

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

The following standard software provided by instrument suppliers was used for data collection:

Flow cytometry: BD FACSCanto II
WB: Amersham Imager 600(GE Healthcare Life Sciences)
Immunofluorescence : Leica DMI8 microscope (Leica); Zeiss LSM 710 confocal microscope(Zeiss)
LC-MS: Agilent 1290 Infinity II LC system (Agilent, Waldbronn, Germany) coupled to either a QTrap 5500 mass spectrometer (Sciex, Darmstadt, Germany) or a 6495C QQQ mass spectrometer (Agilent Technologies, Waldbronn/Germany).
Analyst 1.60:Sciex (Darmstadt, Germany)
Fluorescence reader: Tecan instrument (Infinite 200 Pro, TECAN)

Data analysis

The following software was used for data analysis:

IGV2.8.13, <https://software.broadinstitute.org/software/igv/download>
Image J 1.47v, <https://imagej.nih.gov/ij/download.html>
BD FACSDiva Software (version8.0.1, firmware version 1.49 BD FACSCanto II), <https://www.bdbiosciences.com/en-eu/products/software/instrument-software/bd-facsdiva-software>
FCS Express 7, <https://denovosoftware.com/full-access/download-landing/>
Zen 2.3, <https://www.zeiss.de/mikroskopie/produkte/mikroskopsoftware/zen-lite/zen-lite-download.html>
DAVID v2023q4 , <https://david.ncifcrf.gov/summary.jsp>
Heatmapper, <http://www.heatmapper.ca/expression/>
MUSCLEMOTION V1.0 ,<https://github.com/l-sala/MUSCLEMOTION>
MultiQuant 3.0, :<https://sciex.com/products/software/multiquant-software>
Metaboanalyst 6.0, <https://www.metaboanalyst.ca/>

GraphPad Prism v9.4.1, <https://www.graphpad.com/>
 Calculate and draw custom Venn diagrams, <http://bioinformatics.psb.ugent.be/webtools/Venn/>
 STAR version 2.7.3a, <https://github.com/alexdobin/STAR/blob/master/doc/STARmanual.pdf>
 Trimmomatic version 0.39, <http://www.usadellab.org/cms/?page=trimmomatic>
 BamTools version 2.5.1, <https://github.com/pezmaster31/bamtools>
 MultiQC version 1.6, <https://multiqc.info/>
 DESeq2 version 1.28.0, <http://bioconductor.org/packages/release/bioc/vignettes/DESeq2/inst/doc/DESeq2.html>
 Ngsplot version 2.41.4, <https://github.com/shenlab-sinai/ngsplot>
 Homer version 4.11, <http://homer.ucsf.edu/homer/motif/>
 Bowtie2 version 2.3.4.1, <https://github.com/BenLangmead/bowtie2>
 SAMtools version 1.7, <http://www.htslib.org/>
 Picard-tools version 1.119, <https://broadinstitute.github.io/picard/>
 deepTools version 3.3.0, <https://deeptools.readthedocs.io/en/develop/>
 MACS2 version 2.1.1.20160309, <https://pypi.org/project/MACS2/>
 Bedtools version 2.28.0, <https://bedtools.readthedocs.io/en/latest/>
 R package DiffBind version 2.16.0, <http://bioconductor.org/packages/release/bioc/vignettes/DiffBind/inst/doc/DiffBind.pdf>
 R package ChIPseeker version 1.24.0, <https://guangchuangyu.github.io/software/ChIPseeker/>
 R package rtracklayer version 1.48.0, <https://bioconductor.org/packages/release/bioc/html/rtracklayer.html>
 R package EnhancedVolcano version 1.6.0, <https://github.com/kevinblighe/EnhancedVolcano>
 Cell Ranger (v.7.1.0), https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/installation?src=website&lss=organic/direct/direct&cnm=wbr-2020-08-21-event-ra_g-p_scmage-apac-2020-08-21-event-ra_g-p_scmage-apac&cid=7011P000000oPkw/
 Seurat (v. 4.3.0), <https://satijalab.org/seurat/articles/install>
 LADetector, <https://github.com/thereddylab/LADetector?tab=readme-ov-file>

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](#)

Sequencing data generated in this study have been deposited in GEO database under accession code GSE248534. The proteomics data have been deposited in the PRIDE repository under accession number XXXX

Lamin A DamID (GSE62685) 87, lamin B1 DamID (GSE17051) 18 ATAC-seq data from Lmna-/-, LmnaG609G/+ and LmnaG609G/G609G mESC as well as Hi-C and RNA-Seq data from Lmna-/- ESC (GSE164069) 33 were retrieved from previously published studies. Single cell sequencing data of mouse embryos were retrieved from GSE10059750. ATAC-seq data of naïve and primed mESC were retrieved from E-MTAB-720788. RNA-seq data of young, aged individuals, as well as progeria patients were retrieved from GSE11395789. Source data are provided with this paper.

