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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 Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Collection of qPCR data: ExpressionSuite Software by Applied Biosystems, version 1.2.3. Microscope imaging: confocal, ZEN Black Edition SP1 by Carl Zeiss, version 8.1. Fluorescence, NIS Elements by Nikon, version 4.50. Brightfield, AxioVision by Carl Zeiss, version 4.8.2 SP3. Immunoblot Imaging: Image Studio by LI-COR Biosciences, version 5.2. ELISA plate reader: SoftMax® Pro software by Molecular Devices, version 5.0.1. Luciferase reporter assays: Modulus Fluorometer by Turner Biosystems, version 1.3

Data analysis	Excel was used to perform general statistical analyses (means, s.d., t-tests, etc). For 1-way ANOVA and Tukey's post-hoc test R software for statistical computing (64-bit version 3.3.2) was used. For RNAseq data analyses, the following software were used: Bowtie, HiSat2, featureCounts, EdgeR, RepEnrich and the GenePattern interface for GSEA Preranked. To detect and annotate L1 elements the web front-end L1Xplorer was used. GeneGlobe Data Analysis by Qiagen was used to analyze PCR array data. CellProfiler (version 2.1.1) by Broad Institute was used for image analysis. ImageJ (version 1.50i) was used for western blot quantification.

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 upon request. 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

Sequencing data that support the findings of this study are available in GEO with the primary accession code GSE109700. All source data and exact P values (if applicable) for every figure are included in the supporting information that accompanies the paper.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The nature and size of all samples are described in figure legends for all experiments. Sample sizes used were based on previously published experiments and experience from the Sedivy lab. No statistical test was used to pre-determine sample size.
Data exclusions	No pre-set criterion or data exclusion was used.
Replication	Results shown are representative of several independently performed experiments. Number of biological replicates and independent experiments is described in figure legends. All attempts at replication were successful. There were no findings that were not replicated or could not be reproduced.
Randomization	Genotype of C57BL/6 mice is known to investigators. No pre-established selection criteria for mice were used, other than gender and ages. When mice with desired gender were at appropriate ages, all mice in corresponding cages were used. No selection criteria were applied. Animals were assigned randomly to cohorts (drug-treated, control) by a technician that was blinded to the appearance or other characteristics of the animals.
Blinding	The investigators were blinded when quantifying IF results. Fields or sections of tissues for quantification were randomly selected and scored, as indicated in Methods. The investigators were also blinded when scoring glomerulosclerosis and muscle fiber diameter.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials

Kamuvudine-9 (Ref. Ambati, J.,Fowler, B. & Ambati, K. Compositions and Methods for Treating Retinal Degradation. PCT Patent Publication WO/2016/138425 (2016)) is available upon reasonable request from Dr. J. Ambati.

