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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	Microarray: TMoGene-2_0-st-v1 and Clariom_S_Mouse GeneChip (Affymetrix) and Scanner 3000 (Affymetrix) Confocal: Olympus FV1200 Flow cytometry: LSRII digital flow cytometer (BD) Intravital imaging: Leica SP8 two-photon microscope Cell sorting: FACS Aria Digital Cell Sorter (BD) and MoFlo Astrios EQ from Beckman Coulter qPCR: CFX96 Real-Time PCR machine (Bio-Rad Laboratories)
Data analysis	Microarray: Affymetrix's AGCC software (v4.0) (Affymetrix); Expression Console v1.4.1 (Affymetrix); "R" (http://www.cran.r-project.org) (versions R3.2.0 and R3.3.2); NetAffx Release 35 and Release 36 (Affymetrix); IPA 2015 and 2016 (Ingenuity). Image analysis: Imaris 8.1.2 Flow cytometry: FlowJo software version 9.7.2 Statistical tests: Graphpad Prism 6.0 or Sigma Plot 11.0

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. 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

The microarray .CEL files have been deposited in the NCBI GEO database and are available for download (accession no. GSE108648).

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	For all studies, 1-6 animals per experimental group were used and all experiments were repeated at least 2 times. Sample sizes were determined based on previous studies using this LCMV model.
Data exclusions	Data were not excluded
Replication	Results were reliably reproduced for each experiment. Attempts at replication were successful once the conditions of the experiment were carefully optimized with pilot experiments.
Randomization	For all experiments involving C57BL/6 mice, 6-8 week old male mice were age-matched and randomly assigned to each group. For transgenic mice and imaging experiments, 6-8 week old male or female mice were age- and gender-matched and randomly assigned to each group.
Blinding	There was no blinding in analysis of the experimental data. Blinding was not possible due to the presence of symptoms in infected mice.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	The following antibodies were obtained from BioLegend (BL), BD, or eBioscience (eB), and used at 1.25 µg/ml: IAb/IEb Alexa 647 (M5/114.15.2, BL), IAb/IEb Pacific Blue (M5/114.15.2, BL) or 2.5 µg/ml: CD45 Brilliant Violet 650 (104, BL), CD11b Brilliant Violet 605 (M1/70, BL), CD90.2 (Thy1.2) Brilliant Violet 785 (30-H12, BL), Ly6G Brilliant Violet 711 (RA3-6B2, BL), F4/80 Brilliant Violet 510 (BM8, BL), CD206 Alexa 488 (C068C2, BL), CD206 Alexa 647 (C068C2, BL), CD206 PerCP/Cy7 (C068C2, BL), H-2Db H-2Kb FITC (28-8-6, BL), Ly6C PerCP/Cy5.5 (HK1.4, eB), CD8β.2 PE (53–5.8, BL), Gr1 Alexa647 BD (RB6-8C5) , SIGN-R1 APC (eB), CD80 PE (16-10A1, BL), ICAM Alexa 488 (YN/7.7.4, BL), CD64 Alexa 647 (X54-5/7.1, BL), MERTK PE-Cyanine7 (DS5MMER, eB), CD11c PE-Cyanine7 (N418, BL), CD54 APC (YN1/1.7.4, BL), CD36 Alexa488 (HM36, BL), CD274 biotin (10F.962, BL), IFN-?R biotin (RDI-MCD119-GRBT, Fitzgerald), Streptavidin 647 (BL), SR-A (MRS1, BL), CCR5 Alexa647 (HM-CCR5, BL), TimD4 Alexa647 (RMT4-54, BL), Lyve-1 Alexa488 (ALY7, eB), CD31 Pacific Blue (clone 390; BL), CD31 PE (clone 390; BL) and corresponding isotype controls. For intracellular staining to detect LCMV, we used anti–mouse LCMV (VL-4; Bio X Cell).
Validation	All reagents are commercially available and have been validated by the respective companies as well as in previously published studies. We also evaluated all the antibodies used in this study for the degree of non-specific binding (as measured in samples that do not express the epitope) or by using isotype controls for comparison.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	BHK-21 and Vero cell lines were originally obtained from American Type Culture Collection center (ATCC, Manassas, VA).
Authentication	The cell lines were purchased from ATCC and we did not authenticate them.