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

Reporting on race, ethnicity, or other socially relevant groupings

Population characteristics

Recruitment

Ethics oversight

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	No statistical measures were used to determine sample size. Sample size is based on our experience and on publications by other groups.
Data exclusions	No data were excluded.
Replication	All experiments were performed at least three independent times. The number of independent experiments and biological replicates in each data panel is indicated in the figure legends. All attempts at replication were successful.
Randomization	Randomization was not applicable, as group allocation was determined by mouse genotype or genetic manipulation. Cell culture treatments (compound exposure, gene silencing, or overexpression) were applied in parallel to avoid bias.
Blinding	Whenever possible, investigators were blinded during data acquisition. Samples were labeled with sequential numbers during preparation and, in most cases, throughout data collection, image acquisition, and metabolite analyses.

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
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern
<input checked="" type="checkbox"/>	<input type="checkbox"/> Plants

Methods

n/a	Involved in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> ChIP-seq
<input type="checkbox"/>	<input checked="" type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Antibodies

Antibodies used

Rabbit monoclonal anti-CTH (D1N1D), Cell Signaling Technology, Cat# 19689T, RRID: AB_2798824, 1:100 for IF and 1:1000 for WB
 Rabbit monoclonal anti-CBS (D8F2P), Cell Signaling Technology, Cat# 14782T, RRID: AB_2798609, 1:100 for IF and 1:1000 for WB
 Mouse monoclonal anti-LaminA/C (E-1), Santa Cruz, Cat# sc-376248, RRID:AB_10991536, 1:100 for IF, 1:100 for FACS, 1:1000 for WB
 Mouse monoclonal anti-LaminA/C (131C3), Abcam, Cat# ab8984, RRID:AB_306913, 1:100 for IF, 1:1000 for WB
 Rabbit polyclonal anti-LaminB1, Abcam, Cat# ab16048, RRID: AB_10107828, 1:1000 for WB
 Mouse monoclonal anti-LaminB1, Santa Cruz, Cat# sc-374015, RRID:AB_10947408, 1:1000 for WB, 1:00 for IF
 Rabbit monoclonal anti-Acetyl-Histone H3 (Lys9) (C5B11), Cell Signaling Technology, Cat# 9649S, RRID: AB_823528, 1:1000 for WB
 Rabbit monoclonal anti-Acetyl-Histone H3 (Lys27) (D5E4), Cell Signaling Technology, Cat# 8173, RRID: AB_10949503, 1:1000 for WB
 Rabbit polyclonal anti-Histone H3ac (pan-acetyl), Invitrogen, Cat# PA5-114693, RRID: AB_2899329, 1:1000 for WB
 Rabbit polyclonal anti-Histone H3 (tri methyl K9), Abcam, Cat# ab8898, RRID: AB_306848, 1:5000 for WB, 1:100 for IF
 Rabbit polyclonal anti-trimethyl-Histone H3 (Lys27) Antibody, Millipore, Cat# 07-449, RRID:AB_310624, 1:100 for IF
 Rabbit polyclonal anti-Acetyl-Histone H3 (Lys56), Cell Signaling Technology, Cat# 4243T, RRID: AB_10548193, 1:1000 for WB
 Rabbit polyclonal anti-Acetyl-Histone H4 (Lys8), Cell Signaling Technology, Cat# 2594T, RRID: AB_2248400, 1:1000 for WB
 Rabbit polyclonal anti-Acetylated-Lysine, Cell Signaling Technology, Cat# 9441S, RRID: AB_331805, 1:1000 for WB
 Rabbit polyclonal anti-Histone H2B, Abcam, Cat# ab1790, RRID: AB_302612, 1:1000 for WB
 Rabbit polyclonal anti-Histone H3, Abcam, Cat# ab1791, RRID: AB_302613, 1:1000 for WB
 Rabbit monoclonal anti-Phospho-Histone H2A.X (Ser139) (20E3), Cell Signaling Technology, Cat# 9718T, RRID: AB_2118009, 1:100 for IF and 1:1000 for WB
 Rabbit monoclonal anti-SUV39H1 (D11B6), Cell Signaling Technology, Cat# 8729T, RRID: AB_10829612, 1:1000 for WB
 Rabbit monoclonal anti-AHCYL1/IRBIT (D3A5G), Cell Signaling Technology, Cat# 94248T, RRID: AB_2800225, 1:1000 for WB
 Rabbit monoclonal anti-Thymidylate Synthase (D5B3), Cell Signaling Technology, Cat# 9045T, RRID: AB_2797693, 1:1000 for WB
 Rabbit monoclonal anti-MTHFD1L (D8T7L), Cell Signaling Technology, Cat# 14999T, RRID: AB_2798681, 1:1000 for WB
 Rabbit monoclonal anti-MTHFD2 (D8W9U), Cell Signaling Technology, Cat# 41377T, RRID: AB_2799200, 1:1000 for WB
 Rabbit monoclonal anti-SHMT1 (D3B3J), Cell Signaling Technology, Cat# 80715T, RRID: AB_2799957, 1:1000 for WB
 Rabbit monoclonal anti-MTHFR (D1E4V), Cell Signaling Technology, Cat# 25164T, RRID: AB_2798897, 1:1000 for WB
 Rabbit polyclonal anti-3-MPST, Sigma-Aldrich, Cat# HPA001240, RRID: AB_1079408, 1:1000 for WB
 Rabbit polyclonal anti- α -Tubulin, Cell Signaling Technology, Cat# 2144S, RRID: AB_2210548, 1:1000 for WB
 Mouse monoclonal anti-Alpha-Actinin ACTN2, Boster Biological Technology, Cat# MA1104, RRID: 1:100 for IF
 Goat polyclonal anti-cardiac troponin I, Abcam, Cat# ab56357, RRID:AB_880622, 1:00 for IF
 Mouse monoclonal Anti-phospho-Histone H2A.X (Ser139), Millipore, Cat# 05-636-I, RRID: AB_2755003, 1:100 for IF and 1:1000 for WB
 Mouse monoclonal anti-OCT3/4 (C-10), Santa Cruz, Cat# sc-5279, RRID: AB_628051, 1:100 for IF and 1:50 for FACS

