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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	The RNA-seq data were collected by Illumina NovaSeq6000 and NovaSeq X Plus. The ChIP-seq data were collected by Illumina NovaSeq6000.
Data analysis	For RNA-seq data analysis, read quality was assessed with FastQC (v0.12.1) and adapters trimmed using Cutadapt (v4.4). Reads were then aligned to the mm10 genome (UCSC) using HISAT2 (v2.2.1) and reads in exons were counted using featureCounts function in Subread (v2.0.3) package. Analysis of differentially expressed genes was conducted using DESeq2 (v1.40.1) R package. Count data was transformed to log2 scale and normalized with respect to library size using rlog transformation produces. For ChIP-seq analysis, sequenced reads were aligned to reference mouse genome (mm10 assembly, UCSC) using Bowtie2 (v2.5.1), and clonal reads were removed from further analysis. After mapping reads to the reference genome, we used the MACS2 (v2.1.0) peak calling software to identify regions of IP enrichment over background. p value threshold of 0.0005 was used for all datasets. ChIPseeker (v1.36.0) R package was used to retrieve the nearest genes around the peak and annotate genomic region of the peak. Peak-related genes were used to perform enrichment analysis to identify the function enrichment results. The codes generated or used during the study are available at the GitHub repository (https://github.com/XiaoXxin/Macrophage_Reparative).

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

All the experiment data that support the findings of this study are included within the paper, its Supplementary Information files, Source Data files and public repositories and also available form the corresponding author upon reasonable request. The RNA-seq, ChIP-seq and CUT&RUN-seq data generated in this study are available in Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) under the accession GSE269834. The LC-MS/MS data for macrophage lipidomic analysis are available within the article (Supplementary Data 3). Publicly available datasets used in this study are available in GEO under the accession GSE141259, GSE152501, GSE163465, GSE180420, GSE186986, GSE200843, GSE205037, GSE205690, GSE131364, GSE162698. LIVER scRNA-seq data is available in Zenodo (https://doi.org/10.5281/zenodo.6035873). All the other data supporting the findings of this study are available within the article and Supplementary Information files.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex and gender determination was based on self-reporting by the participants during the initial data collection phase. The individual-level data is shared only when consent has been obtained.
Reporting on race, ethnicity, or other socially relevant groupings	No ethnicity or other socially relevant groupings were involved in this study.
Population characteristics	No population characteristics were involved in this study.
Recruitment	De-identified healthy donor blood samples were collected from 3 healthy donors.
Ethics oversight	All procedures and protocols involving human participants in this study were conducted following the principles of the Declaration of Helsinki and were approved by Shanghai Liquan Hospital (XF-WBC-220809). Informed written consent was obtained from all individuals before their inclusion in the study. The privacy and confidentiality of all participants were rigorously maintained.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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 sizes for each experiment are provided in figure legends. For in vitro experiments, three biological replicates were achieved. Such sample sizes are typical for the in vitro experiments and sufficient for a statistical analysis. For in vivo assay, at least 4 mice were used. No statistical method was used to determine the sample size. The sample sizes are determined empirically, and are similar in size to most existing studies in the field.
Data exclusions	No data were excluded from the analysis.
Replication	Each in vitro experiment was replicated at least triple successfully. At least 4 mice were used in this study and three replicates were successfully carried out for each sample.
Randomization	For animal studies, the mice were allocated randomly to experimental groups by an independent person. And also other in vitro experiments, such as cells/samples were randomly assigned to examination groups.
Blinding	All experiments were conducted in a double blinded fashion in which the researchers were blinded to group allocation.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Antibodies

