increase in p-tau detected around plaques in Trem2−/− mice results from either increased damage from amyloid to surrounding neurites or decreased phagocytic clearance of neurites due to less plaque-associated microglia, whereas the p-tau detected in the PS19 mice is attributable to neuronal tau aggregation. Another report also observed beneficial effects of TREM2 deficiency on neuroinflammation and degeneration. Trem2−/− mice had reduced levels of inflammatory transcripts, less hippocampal atrophy, and rescue of behavioral deficits 120 d after traumatic brain injury (36). Overall, these studies indicate TREM2 signaling is important for facilitating the microglial response to damage in the brain and echo the juxtaposing roles that have been described for microglia in neurodegenerative diseases.

Several mechanisms have been proposed to explain how loss of TREM2 function impacts microglial fitness and contributes to various disease phenotypes. For instance, decreased neuroinflammatory markers in TREM2-deficient stroke, traumatic brain injury, and neuropathic pain models may result from impaired chemotaxis following neuronal injury (30) and decreased microglial activation (36–38). Similarly, we found decreases in the percentage of reactive microglia in regions affected by tauopathy in aged T2−/−PS were associated with reduction in inflammatory transcripts, specifically IL-1β, IL-1α, TNF-α, and C1q, suggesting loss of TREM2 function impacts microglia activation, hindering inflammatory responses. However, these observations cannot be definitively attributed to deficits in microglial activation since microgliosis and astrogliosis were reduced as well, making it unclear whether lower cytokine levels are merely a result of overall decreased gliosis. Administration of an agonistic TREM2 antibody significantly increased TNF-α and IL-1β levels in Trem2−/− microglia (11), indicating a compensatory role for TREM2 signaling (38). However, TREM2 has classically been described as modestly antiinflammatory and loss of function has also been shown to reduce the same inflammatory markers, such as IL-1β and TNF-α, in other studies (21, 39). Therefore, it remains unclear whether and how TREM2 contributes to microglial activation and regulation of neuroinflammation.

TREM2-deficient microglia have also been shown to have impaired proliferative ability and decreased viability. Trem2−/− plaque-associated microglia have increased TUNEL staining indicative of cellular apoptosis (14) and decreased staining of the proliferation marker Ki-67 (19). A recent report further detailed that deficits in cellular metabolism lead to accumulation of autophagic bodies in Trem2−/− microglia and are responsible for decreasing microglial health (40). We did not observe significant differences in microglial proliferation in PS19 mice regardless of Trem2 genotype. Given the reduction in the number of total microglia in T2−/−PS mice is not attributable to cellular proliferation, TREM2-deficient microglia may be undergoing similar metabolic stress which impacts their fitness and capacity to respond to accumulating damage incited by tauopathy, possibly leading to inadvertent cell death. This would also account for the total decrease in microgliosis that was observed. Recent studies provided further evidence that TREM2 promotes microglial survival via the Wnt/β-catenin signaling pathway (41, 42). These results suggest that reduced TREM2 signaling leaves microglia vulnerable to succumbing to pathological insults and injury.

It should be noted that microgliosis deficits do not always equate with increased neuronal injury. Chronic microglial activation has been hypothesized to lead to excessive neuroinflammation that may exacerbate AD pathologies and neurodegeneration (43). Analysis of human AD brain tissue has revealed up-regulation of several inflammatory cytokines in areas of dense tangle pathology and gliosis in AD and other tauopathies (44, 45). Microgliosis induced by protein aggregation may enhance local neuroinflammation and neuronal damage to accelerate disease progression. In this study, we observed that decreased microgliosis, caused by TREM2 deficiency, was associated with less brain atrophy in the context of tau pathology. Since loss-of-function variants in TREM2 are associated with increased risk of AD, we were surprised by this striking protective effect. The attenuation of neurodegeneration and microgliosis observed in TREM2-deficient mice coincides with other recent data from our laboratory in which we found that there was strikingly reduced inflammation and neurodegeneration in PS19 mice lacking ApoE (35). Taken together, these studies suggest that microglial inflammation promotes tau-dependent degeneration. One caveat is that the PS19 mouse is a model of pure tauopathy that expresses a variant of tau that causes FTD and, unlike in AD, does not first develop amyloid plaques. Many groups have reported that loss of TREM2 function exacerbates amyloid-dependent toxicity in mouse models, including accumulation of p-tau and neuritic dystrophy around plaques. Taken together, it is possible that TREM2 function is critical for mitigating amyloid-dependent toxicity early in AD, but subsequently, TREM2-deficient microgliosis becomes detrimental following the onset of tau pathology to promote neurodegeneration. In other words, there may be stage and pathology-specific effects of TREM2 in AD. Moving forward, it is critical that we gain a better understanding of the mechanisms underlying the potential protective and deleterious effects of TREM2 signaling in the setting of AD pathologies. This may be facilitated by mechanistic in vitro studies, further analysis of mouse models, and examining soluble TREM2 fragments detectable in human cerebral spinal fluid throughout the course of AD (46, 47). Elucidating the functions of TREM2 during the progression of AD may lead to increased understanding of the role of innate immunity in AD and aid in developing novel disease-altering treatment strategies.

