nature research

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Last updated by author(s): Apr 20, 2021

Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	FV10-ASW4.2 Software (version 4.02), BD FACS Diva Software (version 6.1.3), CellSens Standard (v1.13), Bowtie2 (version 2.2.6; with default parameters), MACS (version 2.1.1; with default parameters), PreprocessCore package in R (3.3.2) .
Data analysis	Excel 2013, GraphPad PRISM 6 and 8, Image J version 1.51 , TIGRMeV version 4.9 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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Microarray data were deposited in the GEO public database (accession no. GSE131958). RNA-seq data were deposited in the GEO public database (accession no. GSE169173). All ATAC data were deposited in the DDBJ database (accession no. DRA008515). DAVID web-accessible tool is available at https://david.ncifcrf.gov/tools.jsp. GSEA is available at https://www.gsea-msigdb.org/gsea/index.jsp. TIGRMeV is available at http://mev.tm4.org.

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 methods were used to predetermine the sample size. The sample size was empirically selected based on previous experiments in this field such as Liu et al. (Nature 568;344–350 2019), Matsumura et al. (Science 351;6273 4395 2016), Hsu et al. (Cell 157; 4 935 2014).
Data exclusions	No data were excluded.
Replication	Microarray, RNA-seq and ATAC-seq analysis were conducted one time using more than two mice. All other experiments were conducted at least two independent times.
Randomization	Co-housed wild type mice or genetically modified mice were randomly assigned into two groups and fed ND or HFD.
Blinding	For hair loss, blinding test can not be performed as obese mice can be easily identified from their appearance. For other experiments, no blinding tests were performed as there was no subjective measurement.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used

COL17A1 (Abcam, ab186415, EPR14758, 1:400), Keratin 14 (Biolegend, 906004, Poly9060,1:500), ITGA6 (BD, 555734,GoH3, 1:200), Keratin 15 (Biolegend, 833904, Poly18339, 1:300), NFkB (Santa Cruz, sc-101749, 1:50), CD11b (BD, 557686, M1/70, 1:100), F4/80 (Bio-Rad, MCA497A488, Cl:A3-1, 1:100), KI67 (Invitrogen, 14-5698-82, SolA15, 1:300), CD3 (Biolegend, 100235, 17A2, 1:100), MHC2 (Biolegend, 107605, M5/114.15.2, 1:100), CD31(BD Biosciences, 557355, MEC 13.3, 1:200), anti-DNA/RNA Damage (Abcam, ab62623, IgG2b, 1:2000), Tom20 (Thermo Fisher, 11802-1-AP,1:30), Keratin 1 (Abcam, ab185628, EPR17744, 1:300), survivin (Cell signaling, 2808, 71G4B7, 1:100), casp3 (Cell signaling, 9661, 1:200), Tuj1 (Covance, PRB-435P, Poly18020, 1:500), CD34-FITC (Invitrogen, 11-0341-85, RAM34, 1:100), ITGA6-PE (BD, 555736, GoH3,1:100), Sca1-APC (Miltenyi Biotec, 130-102-343, D7, 1:100), CD45-APC-cy7 (BioLegend, 103116, 30F-11, 1:100).

Validation

Validation statements can be obtained from the following websites.
COL17A1 antibody https://www.abcam.com/collagen-xvii-antibody-epr14758-ab186415.html
Keratin 14 antibody https://www.biolegend.com/ja-jp/products/purified-anti-keratin-14-antibody-13379
ITGA6 antibody https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/purified-rat-anti-human-cd49f-goh3/p/555734
Keratin 15 antibody https://www.biolegend.com/ja-jp/products/purified-anti-keratin-15-antibody-13326
NFkB antibody https://www.scbt.com/p/p-nfkappab-p65-antibody-ser-276?productCanUrl=p-nfkappab-p65-antibody-ser-276&_requestid=1975607
CD11b antibody https://www.bdbiosciences.com/eu/applications/research/stem-cell-research/mesenchymal-stem-cell-markers-bone-marrow/mouse/negative-markers/alexa-fluor-647-rat-anti-cd11b-m170/p/557686
F4/80 antibody https://www.bio-rad-antibodies.com/monoclonal/mouse-f4-80-antibody-cl-a3-1-mca497.html?f=purified
KI67 antibody https://www.thermofisher.com/antibody/product/17-5698-82.html?ef_id=EAIaIQobChMI7ZDgkqP47wIVBsEWBR3K-wopEAAYASAAEgI3xfD_BwE:G:s&s_kwcid=AL!3652!3!278870232429!b!!g!!&cid=bid_pca_frg_r01_co_cp1359_pjt0000_bid00000_0se_gaw_dy_pur_con&gclid=EAIaIQobChMI7ZDgkqP47wIVBsEWBR3K-

