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	Olympus IX51 microscope was used to histology images. ZEISS Zen software (v2.3 blue edition) was used to perform confocal imaging. Xcalibur Software version 4.2 is used for metabolomics data collection. Analyst 1.6.3 and Lipidyzer platform were used to collect lipids data.
Data analysis	For image analysis NIH ImageJ (FIJI) software version 2.1.0/1.53c was used. For preparing plots and statistical analysis Prism version 8 (GraphPad Software) was used. Partek Flow Genomic Analysis Software version 2.3 and Enrichr (https://maayanlab.cloud/Enrichr/) were used for analysis of RNA-seq data. Compound Discoverer version 3.1, TraceFinder version 4.1, Polly platform version 1 (Elucidata Corporation) were used for metabolomics data processing. The SCIEX Lipidyzer™ Platform, MultiQuant3.0.2, and Polly platform version 1 (Elucidata Corporation) were used for lipid data analysis

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

DNA methylation and RNA-seq data are deposited in the Gene Expression Ominibus under the accession number GSE190665 and SuperSeries accession number GSE190986. Metabolomics and lipidomics raw data can be found in supplementary tables 8 and 9 (4F mice serum) and 10 and 11 (B6 mice serum). The raw data for

the figures and other data supporting the findings in the study are available upon request from the corresponding author. MassBank of North America (MoNA, https://mona.fiehnlab.ucdavis.edu/), and commercial mzCloud (Thermo Fisher Scientific) mass spectral database were used.

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	The samples sizes for each experiment are indicated in the figure legends. No statistical methods were used to predetermine sample size. Sample size was chosen based on the sample availability and statistic relevance. Sample size was at least n=3 independent biological replicates.
Data exclusions	No data were excluded.
Replication	Number of biological replicates are described in figure legends.
Randomization	No randomization method was used. Animals and samples were randomly allocated into experimental groups. Equal number of both the gender mice were included to minimize sex differences.
Blinding	No blinding was performed during in vivo experiment, tissue collections and statistical analysis. Blinding was done during analysis and quantification of histology data.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	Rabbit Anti-Ki67 mAb, Cell Signaling, #9027 (1:200 dilution) Mouse Anti-Pax7 mAb, DSHB, #Pax7-C (1:200 dilution) Rabbit Anti-Dystrophin pAb, Abcam #ab15277 (1:500 dilution) Goat anti-Mouse IgG2b antibody conjugate Alexa Fluor 488, Invitrogen, #A21141 (1:500 dilution) Goat anti-Mouse IgG2b antibody conjugate Alexa Fluor 647, Invitrogen, #A21242 (1:500 dilution)
Validation	Information from manufacturer website was used for selecting the antibody. Ki67 antibody was validated by using stomach and testes as positive control and primary antibody was excluded for negative control. Anti-Pax7 (DSHB, Pax7-c) has been cited in at least 97 references such as an immunostaining application in mouse muscle tissues:Lineage Tracing Reveals a Subset of Reserve Muscle Stem Cells Capable of Clonal Expansion under Stress. Cell stem cell 24.6 (2019Jun 6): 944-957.e5. Anti-Dystrophin pAb (Abcam #ab15277) and secondary antibodies have been verified in PMID: 28752107.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Mice carrying a single copy of OSKM polycistronic cassette and rtTA transactivator was used. C57BL/B6 were used in some

Laboratory animals	experiments. All animals were in C57BL/6J background. Both males and female mice were used. Young mice were 3 months old. Aged mice were 12-26 months of age. The mice were housed in a temperature-controlled room (21-23 oC) at 40-60% humidity with 12 hr light and dark cycle between 06:00 and 18:00 and free access to water and food.
Wild animals	This study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal procedures were performed according to NIH guidelines and approved by the Committee on Animal Care at the Salk Institute.

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