Rabbit polyclonal anti-NANOG, Cell Signaling Technology Cat# 3580, RRID:AB_2150399, 1:100 for FACS
 Mouse monoclonal anti-SP1, Santa Cruz Biotechnology Cat# sc-17824, RRID:AB_628272, 1:1000 for WB
 CD31 (PECAM-1) Monoclonal Antibody (390), APC, eBioscience™, Thermo Fisher Scientific, Cat# 17-0311-82, RRID: AB_657735, 1:40
 Alexa Fluor® 647 Mouse Anti-Cardiac Troponin T Clone 13-11, BD Biosciences, Cat# 565744, RRID: AB_2739341, 1:40
 Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor 555, Thermo Fisher Scientific, Cat# A-31570, RRID: AB_2536180, 1:500
 Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488, Thermo Fisher Scientific, Cat# A-21202, RRID: AB_141607, 1:500
 Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor 488, Thermo Fisher Scientific, Cat# A-21206, RRID: AB_2535792, 1:500
 Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 555, Thermo Fisher Scientific, Catalog # A-31572, RRID:AB_162543, 1:500
 Donkey anti-Goat IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 555, Thermo Fisher Scientific, Catalog # A-21432, RRID:AB_2535853, 1:500
 Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 647, Thermo Fisher Scientific, Catalog # A-31571, RRID:AB_162542, 1:500

Validation

All antibodies used were purchased from commercial vendors and were selected because they have been validated by the manufacturer and multiple publications. Validation details and relevant publications are detailed in their respective websites.

