nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection

Plasma NfL concentration was measured with NF-Light Simoa Assay Advantage kit on a Samoa HD analyzer (Quanterix). All the FACS sorting was done on BD FACSAria II sorter (BD Biosciences) or CytoFlex SRT (Beckman Coulter). Immunohistochemistry and cresyl violet images were obtained by a NanoZoomer microscope (Hamamatsu Photonics) at a 20X magnification. Immunofluorescent images were obtained by using a Leica Stellaris 5 confocal microscope. Mass spectrometry data were acquired using a nano-ELUTE 2 chromatograph (Bruker. Bremen, Germany) interfaced to a timsTOF Ultra 2 mass spectrometer (Bruker) with a modified nano-electrospray source.The mass spectrometer was operated in the high sensitivity DDA PASEF mode78 . Ion mobility range was set to 0.64 – 1.65 Vs/cm2 (0.64-1.64 Vs/cm2 for MHC-II) with ramp time 100 ms and accumulation time 100 ms. The number of PASEF ramps was set to 5 and the intensity threshold was set to 1,000 – 12,000. Deflection 0 Delta was set at 30.0 V (70.0 V for MHC-II). Quadrupole isolation was set to 2 Th at <700 m/z and 3 Th at 800 m/z. The samples were reconstituted in 5 µl of 0.1% (vol/vol) formic acid (FA) in water, and 4 µl were injected onto a 75 µm i.d. × 25 cm PepSep Ultra column (Bruker) connected to a 10 µm emitter (Bruker). The column temperature was set to 50 °C. The column was equilibrated using constant pressure (800 bar) with 5 column volumes of solvent A (0.1% (vol/vol) FA). Sample loading was performed at constant pressure (800 bar) at a volume of 2 sample pick-up volume plus 2 µl. The peptides were eluted using one column separation mode with a flow rate of 250 nl/min and using solvents A (0.1% (vol/vol) FA) and B (0.1% (vol/vol) FA/Acetonitrile): solvent A containing 2% B increased to 20% B over 40 min, to 37% B over 5 min, to 95% B over 1 min, and constant 95% B for 4 min. The MS1 and MS2 spectra were recorded from m/z 100 to 1700. The collision energy was ramped stepwise as a function of increasing ion mobility: 20 eV at 0.60 Vs/cm2 and 59 eV 1.60 Vs/cm2. The TIMS elution voltage was calibrated linearly using the Agilent ESI-L Tuning Mix (m/z 622, 922,1222).

Data analysis

Flow cytometry data acquired from machines other than Cytek Aurora were exported as Fcs files and analyzed using FlowJo software (version 10.10.0, Tree Star). The data acquired from Cytek Aurora were unmixed using the SpectroFlo software first and then further analyzed using FlowJo software (version 10.10.0, Tree Star). Immunohistochemistry and cresyl violet images were extracted by using the NDP viewer