Methods

Animals. PS19 Tgtau transgenic mice (purchased from The Jackson Laboratory, https://www.jax.org/strain/008169) expressing the T34 isoform (1N4R) with a P301S mutation were crossed with Trem2−/− or Trem2+/+ mice to generate Trem2−/− × PS19 (T2−/−PS) and Trem2+/+ × PS19 (T2+/+PS) mice. Only male T2−/−PS and T2−/−PS mice were used for analysis in this study. All mice were on a C57BL/6 background. Animal procedures were performed in accordance with protocols approved by the Animal Studies Committee at Washington University School of Medicine.

Brain Extraction and Preparation of Tissue Homogenates. Mice were anesthetized with i.p. pentobarbital (200 mg/kg), followed by perfusion with 3 U/mL heparin in cold Dulbecco’s PBS. The brains were carefully extracted and cut into two hemispheres. The left hemisphere was collected for immunostaining and fixed in 4% paraformaldehyde overnight before being transferred to 30% sucrose and stored at 4 °C until they were sectioned. Brains were cut coronally into 50-μm sections on a freezing sliding microtome (SM1020R; Leica) and stored in cryoprotectant solution (0.2 M PBS, 15% sucrose, 33% ethylene glycol) at −20 °C until use. The right hemisphere was dissected to isolate the hippocampus for biochemical analysis, and the tissue was kept at −80 °C until analyzed. Biochemical extractions on brain tissue were performed as previously described (48) to assess tau solubility.

Volumetric Analysis of Brain Sections. Seven coronal brain sections (300 μm between sections) beginning rostrally at the ventricle to the caudal end of the hippocampus were mounted on slides and allowed to dry overnight. These sections correspond to bregma coordinates −1.23 to −2.69 in the mouse brain atlas (49). The following day, sections were stained in cresyl violet for 6 min and dehydrated in increasing ethanol concentrations followed by xylene and


**Supporting Information**

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**SI Methods**

**Antibodies.** Antibodies to Iba1 (1:5,000–1:10,000; 019-19741; Wako), PSD-95 (1:1,000; 18258; Abcam), ERK (1:1,000; 9102; Cell Signaling), biotinylated p-tau AT8 (1:500; MN1020B; Thermo Fisher), biotinylated KI-67 (1:200; SolA15; Thermo Fisher), biotinylated HT7 (1:500; MN1000B; Thermo Fisher), HRP-conjugated antimouse (1:7,000; 115-035-003; Jackson), HRP-conjugated antirabbit (1:7,000; 111-035-003; Jackson), anti-rabbit 568 (1:500; A11011; Thermo Fisher), and biotinylated anti-rabbit (1:1,000; 711-065-152; Jackson ImmunoResearch) were purchased. Biotinylated anti-mouse ApoE HJ6.3 at 1:200 and anti-Tau5 (27) were used.

**Assessment of PSD-95 Levels in Hippocampal Lysates.** Analysis of PSD-95 and ERK levels were performed on 25 μg of total protein from samples processed in SDS-loading buffer and boiled for 10 min. Samples were loaded on an NuPAGE 4–12% Bis-Tris Gel (NP0336; Invitrogen) and transferred onto a nitrocellulose membrane (PowerEase 300W; Life Technologies). Membranes were blocked in 5% milk–TBST for 30 min and incubated in primary antibody diluted in 3% milk–TBST for 3 h, shaking at room temperature. After washing, secondary antibodies were applied for 1 h, shaking at room temperature. Membrane was washed three times for 5 min and imaged using GeneMate Blue Autoradiography Film (9023; Bioexpress) and a medical film processor (Zeiss) with a 20× objective. Manual quantification was aided using Imaris 8.1 software (Bitplane). Representative images were further processed using ImageJ software, version 2.0.0 (National Institutes of Health), and Illustrator and Photoshop CC 2017 (Adobe Systems).