Rabbit monoclonal anti-CTH (D1N1D): <https://www.cellsignal.com/products/primary-antibodies/cystathionine-g-lyase-d1n1d-rabbit-mab/19689>

Rabbit monoclonal anti-CBS (D8F2P): <https://www.cellsignal.com/products/primary-antibodies/cbs-d8f2p-rabbit-mab/14782>

Rabbit polyclonal anti-LaminB1: <https://www.abcam.com/lamin-b1-antibody-nuclear-envelope-marker-ab16048.html>

Mouse monoclonal anti-LaminB1: <https://www.scbt.com/p/lamin-b1-antibody-b-10?srsltid=AfmBOOpNCPeJNBLeUrCQCY9SToD0fuwqRpFdALEBF6VJrDchyNKuyav>

Mouse monoclonal Anti-Lamin A/C Antibody (E-1): <https://www.scbt.com/p/lamin-a-c-antibody-e-1?productCanUrl=lamin-a-c-antibody-e-1&requestid=793642>

Mouse monoclonal anti-LaminA/C (131C3): https://www.abcam.com/en-us/products/primary-antibodies/lamin-a-lamin-c-antibody-131c3-nuclear-envelope-marker-ab8984?srsltid=AfmBOOqXsm9Ah1GRvllhqYM6wJFRgoGc5dN_3cwwU6hH4te-KMKZyQ1K

Mouse monoclonal anti-SP1: https://www.scbt.com/p/sp1-antibody-e-3?srsltid=AfmBOOoZVpIXB_FcgJpZYfmaD7MNKRTreyk_2Tm10oZY1aZ7FYXhrWkl

Rabbit monoclonal anti-Acetyl-Histone H3 (Lys9) (C5B11): <https://www.cellsignal.com/products/primary-antibodies/acetyl-histone-h3-lys9-c5b11-rabbit-mab/9649>

Rabbit monoclonal anti-Acetyl-Histone H3 (Lys27) (D5E4): <https://www.cellsignal.com/products/primary-antibodies/acetyl-histone-h3-lys27-d5e4-xp-174-rabbit-mab/8173>

Rabbit polyclonal anti-Histone H3ac (pan-acetyl): <https://www.thermofisher.com/antibody/product/Histone-H3ac-pan-acetyl-Antibody-Polyclonal/PA5-114693>

Rabbit polyclonal anti-Histone H3 (tri methyl K9): <https://www.abcam.com/products/primary-antibodies/histone-h3-tri-methyl-k9-antibody-chip-grade-ab8898.html>

Rabbit polyclonal anti-trimethyl-Histone H3 (Lys27) Antibody: https://www.merckmillipore.com/DE/en/product/Anti-trimethyl-Histone-H3-Lys27-Antibody,MM_NF-07-449?ReferrerURL=https%3A%2F%2Fwww.google.com%2F

Rabbit polyclonal anti-Acetyl-Histone H3 (Lys56): <https://www.cellsignal.com/products/primary-antibodies/acetyl-histone-h3-lys56-antibody/4243>

Rabbit polyclonal anti-Acetyl-Histone H4 (Lys8): <https://www.cellsignal.com/products/primary-antibodies/acetyl-histone-h4-lys8-antibody/2594>

Rabbit polyclonal anti-Acetylated-Lysine: <https://www.cellsignal.com/products/primary-antibodies/acetylated-lysine-antibody/9441>

Rabbit polyclonal anti-Histone H2B: <https://www.abcam.com/products/primary-antibodies/histone-h2b-antibody-chip-grade-ab1790.html>

Rabbit polyclonal anti-Histone H3: <https://www.abcam.com/products/primary-antibodies/histone-h3-antibody-nuclear-marker-and-chip-grade-ab1791.html>

Rabbit monoclonal anti-Phospho-Histone H2A.X (Ser139) (20E3): <https://www.cellsignal.com/products/primary-antibodies/phospho-histone-h2a-x-ser139-20e3-rabbit-mab/9718>

Rabbit monoclonal anti-SUV39H1 (D11B6): <https://www.cellsignal.com/products/primary-antibodies/suv39h1-d11b6-rabbit-mab/8729>

Rabbit monoclonal anti-AHCYL1/IRBIT (D3A5G): <https://www.cellsignal.com/products/primary-antibodies/ahcyl1-irbit-d3a5g-rabbit-mab/94248>

Rabbit monoclonal anti-Thymidylate Synthase (D5B3): <https://www.cellsignal.com/products/primary-antibodies/thymidylate-synthase-d5b3-xp-rabbit-mab/9045>

