

Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
- An indication of 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 statistics 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
- Clearly defined error bars
State explicitly what error bars represent (e.g. SD, SE, CI)

Our web collection on [statistics for biologists](#) may be useful.

Software and code

Policy information about [availability of computer code](#)

Data collection

RNA/DNA quality check: 2100 Expert Software
 RNA/DNA sequencing: NextSeq System Suite, HiSeq Control Software, Illumina bcl2fastq2 Conversion Software v2.17
 qPCR: StepOne Software
 single nuclei RNA sequencing: C1 System Software
 Imaging : Zen 2011 software
 Flow cytometry: FACSDiva v8.0.1
 Mouse behavior: EthoVision, Home Cage photobeam, Video Freeze
 Software and script usage is described in the method section.

Data analysis

Bulk RNA seq bioinformatics: TopHat2, HTSeq-count (v0.6.0), SPEctRA, DESeq2 package, R (v3.1.1), Enrichr, Ingenuity Pathway Analysis
 Single cell sequencing bioinformatics: STAR (2.4.0a), edgeR (3.10.0), Monocle (1.2.0) toolkit
 ChIP-seq bioinformatics: FastQC (v0.11.2), Bowtie v0.12.7, SAMtools package (v0.1.19), MACS (v2.1.1), region-analysis (v0.1.2), ngsplot (v2.47)
 Published data analysis: GEO2R
 Data representation: Multiple Experiment Viewer 4.8 (v.10.2), IGV Tools, GraphPad Prism v5.01
 Imaging analysis: Imaris, NeuroLucida Explorer, NeuroLucida360, ImageJ, IncuCyte, Image Lab
 Flow cytometry analysis: FCS Express 6
 Software and script usage is described in the method section.

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/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [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 list of figures that have associated raw data
- A description of any restrictions on data availability

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Accession Codes

Sequence data can be downloaded from the National Center for Biotechnology Information Gene Expression Omnibus Accession #GSE108356.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf](https://www.nature.com/authors/policies/ReportingSummary-flat.pdf)

Life sciences study design

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

Sample size	We do not include a justification of sample size for this study. We used the minimum number of animals needed to reliably detect the expected effect size with an alpha rate set at .05 in a standardly powered experiment and based on extensive laboratory experience and literatures in the field.
Data exclusions	For all behavioral data Grubbs test was used to identify significant outliers and these outliers were excluded
Replication	All attempts of replications were successful. Each experiment was reproduced with similar results. Reproducibility has been either indicated in the Figure Legends, or shown as a quantification.
Randomization	For all molecular, imaging and behavioral experiments, animals were randomly assigned to groups.
Blinding	Experimenters were blinded during imaging and behavioral experiments. Gene expression and protein analyses were not performed blind to the conditions of the experiments.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Unique biological materials
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Human research participants

Methods

n/a	Involved in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> ChIP-seq
<input type="checkbox"/>	<input checked="" type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Unique biological materials

Policy information about [availability of materials](#)Obtaining unique materials