**Immunofluorescence.** Free-floating sections were washed three times in PBS for 5 min. They were then placed in a 1% Sudan black solution for 20 min, followed by three washes for 5 min in 0.02% PBS-T and one wash in PBS. Sections were then blocked in 3% BSA and 3% normal goat serum (NGS) in PBS with 1% Triton X-100 (PBSX) for 30 min. Sections were incubated in primary antibodies diluted in blocking buffer overnight, shaking at 4 °C followed by three more washing steps. Fluorescently labeled secondary or streptavidin (1:500; S11223; Thermo Fisher) diluted in blocking buffer and applied to the sections for 2-h shaking at room temperature. After washing sections in PBS for three times for 20 min, they were mounted and coverslipped with Prolong Gold (P36950; Invitrogen). Images were taken as a z stack with a LSM 880 II Airyscan FAST confocal microscope (Zeiss) with a 20× objective. Manual quantification was aided using Imaris 8.1 software (Bitplane). Representative images were further processed using ImageJ software, version 2.0.0 (National Institutes of Health), and Illustrator and Photoshop CC 2017 (Adobe Systems).

**Immunohistochemistry.** For microglial stains, sections were washed three times in TBS for 5 min and blocked in 0.3% hydrogen peroxide for 10 min. After washing, sections were blocked in 3% NGS in TBS with 0.25% Triton X-100 (TBSX) for 30 min. Primary antibody was diluted in 1% NGS–TBSX, and the sections were incubated in the primary antibody overnight at 4 °C. The next day, sections were washed and incubated with secondary diluted in 1% NGS–TBSX for 1 h. After washing, sections were incubated in ABC elite solution (VectorStain; PK-6100), prepared per manufacturer’s instructions, for 1 h followed by another washing step. Sections were developed in DAB solution (catalog no. D5905; Sigma-Aldrich), washed, and mounted on slides. After drying overnight, the slides were dehydrated and increasing ethanol concentrations followed by xylene and coverslipped with Cytoseal 60 (8310; Thermo Fisher). Phospho-tau AT8 staining was performed as previously described (48). Stained tissue was scanned using a NanoZoomer digital pathology system (Hamamatsu Photonics). Images were processed using NDP viewing software (Hamamatsu).
**Fig. S1.** Full scans of immunoblot data. Unedited film from PSD-95 (~83-kDa) and ERK1/2 (~44- and 42-kDa) immunoblots.

**Fig. S2.** No effect of TREM2 deficiency on KI-67–positive microglia in the piriform cortex. (A) Quantification of KI-67–positive microglia in the piriform cortex (P = 0.6844; T2+/+PS: 0.9725 ± 0.2171, n = 13; T2−/−PS: 0.8738 ± 0.2406, n = 22). (B) Representative image of KI-67–positive microglia. Images represent maximum-intensity projections of z stacks. (Scale bars: 50 μm.) Data are mean ± SEM. Significance was determined using an unpaired, two-tailed Student’s t test with *P < 0.05.

**Fig. S3.** Correlations between tau pathology, microgliosis, and degeneration in the hippocampus of T2+/+PS and T2−/−PS mice. Significant correlations were observed between Iba1 microglial staining and (A) AT8 p-tau staining (T2+/+PS: n = 12, *P < 0.01, $R^2 = 0.6743$; T2−/−PS: n = 21, **P < 0.01, $R^2 = 0.3392$) and (B) FA-soluble htau levels (T2+/+PS: n = 12, **P < 0.01, $R^2 = 0.5560$; T2−/−PS: n = 16, *P < 0.05, $R^2 = 0.2475$) in both groups, but were stronger in T2+/+PS mice. Additionally, significant correlations for ventricular size and (C) AT8 p-tau staining (T2+/+PS: n = 13, *P < 0.05, $R^2 = 0.4312$; T2−/−PS: n = 19, not significant $P > 0.05$, $R^2 = 0.0064$) and (D) FA-soluble htau levels (T2+/+PS: n = 13, *P < 0.05, $R^2 = 0.3185$; T2−/−PS: n = 14, not significant $P > 0.05$, $R^2 = 0.0114$) were observed for T2+/+PS but not T2−/−PS mice. Solid, colored lines represent the best-fit line with a linear regression, and black, dashed lines represent 95% confidence intervals.
Fig. S4. Correlations between astrogliosis, tau pathology, and microgliosis in the hippocampus of T2^{+/+}PS and T2^{-/-}PS mice. Strong, significant correlations were observed between GFAP staining and (A) AT8 p-tau staining (T2^{+/+}PS: n = 12, **P < 0.01, R^2 = 0.5130; T2^{-/-}PS: n = 19, ***P < 0.001, R^2 = 0.6311) for both T2^{+/+}PS and T2^{-/-}PS mice. (B) Correlations between GFAP and Iba1 were reduced in T2^{-/-}PS compared with T2^{+/+}PS mice (T2^{+/+}PS: n = 13, **P < 0.01, R^2 = 0.5610; T2^{-/-}PS: n = 19, *P < 0.05, R^2 = 0.2430). Solid, colored lines represent the best-fit line with a linear regression, and black, dashed lines represent 95% confidence intervals.