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Last updated by author(s): Sep 1, 2020

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	Microsoft Excel 2010
Data analysis	Microsoft Excel 2010 and GraphPad Prism 6, Flow cytometry analysis was done using FlowJ0 (FlowJ0, LLC).

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

There is no accession code to be displayed.The data that supports the findings of this study are available from corresponding author upon reasonable request. Source data are available online.

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	Sample sizes were determined based on preliminary studies, our previous publications and publications in the literature that support the samples size of our studies. Sample size of different studies were determined based on specifics of each experiments.
Data exclusions	No data were excluded
Replication	All experiments presented in our manuscript were replicated. In addition, several experiments were further comfiremd using alternative techniques and approaches.
Randomization	In all animal studies groups were randomized.
Blinding	When appropriate investigators were blinded to samples measured

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	TNF alpha (R&D Systems - MAB4101), IL6 (R&D Systems - AB-406-NA), NIMR-5 (Novus Biologicals - NBP1-27951), Isatuximab (TeneoBio, not commercially available from this source), UniAb clone ID 337468 (TeneoBio - not commercially available), UniAb clone ID 337469 (TeneoBio - not commercially available), OKT3 (Acro Biosystems - CDE-M5256), human CD38 (Abcam - ab108403 and Novus Biologicals - NBP1-95323), mouse CD38 (R&D Systems - AF4947), Slc12a8 (Aviva Systems Biology - ARP44039), Actin (Cell Signaling Technology - 8457), Tubulin (Abcam - ab15568), ORF1p (Abcam - ab216324), IL6 (Cell Signaling Technology - 12912), Lamin B1 AF488 (Santa Cruz - sc37415), CD38 AF647 (BD Biosciences - 562769), CD45 FITC (BD Biosciences - 553080), Ter119 APC-Cy7 (BD Biosciences - 560509), CD45 BV786 (BD Biosciences - 564225), B220 PE-Cy7 (BD Biosciences - 552772), CD19 PE-Cy7 (BD Biosciences - 552854), CD19 BUV395 (BD Biosciences - 563557), CD3 BUV395 (BD Biosciences - 563565), CD3 PerCP-EF710 (Invitrogen - 46-0033-82), CD4 BV650 (BD Biosciences - 563747), CD8 BB515 (BD Biosciences - 564422), CD11c PE-CF594 (BD Biosciences - 562454), CD11b BV711 (BD Biosciences - 563168), Ly6G FITC (BioLegend - 127606), NK1.1 APC (BioLegend - 108710), F4/80 BV510 (BioLegend - 123135), Ly6c AF700 (BioLegend - 128024), CD43 BV510 (BD Biosciences - 563206), CD38 PE (BioLegend - 102708 and Miltenyi Biotec - 130-102-607), CD31 VioBright 515 (Miltenyi Biotec - 130-110-306), CD45 BV785 (BioLegend - 103149)
Validation	New antibodies developed for these studies were extensively validated in our manuscript both in vitro and in vivo. Commercially available antibodies were validated by manufacturer. However, in many cases these antibodies were also validated in our laboratory by the use of positive and negative controls. In particular, antibodies for flow cytometry were validated before each experiment.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	The cells lines HEK293T, AML12, CHO cells, and HUVEC were from ATCC, these cells were validated by the company.
Authentication	For HEK293T, AML12, CHO, and HUVEC, authentications were performed by ATCC. Bone marrow derived macrophages were isolated using standard protocols and validated by the use of specific macrophage markers of the M0, M1 and M2 phenotype. Mouse pre-adipocytes were isolated using standard published protocols and validated by their capacity to differentiate into adipocytes. Mouse splenic CD49b NK cells, CD11b microglia, CD4+ T cells, and CD8+ T cells obtained from C&M LABPRO were isolated via

	specific immunomagnetic cell sorting methods with an AutoMACS system, and fully validated by flow cytometry for purity and the presence of cell type-specific markers in a report provided by the company.
Mycoplasma contamination	None of the cells used had mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	None of the cells used were on the list of misidentified lines.

