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Telomere-driven senescence accelerates tau pathology, neuroinflammation and neurodegeneration in a tauopathy mouse model

Debora Palomares¹, Axelle A. T. Vanparys^{1,2}, Joana Jorgji¹, Esther Paître¹, Pascal Kienlen-Campard^{1*} and Nuria Suelves^{1*}

Abstract

The connection between aging and neurodegenerative pathologies like Alzheimer's disease (AD) has long been recognized, with senescent brain cells building up in the brains of AD patients. A causal link has been established between senescence and AD-related tauopathy, but the mechanisms underlying these pathological changes remain largely unknown. To unravel the precise role of cellular senescence in tau-mediated neuropathology, we crossed the *Terc* knockout (*Terc*^{-/-}) mouse model of telomere-induced senescence with the P301S tauopathy model (PS19 line). Using brain sections and protein extracts, an array of biochemical and molecular techniques was applied to investigate the expression of tau-related neuropathological features within a senescent context. Our results showed that the brains of 6- and 9-month-old *Terc*^{-/-} mice exhibit significant telomere attrition and signs of cellular senescence. Additionally, we found evidence that the introduction of a senescent phenotype in a tauopathy mouse model results in increased tau phosphorylation at key residues, particularly in the hippocampus. Over time, this leads to enhanced tau truncation and aggregation, accompanied by exacerbated astrocyte and microglial activation, as well as selective neuronal loss in vulnerable brain regions. Overall, these findings place senescence as a key upstream regulator of tau pathology and tau-related neurodegeneration, suggesting that targeting senescent cells and their detrimental effects may offer promising therapeutic strategies for AD and other related tauopathies.

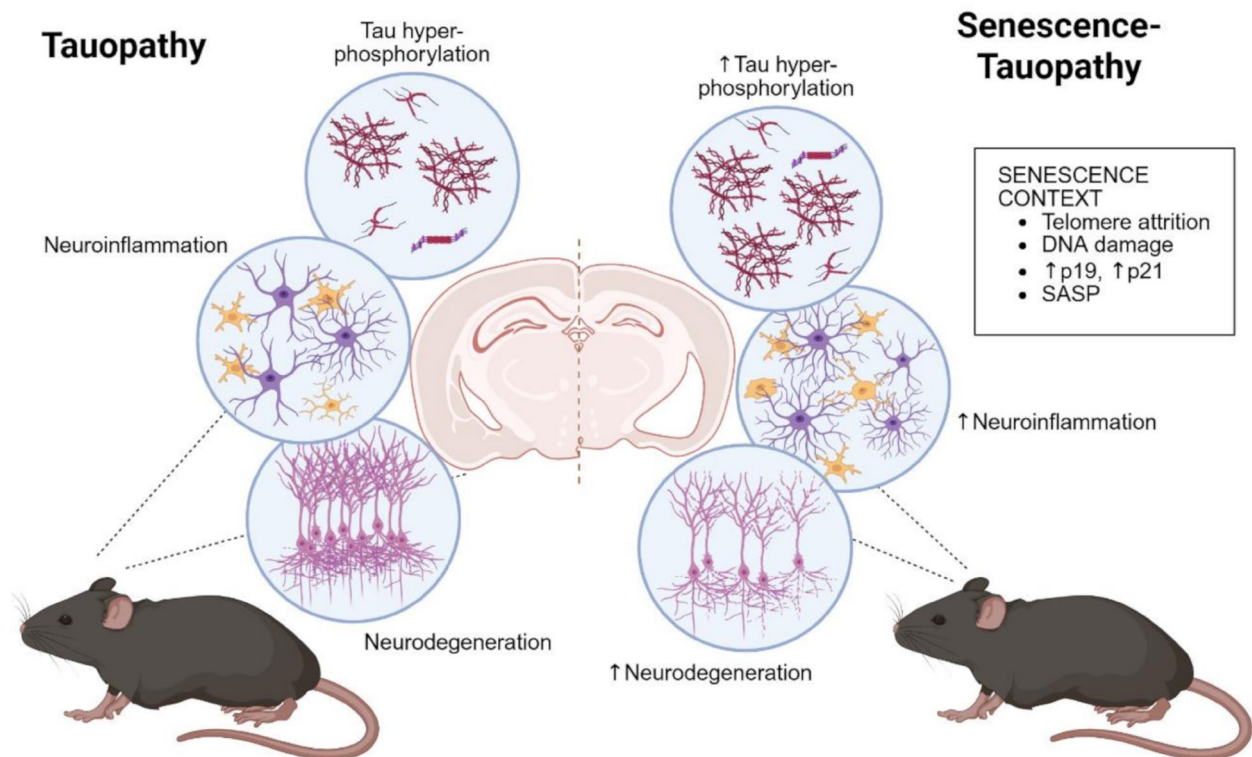
*Correspondence:

Pascal Kienlen-Campard
pascal.kienlen-campard@uclouvain.be
Nuria Suelves
nuria.suelves@uclouvain.be

Full list of author information is available at the end of the article



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Graphical abstract

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Keywords Cellular senescence, Telomere shortening, Alzheimer's disease, Tau pathology, Neuroinflammation, Neurodegeneration

Introduction

Aging is considered one of the sociodemographic predictors most closely associated with chronic diseases and disabilities [62], including many neurodegenerative diseases (NDs), of which Alzheimer's disease (AD) is the most prevalent [39]. With the global increase in life expectancy and the consequent aging population, the prevalence of these diseases is on the rise, putting a significant strain on healthcare systems and progressively becoming a major cause of societal and economic concern worldwide. Furthermore, this burden is expected to intensify in the next few years. In 2019, the estimated global number of people living with AD was around 57 million but could reach 153 million by 2050 [26, 33]. This alarming demographic trend underscores the pressing need to unravel the precise mechanisms underlying pathological aging and its role in the onset and progression of NDs.

Substantial evidence suggests that cellular senescence, a hallmark of aging, contributes to the development of

age-related pathologies [12]. Originally defined in proliferating cells, senescence refers to a state of permanent cell cycle arrest, further characterized by a complex phenotype that includes the secretion of inflammatory factors that cause detrimental effects to surrounding tissues. Telomere attrition, DNA damage, oxidative stress and oncogenic signaling are all well-known triggers of senescence, activating similar molecular pathways that induce and sustain the senescence phenotype. With age, senescent cells accumulate in tissues and promote a state of chronic inflammation. While this has been associated with tissue dysfunction and disease onset in peripheral tissues [55], its specific contribution to the development of disease in the central nervous system remains largely unexplored. A key unresolved question is whether senescence acts as an upstream trigger of neurodegeneration or appears as a consequence of the formation of brain lesions in NDs [71]. Since the precise molecular mechanisms driving senescence pathological effects are still

unexplored, this remains a complex and highly debated issue which requires further investigation.

AD represents the main cause of dementia and is characterized by progressive synaptic dysfunction and neuronal loss caused by two distinct histopathological lesions: amyloid- β (A β)-containing plaques and neurofibrillary tangles (NFTs) of hyperphosphorylated tau. Tau pathology is also found in other neurodegenerative diseases beyond AD, collectively known as tauopathies, including corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and frontotemporal lobe degeneration (FTLD), among others [31]. While amyloid pathology is an early step in AD progression [35], tau hyperphosphorylation and aggregation occur later in the disease and closely correlate with the evolution of cognitive decline and neurodegeneration [1, 61]. Pharmacological treatments for AD are mostly symptomatic, except for very few immunotherapies against amyloid- β , which have shown only modest therapeutic benefits [99].

While a small percentage of AD cases have a known cause, linked to inherited mutations in genes involved in A β production, most cases are sporadic, with an unknown underlying molecular basis. However, the global incidence and prevalence of both sporadic and inherited forms of AD are known to increase with age [36, 47], with an increasing number of studies suggesting that brain cellular senescence may play a role in the development of AD. Senescent neurons and glial cells have been identified in the brains of AD patients [7, 19, 21, 23, 38, 40, 60] as well as in AD-related mouse models, including tauopathy models [11, 40, 93]. Furthermore, the targeted removal of senescent cells through genetic or pharmacological approaches in a tauopathy model has been shown to alleviate tau pathology, reduce neurodegeneration and improve cognitive function [11]. Additionally, increasing evidence suggests a direct correlation between shorter telomere length and increased AD risk [22, 25, 73, 97].

In this project, *Terc* knockout mice, which exhibit senescence due to telomere dysfunction, were crossed with PS19 tauopathy mice. This novel combined model was then used to investigate the involvement of senescence in the progression of tau pathology and associated pathological processes. Our results demonstrate for the first time the causal role of telomere-induced cellular senescence in tauopathy progression and highlight its significance in neuroinflammation and neurodegeneration. In that context, further exploring the molecular mechanisms underlying the relationship between cellular senescence and tauopathy progression could offer valuable insights for developing novel AD treatment strategies.

Materials and methods

Mouse models

Heterozygous *Terc* knockout mice (referred to as *Terc*^{+/-}, Strain #004132, The Jackson Laboratory), carrying a germline deletion of the telomerase RNA component *Terc* [8], and hemizygous *Tau* P301S (PS19 line) transgenic mice (referred to as *Tau*^{Tg}, Strain #008169, The Jackson Laboratory), overexpressing the 1N4R human tau isoform with the P301S mutation found in frontotemporal dementia with parkinsonism-17 (FTDP-17) [96], were purchased and maintained on a C57BL/6 genetic background for a minimum of 6 generations. To procure double mutant *Terc*^{-/-} *Tau*^{Tg} mice of the second (G2) and third (G3) generations, the following breeding strategy was followed. Heterozygous *Terc*^{+/-} mice were first crossed with hemizygous *Tau*^{Tg} mice to obtain *Terc*^{+/-} *Tau*^{Tg} mice. These mice were then crossed with *Terc*^{+/-} mice to generate G1*Terc*^{-/-} *Tau*^{Tg} and G1*Terc*^{-/-} littermates lacking telomerase activity. G1*Terc*^{-/-} *Tau*^{Tg} and G1*Terc*^{-/-} mice and their offspring were subsequently crossbred to produce the later generations. Age- and sex-matched non-transgenic (wild-type, WT) and hemizygous *Tau*^{Tg} control littermates came from a separate breeding setup. Genotype of the mice was confirmed by polymerase chain reaction (PCR) analysis on ear tag DNA samples. All animals were housed in the same standard animal care facilities on a 12 h light/12 h dark cycle, with *ad libitum* access to food and water. Animals were monitored daily and sacrificed if they showed signs of pain or distress. All animal procedures were carried out in compliance with institutional and European guidelines and were approved by the Ethical Committee for Animal Welfare at UCLouvain (References: 2018/UCL/MD/38 and 2021/UCL/MD/18).