Antibodies used

For Western blot the following primary antibodies were used:
Mouse anti-PPARγ (1:200) , Santa Cruz, Cat# sc-7273
Rabbit anti-PPARγ (1:1000), Cell Signaling Technology, Cat# 2443S
Rabbit Phospho-PPAR Gamma (S273) (1:1000), Bioss, Cat# bs-4888R
Rabbit Phospho-PPAR Gamma (S112) (1:500), Abcam, Cat# ab195925
Rabbit Phospho-Stat3 (Tyr705) (1:2000), Cell Signaling Technology, Cat# 9145
Rabbit anti-STAT3 (1:1000), Bioworld, Cat# BS1336
Rabbit anti-ACC1 (1:4000), proteintech, Cat# 21923-1-AP
Rabbit anti-FASN (1:5000), proteintech, Cat# 10624-2-AP
Rabbit anti-Lamin A/C (1:1000), Bioworld, Cat# BS1446
Mouse anti-beta-Actin (1:10000), Zen-Bioscience, Cat# 700068
Mouse GAPDH (1:5000), Zen-Bioscience, Cat# 390035
Mouse Phospho-PPAR Gamma (T166) (1:500), PMID: 36329235

The fluorochrome-labeled antibodies used for FACS analysis are:
FITC anti-CD45 (1:100), Biolegend, Cat# 157214
APC anti-F4/80 (1:100), Invitrogen, Cat# 17-4801-82
PE anti-CD11b (1:100), Invitrogen, Cat# 12-0112-81
PerCP-Cy5.5 anti-Ly-6G and Ly6C (1:100), BD Biosciences, Cat# 552093
PE anti-CD3e (1:100), Invitrogen, Cat# 12-0031-83
PE anti-CD206 (1:100), Biolegend, Cat# 141705
APC anti-CD163 (1:100), Invitrogen, Cat# 17-1631-82
PE anti-CD80 (1:100), Invitrogen, Cat# 12-0801-81
PE anti-MHC class II (1:100), Invitrogen, Cat# 12-5321-82
7-AAD (1:100) Biolegend Cat# 420403

Validation

Mouse anti-PPARγ, mouse, rat and human, WB, IP, IF, IHC(P) and ELISA, (https://www.scbt.com/p/ppargamma-antibody-e-8?requestFrom=search); In this paper for WB.

Rabbit anti-PPARγ, mouse and human, WB, IP, IF and ChIP, (https://www.cellsignal.com/product/productDetail.jsp?productId=2443); In this paper for WB and ChIP.

Rabbit Phospho-PPAR Gamma (S273), mouse and human, WB, ELISA, IHC(P), ICC and IF, (http://www.bioss.com.cn/prolook_03.asp?id=AF08169606015370&pro37=1); In this paper for WB.

Rabbit Phospho-PPAR Gamma (S112), mouse, rat and human, WB, (https://www.abcam.cn/products/primary-antibodies/ppar-gamma-phospho-s112-antibody-ab195925.html); In this paper for WB.

Rabbit Phospho-Stat3 (Tyr705) , mouse, rat and human, WB, IP, IF, IHC,F and ChIP,(https://www.cellsignal.com/product/productDetail.jsp?productId=9145); In this paper for WB.

Rabbit anti-STAT3, mouse, rat and human, WB, IHC and IF, (https://www.bioworlde.com/Primary-Antibodies/142351.html); In this paper for WB.

Rabbit anti-ACC1, mouse, rat and human, FC, IF, IHC, IP, WB and ELISA, (https://www.ptgcn.com/products/ACACA-Antibody-21923-1-AP.htm); In this paper for WB.

Rabbit anti-FASN, mouse, rat and human, FC, IF, IHC, IP, WB and ELISA, (https://www.ptgcn.com/products/FASN-Antibody-10624-2-AP.htm); In this paper for WB.

Rabbit anti-Lamin A/C, mouse, rat and human, WB, IHC and IF, (https://www.bioworlde.com/Primary-Antibodies/142442.html); In this paper for WB.

Mouse anti-beta-Actin, mouse, rat and human, WB, (http://www.zen-bio.cn/prod_view.aspx?IsActiveTarget=True&TypeId=179&Id=535552&FId=t3:179:3); In this paper for WB.

Mouse GAPDH, mouse, rat and human, WB and ELISA, (http://www.zen-bio.cn/prod_view.aspx?IsActiveTarget=True&TypeId=179&Id=535541&FId=t3:179:3); In this paper for WB.

Mouse Phospho-PPAR Gamma (T166), mouse, WB. This antibody has been validated by Yang et al. (PMID: 36329235); In this paper for WB.