Rabbit monoclonal anti-MTHFD1L (D8T7L): <https://www.cellsignal.com/products/primary-antibodies/mthfd1l-d8t7l-rabbit-mab/14999>

Rabbit monoclonal anti-MTHFD2 (D8W9U): <https://www.cellsignal.com/products/primary-antibodies/mthfd2-d8w9u-rabbit-mab/41377>

Rabbit monoclonal anti-SHMT1 (D3B3J): <https://www.cellsignal.com/products/primary-antibodies/shmt1-d3b3j-rabbit-mab/80715>

Rabbit monoclonal anti-MTHFR (D1E4V): <https://www.cellsignal.com/products/primary-antibodies/mthfr-d1e4v-rabbit-mab/25164>

Rabbit polyclonal anti-3-MPST: <https://www.sigmaldrich.com/DE/en/product/sigma/hpa001240>

Rabbit polyclonal anti-α-Tubulin: <https://www.cellsignal.com/products/primary-antibodies/a-tubulin-antibody/2144>

Mouse monoclonal anti-Alpha-Actinin ACTN2: <https://www.bosterbio.com/anti-alpha-actinin-antibody-monoclonal-ma1104-boster.html>

Goat polyclonal anti-cardiac troponin I: <https://www.abcam.com/en-us/products/primary-antibodies/cardiac-troponin-i-antibody-ab56357?srsltid=AfmBOopl8LNpj2lOdbf0klNE3GGADHJsMg6lw6QznfePZOsojZG4l0Cz>

Mouse monoclonal Anti-phospho-Histone H2A.X (Ser139): https://www.merckmillipore.com/DE/de/product/Anti-phospho-Histone-H2A.X-Ser139-Antibody-clone-JBW301,MM_NF-05-636?ReferrerURL=https%3A%2F%2Fwww.google.com%2F

Mouse monoclonal anti-OCT3/4 (C-10): <https://www.scbt.com/p/oct-3-4-antibody-c-10?productCanUrl=oct-3-4-antibody-c-10&requestid=798972>

Mouse monoclonal anti-SP1: https://www.scbt.com/p/sp1-antibody-e-3?srsltid=AfmBOoHlatg7dQ-Br5rpFqhpBVZSWKlii3yyt_M9pJbxRJR_sDU6VC_

Rabbit polyclonal anti-NANOG: https://www.cellsignal.com/products/primary-antibodies/nanog-antibody/3580?srsId=AtmBOopHhn0zYBu5UxvkoAjVUr7A_ZYYJy1VSBHb34qcUCOB-blhemTE
 Alexa Fluor® 647 Mouse Anti-Cardiac Troponin T Clone 13-11: <https://www.bdbiosciences.com/en-nz/products/reagents/flow-cytometry-reagents/research-reagents/single-color-antibodies-ruo/alexa-fluor-647-mouse-anti-cardiac-troponin-t.565744>
 Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor 555: <https://www.thermofisher.com/antibody/product/Donkey-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-31570>
 Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488: <https://www.thermofisher.com/antibody/product/Donkey-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21202>
 Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor 488: <https://www.thermofisher.com/antibody/product/Donkey-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21206>
 Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 555: <https://www.thermofisher.com/antibody/product/Donkey-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-31572>
 Donkey anti-Goat IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 555: <https://www.thermofisher.com/antibody/product/Donkey-anti-Goat-IgG-H-L-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21432>
 Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 647: <https://www.thermofisher.com/antibody/product/Donkey-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-31571>

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	Female HEK293T cells and male R1 mESCs were purchased from ATCC (CRL-3216 and SCRC-1011); male E14-NKX2-5-EmGFP ESCs generated by Hsiao et al as described in : Marking embryonic stem cells with a 2A self-cleaving peptide: a NKX2-5 emerald GFP BAC reporter. PLoS One 3, e2532 (2008).
Authentication	E14-NKX2-5-EmGFP ESCs line authentication was based on the detection of cellular green fluorescent protein. HEK293T cells and R1 mESCs were authenticated by ATCC.
Mycoplasma contamination	Cell lines were mycoplasma negative.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used in the study.