Brain tissue sampling

Mice were anesthetized with a combination of ketamine (100 mg/kg, Dechra) and medetomidine (1 mg/kg, Vetoquinol) diluted in sterile phosphate-buffered saline (PBS), followed by transcardial perfusion with ice-cold sterile PBS. The brains were removed and divided into two hemispheres. The right hemisphere was post-fixed by immersion in 4% paraformaldehyde in PBS for 24 h, cryoprotected in PBS containing 30% sucrose and 0.02% sodium azide, and subsequently frozen for later use in immunofluorescence and staining analyses. The left hemisphere was further dissected into the hippocampus and cortex, which were snap frozen in dry ice and stored at -80 °C to be further processed.

Telomere length analysis by quantitative PCR

Hippocampal brain tissue obtained from male (*m.*) and female (*f.*) WT (*n* = 4 *m.*, *n* = 0 *f.*), G1*Terc*^{-/-} (*n* = 4 *m.*, *n* = 2 *f.*), G2*Terc*^{-/-} (*n* = 4 *m.*, *n* = 3 *f.*) and G3*Terc*^{-/-} (*n* = 3

m., *n* = 3 *f.*) mice at 5 months was digested with proteinase K (100 µg/ml) in lysis buffer (100 mM NaCl, 100 mM Tris-HCl [pH 8.0], 1 mM EDTA, [pH 8.0] and 1% SDS) at 50 °C overnight. DNA was purified using the phenol/chloroform method. To measure the length of mouse telomeres, a quantitative PCR method was used as previously described [84]. Briefly, two separate quantitative PCR reactions were performed, one with telomere primers and the other with single copy gene primers. The relative telomere length (presented as T/S ratio) was calculated by comparing telomere amplification (T) to that of the single copy gene (S) using the $2^{-\Delta\Delta CT}$ method [14].

Quantitative RT-PCR

Total RNA was extracted from hippocampal brain tissue from adult WT (*n* = 4 *m.*, *n* = 4 *f.*) and G3Terc^{-/-} (*n* = 4 *m.*, *n* = 4 *f.*) mice at 5 months and from relatively aged WT (*n* = 3 *m.*, *n* = 3 *f.*) and G2Terc^{-/-} (*n* = 4 *m.*, *n* = 3 *f.*) mice at 9 months using TriPure™ Isolation reagent (Roche) according to the manufacturer's protocol. RNA was resuspended in DEPC-treated water and its concentration (OD 260) and purity (260/280 and 260/230 ratios) were assessed on BioSpec-nano spectrophotometer (Shimadzu Biotech). Reverse transcription (RT) was carried out with the iScript cDNA synthesis kit (Bio-Rad Laboratories) using 1 µg of total RNA in a 20 µl reaction volume. Quantitative PCR was performed for the amplification of cDNAs using the appropriate primers (Table S1) and the GoTaq® qPCR Master Mix (Promega), following manufacturer's instructions. For negative controls, the iScript reverse transcriptase was omitted in the cDNA synthesis step. Relative quantification was calculated by the $2^{-\Delta\Delta CT}$ method using *Gapdh* and *Tbp* as housekeeping genes. Results were then normalized (fold change) to the control condition.

Protein isolation

For the evaluation of senescence biomarkers, hippocampal brain tissue from WT (*n* = 5 *m.*, *n* = 8 *f.*) and G3Terc^{-/-} (*n* = 3 *m.*, *n* = 8 *f.*) mice was collected at 5–6 months, and from WT (*n* = 4 *m.*, *n* = 8 *f.*) and G2Terc^{-/-} (*n* = 6 *m.*, *n* = 5 *f.*) mice at 9 months. Further, for the examination of tau phosphorylation and tau-related pathology, hippocampal and cortical brain tissue from WT (*n* = 5 *m.*, *n* = 3 *f.*), G3Terc^{-/-} (*n* = 3 *m.*, *n* = 4 *f.*), Tau^{Tg} (*n* = 3 *m.*, *n* = 3 *f.*) and G3Terc^{-/-} Tau^{Tg} (*n* = 4 *m.*, *n* = 1 *f.*) mice was collected at 6 months, and from WT (*n* = 3 *m.*, *n* = 11 *f.*), G2Terc^{-/-} (*n* = 1 *m.*, *n* = 7 *f.*), Tau^{Tg} (*n* = 3 *m.*, *n* = 10 *f.*) and G2Terc^{-/-} Tau^{Tg} (*n* = 7 *m.*, *n* = 5 *f.*) mice at 9 months. Mouse cortical and hippocampal tissues were homogenized as follows. Briefly, tissues were sonicated in ice-cold lysis buffer containing 20 mM Tris-base (pH 8.0), 150 mM NaCl, 1% NP-40, 10% glycerol and supplemented with protease and phosphatase inhibitor cocktails (Roche). The total

homogenate was centrifuged at 16,000 ×g and 4 °C for 20 min and the supernatant was collected as the soluble fraction and stored at –80 °C. For the analysis of tau in the insoluble fraction, the pellet was washed in ice-cold PBS and resuspended by sonication in a buffer containing 8 M urea, 5 mM EDTA, 1 mM EGTA and supplemented with protease and phosphatase inhibitor cocktails (Roche). The samples were centrifuged at 16,000 ×g for 15 min and the supernatant was collected as the insoluble fraction and stored at –80 °C.

Western blot

Total protein concentrations in the soluble and insoluble fractions were determined using the Pierce™ BCA Protein assay (Invitrogen, Thermo Fisher Scientific) following appropriate dilution (1:10) of both protein fractions in ultrapure water. NuPAGE™ LDS Sample Buffer (Invitrogen, Thermo Fisher Scientific) and 50 mM dithiothreitol (DTT) were added. Only the soluble protein fraction samples were heated for 10 min at 70 °C. 10 µg to 20 µg of total protein were resolved by SDS-PAGE on precast NuPAGE™ 4–12% Bis-Tris gels (Thermo Fisher Scientific) with MES-SDS running buffer (Thermo Fisher Scientific) and SeeBlue™ Plus2 pre-stained (Thermo Fisher Scientific) as standard. Samples were then transferred to 0.45 µm nitrocellulose membranes (Thermo Fisher Scientific). The nitrocellulose membranes were blocked in 5% (w/v) non-fat powdered milk in PBS/0.1% Tween®20 (PBS-T) for 30 min–1 h at room temperature, before incubation overnight at 4 °C with primary antibodies (Table S2) diluted in PBS-T. Species-specific secondary antibodies conjugated with horseradish peroxidase (HRP, Sigma-Aldrich) diluted in PBS-T were used to bind primary antibodies prior to ECL detection (PerkinElmer). Following ECL detection, the membranes were stripped in boiling PBS for 10 min and Restore™ PLUS Western Blot Stripping Buffer (ThermoFisher) at room temperature for 30 min, re-blocked and re-probed up to a maximum of 3 times. Protein band intensity was quantified using the image processing software ImageJ [75] and normalized to the protein band intensity of actin or total tau (D1M9X, Cell Signaling).

Immunofluorescence and imaging of brain sections

Frozen right brain hemispheres from 6-month-old WT (*n* = 5 *m.*, *n* = 3 *f.*), G3Terc^{-/-} (*n* = 3 *m.*, *n* = 4 *f.*), Tau^{Tg} (*n* = 3 *m.*, *n* = 3 *f.*) and G3Terc^{-/-} Tau^{Tg} (*n* = 4 *m.*, *n* = 1 *f.*) mice, and from 9-month-old WT (*n* = 3 *m.*, *n* = 10 *f.*), G2Terc^{-/-} (*n* = 1 *m.*, *n* = 7 *f.*), Tau^{Tg} (*n* = 3 *m.*, *n* = 10 *f.*) and G2Terc^{-/-} Tau^{Tg} (*n* = 7 *m.*, *n* = 5 *f.*) mice were sliced into 30 µm thick coronal sections using a CryoStar™ NX50 Cryostat (Thermo Fisher Scientific) and stored at –20 °C in cryoprotectant solution (sodium phosphate buffer containing 30% ethylene glycol and 20% glycerol) until use.

For each hemibrain, four to five free-floating sections spaced 240 μm apart containing hippocampus and entorhinal/piriform cortex – between bregma -1.94 and -2.92 based on the mouse brain atlas [27] – were selected, washed three times in 1X PBS and blocked/permeabilized for 30 min at room temperature in blocking solution containing 5% BSA, 3% normal goat serum (Gibco) and 0.5% Triton X-100 in 1X PBS. Subsequently, brain sections were incubated overnight at 4 °C with primary antibodies (Table S2) diluted in blocking solution. The next day, after three washes with 1X PBS, sections were incubated in the dark for 1 h at room temperature with DAPI (1:10,000, Sigma-Aldrich) and the appropriate species-specific fluorophore-conjugated Alexa Fluor™ secondary antibodies diluted in blocking solution. Finally, sections were washed three times in 1X PBS and mounted on Superfrost™ glass slides, air dried and coverslipped using Mowiol mounting medium. Sections were stored at 4 °C. Images were captured using a ZEISS AxioScan 7 Microscope Slide Scanner with a 20X objective lens and analyzed by either ZEN (Carl Zeiss) or ImageJ [75] softwares. Briefly, we quantified the intensity and extent of the pathological phosphorylation of tau and any associated neurodegeneration and neuroinflammation by delineating the areas of interest (i.e., hippocampus, entorhinal/piriform cortex) [27] and measuring the fluorescence intensity and the percentage covered by positive signal within our regions of interest. Additionally, to study the impact of tau pathology and senescence on specific hippocampal subregions, we performed quantification of the number of neuronal cells, positive for NeuN signal. Finally, to examine the morphology of microglia, positive for Iba1 antibody, we captured images using a ZEISS LSM800 Confocal Laser Scanning Microscope with a 40X objective lens.

As negative controls, samples were processed as described in the absence of primary antibody and no signal was detected.

Nissl staining and volume quantifications

To quantify hippocampal volume, ventricular volume and cortical thickness, four to five hemibrain sections spaced 240 μm apart largely spanning the hippocampus and entorhinal/piriform cortex, between bregma -1.94 and -2.92 based on the mouse brain atlas [27] were mounted on Superfrost™ glass slides, air dried overnight at room temperature and stained with Cresyl violet (Nissl staining). After being stained for 45 min in cresyl violet solution (0.04%, Sigma-Aldrich), sections were dehydrated in ethanol, cleared in xylene and mounted with DPX mounting medium (Sigma-Aldrich).

For quantification of hippocampal/ventricular volumes, the brain structures were manually delineated and the areas measured. Volumes between consecutive

sections were then calculated using the following formula

$$V = \frac{(a+b)}{2} \times 240\mu\text{m}$$
, where a and b are the areas of the hippocampal/ventricular structures in each section, and 240 μm is the distance between sections. The volumes of all section pairs were added up to calculate the total hippocampal/ventricular volume [5].