FITC anti-CD45, mouse, FC, (https://www.biolegend.com/en-us/products/fitc-anti-mouse-cd45-antibody-21256); In this paper for FC.

APC anti-F4/80, mouse, IF, ICC and FC, (https://www.thermofisher.cn/cn/zh/antibody/product/F4-80-Antibody-clone-BM8-Monoclonal/17-4801-82); In this paper for FC.

PE anti-CD11b, Mouse, FC, (https://www.thermofisher.cn/cn/zh/antibody/product/CD11b-Antibody-clone-M1-70-Monoclonal/12-0112-81); In this paper for FC.

PerCP-Cy5.5 anti-Ly-6G and Ly6C, mouse, FC, (https://www.bdbiosciences.com/zh-cn/products/reagents/flow-cytometry-reagents/research-reagents/single-color-antibodies-ruo/percp-cy-5-5-rat-anti-mouse-ly-6g-and-ly-6c.552093); In this paper for FC.

PE anti-CD3e, mouse, FC, (https://www.thermofisher.cn/cn/zh/antibody/product/CD3e-Antibody-clone-145-2C11-Monoclonal/12-0031-83); In this paper for FC.

PE anti-CD206, mouse, FC, (https://www.biolegend.com/en-us/products/pe-anti-mouse-cd206-mmr-antibody-7424); In this paper for FC.

APC anti-CD163, mouse, FC, (https://www.thermofisher.cn/cn/zh/antibody/product/CD163-Antibody-clone-TNKUPJ-Monoclonal/17-1631-82); In this paper for FC.

PE anti-CD80 (1:100), mouse, FC, (https://www.thermofisher.cn/cn/zh/antibody/product/CD80-B7-1-Antibody-clone-16-10A1-Monoclonal/12-0801-81); In this paper for FC.

PE anti-MHC class II, mouse, FC and IHC, (https://www.thermofisher.cn/cn/zh/antibody/product/MHC-Class-II-I-A-I-E-Antibody-clone-M5-114-15-2-Monoclonal/12-5321-82); In this paper for FC.

7-AAD, FC, (https://www.biolegend.com/en-us/products/7-aad-viability-staining-solution-1649); In this paper for FC.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	HEK293T (#GNHu17), RAW 264.7 (#TCM13) were purchased from the cell bank of the Committee on Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China). HSF and HaCaT cells were generous gifts from Prof. JinHui Wu's Lab at Nanjing University.
Authentication	RAW 264.7, HEK293T, HSF, and HaCaT cells have been authenticated by STR profiling.
Mycoplasma contamination	Cell lines were routinely tested for potential mycoplasma contamination by using commercial mycoplasma detection kits (Yeasen, 40612ES). All tests were negative.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used in this study.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	C57BL/6J mice (Strain NO. N000013), 6 to 8 weeks old, were purchased from Gempharmtech Co., Ltd (China). C57BL/6J and PPARg T166A/T166A mice were raised in an specific pathogen free (SPF) environment with an ambient temperature of 20-25 °C , a relative humidity of 45-65%, and a 12h light/dark cycle.
Wild animals	The study did not involve wild animals.
Reporting on sex	Sex was not considered for the study design. There are no primary data disaggregated for sex. There is no indication that the results apply to only one sex.
Field-collected samples	No field-collected animals or samples were used in this study.

Ethics oversight	All mouse procedures and experiments for this study were approved by the Institutional Animal Care and Use Committee at Nanjing University (ICAUC-2207009).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	No plants were used in this study.
Novel plant genotypes	No plants were used in this study.
Authentication	No plants were used in this study.