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	The Lmna tm1.1Yxz/J and C57BL/6J mice were obtained from Jackson Laboratory. All animal experiments were performed according to the regulations issued by the Committee for Animal Rights Protection of the State of Baden-Württemberg (Regierungspraesidium Karlsruhe). Mice were housed in a specific pathogen-free animal facility under standard conditions with a 12 hour light/dark cycle , temperature of 20-25 degrees and humidity range of of 30-70%.Both male and female mice at the indicated in the figure legends age were used within the study.
Wild animals	No wild animals were used in this study.
Reporting on sex	Both male and female mice at the indicated in the figure legends age were used within the study.
Field-collected samples	No field-collected samples were used in this study.
Ethics oversight	All animal experiments were performed according to the regulations issued by the Committee for Animal Rights Protection of the State of Baden-Württemberg (Regierungspraesidium Karlsruhe, Experimental protocol Az.: I-25/09 and 35-9185.81/G-17/24).

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

Data deposition

- ☒ Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- ☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links

May remain private before publication.

Sequencing data generated in this study have been deposited in GEO database under accession code GSE248534.

Files in database submission

ES_shControl_RNA_seq_r1
 ES_shControl_RNA_seq_r2
 ES_shControl_Lmna_KO_RNA_seq_r1
 ES_shControl_Lmna_KO_RNA_seq_r2
 ES_shCth_Lmna_KO_RNA_seq_r1
 ES_shCth_Lmna_KO_RNA_seq_r2
 ES_shCbs_Lmna_KO_RNA_seq_r1
 ES_shCbs_Lmna_KO_RNA_seq_r2
 ES_CTH_OE_RNA_seq_r1
 ES_CTH_OE_RNA_seq_r2
 ES_CBS_OE_RNA_seq_r1
 ES_CBS_OE_RNA_seq_r2
 ES_Control_H3K9acChIP_seq_r1
 ES_Control_H3K9acChIP_seq_r2
 ES_Lmna_KO_H3K9acChIP_seq_r1
 ES_Lmna_KO_H3K9acChIP_seq_r2
 ES_CTH_OE_H3K9acChIP_seq_r1
 ES_CTH_OE_H3K9acChIP_seq_r2
 ES_CBS_OE_H3K9acChIP_seq_r1
 ES_CBS_OE_H3K9acChIP_seq_r2
 ES_Control_H3K27acChIP_seq_r1
 ES_Control_H3K27acChIP_seq_r2
 ES_Lmna_KO_H3K27acChIP_seq_r1
 ES_Lmna_KO_H3K27acChIP_seq_r2
 ES_CTH_OE_H3K27acChIP_seq_r1
 ES_CTH_OE_H3K27acChIP_seq_r2
 ES_CBS_OE_H3K27acChIP_seq_r1
 ES_CBS_OE_H3K27acChIP_seq_r2
 ES_Control_inputChIP_seq_r1
 ES_Control_inputChIP_seq_r2
 ES_Lmna_KO_inputChIP_seq_r1
 ES_Lmna_KO_inputChIP_seq_r2
 ES_CTH_OE_inputChIP_seq_r1
 ES_CTH_OE_inputChIP_seq_r2
 ES_CBS_OE_inputChIP_seq_r1
 ES_CBS_OE_inputChIP_seq_r2
 PLKO_LmnaKO_H3K9ac_rep1
 PLKO_LmnaKO_H3K9ac_rep2
 LmnaKO_shCbs_H3K9ac_rep1
 LmnaKO_shCbs_H3K9ac_rep2
 LmnaKO_shCth_H3K9ac_rep1
 LmnaKO_shCth_H3K9ac_rep2
 In_PLKO_LmnaKO_rep1.
 In_PLKO_LmnaKO_rep2
 In_LmnaKO_shCbs_rep1
 In_LmnaKO_shCbs_rep2
 In_LmnaKO_shCth_rep1
 In_LmnaKO_shCth_rep2
 ES_Ctr_H3K9me3_seq_r1
 ES_Ctr_H3K9me3_seq_r2
 ES_Lmna_KO_H3K9me3_seq_r1
 ES_Lmna_KO_H3K9me3_seq_r2
 ES_LmnaG609G_homo_H3K9me3_seq_r1
 ES_LmnaG609G_homo_H3K9me3_seq_r2

Genome browser session
(e.g. [UCSC](#))

No longer applicable

Methodology

Replicates

RNA-Seq, Chip-Seq experiments were performed with at least two independent biological replicates.

