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Reporting Summary

Nature Portfolio 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 Portfolio policies, see our Editorial Policies 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	Flow cytometry data were collected using DIVA (Becton Dickinson) software.
Data analysis	Image lab (Bio-Rad. version 6.1) was used for quantification of of Western blot. FlowJo (Tree Star, Inc.) was used for analysis of flow cytometry data. Statistical analyses were performed using GraphPad Prism 7 software (GraphPad Software, Inc.).

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The authors declare that the data supporting the findings of this study are available within the paper and the Supplementary Information files. The raw data that support the findings of this study are available as source data files.

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	No statistical method was used to predetermine sample size. The sample size for the in vivo MaR2 treatment was chosen based on our previous experience with similar in vivo experiments for other lipid mediators (PMID: 31353262 and PMID: 28346411).
Data exclusions	Statistical outliers were determined by the Grubb's test.
Replication	Most of experiments were replicated at least two times. n values for replicates are reported throughout the manuscript. Experiments in Figure1a-g, Fig2b,d,f,h, and Extended Fig2a,b,d were replicated twice or more than twice independently. All the attempts got similar trend.
Randomization	The experiments were not randomized. Animals were randomly assigned to different groups, to have the same average body weight in each group.
Blinding	Although the primary investigators were not blinded for most of the studies, some of the sample analyses (such as measurement of blood parameters) were performed in different labs or facilities where the researchers were not informed of the grouping during the analyses.

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 and archaeology
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

The antibodies used are listed in Supplementary Table 2.
Purified CD16/32, Biolegend, 101302, 93, B288201, 1/100.
FITC CD11c, Biolegend, 117306, N418, B277030, 1/200.
FITC Armenian hamster IgG, Biolegend, 400605, HTK888, B275653, 1/200.
BV785 CD45, Biolegend, 103149, 30-F11, B255080, 1/200.
PE CD45, Biolegend, 103105, 30-F11, B194415, 1/400.
APC/Fire750 CD11b, Biolegend, 101261, M1/70, B262766, 1/400.
BV421 CD206, Biolegend, 141717, C068C2, B266521, 1/100.
BV421 rat IgG2a, Biolegend, 400535, RTK2758, B259985, 1/100.
BV711 F4/80, Biolegend, 123147, BM8, B261358, 1/200.
TruStain FcXTM PLUS - CD16/32, Biolegend, 156604, S17011E, B330293 1/100.
APC R700 CD45, BD Bioscience, 565478, 30-F11, 1069323, 1/100.
BV605 CD11b, Biolegend, 101257, M1/70, B316880, 1/150.
APC F4/80, Biolegend, 123116, BM8, B298926, 1/150.
BV785 Ly6C, Biolegend, 128041, HK1.4, B325962, 1/100.
BUV496 CCR2, BD Bioscience, 750043, 475301, 1293620, 1/100.
PerCP Cy5.5 MHCII Biolegend 107626 M5/114.15.2 B336919 1/100
PE VSIG4, eBioscience, 12-5752-82, NLA14, 2293904, 1/150.
BUV395 TIM4, BD Bioscience, 742779, 21H12, 1296227, 1/150.
AF488 TREM2, R&D Systems, FAB17291G, 237920, AFGM0320081, 1/100.
AF488 rat IgG2B, R&D Systems, IC013G, 141945, ABWA0420041, 1/100.

12-LOX, Santa cruz, sc-365194, n/a, F0711, 1/2000.
sEH, UC Davis, n/a, n/a, n/a, 1/15000.
Vinculin, Santa cruz, sc-25336, HRP, n/a, G1118, 1/2000.