Antibodies

Antibodies used

Immunostaining: GFP (1:2000, ab6556 and 1:500 ab13970 Abcam, Cambridge, MA), IBA1 (1:500, 019-19741, Wako Chemicals, Richmond, VA), CD68 (1:250, MCA1957, Biorad, Hercules, CA), NeuN (1:500, MAB377, EMD Millipore, Billerica, MA), GFAP (1:500, G3893, Sigma), OLIG2 (1:250, MABN50, EMD Millipore), CD11B (1:1000, MCA711GT, Biorad, Hercules, CA), H3K27me3 (1:500, C36B11, Cell Signaling), CD74 (1:50, sc-5438, Santa Cruz), cCASP3 (1:400, #9661, Cell Signaling), P2RY12 (1:5000, kind gift from O. Butovsky), MHCII (1:200, ab23990, Abcam), ApoE (1:100, AB947, Millipore), AXL (1:100, AF854, R&D Systems), Ki67 (1:200, ab16667, Abcam), Alexa Fluor 488-labeled goat anti-mouse IgGs (H+L) (1:500, Life Technologies, A32723), Alexa Fluor 488-goat anti-rat IgGs (H+L)(1:500, Life Technologies, A-11006), Alexa Fluor 488-goat anti-chicken IgYs (H+L)(1:500, Life Technologies, A-11039), Alexa Fluor 488-goat anti-rabbit IgGs (H+L) (1:500, Life Technologies, A-11008), Alexa Fluor 568-labeled goat anti-mouse IgGs (H+L) (1:500, Life Technologies, A-11004), Alexa Fluor 568-goat anti-rat IgGs (H+L)(1:500, Life Technologies, A-11077), Alexa Fluor 568-goat anti-rabbit IgGs (H+L) (1:500, Life Technologies, A-11011), Alexa Fluor 568- donkey anti-goat IgGs (H+L) (1:500, Life Technologies, A-11057), and Alexa Fluor 647-goat anti-rat IgGs (H+L)(1:500, Life Technologies, A-21247)

ChIP: H3K27me3 (1:100, 07-449, Millipore)

Immunoblotting: AXL (1:500, sc-1097, Santa Cruz), AXL (1:1000, ab227871, Abcam), FSCN1 (1:5000, ab126772, Abcam), MRC1 (1:500, AF2535, R&D Systems), LC3B (1:1000, 2775, Cell Signaling), H3K27me3 (1:1000, 07-449, Millipore), ACTB (1:20,000, ab8227, Abcam), Histone H3 (1:2,000, ab1791, Abcam), horseradish-peroxidase-conjugated anti- mouse (Life Technologies, 31438, 1:10,000), horseradish-peroxidase-conjugated anti-rabbit IgG secondary antibody (GE, NA934V, 1:10,000), and horseradish-peroxidase-conjugated anti-goat IgG antibody (Life Technologies, PI31400, 1:10,000)

TRAP: goat anti-GFP (I9F7 and I9C8, Antibody & Bioresource Core Facility Memorial Sloan Kettering Cancer Center)

Validation

GFP (ab6556), GFP (ab13970), IBA1 (019-19741), CD68 (MCA1957), NeuN (MAB377), CD11B (MCA711GT), H3K27me3 (C36B1), cCASP3 (#9661), MHCII (ab23990), and Ki67 (ab16667) are verified for immunostaining in mouse on the company websites, with the exception of GFP which is an exogenously-expressed protein but endogenous to *A. victoria*.

GFAP (G3893) was verified for immunostaining in mouse by LeComte et al. 2015. OLIG2 (MABN50) was verified for immunostaining in mouse by Moyon et al. 2016. CD74 (sc-5438) was verified for immunostaining in mouse by Sun Hui et al. 2015. P2RY12 and ApoE (AB947) were verified for immunostaining in mouse by Krasemann et al. 2017. AXL (AF854) was verified for immunostaining in mouse by Fourceaud et al. 2016.

H3K27me3 (07-449) was verified for ChIP in mouse on the company website.

AXL (ab227871), FSCN1 (ab126772), MRC1 (AF2535), LC3B (2775), H3K27me3 (07-449), ACTB (ab8227), and Histone H3 (ab1791) are verified for immunoblotting in mouse on the company websites

AXL (sc-1097) was verified for immunoblotting in mouse by Fourceaud et al. 2016.

goat anti-GFP (I9F7 and I9C8, Antibody & Bioresource Core Facility Memorial Sloan Kettering Cancer Center) were verified for TRAP in Heiman et al. and Doyle et al. 2008

Eukaryotic cell lines

Policy information about [cell lines](#)Cell line source(s) Authentication

Mycoplasma contamination

All cell lines tested negative for mycoplasma contamination.

Commonly misidentified lines
(See [ICLAC](#) register)

No commonly misidentified cell lines were used.