Statistical analysis

Statistical analyses were carried out using the GraphPad Prism 10 software. Normality was assessed with the Shapiro-Wilk test. A parametric test was performed if the data followed normal distribution, while a non-parametric test was used otherwise. Comparisons between two groups were made using either a parametric Student's-t-test or a non-parametric Mann-Whitney test. When more than two groups were compared, parametric one-way ANOVA with indicated post-hoc tests or non-parametric Kruskal-Wallis were used. For correlation analyses, the non-parametric Spearman's test was used. Significance is indicated as: ns = non-significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. The number of independent biological samples (i.e., animals) is indicated in figure legends with “n =”.

Results

The brains of G2Terc^{-/-} and G3Terc^{-/-} mice present telomere shortening and elevated expression of senescence markers

Given the well-established role of telomere attrition as a driver of cellular senescence, Terc knockout (Terc^{-/-}) mice, which lack the RNA component of the telomerase, were used as a model of accelerated senescence. Previous data from our group demonstrated progressive telomere shortening in cortical extracts from increasing generations of Terc^{-/-} mice at 5 months of age [84]. In this study, we expanded upon these findings by evaluating telomere length in hippocampal tissue from these mice. The results confirmed a progressive reduction in telomere length across successive generations of Terc^{-/-} mice, with significant attrition observed in the second and third generations, compared to wild-type control mice (Fig. 1a).

Two distinct time points were selected for evaluation in the senescent model. G3Terc^{-/-} mice at 5–6 months of age were chosen as they display a pronounced senescent phenotype, as previously confirmed using cortical extracts and primary neurons derived from this generation of mice [84]. Of note, we observed a dramatic decrease in the life expectancy of G3Terc^{-/-} mice after 6–7 months of age, emphasizing the devastating effects of systemic telomere attrition. In contrast, G2Terc^{-/-} mice live longer but still show significant telomere attrition in the brain (Fig. 1a). Therefore, 9-month-old G2Terc^{-/-} mice were selected to reflect an aged phenotype in a

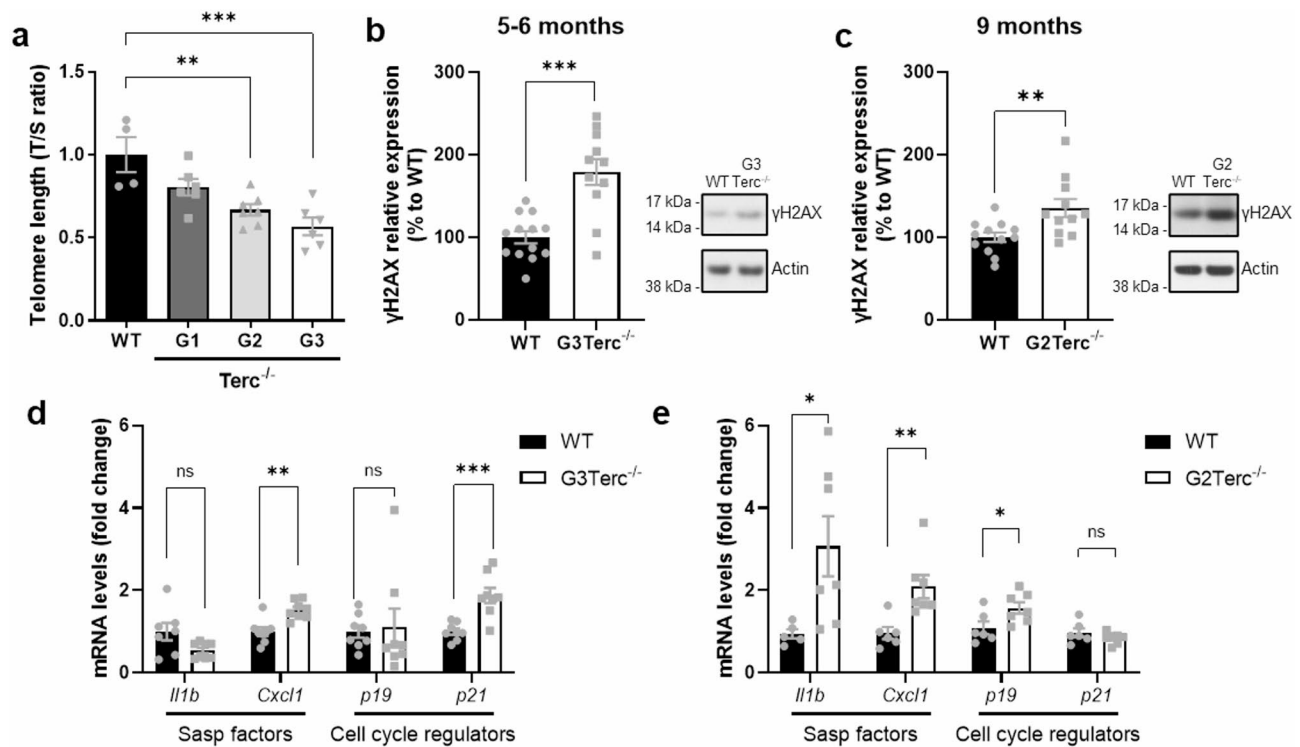


Fig. 1 Telomere shortening in the brains of G3Terc^{-/-} and G2Terc^{-/-} mice triggers the activation of classical senescence markers. **(a)** Relative telomere length detected by qPCR analysis using hippocampal DNA extracts from WT and successive generations (G1–G3) of Terc^{-/-} mice at 5 months of age. The average telomere length was calculated as the ratio (T/S) of telomere repeat copy number (T) to a single-copy gene (S = 36B4). ***P* < 0.01, ****P* < 0.001 (One-way ANOVA with Tukey's post-hoc analysis, *n* = 4–7 mice/group). **(b–c)** Relative levels of the DNA damage biomarker γH2AX detected by Western Blot analysis using hippocampal protein extracts from 5–6-month-old WT and G3Terc^{-/-} mice **(b)** and 9-month-old WT and G2Terc^{-/-} mice **(c)**. ***P* < 0.01, ****P* < 0.001 (two-tailed Student's *t*-test, *n* = 11–13). **(d–e)** mRNA levels of the SASP factors *Il1b* and *Cxcl1*, and the cyclin-dependent kinase inhibitors *p19*^{Arf} (*p19*) and *p21*^{Waf1/cip1} (*p21*), were measured by RT-qPCR in hippocampal extracts from 5-month-old WT and G3Terc^{-/-} mice **(d)** and 9-month-old WT and G2Terc^{-/-} mice **(e)**. **P* < 0.05, ***P* < 0.01, ****P* < 0.001 (two-tailed Student's *t*-test or Mann-Whitney's test, *n* = 5–8 mice/group)

senescent context. As both models will be later used in our study to evaluate the role of senescence in tau pathology, we first validated the presence of senescence biomarkers in their brains. The evaluation of γH2AX, a phosphorylated form of histone H2AX at Ser139 that signals for double-stranded DNA breaks and is recognized as a senescence marker [69], revealed elevated levels in both G3Terc^{-/-} and G2Terc^{-/-} models (Fig. 1b, c). In addition, we performed RT-qPCR analyses of *bona-fide* senescence markers, including the SASP factors *Il1b* and *Cxcl1*, and the cyclin-dependent kinase inhibitors *p19*^{Arf} (*p19*) and *p21*^{Waf1/cip1} (*p21*). Increased mRNA expression of *Cxcl1* and *p21* was observed in 5-month-old G3Terc^{-/-} mice, while *Il1b*, *Cxcl1* and *p19* were upregulated in 9-month-old G2Terc^{-/-} mice (Fig. 1d, e). Interestingly, the fold change in SASP factors was greater in 9-month-old G2Terc^{-/-} mice compared to 5-month-old G3Terc^{-/-} mice, suggesting that the aging phenotype further amplifies the secretion of pro-inflammatory molecules in a senescent context. These findings support our rationale for using both models: while G3Terc^{-/-} at 5–6 months present strong senescent features, G2Terc^{-/-} at 9 months

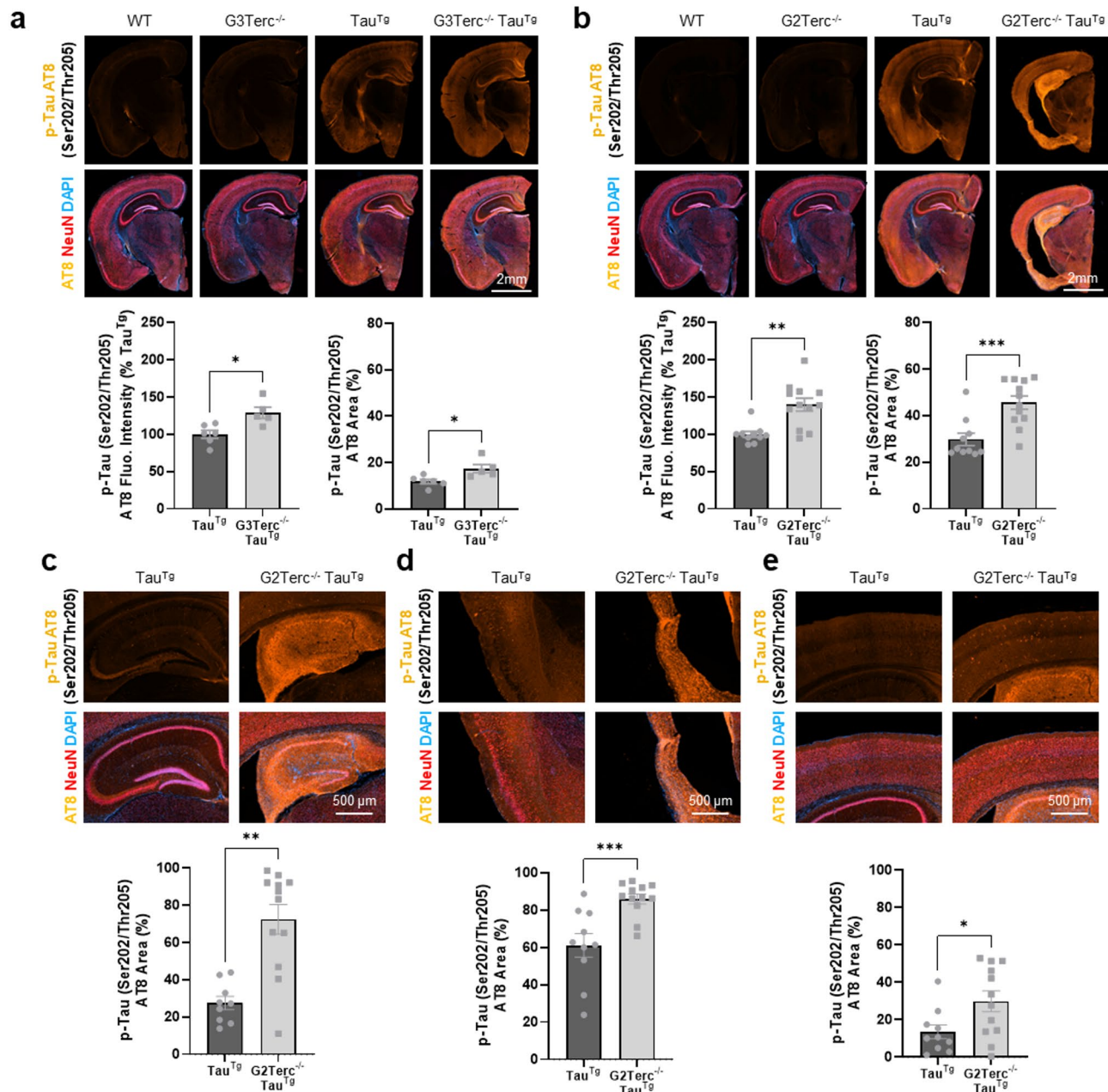
display a combination of moderate senescence and an aged phenotype with enhanced chronic inflammation.