Validation

All antibodies used in this study were validated by the manufacturer by applications listed in the Supplementary Antibody table. The anti-sEH antibody was validated in the laboratory of Dr. Bruce Hammock at UC-Davis (e.g., PMID: 32786492)

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Immortalized mouse brown preadipocytes (WT-1) were derived from the stromal vascular fraction (SVF) of interscapular brown adipose tissue of newborn mice. The SVF cells were immortalized by SV40 T overexpression as described in PMID: 11113206 and PMID: 18719589.
Immortalized human brown brown preadipocytes (A41 hBAT-SVF) were derived from the SVF of deep neck fat collected from a human subject. The SVF cells were immortalized by hTert overexpression as described in PMID: 26076036 and PMID: 28469146.
Primary rat Kupffer cells isolated from male 35-week-old Sprague-Dawley rats Primary rat Kupffer cells isolated from male 35-week-old Sprague-Dawley rats (ThermoFisher, Cat#RTKCCS, Lot # RCC138)

Authentication

The immortalized mouse brown preadipocytes (WT-1) have been deposited to Millipore Sigma and were authenticated by Millipore Sigma (#SCC255)
The immortalized human brown preadipocytes (A41 hBAT-SVF) have been deposited to ATCC and were authenticated by ATCC (#CRL-3385).

Mycoplasma contamination

All the cell lines were routinely tested negative for mycoplasma contamination.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell line was used.

Animals and other organisms

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

Laboratory animals

Mus musculus (C57BL6/J, 6-week-old male and female, 12-week-old male, Stock no. 000664), UCP1-CRE strain (10-week-old, male and female, Stock no. 024670) and homozygous Rosa26-floxed STOP-Cas9 knockin mice (10-week-old male and female, Stock no. 024857) were purchased from the the Jackson Laboratories.
We purchased the primary rat Kupffer cells (originally isolated from male 35-week-old Sprague-Dawley) from ThermoFisher. Thus, we did not directly use the Sprague-Dawley rats.

Wild animals

Study did not include wild animals.

Field-collected samples

Study did not involve samples collected from the field.

Ethics oversight

All animal procedures were approved by the Institutional Animal Care and Use Committee at Joslin Diabetes Center.

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

Single cells of SVF fraction in BAT, pgWAT or ing WAT were isolated by enzymatic digestion with 1.5mg/ml of collagenase I, followed by filtration. Single cells from the liver were isolated by enzymic digestion with 1.5 mg/ml of collagenase I, followed by filtration. Cells were previously blocked with purified anti-mouse CD16/32 antibody (cat# 101302, BioLegend) and True-Stain monocyte Blocker (cat# 426101, BioLegend) to prevent nonspecific binding of Abs and were stained with monoclonal antibodies in staining buffer. Cells were then washed and resuspended in a staining buffer with PI (100 ng/ml) for dead cell exclusion.
Hepatic immune cells from DIO mice in Figure 8, were isolated after liver perfusion with PBS, with 0.75mg/ml of Collagenase

	A and 50ug/ml of DNase I 37°C for 30 min on a shaker, followed by filtration using a 70µm cell strainer. Hepatocytes were separated from non-parenchymal cells (NPCs) by centrifugation. The NPCs were incubated with RBC Lysis Buffer at RT for 5 min and the cell suspension was washed with PBS. The NPCs were resuspended in PBS containing Zombie Aqua for dead cell exclusion and cells were blocked with TruStain FcX™ PLUSt o prevent nonspecific binding of Abs and were stained with monoclonal antibodies in FACs buffer.
Instrument	LSR Fortessa (BD 715 Biosciences)
Software	FlowJo (Tree Star)
Cell population abundance	At least 10,000 cells for each sample were acquired and analyzed. For Figure 8, at least 1,000,000 cells for each sample were acquired and analyzed.
Gating strategy	Live cells were determined by appropriate size (FSC/SSC) and a PI staining. Target cell populations were then gated on CD45+ F4/80+ cells. Live liver cells on Figure 8, were determined by gating on single cells (SSC-A/SSC-H), single cells (FSC-A/FSC-W) and negative staining of Zombie Aqua (cat# 423101, Biolegend). Target cells population were then gated on CD45+ cells. For monocytes, cells were gated on CD11bhi, F4/80-, and then gated according to their differential expression of Ly6C and CCR2. For macrophages, CD45+ cells were gated on CD11bint F4/80+. While KCs were identified by gating on TIM4hiMHCII+VISIG4 +CCR2-, mo-KCs were identified by gating on TIM4loMHCII+VISIG4+CCR2-

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