Mycoplasma contamination	The cell lines were determined to be free of Mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	None of the misidentified cell lines were used in this study.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	C57BL/6J (B6), B6.129S7-Ifntm1Ts/J (Ifng–/–), B6.129P-Cx3cr1tm1Litt/J (Cx3cr1gfp/gfp), B6.129P2(Cg)-Cx3cr1tm2.1(cre/ERT2)Litt/WganJ (Cx3cr1CreER/CreER), C57BL/6N-Ifngr1tm1.1Rds/J (Ifngr1fl/fl), B6.129P2-Lyz2tm1(cre)Ifo/J (LysMCre/Cre), B6.Cg-Gt(ROSA)26Sortm14(CAG-tdTomato)Hze/J (Stopfl/fl TdTomato) were purchased from The Jackson Laboratory. Cx3cr1gfp/gfp, Ifngr1fl/fl, LysMCre/Cre, Rosa26iDTR, and Stopfl/fl TdTomato were then bred and maintained under specific pathogen free conditions at the National Institute of Health (NIH). B6 DbGP33–41 TCR-tg (P14), actin-TFP1 and actin-OFP1 were also bred and maintained at the NIH. Cx3cr1CreER/+ Stopfl/fl TdTomato, Cx3cr1gfp/+ and OFP+ P14 were derived from the following F1 crosses: Cx3cr1CreER/CreER × Stopfl/fl TdTomato mice, B6 × Cx3cr1gfp/gfp mice and actin-OFP × P14. LysMCre/+ Ifngr1fl/fl mice were obtained in the F2 generation by originally crossing LysMCre/Cre and Ifngr1fl/fl mice. Male and female mice in this study were used at 6-8 weeks of age.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All mice in this study were handled in accordance with the guidelines set forth by the NIH Animal Care and Use Committee and the recommendations in the AAALAC Guide for the Care and Use of Laboratory Animals. The protocol was approved by the NINDS Animal Care and Use Committee.

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

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	Anesthetized mice received an intracardiac perfusion with PBS to remove contaminating erythrocytes. Leukocytes were isolated from the meninges using forceps to gently separate them from the underside of skull cap (the same method used to prepare meningeal whole mounts above). This was followed by enzymatic digestion in RPMI containing 2.5 mg/ml collagenase D (Roche) + 0.1 mg/ml DNase (Roche) for 30 min at 37°C with gentle shaking every 10 minutes. Following digestion, supernatants were isolated, washed, and finally passed through a 35-µm pore cell strainer. After this step, meningeal cells were used for staining. Cells from the brain, however, were resuspended in a 90/60/40% discontinuous Percoll (GE Healthcare) gradient in HBSS and centrifuged to remove myelin and debris from the preparation. Afterwards, brain leukocytes were then stained comparably to meningeal cells.
Instrument	Samples were acquired using an LSRII digital flow cytometer (BD).
Software	Data were analyzed using FlowJo software version 9.7.2 (Tree Star).
Cell population abundance	Purity was >95% as determined by flow-cytometry, using a fraction of the sorted samples.
Gating strategy	MM were gated on FSC-A/SSC-A, FSC-W/FSC-H, SSC-W/SSC-H (to eliminate doublets), LiveDead- CD45+ Thy1.2- CD11b+ Ly6C- Ly6G- F4/80+ CD206+ cells and further divided into MHC II+ and MHC II- cells based on IAb/IEb marker. Monocytes were gated FSC-A/SSC-A, FSC-W/FSC-H, SSC-W/SSC-H (to eliminate doublets), LiveDead- CD45+ Thy1.2- CD11b+ Ly6C + Ly6G-. Neutrophils were gated FSC-A/SSC-A, FSC-W/FSC-H, SSC-W/SSC-H (to eliminate doublets), LiveDead- CD45+ Thy1.2- CD11b+ Ly6C- Ly6G+.

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