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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	The following software was used for data collection: BD FACSDIVA™ software for FACS, Affymetrix GeneChip Command Console Scan Control software v 4.0.0.1567 for microarray, HiSeq Control Software 2.0.12.0 and RTA version 1.17.21.3 for Sequencing data.
Data analysis	Methods describe the software used to analyze microarray, ATAC-Seq, and scRNA-Seq samples in detail and are publicly available unless otherwise stated. Latent Cellular State Analysis (LCA), a novel clustering algorithm developed in house for analyzing large-scale scRNA-Seq data (manuscript in preparation). Flowjo 9.3.2 or 9.9.6 (Tree Star) for FACS results; GraphPad Prism 6 for statistics.

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

Transcriptome data have been deposited into NCBI GEO (GSE107521).

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 selected to maximize the chance of uncovering mean difference which is also statistically significant.
Data exclusions	No data were excluded.
Replication	Each experiment used a new cohort of mice with very consistent results. All replicates reported in the manuscript are biological replicates. All the statistics reported in the manuscript are based on at least 3 biologically independent replicates.
Randomization	Age- and sex-matched mice were assigned randomly to experimental and control groups.
Blinding	The assessment of EAE scores and histopathology examination was performed in a blinded fashion. Experimental analyses of mouse samples were obtained by automated methods (cell counter, flow cytometer, realtime PCR machine, et al.). Other experimental techniques were not blinded.

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	The following antibodies were used: anti-CD27 (LG.7F9), anti-CD45.2 (104), anti-IFNg (XMG1.2), anti-KLRG1 (2F1), anti-T-bet (eBio4B10) (all from eBioscience); anti-CD43 (activation-glycoform; 1B11), anti-CD44 (IM7), anti-CD45.1 (A20), anti-CD62L (MEL-14), anti-CD127 (A7R34), anti-CCR6 (29-2L17), anti-CXCR3 (CXCR3-173), anti-IL-17 (TC11-18H10.1), anti-Ly6C (HK1.4), anti-PD-1 (29F.1A12), anti-Sca-1 (D7), anti-TCRb (H57-597) (all from Biolegend); anti-CD95 (Jo2), anti-Foxp3 (FJK-16s), anti-RORgt (Q31-378), anti-pSTAT3 (pY705), anti-pSTAT4 (pY693) (all from BD Biosciences); and anti-CD4 (RM4-5) (from SONY), anti-p4E-BP1 T37/46 (236B4), anti-pS6 S235/236 (D57.2.2E), and anti-TCF-1 (C63D9) (from Cell Signaling Technology) (from Methods section).
Validation	Antibodies were validated by the manufacturer and corroborated with previously observed antibody staining results for FACS.

Animals and other organisms

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

Laboratory animals	Mice were housed and bred at the St. Jude Children's Research Hospital animal care facilities in specific pathogen-free conditions. C57BL/6, TCRa−/−, CD45.1+, Il17aCre, Rag1−/− and 2D2-transgenic mice were purchased from the Jackson Laboratory. Rptorfl, Mycfl, and Hmgcrfl mice were as described previously22-24. Cre-expressing mice were used as controls, and littermates were used when possible. Mice were backcrossed for at least 10 generations to the C57BL/6 background strain. Female and male mice were used at 6-10 weeks of age (from Methods section).
Wild animals	No wild animals were used in the study.
Field-collected samples	No field-collected samples were used in the study.

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	Spleens, peripheral draining lymph nodes (dLN), and spinal cord (SC) samples were gently ground under nylon mesh using the flat end of a 3-mL syringes. Red blood cells were removed by ACK lysing buffer, followed by washing cells with isolation buffer. Cells were then filtered, pelleted and stained for FACS.
Instrument	BD LSR II and LSR-Fortessa.
Software	FACSDIVA 7.0+ for sample collection. FlowJo 9.3.2 or higher or FlowJo 10 (Tree Star) for FACS analysis.
Cell population abundance	The purities of the sorted T cells were more than 99%.
Gating strategy	Based on the pattern of FSC-A/SSC-A, cells in the lymphocyte gate were used for analysis of T cell subsets. Singlets were gated according to the pattern of FSC-H vs. FSC-A. Positive populations were determined by the specific antibodies, which were distinct from negative populations. An example gating strategy is shown in supplementary information.

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