Cellular senescence increases Tau phosphorylation, cleavage and aggregation in PS19 mice

To explore the role of cellular senescence in the onset and development of tau pathology, we generated a novel combined mouse model by crossing Terc knockout mice with the PS19 tauopathy model, hereafter referred to as Tau^{Tg}, a transgenic mouse that overexpresses the 1N4R human tau isoform with the P301S mutation found in familial FTLT. This widely used and well-characterized model exhibits widespread aberrant tau phosphorylation and aggregation by 6 months of age and significant neuronal loss by 9–12 months of age, with a particularly strong effect on the hippocampus and the entorhinal cortex [56, 96]. Importantly, these region-specific vulnerabilities occur despite comparable expression of the tau transgene across different brain regions at both the mRNA and protein levels (Fig. S1). To assess the impact of senescence at two different stages of pathology in Tau^{Tg} mice, adult mice at 6 months and relatively aged mice at 9 months

were selected. For each time point, four different groups of mice were obtained. At 6 months of age, we collected samples from WT, G3Terc^{-/-}, Tau^{Tg}, and G3Terc^{-/-} Tau^{Tg} mice. As mentioned above, G3Terc^{-/-} mice in our facilities hardly survived past 6–7 months, so we also collected samples from WT, G2Terc^{-/-}, Tau^{Tg}, and G2Terc^{-/-} Tau^{Tg} mice at 9 months of age (Fig. S2).

To assess pathological tau phosphorylation, immunofluorescence (IF) staining analyses were conducted on coronal brain sections from all groups of mice (Fig. 2). The AT8 antibody, which detects tau phosphorylated at Ser202 and Thr205, is a well-established marker of tau pathology [9, 29]. Co-labeling with an anti-NeuN antibody enabled the visualization of pathological tau in



neuronal somas. AT8 signal was negligible in 6-month-old WT and G3Terc^{-/-} mice, as well as in 9-month-old WT and G2Terc^{-/-} mice (Fig. 2a, b), whereas strong AT8 labeling was detected in hippocampal and cortical regions from tauopathy and combined senescence-tauopathy models. Image quantification revealed an increase in AT8 signal intensity and signal-covered area in 6-month-old G3Terc^{-/-} Tau^{Tg} compared to Tau^{Tg} mice, which was even more exacerbated in 9-month-old G2Terc^{-/-} Tau^{Tg} mice. Further characterization of AT8 signal in 9-month-old G2Terc^{-/-} Tau^{Tg} mice revealed a striking increase within the hippocampus and the piriform/entorhinal cortex (Fig. 2c, d). The somatosensory/association cortex displayed a milder, yet still significant, increase in tau pathology (Fig. 2e), reaching much lower levels of AT8 intensity than in the hippocampus and piriform/entorhinal cortex. These findings illustrate the region-specific vulnerabilities to the senescent context in the brain.

To conduct a more in-depth evaluation of the effect of senescence on tau phosphorylation status, we performed WB analyses of several tau epitopes known to be hyperphosphorylated in pathological conditions: Thr181, Ser202/Thr205 (AT8), Thr231, Ser262, Ser396/Ser404 (PHF-1) and Ser422 [4]. In the adult Tau^{Tg} mouse brain, endogenous murine tau, which exists primarily as the 0N4R isoform [54, 57], coexists with the human 1N4R tau isoform. This isoform difference results in two bands of different molecular weights in WB analyses using anti-tau antibodies, enabling the discrimination between mouse and human tau and the assessment of their phosphorylation status. However, it has been reported that commonly used phospho-tau antibodies, when evaluated by WB in mouse brain samples, display non-specific bands at ~50 kDa, the molecular size of murine tau. These bands can still be observed in samples from Tau knockout mice and therefore cannot be attributed to phosphorylated endogenous tau [66]. For this reason, we focused our evaluation on the phosphorylation status of human tau, using only the tauopathy and combined senescence-tauopathy models at 6 and 9 months of age. The analyses revealed a marked increase in tau phosphorylation at Thr181 and Ser202/Thr205 (AT8) in both soluble and insoluble protein fractions, and at Thr231 and Ser396/Ser404 (PHF-1) only in the soluble fraction, in the hippocampus of 6-month-old G3Terc^{-/-} Tau^{Tg} (Fig. 3a). No changes in Ser262 and Ser422 residues were found. We additionally established there is a significant correlation between the levels of the senescence biomarker γ H2AX and pathologically phosphorylated tau levels (AT8 signal), as measured by WB, in tauopathy and senescence-tauopathy adult mice, emphasizing the direct link between cellular senescence and tau pathology (Fig. S3). Unlike the hippocampus, the cortical region of these mice showed no changes at any of the evaluated

phosphorylation sites (Fig. 3b). Evaluation of total tau levels revealed no significant differences in either soluble or insoluble protein fractions (Fig. S4). At a later timepoint in the disease progression (9 months), all the evaluated tau phosphorylation residues were significantly increased in the insoluble protein fraction of the hippocampus in G2Terc^{-/-} Tau^{Tg} mice (Fig. 3c), indicating that tau pathology is aggravated under a senescent context. Notably, the fold change differences were greater at 9 months compared to 6 months. Tau phosphorylation at Thr181 and Ser202/Thr205 (AT8) was still increased in the soluble fraction. The cortical region was again relatively spared, although a significant increase was found in phosphorylated tau at Thr231 and Ser422 in the soluble fraction and an almost significant increase was found at the AT8 ($P=0.0819$) site in the insoluble fraction (Fig. 3d). Additionally, total tau levels were significantly elevated in soluble and insoluble protein fractions of these mice (Fig. S4). Overall, our data suggests that the senescent context induces site-specific hyperphosphorylation of tau in a region-dependent manner, eventually leading to an increase in tau accumulation and deposition.

To further investigate the molecular mechanisms underlying these effects, we assessed several major tau kinases, including AMP-activated protein kinase (AMPK), glycogen synthase kinase 3 β (GSK-3 β), mitogen-activated protein kinases ERK1/2 and protein kinase B (also known as AKT), as well as the primary tau phosphatase, protein phosphatase 2 A (PP2A) (Fig. 4). Telomere attrition-induced senescence had no major impact on the protein levels and phosphorylation status of most tau kinases and phosphatases at 6 months of age, although a significant decrease in the active form of AMPK (p-AMPK) was observed in G3Terc^{-/-} Tau^{Tg} mice compared to WT controls. This suggests that the early effects of senescence on tau phosphorylation might not be driven by the over-activation of tau kinases or inactivation of tau phosphatases. In contrast, at 9 months of age (Fig. 4a), p-ERK became hyperactive in the hippocampi of Tau^{Tg} mice, with further enhancement caused by the senescence context, while p-AKT was found significantly increased in G2Terc^{-/-} Tau^{Tg} mice. Additionally, a significant decrease in p-AMPK was found in Tau^{Tg} mice, becoming further inactivated in G2Terc^{-/-} Tau^{Tg}. These results suggest that advanced tau pathology disrupts the activity of AMPK, ERK1/2 and AKT kinases, and that this dysregulation might be accelerated by the senescent environment.

Since our data showed that telomere-driven senescence promotes tau phosphorylation, particularly in the hippocampus, we sought to determine whether it also modulates tau cleavage and aggregation in this region. WB analysis using a total tau antibody (D1M9X clone) on soluble and insoluble hippocampal protein fractions of

