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Corresponding author(s): Ioana I. N. Da Silva and Fred H. Gage, manuscript #NCOMMS-25-64617

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Reporting Summary

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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	For flow cytometry, we used BD FACSDiva v8.0.1. For qPCR, we used QuantStudio v1.5.2. For ddPCR, we used we used QuantaSoft v1.7.4.0917. For confocal microscopy, we used Zeiss Zen Blue v3.4; for slide scanning, we used Zeiss ZEN 3.9 or Akoya Biosciences Fusion 2.3.1. For plate reading, we used Promega GloMax Discover v3.2.3. For Western blot image acquisition, we used LI-COR ImageStudio v5.2.5. For LC-MS/MS, we used a TSQ Quantiva mass spectrometer (Thermo), controlled by Thermo Xcalibur version 3.0.63, or a Fusion Lumos mass spectrometer (Thermo) controlled by Thermo Xcalibur version 4.0.27.10. RNA-seq data was acquired using HiSeq Control Software v2.2.68 (HiSeq 2500) or HiSeq Software Suite v3.4.0 (HiSeq 4000).
Data analysis	Data was analyzed and plotted in GraphPad Prism v9.5.1. We used R v4.0.0 and v.3.3.2, with the following packages: R package TPP v3.10.0, DESeq2 package version 1.20.0, WebGestalt R package version 0.1.1, edgeR package version 3.11, tximeta package v1.8.3, org.Hs.eg.db v3.12.0. FlowJo v10.8.0. For qPCR, we used Thermo Fisher Cloud Software v1.1. For confocal microscopy, we used Zen Blue v3.3, ImageJ v2.1.0, QuPath v0.5.1, and CellProfiler v3.1.8. For immunoblotting, we used LI-COR ImageStudio v5.2.5. For network analysis, Cytoscape v3.5.1 and Cytoscape apps ClueGO v2.5.7 and GeneMania v3.4.1 . For RNA-seq: STAR v.4.0k, DAVID v6.8 , X2K Web (no version specified; accessed April 2020), Expression2Kinases 1.6.1207, SolexaQA v3.1.7.1, cutadapt v2.10, Salmon v1.2.1, STRING v11.0b, cMAP v1.0.2. For MS, we used Integrated Proteomics Pipeline – IP2 (Integrated Proteomics Applications, version 6.0.1), RawConverter version 1.1.0.18, ProLuCID version 1.4.2 , DTASelect version 2.1.4, Census version 2.51, Skyline version 21.2.0.536. For PK modeling, we used WinNonlin 8.2.

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

Source Data from all main and supplementary figures are provided with this paper. Primary RNA-sequencing data are available through SRA at SRP429592 [https://www.ncbi.nlm.nih.gov/sra?term=SRP429592]; source data for gene expression analyses are shown in Supplementary Data 2, 3, and 5. Raw proteomics data are available through ProteomeXchange partner repository MassIVE at MSV000091641 [https://doi.org/doi:10.25345/C5CJ87W3G] and processed and analyzed data are provided in Supplementary Data 1. The publicly available datasets used in this study are the Aging, Dementia, TBI study [https://aging.brain-map.org/download/index]) and syn17009177 [https://www.synapse.org/Synapse:syn17009177] (UPP Proteomics Study).

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	For the generation of patient-derived control and AD astrocytes, patient cohort was assembled to represent both males and females across control and suspected AD donor groups (n =1 male in control, n = 3 males in AD; n = 3 females in control and n = 4 females in AD). For the generation of hiPSC-derived glia-enriched organoids, the 3 cell lines used consisted of 2 males and 1 female. No sex-based analysis was performed due to low sample size.
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	hiPSC derived from fibroblasts or PBMCs from donors with suspected AD as well as age- and sex-matched control donors were obtained from the University of California-Irvine (UCI) MIND iPS Bank. Patients and controls were males and females, ages 63-87. Clinical data is summarized in Supplementary Table 4. For one of the replicates of glia-enriched organoid differentiation, a CRISPR-corrected iPSC line (R88) derived from a 5 year old male with Alexander disease was used. See for more information: Jones, J. R. et al.Cell Rep. 25, 947-958.e4 (2018).
Recruitment	Patients were recruited by the UCI-ADRC. For R88, see for more information: Jones, J. R. et al.Cell Rep. 25, 947-958.e4 (2018).
Ethics oversight	Patient consent and ethics approval was obtained by UCI-ADRC and UCI MIND iPS Bank, and samples were obtained by the authors de-identified. For R88, see for more information: Jones, J. R. et al.Cell Rep. 25, 947-958.e4 (2018).

