

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
<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. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P 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 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	No software was used to collect data.
Data analysis	Softwares for Single cell seq analysis include Cell Ranger (v3.1.0), R (v3.6.3), Python (v3.6), Scanpy(v1.7.1), Seurat (v3.1.1), Velocyto(v0.17.16), scVelo (v0.2.1), SCENIC (v1.2.2) listed in supplementary table 3. Cy5-labeled P-G3 or NPs in living mice or tissues were imaged and analyzed using PerkinElmer IVIS Spectrum Optical Imaging System (Living Image 4.5.5 Software). Most data were analyzed with Prism 9.3.1 (GraphPad) software. Tissue slides and cell Images were processed using ImageJ 2.1.0 (National Institutes of Health) software. Flow cytometry data were analyzed by FCS Express (7.14.0020) software.

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-cell RNA-seq data are available in the Gene Expression Omnibus (GEO) database under accession number GSE209819.

Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender

The biomaterial used in this study was from one female subject.

Population characteristics

Only sample from one subject was used.

Recruitment

The subject's biomaterial was obtained from a cross-sectional study (Next Generation Sequencing for Diabetes and Metabolic Diseases study). Participants of this study were recruited from one of six Weill Cornell Medicine clinics, including Bariatric Surgery, Endocrinology, Gastroenterology, Cardiology, and Internal Medicine from August 2020 – July 2022. Inclusion criteria included a diagnosis of hyperlipidemia, Type-2 Diabetes, Pre-diabetes, or Non-alcoholic Fatty Liver Disease/Non-alcoholic Steatohepatitis.

Ethics oversight

The study has been approved by Weill Cornell Medicine IRB 19-05020126.

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

Sample sizes for experiments were estimated based on previous experiences and reports with similar setups to achieve 80% power of significance.

Data exclusions

No data were excluded from the analyses.

Replication

All the in vitro were repeated at least three times with similar results. Key in vivo experiments were repeated at least two times with similar results.

Randomization

Animals were assigned randomly to experimental and control groups. Cells were also randomly assigned to experimental groups with different treatments.

Blinding

Histological assessments, flow cytometry analysis, and data collection of single cell sequence were performed in blinded manner.

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

Methods

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

Antibodies

Antibodies used

Antibodies used in this study are:

p-mTOR, Cell signaling technology, catalog number: CST #2971;
 p-S6K, Cell signaling technology, catalog number: CST #9205;
 p-4E-BP1, Cell signaling technology, catalog number: CST #2855;
 p-AKT (Ser473), Cell signaling technology, catalog number: CST #9271;
 p-AKT (Thr308), Cell signaling technology, catalog number: CST #13038;
 p-GSK3b (Ser 9), Cell signaling technology, catalog number: CST#9322;
 FASN, Cell signaling technology, catalog number: CST #3180;
 ADIPSIN, R&D Systems, catalog number: # AF5430;
 ADIPONECTIN, Thermo Fisher, catalog number: #PA1-054;
 CEBPA, Santa cruz, catalog number: #sc-61);
 HSP90, Proteintech, catalog number: #13171-1-AP;
 GAPDH, Proteintech, catalog number: #HRP-60004;
 Caveolin-1 (D46G3), Cell signaling technology, catalog number: CST, #3267;
 Rabbit Alexa 488, Thermo Fisher Scientific, catalog number: # A27034;
 F4/80, Cell signaling technology, catalog number: CST, #70076.

The dilution of antibodies were based on the recommendation on the manufacturer's website.

Validation

All antibodies were verified by the supplier. Validation statements are shown on the manufacturer's website.

1. p-mTOR antibody has been validated to be used for western blotting and mentioned species reactivity with mouse. (<https://www.cellsignal.com/products/primary-antibodies/phospho-mtor-ser2448-antibody/2971>)
2. p-S6K has been validated to be used for western blotting and mentioned species reactivity with mouse. (<https://www.cellsignal.com/products/primary-antibodies/phospho-p70-s6-kinase-thr389-antibody/9205>)
3. p-4E-BP1 antibody has been validated to be used for western blotting and mentioned species reactivity with mouse. (<https://www.cellsignal.com/products/primary-antibodies/phospho-4e-bp1-thr37-46-236b4-rabbit-mab/2855>)
4. p-AKT (S473) has been validated to be used for western blotting and mentioned species reactivity with mouse. (<https://www.cellsignal.com/products/primary-antibodies/phospho-akt-ser473-antibody/9271>)
5. p-AKT (T308) has been validated to be used for western blotting and mentioned species reactivity with mouse. (<https://www.cellsignal.com/products/primary-antibodies/phospho-akt-thr308-d25e6-xp-rabbit-mab/13038>)
6. p-GSK3b (Ser 9) has been validated to be used for western blotting and mentioned species reactivity with mouse. (<https://www.cellsignal.com/products/primary-antibodies/phospho-gsk-3-beta-ser9-d3a4-rabbit-mab/9322>)
7. FASN has been validated to be used for western blotting and mentioned species reactivity with mouse. (<https://www.cellsignal.com/products/primary-antibodies/fatty-acid-synthase-c20g5-rabbit-mab/3180>)

Eukaryotic cell lines

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

Cell line source(s)	3T3-L1 and C3H10T1/2 were purchased from ATCC.
Authentication	None of the cell lines used were authenticated.
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

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	6-17 week old male and female C57BL/6 mice were purchased from Jackson Laboratory. All mice were maintained in Columbia University animal facility with at 23 ± 1°C and a 12-hr light and dark cycle with ad libitum access to chow food (PicoLab Rodent 5053) and water.
Wild animals	The study did not involve wild animals.

Reporting on sex

The findings were reproduced in both male and female mice.

Field-collected samples

The study did not involve samples collected from the field.

Ethics oversight

The Columbia University Animal Care and Utilization Committee approved all animal studies.

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

Cell cultures were treated as indicated and harvested by trypsinization. Cells were centrifuged (250 g, 5min) and resuspended in appropriate amount of PBS containing 1% FBS to get concentration of 10^7 cells per 1 mL. Cells were filtered through the cell strainer right before the FACS analysis.

Instrument

BD influx equipped with 405, 488, 561 and 638nm lasers.

Software

FCS Express (7.14.0020) software

Cell population abundance

Cell sorting not employed.

Gating strategy

Using the FSC/SSC gating, debris was removed by gating on the main cell population. Gating strategy were provided in Extended Data Fig. 6e.

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