Animals and other organisms

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

Laboratory animals	Experiments were performed using the following mouse lines: C57BL/6 Wild type, CD38 KO, CD38 CI, and INK-ATTAC mice. Male and female mice were used for experiments.
Wild animals	Did not involve wild animals
Field-collected samples	All samples were collected after animals were sacrificed according to IACUC guidelines. No field collected samples were collected.
Ethics oversight	All protocols requiring use of animals were approved by the Mayo Clinic Institutional Animal Care and Use Committee (IACUC) and studies were conducted in adherence to the NIH Guide for the Care and Use of Laboratory Animals.

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	1) For liver analysis, tissue was minced with scissors and digested with liberase (Sigma) at 37° C for 15 minutes to make single cell suspensions. Cells were incubated with FC-receptor block (Miltenyi), and stained with antibodies for 45 min at 4° C. Live dead exclusion was done with Near IR live dead dye. 2) For WAT tissue, single cell suspension was prepared by mincing the tissue with scissors followed by 0.1% w/v collagenase II digestion (Gibco) at 37 °C for 60 minutes. The digested tissue was filtered through a 70 µm cell strainer. The RBCs were lysed with ACK lysis buffer (Gibco).The cells were then blocked with FcR blocking reagent (Miltenyi Biotec) in staining buffer for 10 minutes on ice. Cells were then stained with specific antibodies. Live dead exclusion was done either with Propidium iodide or Near IR live dead dye. 3) To isolate splenocytes, the spleen was placed on the 70µm cell strainer held on a 50 mL falcon. Using the plunger end of the syringe, spleen was gently pressed through the cell strainer and was rinsed with RPMI media. Cells were centrifuged at 350g for 5 minutes. After supernatant aspiration, cells were suspended in ACK lysis buffer for 5 minutes and then 15 mL PBS was added. Cells were centrifuged at 350g for 5 minutes. 4) For single cell isolation from jejunum, the tissue was first minced and then digested in 20 mL RPMI complete media containing enzyme cocktail of collagenase type 4 (0.6 mg/mL), DNase (9 U/mL) and hyaluronidase (0.06 mg/mL) for 25 minutes at 37° C with 250 rpm. The digested tissue was passed through the 100 µm cell strainer. The flow through was centrifuged for 7 minutes at 1600 rpm and pellet was collected and kept on ice. The remaining tissue on the cell strainer was digested again as described earlier. The two pellets were pooled together and the percoll gradient separation was performed using 44 % and 67% percoll to isolate the immune cells. The single cells suspension from spleen and gut was then stained with live dead dye. Following live dead staining, cells were incubated with FcR block for 10 minutes on ice. Next, cells were stained with specific markers in cell staining buffer for 1 hour on ice. The cells were fixed with 2% paraformaldehyde and samples were run on LSR II.
Instrument	MACSQuant Analyzer 10 (Miltenyi Biotec) and LSR-II (BD Biosciences)
Software	FlowJo (FlowJo, LLC)
Cell population abundance	N/A; cell population abundance is not applicable, as no flow-cytometric cell sorting was performed in the course of these studies.
Gating strategy	For liver, erythrocytes (Ter119) and dead cells were excluded, live/dead discrimination was determined using the amine reactive dye. CD38+ cells were then gated followed by exclusion of doublets (FSC-H vs. FSC-A) and debris (SSC-A vs. FSC-A). Remaining population was gated for pan-lymphocyte marker CD45 (BV786). T-cells were gated as CD19- B220- CD3+ followed by CD4 and CD8 respectively. Granulocytes were gated as CD45+ Ly6G+ while NK cells were NK1.1+ Dendritic cells were gated as CD45+ CD11bneg CD11chi and monocytes as CD11b+. Monocytes were further studied as Classical Ly6chiCD43neg and non-classical as CD43+ Ly6clo-neg. Tissue-resident macrophages are gated as CD11blo F4/80+ and monocyte-derived (or M1) as CD11b+ F4/80+

Ly6chi.
For WAT tissue, After gating on FSCxSSC, single cells were gated followed by live dead exclusion gates. The CD38+ cells were gated on live cells followed by CD45+ or CD45-. For 22 months, Cd45-and Cd45+ population was gated on after live dead exclusion. Then CD38+ population was gated on CD45+ population. F4/80+ was gated on CD45+ and then Cd38+ population was gated on CD45+F4/80+ population.
For gut and spleen samples, single cells were gated on the FSCxSSC gate. The live/dead cells were gated on the single cells gate and then CD38+ cells were gated on live cells gate.

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