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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 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	No software was used for data collection.
Data analysis	BIAevaluation was used to analyse SPR results. ImageJ was used to analyse microscopic images. Prism software (GraphPad v6 or v8) was used to conduct all statistical tests. Flow-cytometry data were analysed via FlowJo (v10). Microsoft Excel was used to carry out simple operations.

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 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 main data supporting the results in this study are available within the paper and its Supplementary Information. The raw and analysed datasets generated during the study are too large to be publicly shared, yet they are available for research purposes from the corresponding authors on reasonable request.

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 size was pre-determined from pilot experiments and/or experiments that have been done in the past to obtain statistically significant data. For example, we referred to the paper with doi:10.4049/jimmunol.1101816, which has reported similar experimental procedures.
Data exclusions	No mice were excluded from the study.
Replication	Experiments were repeated at least once, or data were compiled from two independent experiments, unless otherwise stated in the figure legend. Replicates were reproducible.
Randomization	The mice were randomized.
Blinding	Histological evaluation and EAE disease scoring were performed blindly. Other experiments, such as the in vitro experiments and the flow-cytometric analyses, as well as data collection and analyses, were not blinded.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used

For flow cytometry, the following anti-mouse antibodies were used (all at a 1:200 dilution): CD3e (145-2C11, BD Biosciences, cat no 563565), CD4 (RM4-5, BD Biosciences, cat no 612952), CD8 (53–6.7, BD Biosciences, cat no 612759 and cat no 100714), CD45 (30-F11, BD Biosciences, 557659), CD44 (IM7, BD Biosciences, cat no 560570 and 560569), CD62L (MEL-14, BD Biosciences, 553150), F4/80 (T45-2342, BD Biosciences), CD86 (GL1, BD Biosciences, 564199), Gata3 (eBioscience, TWAJ, cat no 25996642), CD25 (Biolegend, PC61 ,cat no 102054), FoxP3 (BD Biosciences, MF23, cat no 560403), CD206 (C068C2, BioLegend, 141706), Ly6G (1A8, BioLegend, cat no 563005), Ly6C (HK1.4, BioLegend, cat no 128005), CD11b (M1/70, BioLegend, cat no 101229), CD11c (HL3, BD Biosciences, 558079), B220 (RA3-6B2, BD Biosciences, 563894), PD-1 (29F.1A12, BD Biosciences, cat no 562671), PD-L1 (MIH5, BioLegend, cat no 12598282), IL-23R (O78-1208, BD Biosciences, cat no 564828), CD11a; integrin aL (HI111, BD Biosciences, cat no 561387), CD18; integrin b2 (M18/2, BD Biosciences, cat no 744599) , CD29; integrin b1 (HMb1-1, BD Biosciences, cat no 17029180), CD49d; integrin a4 (R1-2, BD Biosciences, cat no 11049281), GM-CSF (MP1-22E9, BD Biosciences, cat no 554406), IL-17 (TC11-18H10.1, BD Biosciences, cat no 506939), IFNg (XMG1.2, BD Biosciences, cat no 11731141), TNFa (eBioscience, MP6-XT22, cat no 147321811), RORgt (Q31-378, BD Biosciences, cat no 562682), T-bet (Biolegend, 4B10, cat no 644817), IL-13 (eBioscience, eBio13A, cat no 25713382).

CD31 BUV395 (clone 390, BD Biosciences cat# 740239), gp38 PE-Cy7 (clone 8.1.1, Biolegend Cat# 127412), PNad (Biotinylated, BioLegend, 120803), FcRn (polyclonal, Novus Biologicals, AF6775), F4/80 PE (clone BM8, Biolegend Cat# 123110), CD11c BV421 (clone N418, Biolegend Cat# 117329), CD11b BV786 (clone M1/70, BD Biosciences Cat# 740861), CD146 BV605 (clone ME-9F1, BD Biosciences Cat# 740434). For PNad staining cells were stained with BUV737 streptavidin (BD Biosciences Cat# 612775), and for FcRn staining cells were stained with donkey anti-goat IgG AF647 (Jackson ImmunoResearch Cat# 705-605-147).

For tetramer staining: MOG(35-55) (MBL International, cat no TSM7041), MOG(38-49), NIH Tetramer Core Facility, APC and PE).

For signalling, AlexaFluor 647 anti-pSTAT6 antibody (Clone J71-773.58.11, BD Biosciences, 558241)
Cell viability was determined using the fixable viability dye eFluor 455UV dye (65-0868-14, eBioscience) , Live/Dead Fixable Violet (eBioscience, cat no L34964), or Live/Dead Fixable Aqua (eBioscience, cat no L34957).

For IHC staining of sections, hamster anti-mouse CD3e antibody (clone: 145-2C11, BioLegend, 100301) and rat anti-mouse PNAd (clone: MECA-79, BioLegend, 120801),Alexa Fluor 647 goat anti-hamster (Jackson ImmunoResearch, 127-605-160) and Alexa Fluor 488 donkey anti-rat (Jackson ImmunoResearch, 122-545-167), anti-mouse aMBP, abcam ab40390).