ChIP-seq

Data deposition

☒ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	The ChIP-Seq data have been deposited in the NCBI BioProject database with accession code GSE252900 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE252900) (reviewer token: edidggianpobtwb)
Files in database submission	WT_PPAR_1.fq.gz WT_PPAR_2.fq.gz WT_Input_1.fq.gz WT_Input_2.fq.gz TA_PPAR_1.fq.gz TA_PPAR_2.fq.gz TA_Input_1.fq.gz TA_Input_2.fq.gz WT_logLR.bigWig TA_logLR.bigWig
Genome browser session (e.g. UCSC)	The bigWig files can be conveniently loaded into and viewed using th IGV web app (https://igv.org/app)

Methodology

Replicates	Each ChIP-seq sample has one replicate.
Sequencing depth	All sequencing was 150 bp length, paired-end. TA Input 19512225 reads; of these: 19512225 (100.00%) were paired; of these: 1319733 (6.76%) aligned concordantly 0 times 13582220 (69.61%) aligned concordantly exactly 1 time 4610272 (23.63%) aligned concordantly >1 times TA PPARg 24537645 reads; of these: 24537645 (100.00%) were paired; of these: 1179019 (4.80%) aligned concordantly 0 times 17175862 (70.00%) aligned concordantly exactly 1 time 6182764 (25.20%) aligned concordantly >1 times WT Input 20026997 reads; of these: 20026997 (100.00%) were paired; of these: 1442165 (7.20%) aligned concordantly 0 times 13852428 (69.17%) aligned concordantly exactly 1 time 4732404 (23.63%) aligned concordantly >1 times WT PPARg 22124151 reads; of these:

22124151 (100.00%) were paired; of these:
1033038 (4.67%) aligned concordantly 0 times
15456892 (69.86%) aligned concordantly exactly 1 time
5634221 (25.47%) aligned concordantly >1 times

Antibodies	Rabbit anti-PPARγ antibody (#2443S, Cell Signaling Technology; 1:100 dilution) was used in this study.
Peak calling parameters	MACS2 (v2.1.0) was used to call peaks by following parameters: callpeak -B --SPMR -f BAMPE -g mm --extsize 200
Data quality	Peaks with p-value <0.0005 were retained.
Software	Bowtie2 (v2.5.1); MACS2 (v2.1.0); Bedtools (v2.31.0); ChIPseeker (v1.36.0); Gviz (v1.44.0).

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	Preparation of skin-cell suspensions for flow cytometry: Mice were sacrificed, dorsal skin was removed and cut into tiny pieces with scissors, followed by incubation with complete medium (RPMI 1640 and 10% FBS) containing 0.1 mg/ml DNase I (Roche), 0.5 mg/ml hyaluronidase (MCE) and 2 mg/ml collagenase IV (MCE) in a shaking water bath (37 °C) for 2 h. The cell suspension was filtered with a 40-μm cell nylon mesh to obtain a single-cell suspension. The remaining red blood cells were lysed using RBC lysis buffer. The acquired single-cell suspensions were processed for flow cytometry. Isolation of bone marrow-derived macrophages (BMDMs): BMDMs were isolated from the femurs and tibiase of C57BL/6J or PPARg A/A mice. Total bone marrow cells were passed into a 40-μm cell strainer and centrifuged. Next, bone marrow cells were differentiated for 7 d in the presence of M-CSF (50 ng/ml, Z03275, GenScript) in RPMI-1640 medium containing 10% FBS and 100 U/ml penicillin-streptomycin. Flow cytometry staining and analysis: After collection, skin digest or BMDMs were resuspended in PBS supplemented with 1% FBS on ice. Non-specific binding was blocked with FcR blocking reagent (Miltenyi Biotech, 130-092-575) for 20 min at 4 °C. Cells were stained with fluorochrome-conjugated antibodies for 40 min at 4 °C. For intracellular staining, cells were fixed and permeabilized using the Intracellular Fixation & Permeabilization Buffer Set (#88-8824-00, eBioscience) and intracellularly stained for 1 h at 4 °C with antibody. The lipid content was assessed with BODIPY 493/503 (D3922, Invitrogen), following 20 min of incubation at 37 °C.
Instrument	NovoCyte Flow Cytometer (Agilent Technologies, Inc.)
Software	NovoExpress (v1.6.2)
Cell population abundance	Purity of isolated BMDMs was assessed by FACS and showed a purity ≥ 90% in all samples. At least 10,000 cells were selected for fluorescence intensity statistics.
Gating strategy	The starting cell population was gated according to FSC/SSC followed by doublet exclusion gate. Usually, population gates were set according to the FMO control including an isotype control wherever possible.

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