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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	EchMRI-TM-130 Analyzer was used to record body composition data acquired using EchoMRI-TM-100H. MRI Analysis was done using a multi spin echo (MSME) sequence (repetition time[TR]= 500 ms, echo time[TE]=7.86 ms, averages =4) with and without fat suppression (fat suppression bandwidth=1401.17 Hz). BD FACS Diva 8.0.1 was used for data collection during flow cytometry analysis.
Data analysis	Graph design and statistical analysis was performed using GraphPad Prism V7.0. Postprocessing of MRI data was performed using ParaVision V6 Quantitative analysis of adipose tissue H/E staining was performed using ImageJ-Adiposoft plugin V1.15. Immunohistochemistry stained sections were scanned using Pannoramic 250 FLAH II (3DHISTECH) Digital Slide Scanner. The images were then analyzed using Cell Profiler V3.0. For flow cytometry data analysis we used FlowJo V10.4.2. For RNA-sequencing data was quinfified and analyzed using the TopHat2 (v2.0.10). Cufflinks (v2.2.1), Cuffdiff (v2.2.1) and the Cuffmerge pipeline. Enrichment analysis was performed with Cytoscape ClueGO 82 (v2.3.3).

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

Accession number for the row data of the RNAseq: GSE118819.

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	All experiments described in this study were done using a sample size varying between n=3-5 as indicated in figure legends.
Data exclusions	No data was excluded from the analysis.
Replication	All data shown are either representative or pooled data from at least two successful independent experiments. In the case of RNA-sequencing data and histology (H/E data and immunofluorescent data), a single experiment was performed, quality control measures were taken to insure the validity of the experiment, this include measurement of viral load and body weight of LCMV-infected mice.
Randomization	age- and sex-matched mice were randomly assigned to the experimental groups prior to the start of the experiment.
Blinding	*Describe whether the investigators were blinded to group allocation during data collection and/or analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.*

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

Rat IgG1 isptype, clone: MOPC-21 (0.5mg) BioXcell BE0083
Hamster IgG1 isotype, clone: N/A (0.2mg) BioXcell BE0091
Rat IgG1 anti-TNFα, clone: XT3.11 (0.5mg) BioXcell BE0058
Rat IgG1 anti-IFNγ, clone: XMG1.2 (0.5mg) BioXcell BE0055
Hamster IgG1 anti-IL1α, clone: ALF-161 (0.2mg) BioXcell BE0243
Rat IgG1 anti-IL6, clone: MP5-20F3 (0.5mg) BioXcell BE0046
Rat IgG2b anti-CD4, clone:YTS191 (0.2mg) BioXcell BE0119
Rat IgG2b anti-CD8, clone: YTS169.4 (0.2mg) BioXcell BE0117
Rat IgG2b anti-CD90, clone: T24 (200µg) BioXcell BE0212
Rat anti-CD16/CD32, clone: 93 (1:200) eBioscience #14-0161-82
Anti-mouse CD8b.2 Pacific Blue, clone: 53-5.8 (1:200) Biolegend #140414
Anti-mouse CD8a PE-Cy7, clone: 53-6.7 (1:200) Biolegend #100721

Anti-mouse CD8a PerCP-Cy5, clone:53-6.7 (1:200) Biolegend #100733
Anti-mouse CD8a FITC , clone: 53-6.7 (1:200) Biolegend #100803
Anti-mouse CD8a AF700, clone: 53-6.7 (1:200) Biolegend #100729
Anti-mouse CD4 Pacific Blue, clone: RM4-4 (1:200) Biolegend #116007
Anti-mouse CD3 APC, clone: 17A2 (1:200) Biolegend #100235
Anti-mouse CD3 PE-Cy7, clone: 145-2C11 (1:200) Biolegend #100319
Anti-mouse CD45.1 Pacific Blue, clone: A20 (1:200) Biolegend #110721
Anti-mouse CD45.1PE-Cy7, clone:A20 (1:200) Biolegend #110729
Anti-mouse CD45.2 PE, clone 104 (1:200) Biolegend #109807
Anti-mouse CD45.2 APC, clone:104 (1:200) Biolegend #109813
Anti-mouse CD44 BV605, clone: IM7 (1:200) Biolegend #103047
Anti-ATGL, (1:1000) Cell Signaling #2138S
Anti-HSL, (1:1000) Cell Signaling #4107S
Anti-phospho HSL Ser660, (1:1000) Cell Signaling #4126S
Anti-D418-Perlipin, (1:1000) Cell Signaling #3470S
Anti-β-Actin, (1:1000) Abcam ab8224
HRP-conjugated anti-rabbit antibody, (1:4000) Dako P0448
Rat anti-mIFN-α capture antibody, (1:54) PBL Interferon Source 22100-1
Rabbit anti-mIFN-α detection antibody, (1:738) PBL Interferon Source 32100-1
Anti-rabbit HRP secondary antibody, (1:5000) Jackson ImmunoResearch 711-036-152
Rat anti-mIFN-β capture antibody, (1:1000) PBL Interferon Source 22400-1
Rabbit anti-mIFN-β detection antibody, (1:1000) PBL Interferon Source 32400-1
Rat anti-CD8a Alexa Fluor 647, clone:4SM15 (1:1000) eBioscience #4SM15
Alexa Fluor 488 anti-LCMV_NP, (1:4000)

