

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	N.A
Data analysis	Partek Flow

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](#)

RNA-seq is available as GEO accession number GSE246231.

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 Sample size of at least 2 for cells or 4 for mice was selected based on variance observed in prior experiments of a similar nature, as well as practical considerations.

Data exclusions Data were not exclude from analysis.

Replication To ensure robust reproducibility, all data presented in the manuscript were repeated at least three times (two times only for initial CRISPRa sgRNA transfection guide selection). All replication attempts were successful.

Randomization N.A

Blinding No blinding was performed in this study. It required to use the correct genotypes of cells and mice

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 Ki67 (SolA15),Fisher Scientific,14-5698-82
Carbonic Anhydrase,Fisher Scientific,AF2188
CD31,Fisher Scientific,BBA7

GAPDH, Cell Signaling, 5174
 Goat anti-rat, Alexa Fluor 647, Fisher Scientific, A21247
 Goat anti-mouse, Alexa Fluor 594, Life Technologies, A11032
 Donkey anti-goat, Alexa Fluor 594, Fisher Scientific, A11055
 Caspase 3, Cell Signaling, CS9661
 CK19, Abcam, Ab203444
 UCP1, R&D, MAB6158

Validation

Ki67- [## Eukaryotic cell lines](https://www.thermofisher.com/antibody/product/Ki-67-Antibody-clone-SolA15-Monoclonal/14-5698-37?gclid=Cj0KCQjw27mhBhC9ARIsAlFsETEvm59r_6344DC3_jxeeelBcjHtvUN6FV_e1JxDJyqy8Z0Ns9dsalaAhu-EALw_wcB&ef_id=Cj0KCQjw27mhBhC9ARIsAlFsETEvm59r_6344DC3_jxeeelBcjHtvUN6FV_e1JxDJyqy8Z0Ns9dsalaAhu-EALw_wcB:G:s&s_kwid=AL13652131278870232429!!lg!!!1454324556!63404918784&cid=bid_pca_frg_r01_co_cp1359_pjt0000_bid00000_0se_gaw_dy_pur_con.CA9-https://www.rndsystems.com/products/human-carbonic-anhydrase-ix-ca9-antibody_af2188CD31-https://www.rndsystems.com/products/human-cd31-pecam-1-antibody-9g11_bba7?gclid=Cj0KCQjw27mhBhC9ARIsAlFsETESGafo_oT07Q0oQgcgGzrDCU8jmY4a2yrvbTshU1rGsCo_-SFX41YaAsWdEALw_wcB&gclidsrc=aw.dsCaspase3-https://www.cellsignal.com/products/primary-antibodies/cleaved-caspase-3-asp175-antibody/9661CK19- https://www.abcam.com/products/primary-antibodies/alexa-fluor-555-cytokeratin-19-antibody-ep1580y-ab203444.htmlGAPDH- https://www.cellsignal.com/products/primary-antibodies/gapdh-d16h11-xp-rabbit-mab/5174UCP1- https://www.rndsystems.com/products/human-mouse-ucp1-antibody-536435_mab6158</p>
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Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

Human preadipocyte cell line was obtained from Dr. Hei Sook Sul lab at UC Berkeley. It was generated by immortalizing human male subcutaneous preadipocytes. DU-415, Panc 10.01, SW-1417, MDA-MB-436, MCF7 and Mouse 3T3-L1 were obtained from ATCC. AAVpro 293T cells were obtained from Takara.

Authentication

Preadipocyte cell lines were subjected adipocyte differentiation and adipogenic markers were checked with qRT-PCR.

Mycoplasma contamination

All lines were tested for mycoplasma.

Commonly misidentified lines
(See [ICLAC](#) register)

N.A

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

SCID mice (JAX, 001303), FVB/N-Tg(MMTV-PyVT)634Mul/J (JAX, 002374), Krastm4Tyj Trp53tm1Brn Tg(Pdx1-cre;Esr1*)#Dam/J (Jax, 032429)

Wild animals

N.A

Reporting on sex

We used both males and females

Field-collected samples

N.A

Ethics oversight

UCSF Institutional Animal Care & Use Program

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