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	The mouse group sizes or biological and technical replicates in in vitro studies are based on numbers having been shown in previous publications to generate statistically significant results for the given experimental question.
Data exclusions	Individual samples were excluded from analysis only in the instance of technical failure within the experiment. For the APP/PS1 staining studies, due to the variability in penetrance of plaque pathology, animals with few or no plaques were excluded from analysis (See Supplementary Figure 13F).
Replication	Experiments were repeated independently at least 1-2 times and conclusions were replicated in all instances. The in vivo PK/PD and tolerability studies and acute inflammation model described in Figure 4 and Figure 6 were conducted only once but samples were analyzed more than once as independent experiments whenever possible. The APP/PS1 in vivo studies in Figure 6 were conducted twice, independently of each other.
Randomization	Samples and mice were randomly allocated to experimental groups (no specific method used).
Blinding	For the in vitro studies, blinding is not relevant because studies involved experimental groups with different reagent treatments. For the in vivo APP/PS1 studies, imaging analysis was performed with blinded images.

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
[ ]	[x] Antibodies
[ ]	[x] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[ ]	[x] Animals and other organisms
[x]	[ ] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[ ]	[x] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used

For IF, the following primary antibodies were used: (a) Glast (EAAT1): mouse anti-EAAT1 (1:1,000; Santa Cruz, sc-15316); S100b: rabbit anti-S100b (1:1,000; Dako, Z031129-2); Vimentin: goat anti-Vimentin (1:500; EMD Millipore, AB1620); (b) rabbit anti-NF-κB (1:400; CST #8242), mouse anti-phospho NF-κB S529 (1:25; R&D MAB7624), mouse anti-CK2A1 (1:500; Santa Cruz sc-12738), rabbit anti-phospho CK2A1 Y255 (1:25; Thermo Fisher PA5-40226); (c) rabbit monoclonal anti-β-Amyloid (D54D2) XP (1:500; CST: 8243), chicken polyclonal anti-GFAP (1:5000; EDM Millipore: AB5541), goat polyclonal anti-Iba1 (1:200; Abcam: ab5076); (d) anti-CK2A1 (Rabbit, Bethyl, A300-198A, 1:5000), anti-CK2A2 (Rabbit, ProteinTech, 10606-1-AP, 1:100), Anti-CK2B (Rabbit, Abcam, ab76025, 1:100), Anti-GFAP (Chicken, EMD, AB5541, 1:1000), anti-IBA1 (Goat, ab5076, Abcam, 1:100), anti-MAP2 (Mouse, Sigma, M1406, 1:500); (e) rabbit anti-GFP (1:1000; Invitrogen: A6455), goat polyclonal anti-hSox9 (1:250; R&D Biosystems: AF3075), rabbit monoclonal anti- NF-κB p65/RelA (1:400; CST: 8242), mouse monoclonal anti-Phospho-RelA/NFkB p65 (S529) (1:50; R&D Systems: MAB7624), Rabbit polyclonal anti-CSNK2A2 (1:100; Proteintech: 10606-1-AP); Chicken polyclonal anti-NeuN (1:250; Millipore: ABN91). The following secondary antibodies were used: (a) mouse IgG-AF488 (Jackson ImmunoResearch Labs, 715-545-151), rabbit IgG-AF488 (Jackson ImmunoResearch Labs, 711-545-152), goat IgG-AF488 (Jackson ImmunoResearch Labs, 705-545-147) (each at 1:200);(b) rabbit IgG-Cy3 (Jackson ImmunoResearch Labs, 711-165-152), mouse IgG-AF488 (Jackson ImmunoResearch Labs, 715-545-151); mouse IgG-Cy3 (Jackson ImmunoResearch Labs, 715-165-151), rabbit IgG-AF488 (Jackson ImmunoResearch Labs, 711-545-152) (each at 1:200); (c) Goat IgG-Cy3 (Jackson ImmunoResearch Labs, 705-165-147), Chicken IgG-AF488 (Jackson ImmunoResearch Labs, 703-545-155), and Rabbit IgG-AF647 (Jackson ImmunoResearch Labs, 711-605-152) (each at 1:250); (d) Anti-Rabbit IgG-AF647 (Invitrogen, A-21245, 1:200), Chicken IgG-AF488 (Invitrogen, A78948, 1:200), Goat IgG-AF594 (Invitrogen, A32758, 1:200), Mouse IgG-AF546 (Invitrogen, A10036, 1:200); (e) chicken IgG-Cy3 (703-165-155), rabbit IgG-AF488 (Jackson ImmunoResearch Labs, 711-545-152), goat IgG-AF647 (705-175-147) (each 1:200); rabbit IgG-AF488 (Jackson ImmunoResearch Labs, 711-545-152); mouse IgG-AF488 (Jackson ImmunoResearch Labs, 715-545-151), rabbit IgG-Cy3 (Jackson ImmunoResearch Labs, 711-165-152).