wopEAAYASAAEgI3xfD_BwE
CD3 antibody https://www.scbt.com/p/cd3-antibody-pc3-188a?gclid=EAIaIQobChMI_5jQo6P47wIVC8WWCh161g-7EAAYASAAEgli7PD_BwE
MHC2 antibody https://www.biolegend.com/ja-jp/search-results?6680&productid=366
CD31 antibody https://www.bdbiosciences.com/eu/applications/research/stem-cell-research/cancer-research/mouse/purified-rat-anti-mouse-cd31-mec-133/p/557355
anti-DNA/RNA damage https://www.abcam.com/dnarna-damage-antibody-15a3-ab62623.html?#description_protocols
Tom 20 antibody https://www.thermofisher.com/antibody/product/TOM20-Antibody-Polyclonal/11802-1-AP
Keratin1 antibody https://www.citeab.com/antibodies/4636852-ab185628-anti-cytokeratin-1-antibody-epr17744
survivin antibody https://www.cellsignal.jp/products/primary-antibodies/survivin-71g4b7-rabbit-mab/2808
casp3 antibody https://www.cellsignal.jp/products/primary-antibodies/cleaved-caspase-3-asp175-antibody/9661
Tuj1 antibody https://www.biolegend.com/ja-jp/products/purified-anti-tubulin-beta-3-tubb3-antibody-11579?GroupID=GROUP32
CD34-FITC https://www.thermofisher.com/antibody/product/CD34-Antibody-clone-RAM34-Monoclonal/11-0341-82
ITGA6-PE https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/pe-rat-anti-human-cd49f-goh3/p/555736
Sca1-APC https://www.labome.com/product/Miltenyi-Biotec/130-102-343.html
CD45-APC-cy7 https://www.biolegend.com/en-us/products/apc-cyanine7-anti-mouse-cd45-antibody-2530?GroupID=GROUP20

Animals and other organisms

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

Laboratory animals	Mice were housed individually in cages at a maximum density of 5 mice per cage and kept on a 12-h light-dark cycle. The ambient temperature was maintained at 22-26°C with 40-60 % humidity. Mice of both sexes were analyzed, ranging in age from 7weeks through 24 months. Both C57BL/6N and C57BL/6J were analyzed as wild type mice. Mutant strains included K15crePR, Rosa-H2B-EGFP (Riken CDB), Rosa-lsl-rtTA (Jackson lab, #005670), tetO-Gli2dC, IL1aKO, IL1bKO, IL1Ra KO, K19creER (Riken BRC), TNFa KO, Nrf2 KO and tetO-Gli2dN.
Wild animals	This study did not involve wild animals.
Field-collected samples	This study did not involve samples collected from the field.
Ethics oversight	Animal care was in accordance with the guidance of the Tokyo Medical and Dental University for animal and recombinant DNA experiments.

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	Dorsal skin was placed dermis side down in 0.25% trypsin (Gibco) or 0.2% Dispase 2 (Roche) for 12-14 h at 4°C. The epidermis and dermis were then obtained by scraping the skin gently. The epidermis was minced with a razor blade and then filtered with strainers (40 um) (BD Falcon, San Jose, CA, USA). The dermis was minced using scissors and the pieces were incubated in 0.2% collagenase (Sigma) for 1 h at 37°C with gentle agitation. Those suspensions were filtered with 70 um strainers and epidermal and dermal cells were obtained after two washes with PBS.
Instrument	BD FACSAria II (BD Biosciences) and BD FACSAria IIIu (BD Biosciences)
Software	FACSDiva and FACSAria software (BD Biosciences)
Cell population abundance	Fluorescent microscopic detection, over 90%
Gating strategy	To distinguish negative and positive events, unstained samples were used as negative control for each antibody. The sample containing only buffer without cells was used as negative control for FSC/SSC gates of starting cells.

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