software (Hamamatsu Photonics, U12388-01) and analyzed with ImageJ software (NIH, V1.54k)., Immunofluorescent images were analyzed with ImageJ software (NIH, v1.54k). scRNA-seq and TCR-seq data were aligned to mm10 using Cell Ranger V7.2.0. The filtered transcriptome alignment output of each sample was loaded into R as Seurat objects for quality control. Cells with mitochondrial RNA percentage > 5% were removed, and doublets were predicted and removed using DoubletFinder with parameters PCs = 1:30, pN = 0.25, pK = 0.09, assuming the doublet formation rate is 5%. Then samples were merged into one dataset and processed using log-normalization. Variable features were identified using the mean.var.plot method with a mean cutoff of 0.0125 ~ 5, dispersion cutoff of > 0.5, and Tra/Trb/Igh/Igk genes removed from variable features. Reads are scaled by regressing out mitochondrial RNA percentage and number of features. All variable features were used for downstream analysis. PCA is performed using default parameters, and batch-effect is corrected using harmony by regressing over the samples. The top 40 harmony-corrected PCs were used for non-linear dimension reduction and clustering. Preliminary annotation was performed using resolution at 0.6, and one additional doublet cluster was removed based on overlapping gene expression signature. Lymphocytes were isolated for further processing and T cell subsets were recursively created until subsets with unanimous Cd8a or Cd4 expression were obtained. Top PCs for analysis of subsets were picked using ElbowPlot. Cell type (NKT, CD8T, CD4T, and proliferating) labels were added to each subset creation. Then, subsets were merged back into T cells and all-compartment objects. Artifact clusters with uniformly higher mitochondrial RNA percentages or non-biologically interpretable markers were removed during subset processing. Ribosomal RNA content was regressed during the scaling of variable features of the T cell subset. Markers were calculated using the FindAll Markers function with only.pos=T. TCR-seq data from four samples were loaded and processed using scRepertoire combineTCR function with removaNA=T and removeMulti=T. Clonotypes were called based on the amino acid sequences with clone frequency and proportion calculated for each sample. The relative abundance bar plot was made using the clonalHomeostasis function. Results from scRepertoire were merged into the T cell Seurat object using combineExpression with group.by = "sample" for further analysis and visualization. CloneSize was defined based on clonalProportion with the following levels: Small (1e-04 < X <= 0.001), Medium (0.001 < X <= 0.01), Large (0.01 < X <= 0.1), Hyperexpanded (0.1 < X <= 1). There were no hyperexpanded clones based on clonalProportion. Gini indices for each sample were calculated separately for each cell type using the Gini function from the DescTools package.
snRNA-seq data were aligned to mm10 using Cell Ranger V9.0.1. The filtered transcriptome alignment output of each sample was loaded into R as Seurat objects for quality control. Cells with outlier miQC: An adaptive probabilistic framework for quality control of sing mitochondrial RNA percentage (determined using is.Outlier() from scater72 package) and miQC.keep label of “discard” were removed, and doublets were predicted and removed using DoubletFinder69 with parameters PCs = 1:12, pN = 0.25, and optimal pK, assuming the doublet formation rate is 5%. Then samples are merged into one dataset and processed using log-normalization. Variable features were identified using the mean.var.plot method with a mean cutoff of 0.0125 ~ 5, dispersion cutoff of > 0.5, and Tra/Trb/Igh/Igk genes removed from variable features. Reads are scaled by regressing out mitochondrial RNA percentage and number of features. All variable features were used for downstream analysis. PCA is performed using default parameters, and batch effect is corre cted using harmony by regressing over the samples. The top 40 harmony-corrected PCs were used for non-linear dimension reduction and clustering. Based on the gating for NeuN+ and PU.1+ cells, we used the following strategy for establishing the neuron and microglia subsets. Neurons were isolated by first extracting the neuronal-like clusters and keeping only the NeuN+ samples, followed by quality controls. The microglia subset was created by isolating and clustering the PU.1 and double-negative samples to establish the non-neuronal subset. Then, microglia-like clusters were isolated after quality control of the non-neuronal subset. After quality control of the microglia-like cells, we retained only the cells from PU.1 samples.
For analysis of mass spec data, Processing and database searching were performed with PEAKS Studio 13 (build 20250623, Bioinformatics Solutions Inc.). files were searched against a Uniprot-Mouse database appended with a human tau sequence (Jan. 2022; 21,821 entries) with no enzyme specificity, carbamidomethylation (C) as a fixed modification, and oxidation (M) as a variable modification. Parent mass tolerance was 20 ppm, and fragment ion tolerance was 0.02 Da. A DeepNovo peptidome search was performed, and peptides were filtered at a peptide-spectrum match false discovery rate of 1% or a -10logP score of 20. To perform unsupervised alignment and clustering of peptides (GibbsCluster 2.0), post-translational modifications were removed and the list was filtered to retain only unique peptide sequences.
Data distribution was assumed to be normal without formal testing. All data were expressed as mean values ± SEMs. Statistical analysis was performed with GraphPad Prism 10. Means between two groups were compared with a two-tailed, unpaired Student’s t test or two-tailed, Mann-Whitney test. Two-way ANOVAs were used to analyze between-subjects designs with two factors. A priori comparisons were made using Sidak’s multiple comparison correction. Fisher’s exact test was used to analyze probability distributions. The strength of the linear relationship between two different variables was analyzed using Pearson’s correlation. The null hypothesis was rejected at the $P < 0.05$ level. Statistical significance was taken as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$. NS, $P > 0.05$, suggesting no statistical significance. For two-way ANOVA, F statistics and p value for factor and interaction terms are reported in Supplementary Table 5. P values for Student’s t test, Mann-Whitney test, Fisher’s exact test and corrected p values for a priori comparisons are provided in the figures except for $^{****}P < 0.0001$. NS, $P > 0.05$, which showed as “****” or “NS”. Sample sizes were determined based on our previous studies2,3. Given the variability in brain pathology observed in TE4 mice, cohorts of 15–20 mice per group were selected to provide sufficient statistical power for robust data analysis and reliable conclusions. Investigators were blinded to group allocation during the experiments and outcome assessments. Mice were randomly assigned to experimental groups, and data collection was performed in a randomized manner. No data were excluded from the analyses except for tissue samples that were lost during processing or failed to generate usable data.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Single-cell RNA sequencing (GEO: GSE279315, GSE311230) data were deposited in the National Center for Biotechnology Gene Expression Omnibus. Mass spectrometry immunopeptidomics data files were deposited to the MassIVE repository with the identifier MSV000099442. Mass spectrometry immunopeptidomics data generated in this study are also provided in the Supplementary Tables. Raw data can be found in the Source Data file. Consolidated R codes for scRNA-seq and snRNA-seq bioinformatic analysis and visualization are deposited at https://zenodo.org/records/17282074