For WB, antibodies used were rabbit anti-CK2α1 (Bethyl #A300-198A, 1:5000), rabbit anti-CK2α2 (Bethyl #A300-199A, 1:5000), mouse anti-GAPDH (Fitzgerald #10-1501, 1:20000), rabbit anti-actin (Sigma #A2066, 1:20000), mouse anti-NF-κB (CST #6956, 1:1000), pNF-κB S529 (ThermoFisher #14-9864-82, 1:100), mouse anti-IkBa (CST #4814, 1:1000), mouse anti-IkBa pS32 (Santa Cruz #8404, 1:500), mouse anti-PTGR1 (Abnova #10563-436, 1:1000), anti-HA-tag (Bethyl #A190-108A, 1:20000), rabbit anti-AKT pS129 1464 (ab133458, 1:1000), mouse anti-AKT1 (Santa Cruz #sc-55523, 1:1000), mouse anti-synaptotagmin antibody (Abcam #ab13259, 1:1000) and rabbit anti-synaptophysin (Abcam #ab32594, 1:5000). Secondary antibodies used were goat anti-mouse IgG IRDye 800CW #925-32210, goat anti-rabbit mouse IgG IRDye 800CW #925-32211, goat anti-mouse IgG IRDye 680RD #926-68070, or goat anti-mouse IgG IRDye 680RD #926-68071.

For immunoprecipitation, either (a) NF-κB primary antibody (Novus NB100-97831, Rabbit polyclonal) was used for pulldown and blots were probed with NF-κB primary antibody (CST D14E12) and anti-rabbit Light Chain-specific IgG AlexaFluor 790 (Jackson Immuno NC0493011) secondary antibody for detection or (b) anti-CK2A2 primary antibody (Bethyl A300-199A) was used for both pulldown and blotting.

For flow cytometry, the following antibodies were used:

Antigen Fluorochrome Volume Concentration Isotype Clone Catalog # Company

IL-8 PerCP 5 ul 100 µg/ml Mouse IgG2b BH0814 514606 Biolegend

TNF-a Pe-Cy7 5 ul 200 µg/ml Mouse IgG1, k MAb11 502930 Biolegend

IL-6 APC 5 ul 50 µg/ml Rat IgG1, k MQ2-13A5 501112 Biolegend

MCP-1 (CCL2) PE 3 ul 200 µg/ml Armenian Hamster IgG 2H5 505904 Biolegend

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For FACS sorting, the following antibodies were used:

Color Antibody Catalog # Volume (µL) Concentration (µg/mL)

APC CD64 305014 5 200

PerCP-Cy5.5 CX3CR1 341614 5 400

488/FITC CD14 325610 5 400

PE CD11b 301306 5 200

PE-Cy7 HLA-DR 307616 5 200
APC-Cy7 CD45 304014 5 100
FITC CD43 315204 5 400
FITC Isotype Ct 400107 5 500
APC Isotype Ct 400122 5 200
PerCP-Cy5.5 Isotype Ct 401623 5 200
PE Isotype Ct 400112 5 200
PE-Cy7 Isotype Ct 400231 5 200
APC-Cy7 Isotype Ct 400127 5 200

Validation

Antibody validation data is available on vendor websites (no further validation was performed).

