

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 (<i>n</i>) 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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ 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 <i>d</i> , Pearson's <i>r</i>), 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	Small Animal Body Composition Analysis and Imaging System (MesoQMR23-060H-I; Nuimap Corp., Shanghai, China) for mice body composition. Promethion Metabolic Monitoring System (Sable Systems International, LV, USA) for metabolic cage measurements. LC-MS (AB6500, AB SCIEX, USA) for NE content measurements. LSM980 confocal microscope (Carl Zeiss, Jena, Germany) or A1RMP confocal microscope (Nikon, Japan) for IF data collection. The NovaSeq 6000 platform for the RNA sequencing libraries.
Data analysis	Image Studio Lite software (version v5.2, LI-COR Odyssey CLx Infrared Imaging System) was used to semi-quantify gray values of Western blots. Image J software (version 1.8.0) was used to semi-quantity of immunofluorescence and immunohistochemistry images. Statistical analyses were performed with GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA).

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 single-nucleus RNA sequencing data generated in this study have been deposited in the NCBI Sequence Read Archive under BioProject accession number PRJNA1321392. The RNA-seq datasets generated in this study have been deposited in GEO dataset under accession code GSE308694. The remaining data generated in this study are available in the main text or the supplementary materials. Source data are provided with this paper.

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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](https://www.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	For animal studies, the sample size was determined based on published literature and previous lab experience. For cellular studies, the sample size was chosen according to preliminary experiments. Sample size is indicated in the figure legend in each experiment. At least three biological replicates per group were collected to perform statistical testing.
Data exclusions	No data were excluded from the analyses.
Replication	All experiments in vitro and in cell based models were performed at least three time independently. In vivo mouse models used at least 5 mice per genotype. All experimental repetitions were successfully performed.
Randomization	All samples were randomly allocated among the groups before experiments.
Blinding	The experiments were not blinded. However, we followed standard laboratory procedures of randomization. Each experiment was associated with the proper controls, and compared samples were collected and analyzed under the same condition.

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

Rabbit anti-GFAP (Abcam, Cat#ab7260, 1:5000); Rabbit anti-GFP (Abcam, Cat#ab6556, 1:1000); Rabbit anti-p-ATGL (S406) (Abcam, Cat#ab135093, 1 µg/mL); Rabbit anti-UCP1 (Abcam, Cat#ab10983, 1:1000); Rabbit anti-ATGL (Cell Signaling Technology, Cat#2138, 1:1000); Rabbit anti-c-Fos (Cell Signaling Technology, Cat#2250, 1:1000); Rabbit anti-F4/80 (Cell Signaling Technology, Cat#70076, 1:400); Rabbit anti-p-AKT (S473) (Cell Signaling Technology, Cat#4060, 1:2000 and 1:400); Rabbit anti-p-CREB (S133) (Cell Signaling Technology, Cat#9198, 1:1000); Rabbit anti-p-HSL (S563) (Cell Signaling Technology, Cat#4139, 1:1000); Rabbit anti-p-HSL (S660) (Cell Signaling Technology, Cat#45804, 1:1000); Rabbit anti-p-PAK Substrate (Cell Signaling Technology, Cat#9624, 1:1000); Rabbit anti-Perilipin-1 (Cell Signaling Technology, Cat#9349, 1:1000); Rabbit anti-PTEN (Cell Signaling Technology, Cat#9188, 1:1000); Rabbit anti-AKT (Huabio, Cat#ET1609-51, 1:5000); Rabbit anti-CREB (Huabio, Cat#ET1601-15, 1:1000); Mouse anti-FLAG (Huabio, Cat#M1403-2, 1:50000 and 1:2000); Rabbit anti-Vimentin (Huabio, Cat#ET1610-39, 1:1000); Rabbit anti-β-Actin (Abclonal, Cat#AC026, 1:100000); Rabbit anti-HSL (Abclonal, Cat#A15686, 1:1000); Rabbit anti-Myc (Abclonal, Cat#AE009, 1:3000); Guinea pig anti-c-Fos (Oasis, Cat#OB-PGP080, 1:800); Rabbit anti-TH (Sigma, Cat#AB152, 1:2000 and 1:200); Rabbit anti-IBA1 (Huabio, Cat#ET1705-78, 1:500); Rabbit anti-NeuN (Huabio, Cat#ET1602-12, 1:500); Rabbit anti-p38 (Huabio, Cat#ET1602-26, 1:1000); Rabbit anti-p-p38 (T180+T182) (Bioss, Cat#BS-2210R, 1:1000); Rabbit anti-POMC (Phoenix Pharmaceuticals, Cat#H-029-30, 1:800); Goat anti-tdTomato (Biorbyt, Cat#orb182397, 1:500).