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Yes, the information can be found in supplementary table 2
Reporting on race, ethnicity, or other socially relevant groupings	Yes, the information can be found in supplementary table 2
Population characteristics	Yes, the information can be found in supplementary table 2
Recruitment	We performed experiments on the donated human tissues: E. Reiman, G. Serrano and T. Beach of the Banner Sun Health Research Institute Brain and Body Donation Program of Sun City, Arizona for the provision of human primary tauopathy brain tissue. The Brain and Body Donation Program has been supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the National Institute on Aging (P30 AG19610 Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium) and the Michael J. Fox Foundation for Parkinson's Research; Washington University Translational Human Neurodegenerative Disease Research (THuNDR) Laboratory for meningeal tissue from Knight ADRC research participants.
Ethics oversight	All participants gave prospective pre-mortem written consent for their brain to be banked and used for research with information to potentially be published under procedures approved by the human institutional review board at the Banner Sun Health Research Institute (BSHRI) Brain and Body Donation Program of Sun City, Arizona. Meningeal tissues were provided and investigated under the procedures approved by Washington University Translational Human Neurodegenerative Disease Research (THuNDR) Laboratory from Knight ADRC research participants.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes were based upon the primary outcome of hippocampal volume. Given our previous data from TE4 mice, n=20 mice per group provides sufficient power to detect an approximately 30% difference in hippocampal volume between experimental groups (b=0.8)
Data exclusions	We did not exclude data in our study.
Replication	All data were reproduced independently as stated in the figure legends. The single cell RNA seq (scRNA-seq) analyses were performed using pooled mice from each group and the conclusions generated from the scRNA-seq data were validated using flow cytometry analysis.
Randomization	The mice were randomly selected. Because we are comparing knockout mice and WT mice, all the knockout mice were grouped together and all the WT mice were grouped together. All the mice were blindly ID registered and experiments were blindly performed.
Blinding	Investigators were blinded to group allocation during experimental setup, data collection, and the analysis. The samples were given a blinded ID and the analyses were done by multiple people who were blinded to the experimental groups.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Information for all the antibodies used in this study can be found in Supplementary Table 3
Fc Block
Rat anti-Mouse CD32/CD16 - Purified (Fc Block Antibody) Leinco Technologies Cat# C247, RRID:AB_2829545 1/200 For all flow cytometry experiments

DC sort and analysis
Biotin Hamster anti-mouse CD3e BD Biosciences Cat# 553060, RRID:AB_394593 1/200 Enrich
Biotin Rat anti-mouse CD19 BioLegend Cat# 115504, RRID:AB_313639 1/200
Biotin Rat anti-mouse/human CD45R/B220 BioLegend Cat# 103204, RRID:AB_312989 1/200
Biotin Rat anti-mouse Ly-6G BioLegend Cat# 127604, RRID:AB_1186108 1/200
Biotin Rat anti-mouse TER-119/Erythroid Cells BioLegend Cat# 116204, RRID:AB_313705 1/200
Biotin Rat anti-mouse CD105 Antibody BioLegend Cat# 120404, RRID:AB_961062 1/200
BV421 Rat Anti-Mouse CD117 BD Biosciences Cat# 562609, RRID:AB_11154585 1/200 Sort
APC Rat Anti-Mouse CD135 BD Biosciences Cat# 560718, RRID:AB_1727425 1/200
APC/Cyanine7 Rat anti-mouse I-A/I-E BioLegend Cat# 107627, RRID:AB_1659252 1/200
PE/Cyanine7 Rat anti-mouse CD115 (CSF-1R) BioLegend Cat# 135523, RRID:AB_2566459 1/200
FITC Hamster anti-mouse CD11c BioLegend Cat# 117306, RRID:AB_313775 1/200
PE Rat anti-mouse CD24 BioLegend Cat# 101807, RRID:AB_312840 1/200
PerCP/Cyanine5.5 Rat anti-mouse Siglec H BioLegend Cat# 129613, RRID:AB_10639936 1/200
Brilliant Violet 510 Rat anti-mouse CD45 BioLegend Cat# 103138, RRID:AB_2563061 1/200 DC tissue analysis
eFluor 780 Fixable Viability Dye Invitrogen Cat# 65-0865-14 1/1000
PerCP-Cy5.5 Rat Anti-Mouse CD45RA BD Biosciences Cat# 564359, RRID:AB_2738767 1/200
Brilliant Violet 421 Rat anti-mouse I-A/I-E BioLegend Cat# 107632, RRID:AB_2650896 1/400
PE-Cyanine7 Hamster anti-mouse CD11c Thermo Fisher Scientific Cat# 25-0114-82, RRID:AB_469590 1/200
FITC Rat anti-mouse F4/80 BioLegend Cat# 123108, RRID:AB_893502 1/200
PE Rat anti-mouse CD172a (SIRPα) BioLegend Cat# 144012, RRID:AB_2563550 1/200
APC Mouse anti-mouse/rat XCR1 BioLegend Cat# 148206, RRID:AB_2563932 1/200