Antibodies

Antibodies used

Immunoblotting – GAPDH – (Cell Signaling Technology, Rabbit, cat.no. 5174, clone: n/a, 1:5000)
Immunoblotting – GAPDH – (Sigma, Mouse, cat.no. G8795, clone: n/a, 1:5000)
Immunoblotting – p16 – (Santa Cruz, Mouse, cat.no. sc-1661, clone: F-12, 1:1000)
Immunoblotting – p21 – (Santa Cruz, Rabbit, cat.no. sc-756, clone: H-164, 1:1000)
Immunoblotting, ChIP – RB1 – (BD Biosciences, Mouse, cat.no. 554136, clone: G3-245, 1:1000 WB, 1:50 ChIP)
Immunoblotting – TREX1 – (Cell Signaling Technology, Rabbit, cat.no. 12215, clone: n/a, 1:1000)
Immunoblotting – FOXA1 – (Abcam, Rabbit, cat.no. ab170933, clone: EPR10881, 1:1000)
Immunoblotting – STAT2 – (Cell Signaling Technologies, Rabbit, cat.no. 4594, clone: n/a, 1:1000)
Immunoblotting – IRF7 – (Abcam, Rabbit, cat.no. ab109255, clone: EPR4718, 1:1000)
ChIP – FOXA1 – (Abcam, Goat, cat.no. ab5089, clone: n/a, 1:50)
Immunofluorescence – p16 – (Santa Cruz, Mouse, cat.no. sc-56330, clone: JC8, 1:100)
Immunofluorescence – Phospho-STAT1 – (Santa Cruz, Mouse, cat.no. sc-8394, clone: A-2, 1:50)
Immunofluorescence – Phospho-STAT2 – (Millipore, Rabbit, cat.no. 07-224, clone: n/a, 1:50)
Immunofluorescence – IRF9 – (Novus Biologicals, Rabbit, cat.no. NBP2-16991, clone: n/a, 1:100)
Immunofluorescence, Immunoprecipitation – BrdU – (BD Biosciences, Mouse, cat.no. 555627, clone: 3D4, 1:100)
Immunofluorescence – p-H2A.X – (Millipore, Mouse, cat.no. 05-636, clone: JBW301, 1:100)
Immunofluorescence – F4/80 – (Abcam, Rat, cat.no. ab6640, clone: CI:A3-1, 1:200)
Immunofluorescence – ssDNA – (Enzo, Mouse, cat.no. ALX-804-192, clone: F7-26, 1:100)
Immunofluorescence – DNA:RNA – (Kerafast, Mouse, cat.no. ENH001, clone: S9.6, 1:100)
Immunofluorescence – LaminB1 – (Santa Cruz, Goat, cat.no. sc-6216, clone: C-20, 1:200)
Immunofluorescence – IL-6 – (Cell Signaling Technologies, Rabbit, cat.no. 12912, clone: D5W4V, 1:200)
Immunofluorescence – Human LINE-1 ORF1 – (Gift of K.H. Burns, Johns Hopkins)
Immunofluorescence – Mouse LINE-1 Orf1 – (J.D. Boeke, abEA02, RabMAb clone: NYU-2-1_2)

Validation

With the exception of LINE-1 ORF1 antibodies, all antibodies are from commercially available sources and have been validated from the manufacturer with supporting publications found on manufacturer websites. Antibodies were further validated in-house using relevant positive and negative controls.

The human LINE-1 ORF1 antibody was validated in the lab of K.H. Burns, Johns Hopkins, as described in Rodic et al. Am. J. Pathol. 184, 1280-6 (2014).

The mouse LINE-1 Orf1 antibody was developed and validated in the lab of J.D. Boeke by transfection experiments and peptide blocking.

See below for summary of commerically available antibodies:
Immunoblot – p16 – Santa Cruz, sc-1661
Species: Human, Mouse, Rat
Application: ELISA, Immunocytochemistry, Immunofluorescence, Immunohistochemistry, Western Blot

Immunoblot – p21 – Santa Cruz, sc-756
Species: Mouse, Rat and Human
Application: ELISA, Immunoprecipitation, Immunofluorescence, Western Blot

Immunoblot, ChIP – RB1 – BD Biosciences, 554136
Species: Human, Mouse, Rat, Monkey, Quail, Mink (Reported)
Application: Western blot, Intracellular staining (flow cytometry), Bioimaging, Immunohistochemistry-formalin, Immunoprecipitation, Immunohistochemistry-frozen

Immunoblot – TREX1 – Cell Signaling Technologies, 12215

Species: Human
Application: Western blot

Immunoblot – FOXA1 – Abcam, ab170933
Species: Human, Mouse, Rat
Application: Western blot, Intracellular staining (flow cytometry), Bioimaging, Immunohistochemistry-formalin, Immunohistochemistry-frozen

Immunoblot – STAT2 – Cell Signaling Technologies, 4594
Species: Human
Application: Western blot

Immunoblot – IRF7 – Abcam, ab109255
Species: Human, Mouse, Rat
Application: Western blot, Intracellular staining (flow cytometry), Immunofluorescence, Immunohistochemistry-formalin, Immunoprecipitation, Immunohistochemistry-frozen

ChIP – FOXA1 – Abcam, ab5089
Species: Human, Mouse
Application: ChIP, Western blot, Immunohistochemistry-formalin, Immunoprecipitation

Immunofluorescence – p16 – Santa Cruz, sc-56330
Species: Human
Application: Western blot, Immunofluorescence, Immunohistochemistry, Immunoprecipitation, solid-phase ELISA

Immunofluorescence – p-STAT1 – Santa Cruz, sc-8394
Species: Human, Mouse and Rat
Application: Western blot, Immunofluorescence, Immunoprecipitation, Flow-cytometry, solid-phase ELISA

