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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.

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	FACSDiva (BD Biosciences), Seahorse XF96 Analyzer (Agilent, v 1.4.2)
Data analysis	FlowJo (Treestar Inc., v10), Prism (GraphPad Inc., v5 and v7) and Photoshop (Adobe Inc., v6).

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 are available from the corresponding author upon reasonable request.

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

Life sciences study design

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

Sample size	Sample size was determined using the resource equation method approach.
Data exclusions	No data points were excluded from any results.
Replication	Experiments were repeated at least three times and/or with sufficient cells /animals per group to demonstrate statistical significance.
Randomization	Animals were randomly allocated for infection and treatment groups. Since we used laboratory mice in specific pathogen free-conditions as sources, these animals have similar baseline immune conditions as shown by extensive literature in our field.
Blinding	When measurements involved immediate investigator interpretation (e.g. pain measurement with or without pharmacological treatment), blinding was used.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Antibodies

Antibodies used	Details of all antibodies used are listed in the Supplementary Table 1.
Validation	As indicated in Supplementary Table 1, all antibodies used came from commercial vendors, and we based specificity on their provided description and data sheets.

Animals and other organisms

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

Laboratory animals	We used laboratory mouse (Mus musculus) in this study, from C57BL/6 or BALB/c background, female, between 6-12 weeks of age.
Wild animals	None
Field-collected samples	None

Human research participants

Policy information about studies involving human research participants

Population characteristics	We used peripheral blood-mononuclear cell (PBMC) samples from de-identified adult healthy donors, age 18-60, males and

Population characteristics	females.
Recruitment	Samples were randomly selected from available leukapheresis products

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	A description of the sample preparations for flow cytometry is detailed in the Methods section.
Instrument	We used a LSR Fortessa II flow cytometry machine (BD Biosciences; 5 lasers - blue, red, UV, violet, Yellow-Green; 18 fluorescent parameters). For sorting, we used a FACSAria machine (BD Biosciences).
Software	We used the software FACSDiva (BD Biosciences) to collect the data and the software FlowJo v10 (Treestar Inc.) to analyze the data.
Cell population abundance	After cell sorting, we obtained between 10e5 and 5x10e5 cells from each target population (which were then used for RNA sequencing or "Seahorse" metabolism assays). Post-sort analysis showed >95% purity of target subpopulations.
Gating strategy	For all experiments, we first selected lymphocytes based on FSCxSSC; then, we selected the singlets based on SSC-H x SSC-W; then we selected viable cells based on SSC x Live-Dead gating. After, we selected CD8+ cells based on CD8 x SSC-A, or CD8 x CD4 gating. To select antigen-specific cells we either used congenic CD45 labeling (as determined in Fig. 1b) or we used gp33-tetramer x CD44 gating, selecting the double-positive cells.

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