Brain cell analysis
APC/Cyanine7 Rat anti-mouse/human CD11b BioLegend Cat# 101226, RRID:AB_830642 1/200 Microglia sort
Brilliant Violet 421 Rat anti-mouse CD45 BioLegend Cat# 103134, RRID:AB_2562559 1/200
Propidium Iodide BioLegend Cat# 421301 1/500
APC/Cyanine7 Rat anti-mouse/human CD11b BioLegend Cat# 101226, RRID:AB_830642 1/200 Microglia analysis
Brilliant Violet 510 Rat anti-mouse CD45 BioLegend Cat# 103138, RRID:AB_2563061 1/200
PerCP-eFluor710 mouse anti-human/mouse IRF8 Thermo Fisher Scientific Cat# 46-9852-82, RRID:AB_2573904 1/100
Brilliant Violet 510 Rat anti-mouse CD45 BioLegend Cat# 103138, RRID:AB_2563061 1/200 Brain leukocytes analysis
APC Hamster Anti-Mouse TCR β Chain BD Biosciences Cat# 553174, RRID:AB_398534 1/200
PE Mouse anti-mouse NK-1.1 BioLegend Cat# 108708, RRID:AB_313395 1/200
Alexa Fluor 488 Rat Anti-mouse CD4 BD Biosciences Cat# 557667, RRID:AB_396779 1/200
PE/Cyanine7 Rat anti-mouse CD8a BioLegend Cat# 100722, RRID:AB_312761 1/200
Brilliant Violet 421 Rat anti-mouse I-A/I-E BioLegend Cat# 107632, RRID:AB_2650896 1/400
APC/Cyanine7 Rat anti-mouse/human CD11b BioLegend Cat# 101226, RRID:AB_830642 1/200
PerCP-eFluor 710 Rat anti-mouse/human CD45R (B220) Thermo Fisher Scientific Cat# 46-0452-82, RRID:AB_10717389 1/200
eFluor 780 Fixable Viability Dye Invitrogen Cat# 65-0865-14 1/1000 Brain ILC2/3, T cells, and T cell subsets analysis
Brilliant Violet 510 Rat anti-mouse CD45 BioLegend Cat# 103138, RRID:AB_2563061 1/200
BUV615 Rat Anti-mouse CD11b BD Biosciences Cat# 751140, RRID:AB_2875166 1/200
BUV737 Hamster Anti-Mouse TCR β Chain BD Biosciences Cat# 612821, RRID:AB_2870145 1/200
BUV395 Mouse anti-mouse NK-1.1 Thermo Fisher Scientific Cat# 363-5941-82, RRID:AB_2925297 1/200
Brilliant Violet 785 Hamster anti-mouse CD11c BioLegend Cat# 117336, RRID:AB_2565268 1/200
PE-CF594 Mouse Anti-Mouse RORγt BD Biosciences Cat# 562684, RRID:AB_2651150 1/100
Brilliant Violet 421 Mouse anti-mouse GATA3 BioLegend Cat# 653814, RRID:AB_2563221 1/100
Alexa Fluor 488 Rat Anti-mouse CD4 BD Biosciences Cat# 557667, RRID:AB_396779 1/200
BUV496 Rat anti-mouse/human CD44 Thermo Fisher Scientific Cat# 364-0441-82, RRID:AB_2925331 1/200
BUV805 Rat anti-mouse CD62L Thermo Fisher Scientific Cat# 368-0621-82, RRID:AB_2896124 1/200
eFluor 450 Rat anti-mouse FOXP3 Thermo Fisher Scientific Cat# 48-5773-82, RRID:AB_1518812 1/100
Alexa Fluor 700 Rat anti-mouse CD8a BioLegend Cat# 100730, RRID:AB_493703 1/200
Brilliant Violet 711 Rat anti-mouse CD279 (PD-1) BioLegend Cat# 135231, RRID:AB_2566158 1/200
Vio B515, REAfinity human anti-human/mouse TOX Miltenyi Biotec Cat# 130-129-208, RRID:AB_2922006 1/100