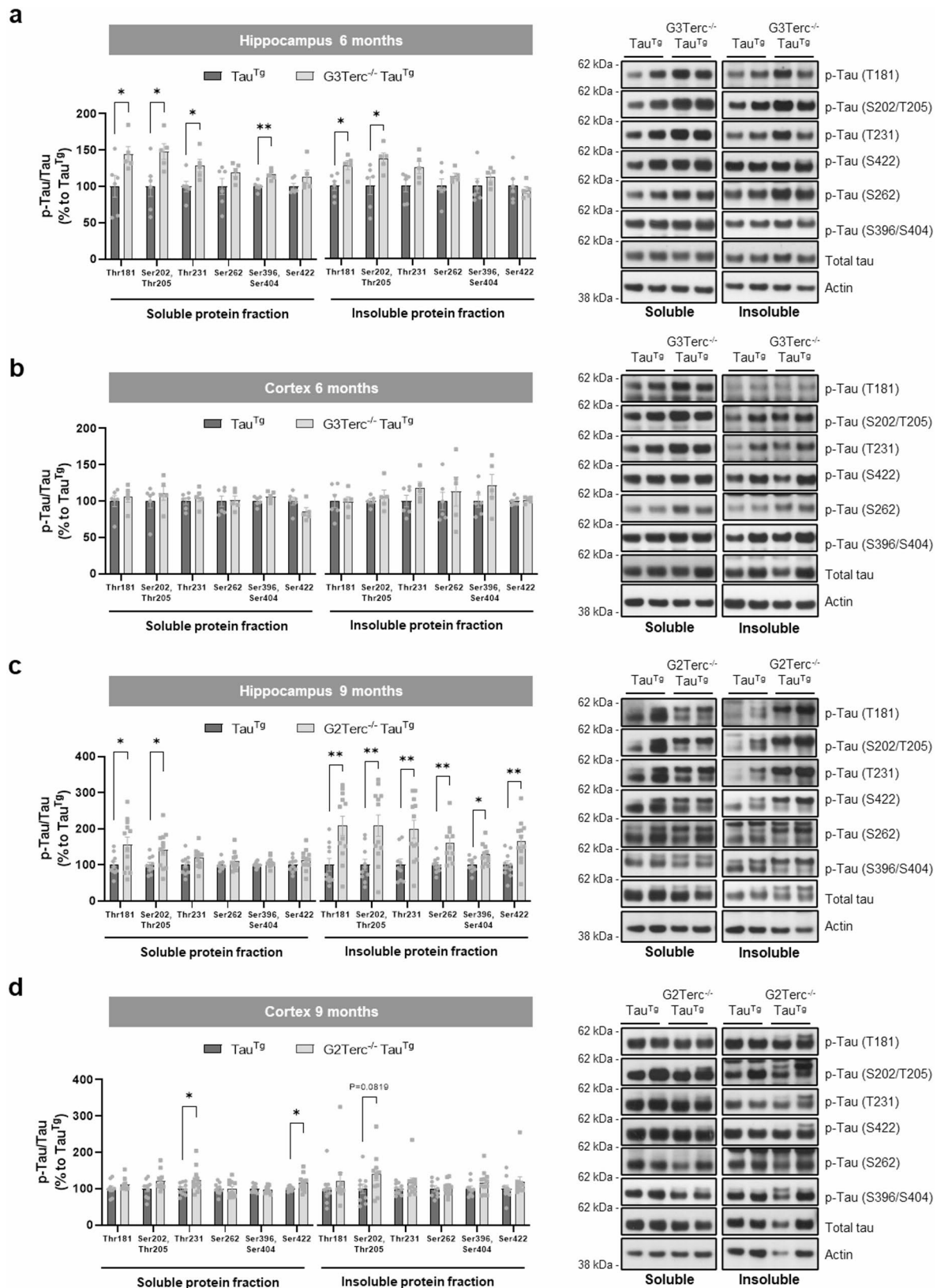


Fig. 3 Senescence induces site-specific hyperphosphorylation of tau in PS19 mice. WB analysis of phosphorylated tau (Thr181, Ser202/Thr205 – AT8, Thr231, Ser262, Ser396/Ser404 – PHF-1 and Ser422) normalized to total tau (D1M9X clone) in soluble and insoluble protein extracts from 6-month-old Tau^{Tg} and $\text{G3Terc}^{-/-} \text{Tau}^{\text{Tg}}$ hippocampal (**a**) and cortical (**b**) samples and from 9-month-old Tau^{Tg} and $\text{G2Terc}^{-/-} \text{Tau}^{\text{Tg}}$ hippocampal (**c**) and cortical (**d**) samples. * $P < 0.05$, ** $P < 0.01$ (Student's t -test or Mann-Whitney's test, $n = 5$ –12 mice/group)

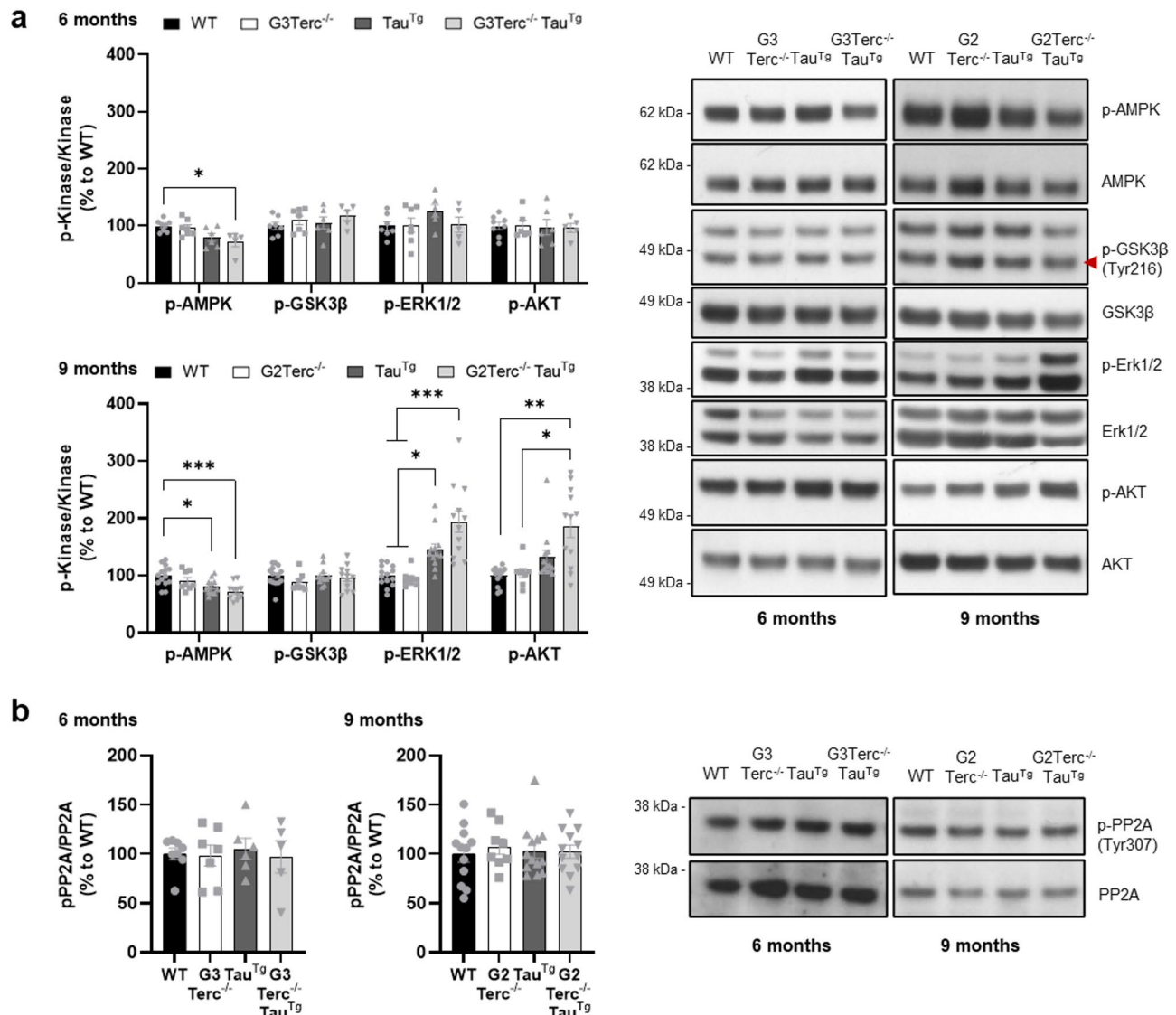


Fig. 4 Telomere-induced senescence does not modify protein levels of tau kinases and phosphatases, nor their phosphorylated status at early stages of the pathology. WB evaluation of major tau kinases (**a**) and the main tau phosphatase PP2A (**b**) in hippocampal protein extracts from 6-month-old WT, G3Terc^{-/-}, Tau^{Tg} and G3Terc^{-/-} Tau^{Tg}, and 9-month-old WT, G2Terc^{-/-}, Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} mice. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (One-way ANOVA with Tukey's post-hoc analysis or Kruskal-Wallis test, $n = 5-13$ mice/group)

9-month-old mice revealed several bands below 50 kDa in Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} mice, which were absent in WT and G2Terc^{-/-} samples (Fig. S5). This suggests that the observed bands correspond to specific fragments of the tau transgene, as previously indicated [20, 95]. Tau truncation by different proteases in the brains of AD patients and tauopathy models has been involved in tau aggregation and neurotoxicity [32, 102]. WB evaluation of truncated tau in hippocampal samples showed a significant increase in the soluble and insoluble fractions in G2Terc^{-/-} Tau^{Tg} mice compared to Tau^{Tg} mice (Fig. 5). Similarly, the total tau antibody in soluble and insoluble protein fractions from 9 months-old Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} revealed several bands of high-molecular weights,

indicative of tau oligomers [20, 95]. Again, these bands were absent in WT and G2Terc^{-/-} samples (Fig. S5). WB analyses demonstrated increased levels of oligomeric tau species in the hippocampus of G2Terc^{-/-} Tau^{Tg} mice compared to Tau^{Tg} mice, in both soluble and insoluble protein fractions (Fig. 5). These data suggest that telomere-induced senescence increases tau truncation and aggregation in relatively aged PS19 mice.

Cellular senescence enhances glial activation in the presence of tauopathy

It is currently well established that glial activation and inflammation are both processes heavily involved in the development and evolution of NDs, including AD [37,

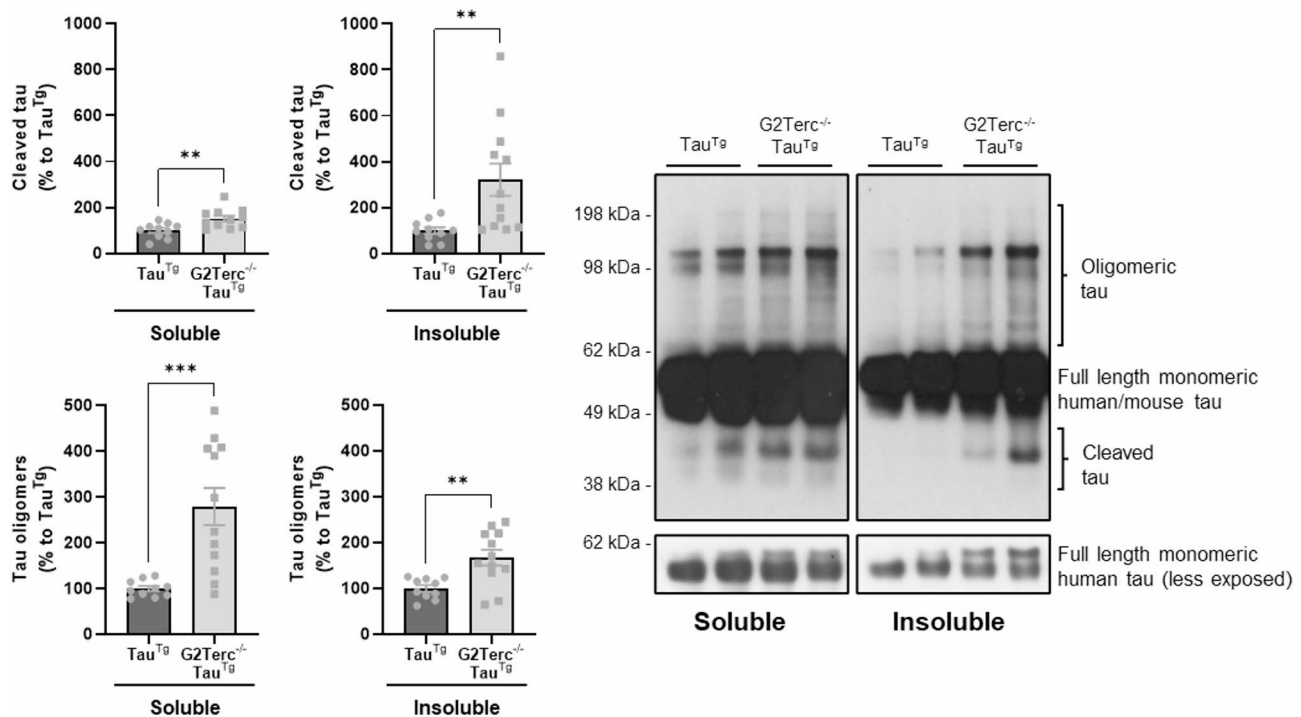


Fig. 5 Senescence exacerbates truncated and aggregated tau. WB evaluation of truncated and oligomeric tau normalized to full length monomeric human tau in soluble and insoluble protein extracts from 9-month-old Tau^{Tg} and $G2Terc^{-/-} Tau^{Tg}$ mouse hippocampi, using a total tau antibody (D1M9X clone). ** $P < 0.01$, *** $P < 0.001$ (Student's *t*-test or Mann-Whitney's test, $n = 10$ –12 mice/group)