ES_shControl_RNA_seq_r1.fq.gz, 36527932, single end
 ES_shControl_RNA_seq_r2.fq.gz, 38941414, single end
 ES_shControl_Lmna_KO_RNA_seq_r1.fq.gz, 34352653, single end
 ES_shControl_Lmna_KO_RNA_seq_r2.fq.gz, 40680629, single end
 ES_shCth_Lmna_KO_RNA_seq_r1.fq.gz, 34027415, single end
 ES_shCth_Lmna_KO_RNA_seq_r2.fq.gz, 36305274, single end
 ES_shCbs_Lmna_KO_RNA_seq_r1.fq.gz, 33410706, single end
 ES_shCbs_Lmna_KO_RNA_seq_r2.fq.gz, 39094061, single end
 ES_CTH_OE_RNA_seq_r1.fq.gz, 34883870, single end
 ES_CTH_OE_RNA_seq_r2.fq.gz, 40336328, single end
 ES_CBS_OE_RNA_seq_r1.fq.gz, 36172886, single end
 ES_CBS_OE_RNA_seq_r2.fq.gz, 32936885, single end
 mES_Ctr_LA_exp1_r1,20897825, pair end
 mES_Ctr_LA_exp1_r2,21016738, pair end
 mES_Ctr_LA_exp1_r3,21322334, pair end
 mES_LA_G609G_het_exp1_r1,21831933, pair end
 mES_LA_G609G_het_exp1_r2,231922/4, pair end
 mES_LA_G609G_het_exp1_r3,21976860, pair end
 mES_LA_G609G_homo_exp1_r1,22956566, pair end
 mES_LA_G609G_homo_exp1_r2,23249595, pair end
 mES_LA_G609G_homo_exp1_r3,22928374, pair end
 mES_Ctr_Lmna_exp2_r1, 26622967, pair end
 mES_Ctr_Lmna_exp2_r2,20444308, pair end
 mES_LA_G609G_homo_exp2_r1,20939375, pair end
 mES_LA_G609G_homo_exp2_r2,20474256, pair end
 mES_LA_G609G_homo_CBSOE_exp2_r1,23471993, pair end
 mES_LA_G609G_homo_CBSOE_exp2_r2,21856010, pair end
 ES_Control_H3K9acChIP_seq_r1, 13500280, pair end
 ES_Control_H3K9acChIP_seq_r2, 18198267, pair end
 ES_Lmna_KO_H3K9acChIP_seq_r1, 17602321, pair end
 ES_Lmna_KO_H3K9acChIP_seq_r2, 14343527, pair end
 ES_CTH_OE_H3K9acChIP_seq_r1, 15114927, pair end
 ES_CTH_OE_H3K9acChIP_seq_r2, 12930648, pair end
 ES_CBS_OE_H3K9acChIP_seq_r1, 18232789, pair end
 ES_CBS_OE_H3K9acChIP_seq_r2, 16344770, pair end
 ES_Control_H3K27acChIP_seq_r1, 15766339, pair end
 ES_Control_H3K27acChIP_seq_r2, 18497279, pair end
 ES_Lmna_KO_H3K27acChIP_seq_r1, 15627205, pair end
 ES_Lmna_KO_H3K27acChIP_seq_r2, 16276725, pair end
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 ES_CTH_OE_H3K27acChIP_seq_r2, 14818565, pair end
 ES_CBS_OE_H3K27acChIP_seq_r1, 15465764, pair end
 ES_CBS_OE_H3K27acChIP_seq_r2, 20599038, pair end
 ES_Control_inputChIP_seq_r1, 15001581, pair end
 ES_Control_inputChIP_seq_r2, 14271097, pair end
 ES_Lmna_KO_inputChIP_seq_r1, 14198892, pair end
 ES_Lmna_KO_inputChIP_seq_r2, 12555791, pair end
 ES_CTH_OE_inputChIP_seq_r1, 16341109, pair end
 ES_CTH_OE_inputChIP_seq_r2, 11350261, pair end
 ES_CBS_OE_inputChIP_seq_r1, 2313708, pair end
 ES_CBS_OE_inputChIP_seq_r2, 1293000, pair end
 PLKO_LmnaKO_H3K9ac_rep1,24948564,single end
 PLKO_LmnaKO_H3K9ac_rep2,25631029,single end
 LmnaKO_shCbs_H3K9ac_rep1,29787426,single end
 LmnaKO_shCbs_H3K9ac_rep2,29083801,single end
 LmnaKO_shCth_H3K9ac_rep1,26801692,single end
 LmnaKO_shCth_H3K9ac_rep2,26672179,single end
 In_PLKO_LmnaKO_rep1,19718408,single end
 In_PLKO_LmnaKO_rep2,11812384,single end
 In_LmnaKO_shCbs_rep1,13755481,single end
 In_LmnaKO_shCbs_rep2,15537788,single end
 In_LmnaKO_shCth_rep1,25698816,single end
 In_LmnaKO_shCth_rep2,18168241,single end
 ES_Ctr_H3K9me3_seq_r1, 24959930, pair end
 ES_Ctr_H3K9me3_seq_r2, 23706959, pair end
 ES_Lmna_KO_H3K9me3_seq_r1, 23096993, pair end
 ES_Lmna_KO_H3K9me3_seq_r2, 21754969, pair end
 ES_LmnaG609G_homo_H3K9me3_seq_r1, 25998548, pair end
 ES_LmnaG609G_homo_H3K9me3_seq_r2, 21665543, pair end
 Day10_EB_Control_scrRNA_seq_r1.fq.gz 388105318, pair end
 Day10_EB_Lmna_KO_scrRNA_seq_r1.fq.gz 375739739, pair end
 Day10_EB_Lmna_KO_CTH_KD_scrRNA_seq_r1.fq.gz 367193535, pair end