PE Mouse anti-mouse T-bet Thermo Fisher Scientific Cat# 12-5825-82, RRID:AB_925761 1/100
Alexa Fluor 647 Mouse Anti-mouse/human TCF-7/TCF-1 BD Biosciences Cat# 566693, RRID:AB_2869823 1/100
PE-Cyanine7 Rat anti-mouse CD39 Thermo Fisher Scientific Cat# 25-0391-82, RRID:AB_1210766 1/200
APC Mouse anti-mouse Ly108 (SLAMF6) BioLegend Cat# 134610, RRID:AB_2728155 1/200
Brilliant Violet 510 Rat anti-mouse CD45 BioLegend Cat# 103138, RRID:AB_2563061 1/200 Brain pDC identification
APC/Cyanine7 Rat anti-mouse/human CD11b BioLegend Cat# 101226, RRID:AB_830642 1/200
PE-Cyanine7 Hamster anti-mouse CD11c Thermo Fisher Scientific Cat# 25-0114-82, RRID:AB_469590 1/200
FITC Hamster anti-mouse CD3ε BioLegend Cat# 100306, RRID:AB_312671 1/200
PerCP-Cy5.5 Rat Anti-Mouse CD45RA BD Biosciences Cat# 564359, RRID:AB_2738767 1/200
Brilliant Violet 421 Rat anti-mouse I-A/I-E BioLegend Cat# 107632, RRID:AB_2650896 1/400
Zombie UV™ Fixable Viability Kit BioLegend Cat# 423108 1/200 Brain T, B, γδ T, NK cells identification
Brilliant Violet 510 Rat anti-mouse CD45 BioLegend Cat# 103138, RRID:AB_2563061 1/200
Brilliant Violet 605 Rat anti-mouse CD19 BioLegend Cat# 115540, RRID:AB_2563067 1/200
Brilliant Violet 421 Mouse anti-mouse CD64 (FcγRI) BioLegend Cat# 139309, RRID:AB_2562694 1/200
APC/Cyanine7 Hamster anti-mouse TCR γ/δ BioLegend Cat# 118143, RRID:AB_2892275 1/200
PerCP/Cyanine5.5 Rat anti-mouse I-A/I-E BioLegend Cat# 107626, RRID:AB_2191071 1/200
Alexa Fluor 700 Rat anti-mouse CD8a BioLegend Cat# 100730, RRID:AB_493703 1/200
Brilliant Violet 711 Rat anti-mouse CD4 BioLegend Cat# 100447, RRID:AB_2564586 1/200
BUV395 Mouse anti-mouse NK-1.1 Thermo Fisher Scientific Cat# 363-5941-82, RRID:AB_2925297 1/200
PE/Cyanine7 Rat anti-mouse CD38 BioLegend Cat# 102718, RRID:AB_2275531 1/200
Brilliant Violet 510 Rat anti-mouse CD45 BioLegend Cat# 103138, RRID:AB_2563061 1/200 Brain iNKT cell identification
FITC Hamster anti-mouse CD3ε BioLegend Cat# 100306, RRID:AB_312671 1/200
APC PBS57-CD1d tetramer NIH Tetramer Core 1/200

Antigen presentation assay
Biotin Rat anti-mouse CD4 BioLegend Cat# 100404, RRID:AB_312689 1/200 OT-1 T cells enrichment
Biotin Rat anti-mouse I-A/I-E BioLegend Cat# 107604, RRID:AB_313319 1/200
Biotin Rat anti-mouse TER-119/Erythroid Cells BioLegend Cat# 116204, RRID:AB_313705 1/200
Biotin Rat anti-mouse Ly-6G BioLegend Cat# 127604, RRID:AB_1186108 1/200
Biotin Mouse anti-mouse NK-1.1 BioLegend Cat# 108704, RRID:AB_313391 1/200
Biotin Rat anti-mouse/human CD45R/B220 BioLegend Cat# 103204, RRID:AB_312989 1/200
Biotin Rat anti-mouse CD19 BioLegend Cat# 115504, RRID:AB_313639 1/200
APC Rat anti-mouse/human CD44 BioLegend Cat# 103012, RRID:AB_312963 1/200 Naïve OT-1 T cells sort
PE Rat anti-mouse TCR Vα2 BioLegend Cat# 127808, RRID:AB_1134183 1/200
APC/Fire 750 Mouse anti-mouse TCR Vβ5.1, 5.2 BioLegend Cat# 139511, RRID:AB_2750130 1/200
PE/Cyanine7 Rat anti-mouse CD8a BioLegend Cat# 100722, RRID:AB_312761 1/200
Alexa Fluor 488 Rat Anti-mouse CD4 BD Biosciences Cat# 557667, RRID:AB_396779 1/200
PerCP/Cyanine5.5 Rat anti-mouse CD62L BioLegend Cat# 104432, RRID:AB_2285839 1/200
Brilliant Violet 510 Streptavidin BioLegend Cat# 405233 1/200
CellTrace Violet staining kit Thermo Fisher Scientific Cat# C34557 1μM
FITC Mouse anti-mouse CD45.1 BioLegend Cat# 110706, RRID:AB_313495 1/200 OT-1 in vivo proliferation analysis
APC/Cyanine7 Mouse anti-mouse CD45.2 BioLegend Cat# 109824, RRID:AB_830789 1/200
PE/Cyanine7 Rat anti-mouse CD172a (SIRPα) BioLegend Cat# 144007, RRID:AB_2563545 1/200
PE Rat anti-mouse TCR Vα2 BioLegend Cat# 127808, RRID:AB_1134183 1/200
Alexa Fluor 700 Rat anti-mouse CD8a BioLegend Cat# 100730, RRID:AB_493703 1/200
Brilliant Violet 785 Hamster anti-mouse CD11c BioLegend Cat# 117336, RRID:AB_2565268 1/200
PerCP-eFluor 710 Rat anti-mouse/human CD45R (B220) Thermo Fisher Scientific Cat# 46-0452-82, RRID:AB_10717389 1/200
BV650 Mouse Anti-Mouse β2-Microglobulin BD Biosciences Cat# 745291, RRID:AB_2742865 1/200 MHC-I 3xKO confirmation
Biotin Mouse anti-mouse H-2Kb BioLegend Cat# 116504, RRID:AB_313731 1/200
Biotin Mouse anti-mouse H-2Db BioLegend Cat# 111504, RRID:AB_313509 1/200
Brilliant Violet 605 Streptavidin BioLegend Cat# 405229 1/200