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals

Mice of C57Bl/6 background were used. For imaging and behavior experiments, young adult 2-4 mo or aged 17-20mo male and female mice were used. For gene expression analyses 3mo male, 6mo male, and 9 mo female mice are used. For TRAP proof of principle 3-6mo male mice were used. For phagocytosis assay and protein analysis, 2-4mo male and female mice were used. For ChIP sequencing assay adult 6-9mo male and female mice were used. For single nuclei sequencing adult 4-5mo female mice were used. Whenever male and female mice were used together, the ratio in control and treatment groups were equal.

Wild animals

This study did not involve wild animals.

Field-collected samples

This study did not involve samples collected from the field.

ChIP-seq

Data deposition

Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).

Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links

May remain private before publication.

GSE108356

Files in database submission

CB_H3K27me3_ChIP
 CB_input
 ST_H3K27me3_ChIP
 ST_input
 H3K27_MGCX_NoIndex_L002_R1.fastq.gz
 Input_MGCX_NoIndex_L003_R1.fastq.gz
 24_ST_ACAGTG_L007_R1_001.fastq.gz
 22_ST_ACAGTG_L005_R1_001.fastq.gz
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 22_CB_ACAGTG_L001_R1_001.fastq.gz
 24_CB_ACAGTG_L006_R1_001.fastq.gz
 38-ST_S1_R1_001.fastq.gz
 48-ST_S2_R1_001.fastq.gz
 70-ST_S3_R1_001.fastq.gz
 74-ST_S4_R1_001.fastq.gz
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 78-ST_S4_R1_001.fastq.gz
 38-CB_S1_R1_001.fastq.gz
 48-CB_S2_R1_001.fastq.gz
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 52-ST_S2_R1_001.fastq.gz
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 Cb_M92_TCCTGAGCAGAGTAGA_L002_R1_001.fastq.gz
 H3K27me3 cbMg stMg counts TSS 1kb.xlsx
 supplementary table 6 - single nuclei gene expression.xlsx
 TRAP rpkm table.txt
 H3K27me3 cxMg TSS 1kb.xlsx

Genome browser session
 (e.g. [UCSC](#))

No longer applicable

Methodology

Replicates

Given the large number of mice (25) we had to utilize for a single ChIP experiment, we omitted doing replicates.

Sequencing depth

Total reads: CB H3K27 ChIP: 134508639, ST H3K27 ChIP: 128561066, CB H3K27 IN: 143429718, ST H3K27 IN: 128306483, H3K27 MG CX: 177410280, INPUT MG CX: 92850211 ; uniquely mapped reads: CB H3K27 ChIP: 91203884, ST H3K27 ChIP: 82130491, CB H3K27 IN: 87850086, ST H3K27 IN: 86077596, H3K27 MG CX: 121583596, INPUT MG CX: 60709894 . Reads were 50 bp single-end reads.

Antibodies

H3K27me3 (07-449, Millipore, 1:100)

Peak calling parameters	Peak-calling was performed using MACS (v2.1.1) with default settings. Annotation of called peaks and differential regions to their genomic features (promoters, gene bodies, intergenic, etc) was performed using region-analysis (v0.1.2).
Data quality	<p>The ChIP-seq data was first checked for quality using the various metrics generated by FastQC (v0.11.2). Raw sequencing reads were then aligned to the mouse mm9 genome using the default settings of Bowtie (v2.2.0). Only uniquely mapped reads were retained, and the alignments were subsequently filtered using the SAMtools package (v0.1.19) to remove duplicate reads.</p> <p>To select for H3K27me3-positive genes in cbMg, stMg and cxMg, the log₂ fold enrichment (log₂FE) of ChIP signal over the corresponding input signal was calculated for a region spanning TSS ± 1 kb for each gene. A cutoff of log₂FE > 0 was used to define H3K27me3-positive genes for stMg, cbMg and cxMg. To compare H3K27me3 targets between cbMg and stMg, a goodness-of-fit G-test was applied to the normalized read counts mapping within TSS ± 1 kb of each gene. A cutoff of p-value < 0.05 was used to define genes differentially marked with H3K27me3 in cbMg and stMg.</p>
Software	<p>Sequencing: HiSeq 2000 platform</p> <p>Raw sequencing data processing: Illumina bcl2fastq2 Conversion Software v2.17</p> <p>Quality control: FastQC (v0.11.2)</p> <p>Alignment: Bowtie (v2.2.0)</p> <p>Filtering: SAMtools package (v0.1.19)</p> <p>Peak-calling: MACS (v2.1.1)</p> <p>Annotation of called peaks: region-analysis (v0.1.2)</p> <p>Profile plots and heatmaps: ngsplot (v2.47) and Multiple Experiment Viewer 4.8.</p>