98]. Moreover, it is believed that astrocyte and microglial alterations associated with aging can further contribute to the process of neurodegeneration [28, 82, 88]. Given that our results revealed strong tau pathology in the combined senescence-tauopathy model at 9 months of age, we initially assessed the presence of astrogliosis and microgliosis across all mouse groups by performing WB analyses of GFAP and Iba1 protein, which are specific markers of astrocytes and microglia, respectively (Fig. 6a). Although GFAP levels already showed a non-significant increasing trend ($P = 0.1184$) in Tau^{Tg} mice compared to WT mice in the hippocampal region, the addition of a senescent context strongly upregulated GFAP levels. Similarly, cortical samples of $G2terc^{-/-} Tau^{Tg}$ mice displayed raised GFAP levels compared to WT and Tau^{Tg} mice. Iba1 levels displayed similar changes, with $G2terc^{-/-} Tau^{Tg}$ hippocampal and cortical samples revealing increased Iba1 levels. Notably, the change in Iba1 levels was more pronounced in the hippocampus compared to the cortex, suggesting stronger microglial activation in this region. Immunofluorescence staining for Iba1 and GFAP confirmed the activation of astrocytes and microglia in the hippocampus of 9-month-old $G2terc^{-/-} Tau^{Tg}$ mice (Fig. 6b), showing a significant increase in the biomarker-positive area for both glial cell types, when compared to WT but also to Tau^{Tg} mice.

An in-depth evaluation of the morphology of Iba1-positive cells revealed that microglial activation in the

hippocampus of 9-month-old $G2terc^{-/-} Tau^{Tg}$ mice was accompanied by the presence of dystrophic microglia [2], characterized by beading and apparent fragmentation of their projections (Fig. S6). Interestingly, this phenotype was not observed in Tau^{Tg} mice, despite the aforementioned increase in Iba1 levels. Altogether, these findings show that telomere-induced brain senescence, typically associated with low-grade chronic inflammation, results in the abnormal activation and proliferation of astroglia and microglia over time, particularly within a pathological background.

Senescence-induced tauopathy in PS19 mice correlates with neurodegeneration

Synaptic impairment is a pathological hallmark of neurodegeneration associated with AD and thought to precede neuronal loss in humans and in preclinical models of the disease, including the PS19 tauopathy mouse model [85, 96]. It is believed that reactive astroglia and activated microglia play an active role in the process of synaptic loss in tau pathology via enhanced synaptic phagocytosis [87, 91]. To assess the impact of tau hyperphosphorylation and neuroinflammation in neurodegeneration, levels of well-established synaptic markers were initially examined via WB. At 6 months of age, no significant changes in the protein levels of NMDAR2B, GluR1, PSD95 and synaptophysin were observed (Fig. 7a). We then examined the same synaptic markers in the hippocampus of

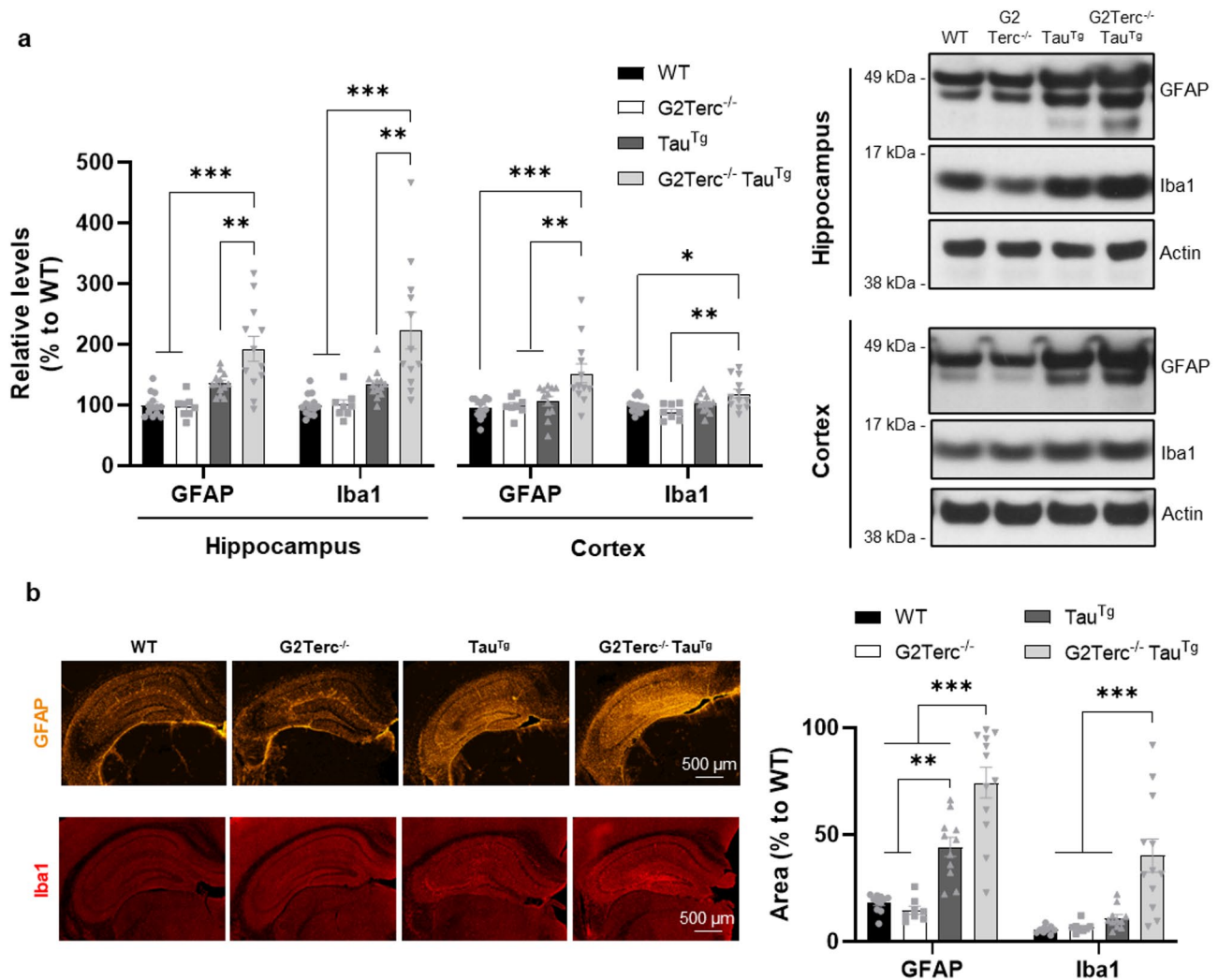


Fig. 6 Senescence increases glial activation within a tauopathy context. **(a)** WB evaluation of GFAP and Iba1 expression in hippocampal and cortical protein extracts from 9-month-old WT, G2Terc^{-/-}, Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} mice. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (One-way ANOVA with Tukey's post-hoc analysis, $n = 8-13$ mice/group). **(b)** Immunofluorescence analysis of GFAP (orange) and Iba1 (red) in the hippocampal region of brain sections from 9-month-old WT, G2Terc^{-/-}, Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} mice. Histograms represent the percentage of staining area. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (One-way ANOVA with Tukey's post-hoc analysis, $n = 8-13$ mice/group)

9-month-old G2Terc^{-/-} Tau^{Tg} mice, and we observed a significant decrease for GluR1 (Fig. 7b).

Next, neuronal degeneration was assessed using Nissl staining and NeuN immunoreactivity analysis. While increased tau phosphorylation was observed in the hippocampus of 6-month-old G3Terc^{-/-} Tau^{Tg} mice (Fig. 2a), neuronal integrity was largely preserved at this age, with no detectable changes in NeuN protein levels (Fig. S7a) and no gross morphological changes (Fig. S7b). In contrast, G2Terc^{-/-} Tau^{Tg} brains at 9 months of age exhibited important brain atrophy, with a significant reduction in hippocampal volume, as well as a shrinkage of the piriform/entorhinal cortex (Fig. 8a), compared to either WT or Tau^{Tg} controls. In contrast, cortical thickness at the level of the somatosensory/association area was unchanged between groups. In addition, G2Terc^{-/-} Tau^{Tg}

mice also displayed marked enlargement of the lateral ventricles, which is frequently associated with hippocampal and cortical atrophies. Moreover, NeuN protein levels of 9-month-old G2Terc^{-/-} Tau^{Tg} hippocampal extracts showed a significant decrease when compared with WT, G2Terc^{-/-} and Tau^{Tg} samples, which was not present in cortical extracts (Fig. 8b). Detailed examination of specific hippocampal subregions of G2Terc^{-/-} Tau^{Tg} mice revealed significant neuronal loss in the CA1, CA3 and DG (Fig. 8c). Our findings further revealed that hyperphosphorylated tau (AT8) and markers of neuroinflammation (GFAP/Iba1) are negatively correlated with hippocampal volume in the brains of 9-month-old Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} mice (Fig. S8), suggesting a potential causal relationship. Together, these results suggest that