Antibodies	H3K9ac antibody: Cell Signaling Technology, 96495; H3K27ac antibody: Active motif, 39135; H3K9me3 antibody: Abcam, ab8898;
Peak calling parameters	MACS14 (default settings)
Data quality	ChIP-seq reads were trimmed with Trimmomatic, aligned to mm10 using Bowtie2, and PCR duplicates removed using Picard MarkDuplicates.
Software	Bowtie2 version 2.4.4, STAR version 2.7.3a, ngsplot version 2.47.1, Deseq2 version 1.28.1

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	EBs were washed twice with HBSS and dissociated with 1 mg/ml collagenase I (Cell Systems, LS004196) at 37°C for 30 min. Single cells were washed with 5% FCS/PBS and then blocked in 10% FCS/PBS buffer for 30 min at room temperature. For FACS staining of intracellular markers, 400,000 single cells obtained from EBs were fixed with 3.7% (wt/vol) paraformaldehyde for 30 minutes at room temperature. After washing twice in 5% FCS/PBS, cells were permeabilized with 0.5% saponin/5% FCS/PBS for 15 minutes on ice and incubated with 2.5 µl APC-conjugated anti-troponin T antibody (BD Biosciences, 565744) in 100µl permeabilization buffer for 2 hours at room temperature in a dark place. Cells were washed three times with PBS and resuspended in FACS buffer for FACS analysis. For FACS analysis of OCT4, NANOG and Lamin A/C expression, cells were first stained with OCT4 (Santa Cruz, sc5279, 1:40), NANOG (Cell Signaling, 3580S, 1:100) and lamin A/C (Santa Cruz, sc-376248; 1:100) for 2 hours followed by staining with corresponding secondary antibody (Thermo Fisher Scientific, 1:200) for 1 hour at room temperature. After washes with PBS, cells were resuspended in 300µl FACS buffer for FACS analysis. For the apoptosis assay by FACS, one million cells were stained with 5 µl APC Annexin V and 5 µl 7-AAD in 100 µl Annexin V Binding Buffer for 15 min at room temperature, following the manufacturer's instructions for the APC Annexin V Apoptosis Detection Kit with 7-AAD (BioLegend, 640930). Cells were then resuspended in 400 µl Annexin V Binding Buffer and analyzed by FACS. Cardiomyocytes (CMs) and non-CMs were distinguished based on Nkx2-5 GFP expression. For ROS detection, mESCs were incubated with 1µM of MitoSOX green (Invitrogen™, M36006) for 30 min at 37°C in a 5% CO2 in HBSS. After 3 washes with pre-warmed HBSS, cells were analyzed by flow cytometry with GFP channel.
Instrument	BD FACSCanto II, BD FACSAria IIu
Software	Data were collected and analyzed using BD FACSDiva™ software(version8.0.1) and FCS Express™ 7.
Cell population abundance	Post sorting confirmed the high purity of the sorted populations.
Gating strategy	Unstained cells were used to define negative cell populations and set gates for analysis.

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