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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	FlowJo v9.9 (Mac OS) flow cytometry
Data analysis	Phoenix WinNolin software, version 8.0 for PK analysis, Graphpad Prism V5 for other analyses.

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 authors declare that all data supporting the findings of this study are available within the paper and its Supplementary Information. Source data for the figures and encoding genes are available on figshare at https://figshare.com/s/f14f13bf582ce99165a1.

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

Life sciences study design

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

Sample size	The sample sizes of this study were determined on the basis of similar published studies. For most in vivo studies, the experimental groups have 5 or 6 samples. These sizes ensure a parametric test with 90% power and a significance level of 0.05.
Data exclusions	No data were excluded.
Replication	All data were generated from at least two repeated experiments, except for Figure 3c.
Randomization	All mice/experimental subjects were randomly assigned into experimental groups.
Blinding	During data acquisition, mice were recorded according to their non-descriptive group number, such as A, B, C. The groups were linked to their treatment after data analysis.

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	Capture anti-mouse IFN-γ mAb (clone: R4-6A2) and biotinylated, detection anti-mouse IFN-γ mAb (clone: XMG1.2-Biotin) were purchased from BioLegend, San Diego, CA. Peroxidase-conjugated AffiniPure Donkey Anti-Mouse IgM and Peroxidase AffiniPure Goat Anti-Mouse IgG (H+L) were purchased from Jackson ImmunoResearch Inc. Anti-mouse?CD-3 antibody (clone: 145-2C11) was purchased from BioXCell, West Lebanon, NH. FITC-, PE-, APC- or biotin-conjugated monoclonal antibodies to Foxp3 (clone: MF-14), B220 (clone: RA3-6B2), CD4 (clone: GK1.5), and CD8 (clone: 53-6.7) were purchased from BioLegend, San Diego, CA.
Validation	All antibodies are validated by the commercial source.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Cell lines were purchased from ATCC.
Authentication	Cell lines were verified: EL4 cells (surface marker, morphology), B16-F10 (morphology, in vivo growth). We specifically verified the PD-1 expression of these cell lines.
Mycoplasma contamination	Cell lines were tested for mycoplasma contamination and found to be negative of 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	NOD/ShiLt: Ten-to-eighteeen-week-old female (from the Jackson Laboratory and from in-house breeding). Specific ages indicated in the manucript. C57BL/6: Ten-week-old female (from Charles River).

Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	Animal studies were conducted following a protocol approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Utah. The group sizes of mice were determined and approved by the regulatory authorities for animal welfare after a balanced consideration of statistical and scientific needs and ethical aspects. All procedures related to animal studies are in compliance with relevant ethical regulations on animal research at the University of Utah.

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	Please refer to the Methods section for details.
Instrument	BD FACSCanto Analyzer
Software	FlowJo v9.9 (Mac OS)
Cell population abundance	Cell populations were identified by their protein marker after the cells were stained with labelled antibodies.
Gating strategy	Cells were gated either against prepared negative samples (isotype control, no antibody staining) or the self-control negative populations. Supplementary Fig. 5 is one example.

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