Validation

Antibodies used were commercially available and were validated in multiple previous studies:

Rabbit anti-GFAP: <https://www.abcam.cn/products/primary-antibodies/gfap-antibody-ab7260.html>

Rabbit anti-GFP: <https://www.abcam.cn/products/primary-antibodies/gfp-antibody-ab6556.html>

Rabbit anti-p-ATGL (S406): <https://www.abcam.cn/products/primary-antibodies/adipose-triglyceride-lipase-phospho-s406-antibody-ab135093.html>

Rabbit anti-UCP1: <https://www.abcam.cn/products/primary-antibodies/ucp1-antibody-ab10983.html>

Rabbit anti-ATGL: <https://www.cellsignal.cn/products/primary-antibodies/atgl-antibody/2138>

Rabbit anti-c-Fos: <https://www.cellsignal.cn/products/primary-antibodies/c-fos-9f6-rabbit-mab/2250>

Rabbit anti-F4/80: <https://www.cellsignal.cn/products/primary-antibodies/f4-80-d2s9r-xp-rabbit-mab/70076>

Rabbit anti-p-AKT (S473): <https://www.cellsignal.cn/products/primary-antibodies/phospho-akt-ser473-d9e-xp-rabbit-mab/4060>

Rabbit anti-p-CREB (S133): <https://www.cellsignal.cn/products/primary-antibodies/phospho-creb-ser133-87g3-rabbit-mab/9198>

Rabbit anti-p-HSL (S563): <https://www.cellsignal.cn/products/primary-antibodies/phospho-hsl-ser563-antibody/4139>

Rabbit anti-p-HSL (S660): <https://www.cellsignal.cn/products/primary-antibodies/phospho-hsl-ser660-antibody/45804>

Rabbit anti-p-PAK Substrate: <https://www.cellsignal.cn/products/primary-antibodies/phospho-pka-substrate-rxrs-t-100g7e-rabbit-mab/9624>

Rabbit anti-Perilipin-1: <https://www.cellsignal.cn/products/primary-antibodies/perilipin-1-d1d8-xp-rabbit-mab/9349>

Rabbit anti-PTEN: <https://www.cellsignal.cn/products/primary-antibodies/pten-d4-3-xp-rabbit-mab/9188>

Rabbit anti-AKT: <https://huabio.cn/products/AKT1-2-3-antibody-ET1609-51>

Rabbit anti-CREB: <https://huabio.cn/products/CREB-antibody-ET1601-15>

Mouse anti-FLAG: <https://huabio.cn/products/DYKDDDDK-Tag-FLAG-antibody-M1403-2>

Rabbit anti-Vimentin: <https://huabio.cn/products/Vimentin-antibody-ET1610-39>

Rabbit anti-β-Actin: <https://abclonal.com.cn/catalog/AC026>

Rabbit anti-HSL: <https://abclonal.com.cn/catalog/A15686>

Rabbit anti-Myc: <https://abclonal.com.cn/catalog/AE009>

Guinea pig anti-c-Fos: <https://www.oasisbiofarm.net/#/productdetails?prold=9638ffec3ee34256908d087e3bda1797&exp2=%E6%8A%E9%7E%E4%BD%93>

Rabbit anti-TH: <https://www.sigmaaldrich.cn/CN/zh/product/mm/ab152>

Rabbit anti-IBA1: <https://huabio.cn/products/Iba1-antibody-ET1705-78>

Rabbit anti-NeuN: <https://huabio.cn/products/NeuN-antibody-ET1602-12>

Rabbit anti-p38: <https://huabio.cn/products/p38-alpha-MAPK14-antibody-ET1602-26>

Rabbit anti-p-p38 (T180+T182): https://www.biosschina.com/#/productDetail?goods_id=18781

Rabbit anti-POMC: https://phoenixpeptide.com/?s=H-029-30&jet_search_suggestions_settings=%7B%22search_source%22%3A%22any%22%7D

Goat anti-tdTomato: <https://www.biorbyt.cn/tdtomato-antibody-orb182397.html>

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	GT1-7 cells and N2a cells were provided by Prof. Lu Gan (West China Hospital of Sichuan University, Sichuan China)
Authentication	Cell lines were authenticated by morphology, gene expression profile and differentiation potentiality.
Mycoplasma contamination	Cell lines were tested negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell line was involved 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	Eight-week-old C57BL/6J mice were purchased from Beijing HFK Bioscience (Beijing, China). Tox3flox/flox mice were provided by Prof. Tao Huang (Shandong University, Shandong, China). POMC-Cre, AgRP-Cre, and Rosa26-lox-stop-lox-tdTomato (Ai9) reporter mice were purchased from the Jackson Laboratory (BarHarbor, ME, USA). Six-week-old mice were fed with chow diet or high-fat diet for another 12-16 weeks. Mice were group-housed in individually ventilated cages under controlled temperature and humidity with a 12-h light-dark cycle.
Wild animals	This study did not involve wild animals.
Reporting on sex	Males and females were used for analyze metabolic phenotypes.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal protocols were approved by Sichuan University Animal Care and Use Committee.

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

Plants

Seed stocks	This study did not involve plants.
Novel plant genotypes	not applicable
Authentication	not applicable