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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 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	IDEAS 6.2 software (Amnis), Living Image 4.5.5 software (PerkinElmer), and BD FACSDiva Software v8.0.1 (BD Biosciences) were used to collect data.
Data analysis	Data was analyzed using Prism 7 (Graphpad Inc.). Imange was analyzed using ImageJ (v1.51g) software. Flow data was analyzed using FlowJo V10.7 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 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

The raw data that support the findings of this study are provided as source data files. The link for Tabula Muris Senis database is https://tabula-muris-senis.ds.czbiohub.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	Sample sizes were determined using power analysis based on the means and variation of pilot experiments and previous publications (doi: 10.1073/pnas.1515386112; 10.1038/s41591-018-0092-9).
Data exclusions	No data was excluded.
Replication	All the key findings were reliably reproduced in several independent cohorts with large Ns.
Randomization	Mice were assigned to experimental groups based on their genotypes.
Blinding	Investigators were blinded to allocation during experiments and outcome assessments.

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	Anti-Lamin B1, Proteintech 12987-1-AP (lot#:00092016) 1:100 dilution; Anti-p21 , Thermo Fisher Scientific 14-6715-81 (lot#:2343102) 1:40 dilution
Validation	Both antibodies were commercially available and validated by companies. For Lamin B1, validation can be found at https://www.ptglab.com/products/LMNB1-Antibody-12987-1-AP.htm. For p21, validation can be found at https://www.thermofisher.com/antibody/product/p21-WAF1-Cip1-Antibody-Polyclonal/14-6715-81. In addition to these validations, we also had negative controls (same samples with secondary antibody but without primary antibody) as validation for every experiment.

Animals and other organisms

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

Laboratory animals	Floxed tdTomato mice (#007914, C57BL/6, 2-4 months, female), floxed LUC mice (#005125,FVB.129S6, 2-4 months, female), floxed DTA mice (#009669,C57BL/6, 2-4 months, female), CAG-Cre mice (#004682,C57BL/6, 2-4 months, female), and Relafl/fl mice (#024342,C57BL/6, 2-4 months, female and male) were used for breeding to generate various transgenic mice. The age and sex information is listed below for the mice used in this study. Fig.2b, 4-month-old male and female mice; Fig.2c, 6-7 months old male mice;Fig.2d, 3 and 23 months old male and female mice ;Fig.3b, 3 and 23 months old male and female mice;Fig.4a and b, 3 and 23 months old male and female mice;Fig.4c, 3-month-old male and female mice;Fig.4d, 5 months old male mice;Fig.5, 7-8 months old male and female mice; Fig.6b, 6-7 months old male and female mice; Fig.6c, 3 and 23 months old male and female mice;Fig.8, 23 months old male and female mice;

Wild animals	No wild animals were used in the study.
Field-collected samples	No field collected samples were used in the study.
Ethics oversight	All animal experiments were performed according to protocols approved by the Institutional Animal Care and Use Committee (IACUC) at UConn Health.

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	The detailed information is included in the Methods section.
Instrument	BD LSR II flow cytometer (BD Biosciences)
Software	FlowJo software v10.7 (Becton, Dickinson and Company) and IDEAS 6.2 software (Amnis)
Cell population abundance	Sorted GFP+ cells were between 10-15% of the whole population.
Gating strategy	Gating strategies were described in the Methods section. For GFP and tdTomato expression, cells from mice without GFP or tdTomato transgene were used as negative control for gating. For SA-β-gal expression, low passage wildtype mouse ear fibroblasts stained with SA-β-gal were used as control. For EdU expression, wildtype young mice SVF cells with staining buffer but without EdU injection were used as control. For Lamin B1 expression, the SVF cells from same obese PL mice but without anti-Lamin B1 primary antibody were used as control. For p21 expression, the SVF cells from same old PT mice but without anti-p21 primary antibody were used as control for p21 expression.

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