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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	Step-OnePlus Real-Time PCR Software v2.3; Gen5 1.11; Wave Desktop Software 2.6.1.; CytExpert 2.3; FSX-BSW(02.02); GitHub (https://github.com/menchelab/Marco)
Data analysis	Microsoft Excel for Mac 16.41 and Microsoft Excel 2013; TraceFinder 4.1 software; FlowJo 10; CytExpert 2.3; Prism 8; Adobe Illustrator CS6; Adobe Photoshop CS6; Python v. 3.7.2; SciPy v. 1.2.0; Circos v. 0.69-3; numpy v. 1.16.0; pandas v. 0.24.0; sklearn v. 0.20.3; matplotlib v. 3.0.2; statsmodels v. 0.10.1; seaborn v. 0.9.0

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 data that support the findings of this study are available from the corresponding authors upon reasonable request. Lipidomics raw data is available on GitHub (https://github.com/menchelab/Marco). Data that support the findings of this study are available in Gene Expression Omnibus (GEO) under accession number GSE8831.

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 calculations were based on effect size with a power=0.8 and alpha level=0.05 and were based on previous experience. Sample sizes for animal experiments was approved by the local ethics committee. Please see Frommlet & Heinze, 2020 (https://doi.org/10.1177/0023677220907617).
Data exclusions	No data except statistical significant outliers were excluded in this study. Statistical outliers have been excluded based on alpha=0.05 on Prism 8 software using Grubbs' Outlier Test (GraphPad, La Jolla, CA). No other exclusion criteria were established or applied.
Replication	All experiments were performed at least two times and represent reproducible findings, except stated otherwise. If possible, we usually use at least three independent biological replicates. Lipidomics data represent single experiments using biological replicates, showed low sample variation and were verified using complementary in vitro approaches.
Randomization	Mice were grouped randomly per cage.
Blinding	Steatosis scores were recorded by a blinded, experienced pathologist. For most other experiments the investigators were not blinded to group allocations.

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	The following antibodies were used: CD45.2-BV650 (Clone 104, BioLegend #109836, 1:100), CD45-V500 (Clone 30-F11, BD Horizon #561487, 1:100), F4/80-BV605 (Clone BM8, BioLegend #123133, 1:80), F4/80-FITC (Clone BM8, BioLegend #123108, 1:100), CD11b-PeCy7 (Clone M1/70, eBioscience #25-0112, 1:500), CD11b-PB (Clone M1/70, Invitrogen #RM2828, 1:100), CD11c-APC-eF780 (Clone N418, eBioscience #47-0114, 1:100), CD11c-PC5.5 (Clone N418, eBioscience #35-0114-82, 1:80), CD206-AF700 (Clone C068C2, BioLegend #141733, 1:200), CD206-PE (Clone C068C2, BioLegend #141705, 1:100), MARCO-APC (Clone 579511, R&D #FAB2956A, 1:25), MARCO-PE (Clone ED31, Invitrogen #15225929, 1:50), CD9-PE (Clone MZ3, BioLegend #124805, 1:200), TREM2-PE (Clone 237920, R&D #FAB17291P, 1:15), Ly6G-AF700 (Clone 1A8, BioLegend #127622, 1:200), Ly6C-BV605 (Clone HK1.4, BioLegend #128035, 1:80), Ly6C-PE/Cy7 (Clone HK1.4, BioLegend #128017, 1:100), B220-PE-Cy5 (Clone RA3-6B2, Tonbo #55-0452, 1:80), CD3-PerCP-Cy5.5 (Clone 145-2C11, Tonbo #65-0031, 1:80), CD3-APC (Clone 17A2, eBioscience #17-0032-82, 1:160), CD19-BV605 (Clone 6D5, BioLegend #115540, 1:200), CD4-AF700 (Clone RM4-5, eBioscience #56-0042-82, 1:100), CD8-Pe/Cy7 (Clone 53-6.7, BioLegend #100721, 1:200). Intracellular staining was performed by using the fixation and permeabilization buffer set (eBioscience #88-8824-00) or True-Phos Buffer Set (Biolegend #425401) according to the manufacturer's instruction and included p-AKT-APC (Clone SDRNR, eBioscience #17-9715-42, 1:50) and PTEN-BV421 (Clone A2B1, BD #566637, 1:30) or isotype controls mouse IgG2a-APC (Clone eBM2a, eBioscience #17-4724-81, 1:50) and mouse IgG1k-BV421 (Clone X40, BD #562438, 1:30).
Validation	All antibody are commercially available and their validation statements are available on the manufacturer's website. All antibodies were validated as per manufacturer instruction. For FACS antibodies unstained control, single stainings and fluorescent minus one stainings were included to control for auto-fluorescence and over- or undercompensation.