Validation

CD3e, validated for mouse (QC testing) for flow cytometry (routinely tested)
CD4, validated for mouse (QC testing) for flow cytometry (routinely tested)
CD8, validated for mouse (QC testing) for flow cytometry (routinely tested)
CD11a, validated for human, african green, baboon, cattle (bovine, cow), capuchin monkey, chimpanzee, cynomolgus, dog (canine), horse (equine), rabbit (lapine), sheep (ovine), and mouse in laboratory, for flow cytometry
CD11b, validated for mouse, human, cross-reactivity: chimpanzee, baboon, cynomolgus, rhesus, rabbit (lapine) for flow cytometry (quality tested)
CD18, validated for mouse (tested in development) for flow cytometry (qualified)
CD25, validated for mouse for flow cytometry (quality tested)
CD29, validated for mouse, rat for flow cytometry
CD44, validated for mouse (QC testing) for flow cytometry (routinely tested)
CD49d, validated for mouse for flow cytometry
FoxP3, validated for mouse (QC testing) for flow cytometry (routinely tested)
Gata3, validated for human, mouse, pig, rhesus monkey for flow cytometry
GM-CSF, validated for mouse (QC testing) for flow cytometry (routinely tested) and ELISA capture (tested during development)
IFNg, validated for mouse for flow cytometry
IL-13, validated for mouse for flow cytometry
IL-17, validated for mouse for intracellular flow cytometry
IL23R, validated for mouse (QC testing) for flow cytometry (routinely tested)
Ly6C, validated for mouse for flow cytometry (quality tested)
Ly6G, validated for mouse (QC testing) for flow cytometry (routinely tested)
PD-1, validated for mouse (QC testing) for flow cytometry (routinely tested)
PD-L1, validated for mouse, human for flow cytometry
Rorgt, validated for mouse (QC testing) for intracellular flow cytometry (routinely tested)
T-bet, validated for mouse and human for flow cytometry (quality tested)
TNFa, validated for mouse, human for flow cytometry
CD86, validated for mouse (QC testing) for flow cytometry (routinely tested)
CD206, validated for mouse for flow cytometry
CD45, validated for mouse (QC testing) for intracellular flow cytometry (routinely tested)
CD62L, validated for mouse (QC testing) for intracellular flow cytometry (routinely tested)
B220, validated for mouse (QC testing) for intracellular flow cytometry (routinely tested)
CD11c, validated for mouse (QC testing) for intracellular flow cytometry (routinely tested)
CD31, validated for mouse (QC testing) for intracellular flow cytometry (routinely tested)
gp38, validated for mouse (QC testing) for intracellular flow cytometry (routinely tested)
CD146, validated for mouse (QC testing) for intracellular flow cytometry (routinely tested)
CD3e, validated for mouse in IHC and flow cytometry
PNAd, validated for mouse, human for IHC
aMBP, validated for mouse, rat for ICC/IF, WB, IHC-FoFr, IHC-Fr, IHC-P
Goat anti-hamster IgG, validated for hamster with minimal cross-reactivity to bovine, human, mouse, rabbit, rat serum proteins; for IHC
Donkey anti-rat IgG, validated for rate with minimal cross-reactivity to human, bovine, horse, mouse, rabbit serum proteins

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK-293F cells were purchased from Thermo Fisher. The HEK-Blue mTLR4 cell line was purchased from Invivogen. HUVECs were purchased from Lonza.
Authentication	Cell lines were not authenticated.
Mycoplasma contamination	Cells were routinely checked for mycoplasma contamination, and tested negative.
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	8-week-old female C57Bl/6 mice were purchased from Charles River Laboratories, and bred at least for a week at the University of Chicago animal facility before starting the experiments.
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 animal experiments were approved by the University of Chicago's Institutional Animal Care and Use Committee (IACUC).

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	Mice were perfused through the left ventricle of the heart with 10 mL of PBS. The lung lobes were then isolated and digested. Briefly, the spinal cord was collected and then digested in 5 mL DMEM (Gibco) with 2 mg/mL Collagenase D (Sigma), 20 ug/mL DNAse I (Worthington Biochemical) and 1.2 mM CaCl2 for 60 min at 37 C on a shaker for 30 min. After quenching the media with 5 mM EDTA (Gibco), single-cell suspensions were prepared using a 70-um cell strainer (Fisher). Spinal cord, LN and spleen single cell samples were prepared by mashing tissue on the a 70-um cell strainer (Fisher). For spleen samples, red blood cells were lysed with 1 mL ACK lysing buffer (Gibco) for 90 sec and neutralized with 10 mL DMEM media with 5% FBS.
Instrument	Sample collection was done on the BD Fortessa flow cytometer.
Software	FlowJo (v10) was used to analyze flow-cytometry data.
Cell population abundance	Cells were not sorted for any of the experiments.
Gating strategy	The gating strategy is provided in Supplementary Fig. 10.

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