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Primary astrocytes were obtained from ScienCell. THP-1 NF-kB Lucia cells were obtained from InVivoGen. HEK293T cells were obtained from the Verma Lab at the Salk Institute. H1 were obtained from WiCell Research Institute. EC11 and Clue 4-7 hiPSCs were generated from neurotypical donor fibroblasts at the Salk Institute Stem Cell Core and Laboratory of Genetics. AD and control hiPS cell lines were obtained from UCI MIND iPS Bank and differentiated into astrocytes at the Salk Institute Laboratory of Genetics. Control hiPSC line R88 was a kind gift from Jeffrey Jones. Supplementary Tables 4 and 8 contain available subject information.
Authentication	The following lines were used: neurotypical control iPSC lines (Clue 4-7) as previously described in (Schafer, S.T., Paquola, A.C., Stern, S., Gosselin, D., Ku, M., Pena, M., Kuret, T.J., Liyanage, M., Mansour, A.A., Jaeger, B.N. and Marchetto, M.C., 2019. Pathological priming causes developmental gene network heterochronicity in autistic subject-derived neurons. Nature neuroscience, 22(2), pp.243-255.) and Ec11 as previously described in (Firth, A.L., Dargitz, C.T., Qualls, S.J., Menon, T., Wright, R., Singer, O., Gage, F.H., Khanna, A. and Verma, I.M., 2014. Generation of multiciliated cells in functional airway epithelia from human induced pluripotent stem cells. Proceedings of the National Academy of Sciences of the United States of America, 111(17), pp.E1723-E1730.) R88: Jones, J. R. et al.Cell Rep. 25, 947-958.e4 (2018). All other cell lines were authenticated by the commercial source.
Mycoplasma contamination	All cell lines regularly tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used in this study.

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	Male C57Bl/6NHsd mice 2-4 months of age were used for the studies in Figures 4 and 6D. For the IP PK study of TAL606, adult male C57Bl/6J mice were used. For the IV and PO PK studies of TAL606, 6- to 8-week-old male CD-1 mice were used. For the APP/PS1 mouse studies in Figure 6, hemizygous APP/PS1 transgenic mice and their wild-type littermates 7-10 months of age (Jax stock #005864) were used.
Wild animals	No wild animals were involved.
Reporting on sex	For the PK/PD studies, we performed experiments only on males to limit animal numbers required for these particular studies. For the APP/PS1 studies, we used both males (n = 36) and females (n = 27) to ensure adequate sample sizes to detect group-based differences. Due to inadequate sample sizes to account for cohort (batch) effects, we did not perform sex-based analyses of the data.
Field-collected samples	No field-collected samples were involved.
Ethics oversight	All animal procedures were approved by the Institutional Animal Care and Use Committees of The Salk Institute for Biological Studies, University of California San Diego, or Shanghai Chempartner Co, Ltd.

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 each well of HCAs in a 6-well plate, 2 mL of fresh medium with GolgiPLUG (BD #555029, 1:1000) and GolgiSTOP (BD # 554724, 1:1000) with 20 uM compound or vehicle (DMSO) and IL1-β 10 ng/mL or DPBS was added. The cells were incubated for 5 hours at 37˚C. Cells were collected with TrypLE and plated into a 96-well V-bottom plate for staining. The plate was centrifuged for 5 min at 1,300 rpm, 4˚C to pellet cells that were subsequently resuspended in 100 µL DPBS with 1 µL Zombie Violet (Biolegend #423113) and 5 µL Human Trustain FC block (Biolegend #422302) per well for 15 min at room temperature (RT) in the dark. The plate was centrifuged, supernatant was aspirated, and the cells were washed with 100 µL/well DPBS. Cells were fixed with 100 µL/well of Cytofix/Cytoperm (BD) for 20 min at 4°C. The plate was centrifuged, supernatant was aspirated, and cells were resuspended in 100 µL Permwash (BD) and incubated for 15 min at 4°C. The plate was centrifuged, supernatant was aspirated, and cells were incubated with 100 µL/well of Ab mix or isotype mix in Permwash (see antibodies list above) for 20 min at 4°C, followed by centrifugation and 2x PermWash washes. The cells were resuspended in 100 µL DPBS and transferred to FACS tubes containing 200 µL of PBS (total volume per tube 300 µL) for analysis.

Instrument

BD LSRII or Fortessa instruments were used.

Software

BD FACSDiva was used for collection and FlowJo was used for analysis.

Cell population abundance

Total alive cell population ~80-100% (via FSC/SSC gating and negative for Zombie Violet staining). TNFa/IL6/IL8/MCP1 positive cell populations varied from <1-100% depending on each treatment group and are clearly shown in Figure 1A and Extended Data Figure 1.

Gating strategy

FSC-A and SSC-A gates comprised a polygon around ~30K-100K. Antibody isotype controls were used as negative controls in order to positive staining for each target.

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