Immunohistochemistry/Immunofluorescence assays
Biotin Phospho-Tau (Ser202, Thr205) (AT8) Thermo Fisher Scientific Cat# MN1020B, RRID:AB_223648 1/500 AT8 DAB staining
AIF-1/Iba1 Antibody Novus Cat# NB100-1028, RRID:AB_3148646 1/500 Reactive glia staining
Biotin Rat anti-mouse I-A/I-E BioLegend Cat# 107603, RRID:AB_313318 1/1000
Rabbit anti-mouse P2RY12 AnaSpec Cat# 55043A, RRID:AB_2298886 1/1000
Alexa Fluor 488 mouse anti-mouse GFAP (GA5) Novus Cat# NBP2-33184AF488, RRID:AB_3284409 1/1000
Chicken anti-Vimentin Polyclonal Antibody Thermo Fisher Scientific Cat# PA1-16759, RRID:AB_2257294 1/1000
RecombiMAb anti-mouse CD16/CD32 BioxCell Cat# CP025 1/400 T cell staining
Rat anti-Mouse CD3 (Clone 17A2) Leinco Technologies Cat# C2457 1/400
REAfinity Biotin Human anti-mouse CD4 Miltenyi Biotec Cat# 130-123-215, RRID:AB_2811468 1 to 50
Rabbit anti-mouse CD8a Thermo Fisher Scientific Cat# MA5-29682, RRID:AB_2785507 1/200
AIF-1/Iba1 Antibody Novus Cat# NB100-1028, RRID:AB_3148646 1/500
Alexa Fluor 488 Donkey anti-rat secondary antibody Thermo Fisher Scientific Cat# A-21208, RRID:AB_2535794 1/500 Secondary staining
Alexa Fluor 594 Donkey anti-mouse secondary antibody Thermo Fisher Scientific Cat# A-21203, RRID:AB_2535789 1/500
Alexa Fluor 594 Donkey anti-rabbit secondary antibody Thermo Fisher Scientific Cat# A-31573, RRID:AB_2536183 1/500
Alexa Fluor 405 Donkey anti-goat secondary antibody Thermo Fisher Scientific Cat# A48259, RRID:AB_2890272 1/500
Alexa Fluor 647 Donkey Anti-Human secondary antibody Jackson ImmunoResearch Labs Cat# 709-605-098, RRID:AB_2340577 2μg/ml