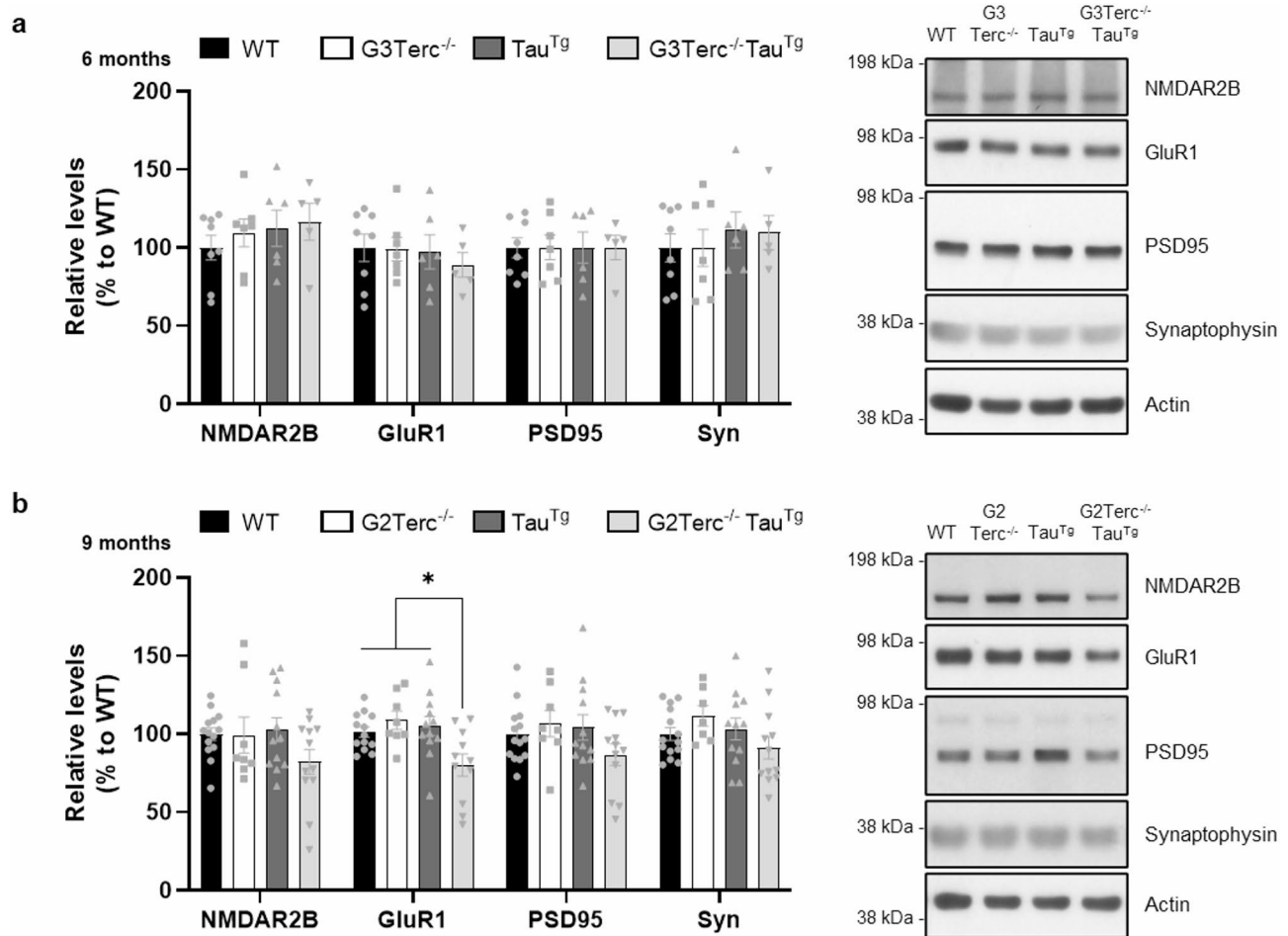


Fig. 7 Senescence slightly impairs synaptic marker expression within a tauopathy context. WB evaluation of relative levels of the synaptic markers NMDAR2B, GluR1, PSD95 and synaptophysin in hippocampal protein extracts from 6-month-old WT, G3Terc^{-/-}, Tau^{Tg} and G3Terc^{-/-} Tau^{Tg} mice (**a**) and 9-month-old WT, G2Terc^{-/-}, Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} mice (**b**). * $P < 0.05$ (One-way ANOVA with Tukey's post-hoc analysis, $n = 5-13$ mice/group)

increased tauopathy caused by senescence activation in PS19 mice leads to region-specific neuronal vulnerability.

Discussion

Given that cellular senescence is closely associated with pathological aging, its role in age-related NDs like AD has attracted increasing attention in recent years [100]. Senescent neurons and glial cells have been found in AD brains [7, 23, 38, 40, 60], and considerable efforts have been made to evaluate their contribution to disease pathogenesis. Since telomere attrition is a primary driver of senescence, the telomerase-deficient Terc knockout mice [8] provide an excellent model for studying the role of brain senescence in the onset and progression of AD pathology. Prior work from our group demonstrated that the senescence context present in Terc knockout mouse brains can drive toxic intraneuronal A β accumulation upon overexpression of human APP carrying familial AD (FAD) mutations [84]. In this project, we explored the potential contribution of senescence on another hallmark

of AD pathology, tau aggregation, by crossing Terc knockout mice with the PS19 tauopathy mouse model. The introduction of a senescent phenotype was found to increase tau phosphorylation and aggregation in specific brain regions, ultimately resulting in excessive neuroinflammation and neuronal loss.

While mounting evidence suggests that AD-related features, particularly tau aggregation, can trigger cellular senescence [23, 60], the inverse relationship seems less well-established [71]. Our study reinforces the idea that senescence is an upstream regulator of the tauopathy process. This finding aligns itself with recent studies exploring the causal role of cellular senescence in tau-related pathology, where it was shown that the pharmacological or genetic elimination of senescent astrocytes and microglial cells in a tauopathy mouse model reduced tau aggregation and associated cognitive deficits [11]. Further supporting that senescence and telomere attrition are drivers of tau pathology, existing literature reports the presence of increased tau phosphorylation in the

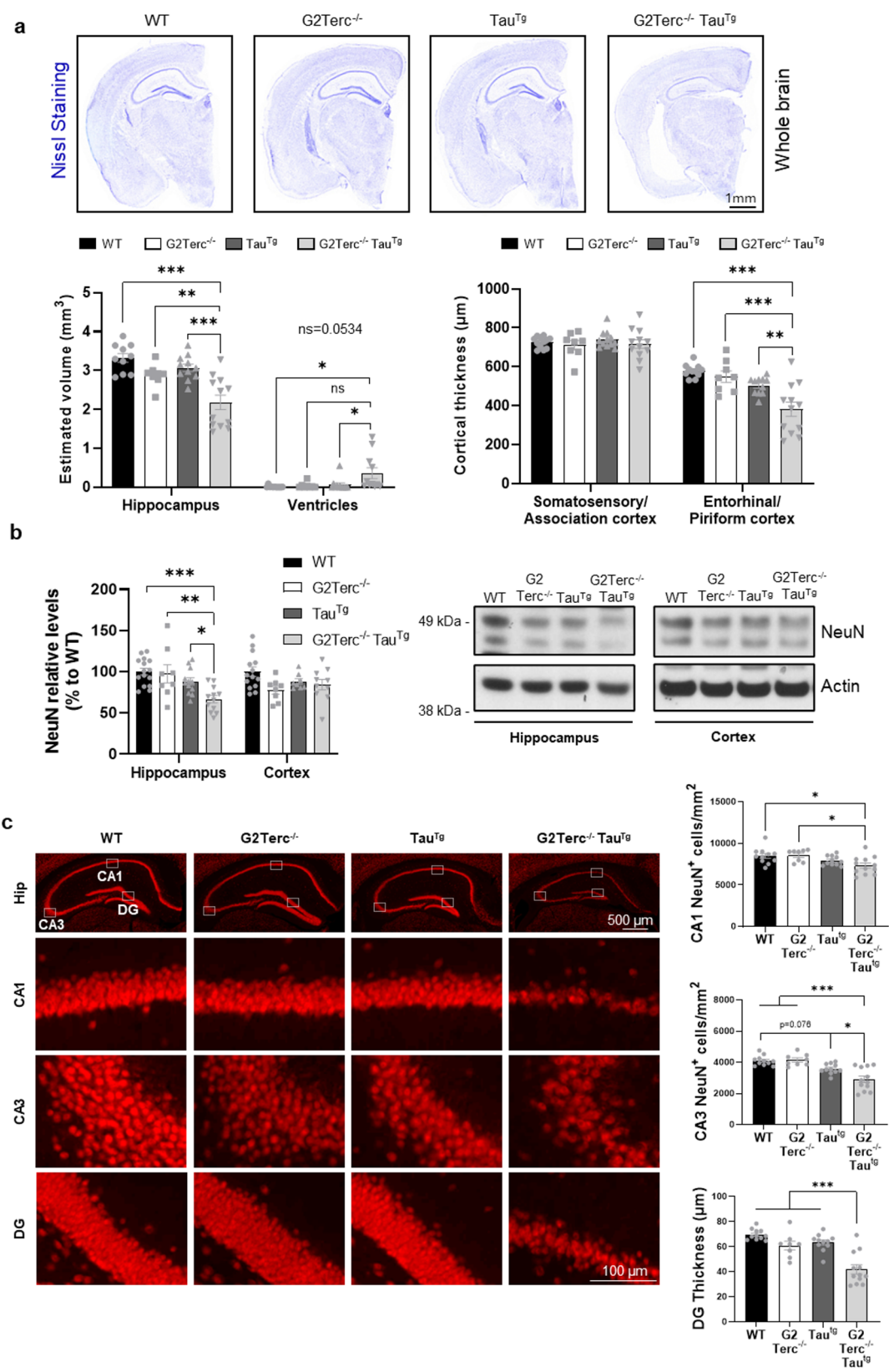


Fig. 8 (See legend on next page.)

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Fig. 8 Senescence induces neurodegeneration in vulnerable brain regions of tauopathy mice. **(a)** Representative Nissl staining images from 9-month-old WT, G2Terc^{-/-}, Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} mice. Quantitative analyses include measurements of lateral ventricles and hippocampal volumes, as well as thickness of the somatosensory/association and entorhinal/piriform cortices. **(b)** WB evaluation of NeuN expression in hippocampal and cortical extracts from 9-month-old WT, G2Terc^{-/-}, Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} mice. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (One-way ANOVA with Tukey's post-hoc analysis, $n = 8–13$ mice/group). **(c)** NeuN immunofluorescence analysis in 9-month-old WT, G2Terc^{-/-}, Tau^{Tg} and G2Terc^{-/-} Tau^{Tg} mice. Histograms show the density of NeuN-positive cells in the CA1 and CA3 areas, as well as the thickness of the DG granule cell layer. $P < 0.05$, *** $P < 0.001$ (One-way ANOVA with Tukey's post-hoc analysis, $n = 8–12$ mice/group)

hippocampi of the senescence-accelerated mouse prone 8 (SAMP8) model [13, 63], and of increased tau-induced pathology in primary neurons derived from G2TERT^{-/-} mouse embryos, which lack the catalytic component of the telomerase [81]. Based on the existing experimental evidence [23, 60], we propose that the initial effects of senescence can become progressively amplified through a negative feedback loop as the disease advances, accelerating neurodegeneration and cognitive decline over time.

Controversial data exists regarding the presence of telomere erosion in brain tissue from AD patients, mainly due to technical limitations inherent to postmortem samples [22]. However, it seems well established that cellular senescence occurs in AD and is more prevalent than in non-affected individuals [7, 19, 21, 23, 38, 40, 60]. In fact, oxidative stress and DNA damage, which are consistently elevated in aged and AD brains, are also well-known inducers of cell senescence and are prevalent in postmitotic cells like neurons [78]. The Terc knockout mouse model of accelerated senescence used in our study is designed to create the ideal conditions for inducing senescence in a controlled, reproducible and time-efficient manner. Indeed, our findings confirm that the presence of significantly shorter telomeres in the mouse brain exacerbates classical senescent features, including the upregulation of cell cycle inhibitors and SASP factors. Telomerase inactivity is also translated into brain DNA damage, as demonstrated by increased γ H2AX levels in G2Terc^{-/-} and G3Terc^{-/-} mouse hippocampi. A recent study demonstrated that the specific accumulation of undigested damaged DNA in the cytosol of neurons [52] or microglia [53] due to DNase II inactivation can lead to increased tau phosphorylation and neurodegeneration.

