nature portfolio

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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	Data collection for 19F NMR was performed with Bruker IconNMR (v5.0.11) and Bruker TopSpin (v3.6.3) software. Data collection for all ELISA and luciferase reporter assay was performed with Agilent BioTek Gen5 (v3.09.07). Data collection for RT-qPCR was performed using Bio-Rad CFX manager (v3.1). For LC-MS, OpenLAB CDS ChemStation Edition (C.01.08) was used. For BLI, Octet BLI Discovery (v12.2.2.20) was used. Thermo Scientific Xcalibur (v4.1.50) was used to collect proteomics data. Data collection for palmitoyl-CoA oxidation was performed with Agilent Cary WinUV (v6.2.0.1588).
Data analysis	GraphPad Prism (v10.1.1) was used for statistical analysis. MestReNova (v14.2.3) was used for 19F NMR analysis. Octet Analysis Studio (v12.2.2.26) was used for BLI analysis. For RNA-seq, NF-core RNAseq (v3.5), Trim Galore (v0.6.7), Star (v2.6.1d), Salmon (v1.5.2), DESeq2 (v1.28.0), R (v4.0.2) and pathfindR (v1.6.3) were used. SAMSA2 (v2.2.0) was used for meta-transcriptomics and Qiime2 (v2023.2) was used for 16S analysis. XCMSOnline (v3.7.1) was used for untargeted metabolomics analysis. For proteomics analysis, Proteome Discoverer (v3.0) and FragPipe (v20.0) were used. The detailed information for data analysis is described in the Method section.

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 RNA-seq data is deposited in the NCBI database under BioProject accession number PRJNA917696. The raw metabolomics data is deposited into the National Metabolomics Data Repository with the Study ID ST003595. The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD057035.

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	No human participants were involved in this study.
Reporting on race, ethnicity, or other socially relevant groupings	No human participants were involved in this study.
Population characteristics	No human participants were involved in this study.
Recruitment	No human participants were involved in this study.
Ethics oversight	No human participants were involved in this study.

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	No statistical method was used to predetermine sample size. Instead, we ensured that the number of samples was sufficient for statistical analysis and adjusted according to the specific experimental context, for example, larger sample sizes were used in animal studies because of greater biological variability. Based on previous experience and common practice in the field, at least four mice per group were included, which is the minimal number required to detect significant differences between groups.
Data exclusions	No data were excluded.
Replication	All the studies were replicated for several times and were successful.
Randomization	All the mice were randomly allocated to different experimental groups.
Blinding	Data analyses were not blinded. We performed an unbiased analysis for all datasets from different experiments.

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

anti-PMP70 antibody (Thermo Fisher Scientific, cat. PA1-650, lot WC318369)
anti-GAPDH antibody (Thermo Fisher Scientific, cat.PA1-987, lot WE322623)

Validation

The PMP70 antibody was validated for both Western Blot and Immunohistochemistry, as described in the Thermo Fisher web page. A total of 31 references have cited and reported the use of this antibody in the Thermo Fisher web page. For more information please see https://www.thermofisher.com/antibody/product/PMP70-Antibody-Polyclonal/PA1-650

The GAPDH antibody was validated for Western Blot with 84 references as described in the Thermo Fisher web page . For more information please see https://www.thermofisher.com/antibody/product/GAPDH-Antibody-Polyclonal/PA1-987

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

HepG2, obtained from ATCC, is a human liver cancer cell line derived from a hepatocellular carcinoma in a 15-year-old White male.
FAO, obtained from Sigma-Aldrich, is a differentiated rat liver cell line derived from H4-11-E-C3, which originates from the hepatocellular carcinoma of a male rat.

Authentication

Cell lines were authenticated by the suppliers and further verified in our lab. Experiments were performed using low-passage cells to minimize genetic drift and phenotypic variation.

Mycoplasma contamination

All cell lines used in this study tested negative for Mycoplasma contamination.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell 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

LDLr-/- mice (male and female, 10-12 weeks), ApoE-/- mice (male and female, 6-7 weeks), C57BL/6J mice (male, 10 weeks) were used in this study. All experiments were performed with mice aged 6-12 weeks at the start of the study.

Wild animals

No wild animals were involved in this study.

Reporting on sex

Mechanistically, our findings apply to both male and female mice. However, we observed some phenotypic differences between sexes, as described in the manuscript. Only male wild-type C57Bl mice were used for the metabolic disease model because male mice are more susceptible to metabolic disease in this model.

Field-collected samples

No field-collected samples were involved in this study.

Ethics oversight

The TSRI Institutional Animal Care and Use Committee approved all experimental protocols involving live animals.

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 the study.
Novel plant genotypes	No plants were used in the study.
Authentication	No plants were used in the study.