Animals and other organisms

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

Laboratory animals	Mice were bred and housed in pathogen-free facilities at the Medical University of Vienna and were kept in a 12 hour light cycle, 21-23°C temperature and 45-65% humidity in cages with maximum 4 male and 5 female animals per cage. Wildtypes were on the C57BL/6J background and purchased from Charles River Laboratories (JAX™ Mice Strain, Code #632). PtenloxP/loxPLysMCre +/- (MGI ID 2182005 and 1934631, PtenDmyel) mice were backcrossed to a C57BL/6J background for at least eight generations. For deletion efficiency experiments, PtenDmyel were further crossed to R26tdTomato mice (C57BL/6J background, MGI ID 3813512), which were a kind gift from Christoph Österreicher. PtenTg/+ mice (MGI ID 5645732) on a C57BL6/CBA background were supplied by the M. Serrano Lab and bred with C57BL/6J females (at least for 5 generations). Resulting male 8-12 week old mice were used as donors for bone marrow transplantations. Marco-/- mice (C57BL/6 background, MGI: 1309998) were backcrossed for at least 5 generation to a C57BL/6J background and were a kind gift from K. Tryggvason. PtenDmyel and Marco-/- were in house inter-crossed to generate Pten and Marco double deficient mice (PtenDmyelMarco-/-). Nrf2-/- mice (C57BL/6 background, Riken BRC #RBRC01390) were kindly provided by Masayuki Yamamoto and Florian Gruber. Ccr2gfp/gfp mice were bought from the Jackson Laboratories (#027619). PI3KgKD/KD (C57BL/6J background, MGI ID 3051886) mice were kindly provided by Emilio Hirsch. Akt1loxP/loxPAkt2loxP/loxPLysMCre+/- mice (C57BL/6J background, Jackson Laboratory #026474 #026475) were a kind gift from Christos Tsatsanis. Eight to twelve weeks old sex and age-matched littermates were used for in vitro approaches. For in vivo experiments male, eight to twelve weeks old, age-matched mice and their respective littermate controls were used unless otherwise stated. Mice were maintained on a normal chow diet (#V1536 Ssniff). Dietary interventions commenced at 6 weeks of age using a diet that contained 60% calories from fat (Research Diets, #D12492) or in the case of normal diet studies, mice were maintained on the chow diet (Ssniff #V1536).
Wild animals	No wild animals were used in this study.
Field-collected samples	No field collected samples were used in this study.
Ethics oversight	All experimental procedures were approved by the Austrian Ministry of Sciences under the project numbers 66.009/0066-WF/V/3b/2016, 66.009/0097-WF/V/3b/2017, 66.009/0377-V/3b/2019 and 66.009/0264-V/3b/2019 and were conducted in strict accordance with Austrian law. Animal experiments performed in Australia were granted permission under project number 17-04 at the Garvan and St. Vincent's Ethics Committee, NSW, Australia.

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	Regarding peritoneal macrophage isolation, animals were sacrificed by cervical dislocation and their peritoneal cavity was flushed with sterile 1x PBS. Cells were plated, washed after 3 hours and supplemented with complete RPMI medium. On the following day, cells were stimulated as indicated. For flow cytometry, cells were detached using Enzyme Free (Milipore #S-014-B) and subsequently stained. Regarding immune cell isolation, epididymal fat pads were harvested from indicated animals, cut into small pieces and washed twice with DMEM:F12 media (Gibco, #11320-074) followed by centrifugation for 8 min at 1,800 rpm at room temperature. Digestion was carried out in 10 mL of freshly prepared collagenase II solution (1 mg/mL in 1.5% sterile BSA, in DMEM:F12) at 37° C for 1 hour. Subsequently, 100 µL of 0.5M EDTA was added and the digested adipose-enzyme solution was filtered through a 100 µm strainer into 20 mL DMEM:F12 media supplemented with 10% FBS and centrifuged as previously. Post centrifugation, the pellet was washed twice and resuspended in 1 mL of erythrocyte lysis buffer (Qiagen #79217) for 5 min, after which 12 mL of media was added. The resulting cell suspension was counted, centrifuged and further stained for flow cytometric analysis. For cell sorting, murine ATMs were filtered through a 40 µM cell strainer and sorted as live, CD45+CD3-CD11b+F4/80+CD11c+CD206 +/- on a FACSAria™ II flow cytometer (BD). Isolation of liver mononuclear cells was performed as previously described. Briefly, via the portal vein, livers were perfused with HBSS, cut into small pieces and digested in RPMI containing 0.05% collagenase/dispase (Roche #10269638001) and 0.01% trypsin inhibitor (Thermo Fisher Scientific #17075029) for 1 hr at 37°C. The resulting liver suspension was passed through a 40 µm cell strainer, centrifuged at 800 g (10 min, 4°C) and the cell pellet was resuspended in 10 ml RPMI. Cell suspensions were overlayed onto 15 ml of 33% (Vol/Vol) Percoll solution (Sigma-Aldrich #P1644) and centrifuged for 30 min at room temperature with no brake. The supernatant was removed and erythrocytes were lysed by resuspending the pellet in 2 ml of red blood cell lysis buffer for 4 min, after which 8 ml of RPMI was added. Cell suspensions were spun at 800 g (5-10 min, 4°C), supernatant removed and the cells were washed twice with 10 ml RPMI. Cells were subsequently resuspended in PBS/2%FBS and total cell numbers per liver were enumerated using a haemocytometer (Turck chamber) before staining for flow cytometry. For flow cytometric analysis of blood monocytes, EDTA-blood was stained with antibodies and subsequently fixed with 2% PFA

	for 15 min. The cell suspension was further subjected to red blood cell lysis prior to processing for intracellular staining or flow cytometric analysis.
Instrument	CytoFLEX S Flow Cytometry (Beckman Coulter), FACSAria™ II flow cytometer (BD)
Software	CytExpert (Version 2.0) and FlowJo (Version 10, LLC) software
Cell population abundance	Post peritoneal macrophage detachment, a minimum of 10,000 live macrophages were recorded per sample. Post sample harvest from tissue and blood, a minimum 50,000 live immune cells were recorded per sample.
Gating strategy	Cells were gated on FSC-A/SSC-A. Where appropriate, cells were gated on live using fixable viability dye (Invitrogen #65-0865-14). A detailed gating strategy is provided in Extended Data Fig. 4a-c.

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