Validation

Antibodies are commercially available and validation materials are available on the appropriate websites.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Cells are maintained by Hope Center Viral Vectors Core at Washington University School of Medicine
Authentication	HEK293 cells were maintained by Hope Center Viral Vectors Core at Washington University School of Medicine and were not further authenticated
Mycoplasma contamination	No Mycoplasma contamination has been detected by PCR based analysis
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	P301S tau transgenic mice (PS19tg; Stock No. 008169, Jackson Laboratories) containing a transgene of the human P301S tau mutant driven by a mouse prion protein (Prnp) promoter were backcrossed to C57BL/6 mice (Stock No. 027, Charles River) for more than 10 generations. These mice were crossed with human APOE4 knock-in mice (C57BL/6 background) in which the endogenous mouse ApoE gene was replaced by a human APOE gene flanked by LoxP sites51 to generate a APOE4 homozygous P301S tau transgenic mice on a C57BL/6 background (abbreviated as TE4 mice). The TE4 mice were then crossed with Irf8+32-/- mice with B57BL/6 background (Stock No. 032744, Jackson Laboratories) for two generations to generate E4WT, E4Δ+32, TE4WT, TE4Δ+32 mice. TE4WdKO mice were generated by crossing TE4 mice with Wdfy4 KO mice10. OT-1 mice (Stock No. 003831) containing transgenic inserts for mouse Tcra-V2 and Tcrb-V5 genes, encoding TCR receptors that recognize ovalbumin residues 257-264, were purchased from Jackson Laboratories. B6/CD45.1 mice (Stock No. 002014) carrying a differential pan leukocyte marker Prprca (known as CD45.1) were purchased from Jackson Laboratories. OT-1 mice were crossed with B6/CD45.1 mice for two generations to generate OT-1/CD45.1 mice for further experiments. MHC-I 3xKO (H-2Kb-/-, H-2Db-/-, β2m-/-) mice were previously reported52 . B6.hMAPTN279K mice (Stock No. 035794) expressing human MAPT with the pathogenic N279K mutation and control mice B6.hMAPTWT (Stock No. 035398) expressing the typical human MAPT protein isoforms were purchased from Jackson Laboratories and maintained in the laboratory of Dr. Timothy Miller. All mice were bred, maintained, and used in experiments in our specific pathogen-free (SPF) animal facility under a 12-h light/12-h dark cycle at an ambient temperature of 20–24 °C and relative humidity of 30–70%, with ad libitum access to food and water. These are in accordance with the guidelines of the Division of Comparative Medicine under the protocols approved by the Institutional Animal Care and Use Committee (IACUC) at Washington University School of Medicine.
Wild animals	This study did not include wild animals.
Reporting on sex	The sex of the mice used for the experiments was stated in the main text of the manuscript as well as in the figure legends
Field-collected samples	This study did not include samples collected from the field.
Ethics oversight	All mice were bred, maintained, and used in experiments in our specific pathogen-free (SPF) animal facility in accordance with the guidelines of the Division of Comparative Medicine under the protocols (24-0098) approved by the Institutional Animal Care Care and Use Committee (IACUC) at Washington University School of Medicine.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	For histopathology and biochemistry experiments, mice were euthanized at 285 days (around 9.5-month-old) of age by intraperitoneal injection of pentobarbital (200 mg/kg). Blood samples were collected in EDTA-treated tubes before cardiac perfusion with 3 U/ml heparin in cold Dulbecco's PBS (DPBS, Gibco, Cat# 14040133). Blood samples were spun down (10 min, 2,000g, 4°C), and plasma was collected. Brains were carefully extracted, weighed, and cut into two hemispheres. The left hemisphere was collected for immunostaining/immunohistochemistry analysis and immerse-fixed in 4% PFA overnight before being transferred to 30% sucrose and stored at 4°C until frozen in powdered dry ice and sectioned. Brains were cut coronally into 50µm sections on a freezing sliding microtome (Leica SM1020R) and stored in cryoprotectant solution (0.2 M DPBS, 15% sucrose, 33% ethylene glycol, 0.2µm filter for sterilization, made in house) at −20°C until used for experiments. The right hemisphere was dissected to isolate the hippocampus and the cortex for biochemical analysis, and the tissue was kept at −80°C until being analyzed. For the flow cytometry experiments, mice were perfused using cold, heparinized DPBS. Spleens were collected and kept in cold DPBS for single cell preparation. Deep cervical lymph nodes (dCLN) were collected under the dissection scope in cold DPBS for single cell preparation. To isolate meninges and brains, the bottom part of the skull was carefully removed, exposing the undamaged brain parenchyma. Brains were carefully collected and kept in cold DPBS for single cell preparation and skullcaps with the adhered meninges were stored in cold RPMI1640 (Gibco, Cat# 11875085) supplemented with 2% FBS medium for single cell preparation. To isolate single cells from different tissues, the following procedures were conducted (all procedures were performed on ice unless noted otherwise) regarding each tissue type. For spleen, single cells were prepared by mechanically smashing the tissue through a 70µm pre-wet strainer (Corning) and red blood cells were removed by adding 1-2ml of red blood cell lysis buffer (8.3g NH4Cl, 1.0g KHCO3, 200µl of 0.5M EDTA diluted in 1L distilled H2O, filtered through 0.2µm filter for sterilization, made in house), agitating vigorously by pipetting and left at room temperature (RT) for 5min before neutralizing with 5-10 ml of DMEM media (Gibco, Cat# 11965084) supplemented with 10% FBS. For dCLN, the lymph nodes were digested with 250µg/ml of Collagenase B (Roche, Cat# 11088807001) and 30U/ml of DNase I (Roche, Cat# 11284932001) diluted in DPBS (~1ml of digestion buffer for each sample) at 37°C for 30 min, agitating every 15min, and the enzymatic activity was neutralized by adding 5ml of cold MACS buffer (3% BSA, 2mM EDTA in DPBS, made in house) For dural meninges digestion, the meninges were digested in 2ml of digestion buffer in a 2ml eppendorf tube containing 0.5mg/ml collagenase P (Roche, Cat# 11213857001), 0.1mg/ml DNAse I (Roche, Cat# 11284932001) diluted in RPMI1640 supplemented with 2% FBS and incubated with shaking at RT for 1h. After digestion, the meninges were mechanically dissociated with pipetting up and down 15 times and the cell mixture was filtered through a pre-wet 100µm strainer (Corning) with cold RPMI1640 supplemented with 2% FBS and the filters were then washed at least twice to maximally recover the cells. Brains were dissected carefully to keep the hippocampal and cortical tissues. The tissues were put in 2ml of the digestion buffer containing 1mg/ml of the Collagenase IV (Sigma, Cat# C4-28-100MG) and 10 µg/ml DNase I ((Roche, Cat# 11284932001) and incubated in a 37°C incubator for 30 min (pipetting every 15 min). The dissociated cells were filtered through pre-wet 70µm strainer. Cells were spun down in a centrifuge at 500g X 5min except when noted otherwise (Cells isolated from meninges were spun down at 520g X 6min) and cell pellets were washed once with DPBS and supernatants were discarded. Cells containing myelin debris were resuspended with 40% isotonic Percoll (Sigma, Cat# P1644-1L) [the Percoll stock solution was first diluted to isotonic "100%" Percoll by adding 9 parts of Percoll with 1 part of 10X HBSS solution (Gibco, Cat# 14065056) and the "100%" Percoll solution was further diluted to 40% by adding 2 parts of the "100%" Percoll solution and 3 parts of the 1X HBSS solution (Gibco, Cat# 14025076)] and spun at 1000g for 10 min at RT with deceleration of "2". After centrifugation, the tubes were carefully taken out and the myelin layer (at top) as well as the supernatant was carefully removed, and the cell pellets were washed twice with DPBS and spun down for antibody labeling. For isolation of BM progenitor cells, BM was harvested from the tibia and femurs. Single cells were prepared by passing through a 70µm pre-wet strainer (Corning) and red blood cells were removed by red blood cell lysis buffer. To enrich CDP, pre-cDC1 and pre-cDC2 cells before subjected to cell sorting which was reported previously43, BM cells underwent negative selection by adding biotinylated antibody mastermix including antibodies specific to CD3, CD19, CD105, CD127, TER-119, Ly-6G?and B220, followed by depletion with MagniSort Streptavidin Negative Selection Beads (Invitrogen, Cat# MSNB-6002-74). The remaining lineage− BM cells were then stained with fluorescent antibodies before sorting. CDPs were identified as lineage−SiglecH-CD117intCD135+CD115+MHCII−CD11c− BM cells; pre-cDC1s were identified as lineage−SiglecH-CD117intCD135+MHCIIint−negCD11c+CD24+ BM cells; pre-cDC2s were identified as lineage- SiglecH-CD117int-lowCD135 +MHCII-CD11C+CD115+ BM cells.
Instrument	All the FACS sorting was done on BD FACSAria II sorter (BD Biosciences) or CytoFlex SRT (Beckman Coulter). Flow cytometry data acquired from FACS CantoII or Cytek Aurora
Software	Flow cytometry data acquired from machines other than Cytek Aurora were exported as Fcs files and analyzed using FlowJo software (version 10.10.0, Tree Star). The data acquired from Cytek Aurora were unmixed using the SpectroFlo software first and then further analyzed using FlowJo software (version 10.10.0, Tree Star).
Cell population abundance	The post sort was performed to confirm a purity above 98%.