Immunofluorescence – p-STAT2 – Millipore, 07-224
Species: Human, Mouse
Application: Western blot, Immunofluorescence, Immunoprecipitation

Immunofluorescence – IRF9 – Novus Biologicals, NBP2-16991
Species: Human, Monkey
Application: Western blot, Immunofluorescence, solid-phase ELISA, Immunohistochemistry

Immunofluorescence, Immunoprecipitation – BrdU – BD Biosciences, 555627
Species: Human
Application: Flow cytometry, Immunofluorescence, Immunoprecipitation, Immunohistochemistry

Immunofluorescence – IRF9 – Novus Biologicals, NBP2-16991
Species: Human, Monkey
Application: Western blot, Immunofluorescence, solid-phase ELISA, Immunohistochemistry

Immunofluorescence - p-H2A.X – Millipore, 05-636
Species: Vertebrates
Application: Immunocytochemistry, Immunofluorescence, Western Blot, ChIP, Immunohistochemistry

Immunofluorescence – F4/80 – Abcam, ab6640
Species: Mouse
Application: Immunocytochemistry, Immunofluorescence, Western Blot, Radioummunoassay, Immunohistochemistry

Immunofluorescence – ssDNA – Enzo Life Sciences, F7-26
Species: Species Independent
Application: Flow Cytometry, Immunocytochemistry, Immunofluorescence, Immunohistochemistry

Immunofluorescence – RNA:DNA – Kerafast, S9.6
Species: Species Independent
Application: Dot Blot, Affinity Binding Assay, ChIP, Immunocytochemistry, Immunofluorescence, Immunohistochemistry, Immunoprecipitation

Immunofluorescence – Lamin B1– Santa Cruz, sc-6216
Species: Human, Mouse and Rat
Application: Western Blot, Immunoprecipitation, Immunofluorescence, Immunohistochemistry, solid-phase ELISA

Immunofluorescence – IL-6 – Cell Signaling Technologies, 12912
Species: Mouse
Application: Western Blot, Immunoprecipitation, Immunofluorescence, Flow cytometry

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	LF1 cells were derived from embryonic lung tissue as described (Brown et al., Science, 1997). These cells have been in continuous use in our laboratory since their isolation in 1996. IMR-90 and WI-38 cells were obtained from the ATCC. HeLa cells were also obtained from the ATCC. 293T cells were only used for lentiviral packaging, and were obtained from Clontech.
Authentication	LF1 fibroblasts were authenticated by in-depth genome-wide sequencing analyses. IMR-90, WI-38, HeLa, and 293T cell lines were obtained from the sources above and used at low passage. They were not further authenticated.
Mycoplasma contamination	All cell cultures were periodically tested for mycoplasma. All cell lines tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	None of these cell lines are listed in the International Cell Line Authentication Committee (ICLAC) database.

Animals and other organisms

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

Laboratory animals	C57BL/6 mice were purchased from the Aged Rodent Colonies operated by the National Institute on Aging. Mice of both sexes were obtained at 5 and 18 months of age. The 5 month old animals were sacrificed after a short (1 week) acclimatization period. The 18 month old animals were housed until they reached a desired age. Mice were fed ad libitum on a regular diet, and handled following institutional regulations and guidelines. Both sexes were included in the study.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve field-collected samples.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Human skin specimens were collected as part of the Leiden Longevity Study (Schoenmaker, M. et al., Eur. J. Hum. Genet., 2006) and were provided by P. Eline Slagboom, Leiden University Medical Centre, Netherlands. 420 families of Caucasian origin took part in the Leiden Longevity Study (LLS). This group consisted of 991 long-lived brothers and/or sisters, their children and partners of their children. The samples were collected as 4 mm thickness full depth punch biopsies, embedded in optimal cutting compound (OCT), flash frozen, and stored at -80°C. Samples were shipped on dry ice to Brown University. The Brown investigators were blinded to everything except the age and sex of the subjects
Recruitment	The men were considered to be long-lived if they were 89 years or older, and the women if they were 91 years or older. Families were invited to participate when there were at least two long-lived brothers and/or sisters alive. Informed consent was obtained and all protocols were approved by the ethical committee of the Leiden University Medical Centre. The results of this study are purely observational and are not affected by any bias in cohort recruitment.