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

Nuclei isolation: Microglial nuclei from different brain regions of 4-/8-month-old Cx3cr1CreErt2/+(Litt);Eef1a1LSL.eGFPL10a/+ mice were isolated based on the eGFP-L10a fluorescence of newly formed ribosomes in the microglia nucleoli. All mice were gavaged at 4-6 weeks of age with five doses of 100 mg/kg of Tamoxifen with a separation of at least 48 hours between doses. Briefly, mice were euthanized with CO₂ and brain regions were quickly dissected and homogenized with a glass homogenizer. The homogenate was cross-linked with 1% formaldehyde for 8 min at room temperature and the reaction was quenched with glycine for 5 min at RT. The homogenate was then spun through a 29% iodixanol cushion. The resulting nuclear pellet was resuspended for FACS.

Microglia isolation: All mice were gavaged at 4-6 weeks of age with five doses of 100 mg/kg of tamoxifen with a separation of at least 48 hours between doses. Brain regions from adult mice were dissected, cut into small pieces and homogenized by manual compression. The tissue was incubated in digestion reaction at 37°C for 30 minutes with titration and was stopped by addition of EDTA. The homogenate was centrifuged, the pellet was resuspended and filtered. Sample was resuspended in 70% Percoll. A Percoll gradient (70% , 37% , and PBS in 4:3:1 ratio) was centrifuged to obtain the interphase containing the microglia. Interphase was collected and resuspended for FACS.

Early apoptotic Jurkat cells (EAJ): The Jurkat human T cells were transferred to fresh growth medium at 1 million/ml and treated with 1 μM Staurosporine for 3 hours. After treatment cells were collected and washed. Induction of apoptosis was verified using FITC-Annexin V / propidium iodide kit.

Phagocytosis assay: EAJ were incubated with 10 μg pHrodo dye per 10⁶ cells for 1 hour at RT in the dark. The cells were then washed with PBS and resuspended in microglia medium at 10 million/ml. Primary microglia from the cerebellum and striatum of adult mice that were cultured for 5h were given an equal number of pHrodo-labeled EAJ. Cells pretreated with 2 μM Cytochalasin D for 30 min before and during the incubation of microglia with pHrodo-EAJ were used as a negative control. After 3 hours, the supernatant was discarded and microglia were trypsinized. Pooled wells were collected in one tube, centrifuged at 400 × g for 5 min, and resuspended in 500 μl 1% BSA in PBS with 1μg/ml DAPI and placed on ice.

More detail is provided in the Methods section.

Instrument	BD FACSAria II and BD LSR II
Software	BD FACSDiva v8.0.1 and FCS Express 6
Cell population abundance	The purity of the samples were >95% as determined by re-analyzing the post-sort fractions.
Gating strategy	Gates were made for live cells (FSC-A by SSC-A), then singlets (FSC-W by FSC-A) for all samples. Singlets of nuclei were

Gating strategy

additionally selected by lowest DyCycle Ruby signal. Microglial cells and nuclei were gated by high GFP/YFP signal from mice expressing GFP/YFP under Cx3cr1 promoter. For apoptotic Jurkat cells, high and low Annexin V and Propidium Iodide signals were quantified to measure percentage of early apoptotic cells. For phagocytosis assay, events were gated on the SSC-A and FSC-A to exclude debris, then on GFP+ microglia, and finally to quantify the percent of GFP+/pHrodo+ cells. pHrodo gate was determined by using the phagocytosis inhibitor as negative control.

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