Gating strategy

Microglia are defined as: CD45int,CD11b+
Brain ILCs are defined as: CD45hi,CD11b-,TCRβ-,CD11c-,MHC-II-,GATA3+(ILC2) or RORγT+(ILC3)
Brain pDC are defined as: CD45hi,CD11b-,CD11c+,B220+,MHC-II+
Brain αβT cells are defined as: CD45hi,CD11b-,TCRβ+,NK1.1-,CD4 (or CD8)+
Brain B cells are defined as: CD45hi,CD11b-,TCRβ-,CD19+
Brain γδT cells are defined as: CD45hi,CD11b-,TCRβ-,CD19-,MHC-II-,TCRγδ+
Brain NK cells are defined as: CD45hi,CD11b-,TCRβ-,NK1.1+
Brain NKT-like and iNKT cells are defined as: CD45hi,CD11b-,TCRβ+,NK1.1+ (NKT-like) or CD1d-PBS57 tetramer+ (iNKT cells)
cDC1 cells are defined as: CD45+,F4/80-.B220-,CD11c+,MHC-II+,XCR1+,Sirpα-
cDC2 cells are defined as: CD45+,F4/80-.B220-,CD11c+,MHC-II+,XCR1-,Sirpα+
Brain naïve T cells are defined as: CD45hi,CD11b-,TCRβ+,NK1.1-,CD4 (or CD8)+,CD62L+,TCF1+
Treg cells are defined as: CD45hi,CD11b-,TCRβ+,NK1.1-,CD4+,CD44int-pos,FOXP3+
CD8 exhausted-like (or Taa) cells are defined as: CD45hi,CD11b-,TCRβ+,NK1.1-,CD8+,PD1+,TOX+
Taa cells can be further separated as: TCF1+SLAMF6+CD39-, TCF1intSLAMF6-CD39+, TCF1-SLAMF6-CD39+
CDPs are defined as lineage−SiglecH-CD117intCD135+CD115+MHCII−CD11c− BM cells
pre-cDC1s are defined as lineage−SiglecH-CD117intCD135+MHCIIint−negCD11c+CD24+ BM cells
pre-cDC2s are defined as lineage- SiglecH-CD117int-lowCD135+MHCII-CD11C+CD115+ BM cells
All gating strategy can be found in the manuscript.
All gating strategy can be found in Supplementary Figure

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.