Validation

All antibodies were validated as per manufacturer instruction. For FACS antibodies unstained samples were included in every run, to control for auto-fluorescence. The LCMV_NP Alexa Fluor antibody has been previously validation in Kosak et al. Sci Rep. 2017 Sep 12;7(1):11289. DOI: 10.1038/s41598-017-10637-y

Animals and other organisms

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

Laboratory animals

Mouse: C57BL/6, The Jackson Laboratory JAX: 000664
Mouse: Ifnγ-/-:B6.129S7-Ifngr1tm1Agt/J, The Jackson Laboratory JAX: 003288
Mouse: Tnf-/-: B6.129S-Tnftm1gkl/J, The Jackson Laboratory JAX: 005540
Mouse: TnfrI-/-: C57BL/6- Tnfrsf1atm1/mx/J, The Jackson Laboratory JAX: 003242
Mouse: Ifnar1-/-: B6.129S2-Ifnar1tm1Agt/Mmjax, The Jackson Laboratory JAX: 032045
Mouse: Ifnar1fl/fl: B6(Cg)-Ifnar1tm1.1Ees/J, The Jackson Laboratory JAX: 028256
Mouse: AdipoqCre/+: B6;FVB-Tg(Adipoq-cre)1Evdr/J, The Jackson Laboratory JAX: 010803
Mouse: Atglfl/fl: B6N.129S-Pnpla2tm1Eek/J, The Jackson Laboratory JAX: 024278
Mouse: Hslfl/fl: B6.129P2-Lipetm1Rze/J, Laboratory of Rudolf Zechner, Graz, Austria. N/A
Mouse: Cd4Cre/+: STOCK Tg(Cd4-cre)1Cwi/BfluJ, The Jackson Laboratory JAX: 017336
Mouse: Ob/Ob: B6.Cg-Lepob/J, The Jackson Laboratory JAX: 000632
Mouse: Cd45.1, Ly5a, PtprcSJL Komuro et al., 1974 MGI:4819849
Mouse: Cd8-/-: B6.129S2-Cd8atm1Mak/J, The Jackson Laboratory JAX: 002665
Mouse: Rag2-/-: B6(Cg)-Rag2tm1.1Cgn/J, The Jackson Laboratory JAX: 008449
Mouse: OT-I Rag1-/- CD45.1: C57BL/6-Tg(Tcratcrb)1100Mjb/J, B6.129S7-Rag1tm1Mom/J, The Jackson Laboratory JAX: 003831, 002216
Mouse: Prf1-/-: CD57BL/6-Prf1tm1Sdz/J, The Jackson Laboratory JAX: 002407

All animals within each experiment were age- and sex-matched. Animals were 8-12 weeks old by the start of the experiment. Between different experiments males and females were used interchangeably, as no sex-specific differences were observed in relevant parameters.

Wild animals

The study did not involve wild animals.

Field-collected samples

The study did not involve field-collected samples.

Ethics oversight

Ethical approval was obtained from the Department of Biomedical Research of the Medical University of Vienna, Vienna, Austria, as well as the Central Facility for Animal Research and Scientific Animal Welfare (ZETT) in Dusseldorf, Germany, the state of Beden-Wurttemberg, Germany, and the Institutional Animal Case and Use Committees of the Institute of Systems Biology in Seattle.

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	For flow cytometry analysis samples were obtained from either blood, spleen or inguinal lymph nodes. Blood samples were collected in MEM-1000UHeparin, then treated with RBC lysis buffer. Spleens and lymph nodes were collected in PBS-2%FCS on ice, then mechanically distrupted against 40-70µm cell trainers.
Instrument	Flow cytometry data was collected using LSRFortessa.
Software	BD FACS Diva 8.0.1 was used for data collection. For data analysis we used FlowJo V10.4.2.
Cell population abundance	No cell sorting was performed in this study.
Gating strategy	Among live, single cells: CD4 T cells were gated as: CD3+CD8+ CD8 T cells were gated as: CD3+CD8+ or CD44+ CD8+ Virus-specific CD8 T cells were gated as: CD3+ CD8+ and either GP33+ or NP396+ For Chimeric mice: endogenous CD8 T cells were gated as: CD45.2+CD8+ the transferred CD8 T cells were gated as CD45.1+CD8+

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