This study provides critical insights into the accumulating effect of chronic senescence on tau phosphorylation and aggregation. We found that senescence initially affects specific phosphorylation residues on tau protein, with Thr181, Ser202 and Thr205 being particularly impacted during the early phases of tauopathy progression. As the disease advances in relatively aged G2Terc^{-/-} Tau^{Tg} mice, senescence leads to a shift from detergent-soluble to detergent-insoluble phosphorylated tau forms, affecting numerous residues. This suggests that senescence plays a crucial role in the progression of tau pathology, further confirmed by the observed increase in high-molecular-weight tau species, indicative of tau oligomers, both in soluble and insoluble protein

fractions. These tau oligomers are in turn associated with enhanced neurotoxicity, prompting worsened synaptic dysfunction and neurodegeneration [48, 64]. While our results showed that tau kinases such as AMPK, GSK3 β , ERK1/2 or AKT, along with the primary tau phosphatase PP2A, may not be involved in the early effects of senescence on tau phosphorylation, further investigation is needed to determine the underlying molecular mechanisms. In contrast, during advanced disease stages, our findings highlight that senescence activates the kinases ERK1/2 and AKT, which regulate tau phosphorylation [46, 65]. In addition, several cellular pathways known to be altered during senescence could have contributed to the observed effects. Results from our previous study suggest that the autophagy flux is altered in the brains of Terc knockout mice [84], and a direct link between autophagy defects and increased tau phosphorylation and aggregation has been made [80]. While hyperphosphorylated tau is degraded by either the proteasome or the autophagy-lysosome systems in physiological conditions [16, 51], under pathological circumstances such as senescence, the increase in hyperphosphorylated tau cannot be efficiently cleared by these pathways [34]. Similarly, Terc knockout mice also present mitochondrial dysfunction and increased oxidative stress [43], two interrelated features that have been correlated with increased tau phosphorylation [3, 58, 72, 83].

Aside from tau phosphorylation, the proteolytic processing of tau has also been involved in promoting its aggregation [32, 102]. Tau can be cleaved by multiple proteases, including calpains, caspases and endopeptidases, and the resulting fragments can be found in AD and other tauopathies at early disease stages and correlate with the degree of cognitive dysfunction [15, 68, 70, 94]. Additionally, truncated tau has been shown to play a key role in promoting tau aggregation and inducing neurodegeneration, as demonstrated in animal models [24, 45, 50] and in vitro systems [17, 32, 90]. Our data demonstrate that telomere-induced senescence accelerates tau cleavage in PS19 mice, potentially contributing to the increased tau aggregation and neurodegeneration observed in our study. Although the precise molecular mechanisms behind this effect were not investigated, it is likely that the reported increase in calpain/caspase-3 activities during DNA damage contributes to tau fragmentation [76, 86].

While the hippocampal region appeared particularly vulnerable to the impact of senescence on tauopathy induction, the cortical region as a whole remained relatively unaffected, particularly at early stages of the disease. WB analyses revealed no significant changes in cortical tau phosphorylation at 6 months of age, while 9-month-old senescent mice displayed increased tau phosphorylation at only a few residues in the soluble protein fraction. Similarly, volume reduction and neuronal loss were found in *G2Terc^{-/-} Tau^{Tg}* hippocampi, but cortical extracts showed unaltered NeuN levels and no thinning of the somatosensory/association cortical area was detected. A previous study similarly observed that the SAMP8 senescence model exhibits gene expression alterations related to AD pathology more prominently in the hippocampus than in the cerebral cortex [92]. However, in our study, not all cortical subregions seemed equally spared. Immunostaining analyses revealed a specific vulnerability of the piriform/entorhinal cortical regions, displaying exacerbated tau phosphorylation and atrophy. Collectively, our findings provide a detailed insight into the region-specific changes associated with pathological aging. This distinct vulnerability to tau pathology in the brain across different regions is also present in AD, where brain structure imaging and post-mortem examinations suggest that some areas remain relatively spared until the late stages of the pathology [10, 59].

Neuroinflammation has been shown to play a dual role in neurodegenerative conditions: while it facilitates repair during acute stages, it can promote neuronal loss and aggravate disease progression in chronic stages [37]. Our findings demonstrate that the senescence impact on tau pathology induces neuroinflammation by increasing the activation of astrocytes and microglia in the hippocampi of old *G2Terc^{-/-} Tau^{Tg}* mice. On the other hand, despite a significant transcriptional upregulation of inflammatory markers in the hippocampi of the senescent model (i.e., *Il1b*, *Cxcl1*), levels of specific astrocyte and microglia markers, as well as the total area they occupied in this region, were not altered in the absence of tauopathy. This suggests a lack of glial activation in non-pathological contexts, consistent with our previous data [84]. Results of this study also indicate that microglial/astrocytic activation might be a direct consequence of tau pathology, as previously suggested [49], rather than merely a result of senescence activation. Indeed, previous studies have shown that microglia and astrocytes from *Terc* knockout brains do not display major functional alterations, unless in the presence of pathological protein aggregates or inflammatory stimuli [44, 67, 74]. Notably, dystrophic microglia, a particular type of microglia which has been closely associated with the progression of AD [77], were observed in the hippocampus of 9-month-old *G2terc^{-/-} Tau^{Tg}* mice, but not in *Tau^{Tg}* mice, suggesting for the first

time that the combination of senescence and tauopathy has a distinct and more detrimental impact on microglia than tauopathy alone.

Mouse models genetically engineered to express human genes associated with neurodegenerative diseases, including AD, have significantly advanced our understanding of the underlying pathogenic mechanisms driving these conditions. However, the relative resistance to neurotoxicity observed in these mice has puzzled scientists for decades [18]. As laboratory mice have long telomeres and short lifespans, it could be hypothesized that they are particularly resistant to certain forms of senescence. Specifically, laboratory mice only live 18 to 24 months and present telomeres that are 25–150 kb long at birth, while human telomeres are around 10–15 kb long [30, 42]. Our results demonstrate that a pathological aging context, modeled here by inducing senescence through telomere damage, may be required to trigger extensive brain atrophy and neuronal loss in transgenic mice overexpressing aggregation-prone human tau. Consequently, this combined model of senescence and tauopathy could serve as a valuable preclinical research model to more accurately recapitulate the extent of neuronal death observed in tau-related human diseases.

Given the observed involvement of telomere-induced senescence in promoting pathological tau progression, as well as associated inflammation and neurodegeneration, investigating key cellular pathways and protein/genes altered in the models described in this study could reveal promising therapeutic targets that act upstream of the neurodegenerative process. These targets may also serve as biomarkers that could be measured in accessible tissues (e.g., blood samples, CSF), in order to track pathological progression or assess AD risk. In fact, it could be argued that telomere length evaluation might be useful as a prognostic biomarker for AD, especially in pre-clinical cases. One could also hypothesize that therapeutic strategies aimed at preserving or recovering telomere length, for example by enhancing telomerase activity, would offer potential benefits. Indeed, recent studies have shown that telomerase activation reduces amyloid [79] and α -synuclein pathology in transgenic mouse models [89]. Given the undoubtable role of telomeres in cancer prevention [41], one valid concern could be the potential carcinogenic effects of such treatments. However, transgenic mouse models and gene therapy studies in mice have demonstrated no increased risk of cancer following telomerase activation, providing a proof-of-principle for harmless telomere-based therapies [6, 101].

Conclusions

Aging is strongly associated with neurodegenerative diseases, yet an ongoing debate persists regarding whether senescence is a cause or consequence of their onset and

progression. Results from this study proved that senescence acts as an upstream modulator of tauopathy, driving tau hyperphosphorylation and aggregation, which in turn promotes neuroinflammation and neurodegeneration. Taken together, our data highlights the critical need to study brain senescence as a key step towards identifying therapeutic targets for AD and other neurodegenerative diseases cursing with tauopathy.

Abbreviations

AD	Alzheimer's disease
APP	Amyloid precursor protein
A β	Amyloid β
CA	Cornu Ammonis
DG	Dentate gyrus
ND	Neurodegenerative disease
NFT	Neurofibrillary tangles
SASP	Senescence-associated secretory phenotype
WB	Western blot
WT	Wild-type

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s40478-025-02118-5>.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We thank Caroline Bouzin and Aurélie Daumerie from the 2IP Imaging Platform (Institut de Recherche Expérimentale et Clinique – IREC, UCLouvain, Brussels, Belgium) for their technical support. We also thank the team of Peter Davies (The Feinstein Institutes for Medical Research, New York, United States) for kindly providing the PHF-1 antibody.

Author contributions

DP and NS designed and performed research, analyzed and interpreted data and wrote the manuscript. AV, JJ and EP performed experiments and analyzed and interpreted data. NS and PKC conceived, designed and supervised the research project. All authors reviewed and approved the final version of the manuscript.

Funding

DP was supported by a FRIA fellowship from the Belgian FRS-FNRS (Fonds National pour la Recherche Scientifique, 40015405/40030154). AV was supported by an Aspirant fellowship from the FNRS. NS was funded by a Chargé de Recherche postdoctoral fellowship from the FNRS. This work was supported by grants from the SAO-FRA Alzheimer Research Foundation (SAO-FRA 2018/0025), UCLouvain Action de Recherche Concertée (ARC21/26–114), Fondation Louvain, Queen Elisabeth Medical Foundation (FMRE AlzHex), F.R.S.-FNRS (FNRS J.0106.22) attributed to PKC and grants from the SAO-FRA Alzheimer Research Foundation (SAO-FRA 2020/0028, SAO-FRA 2022/0028) attributed to NS.

Data availability

All datasets generated and analyzed during this study are included in this published article and its supplementary material.

Declarations

Ethics approval and consent to participate

All animal procedures were carried out in compliance with institutional and European guidelines and were approved by the Ethical Committee for Animal Welfare at UCLouvain (References: 2018/UCL/MD/38 and 2021/UCL/MD/18).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Aging and Dementia Group, Cellular and Molecular Division (CEMO), Institute of Neuroscience (IoNS), UCLouvain, Brussels, Belgium

²Louvain Aging Brain Lab, Clinical Division (NEUR), Institute of Neuroscience (IoNS), UCLouvain, Brussels, Belgium

Received: 30 June 2025 / Accepted: 5 September 2025

Published online: 29 September 2025

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