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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	Data collection was performed using a Zeiss Axio Observer Z1 inverted fluorescence microscope and Leica SP8-STED/FLIM/FCS confocal microscope for fluorescence imaging; plate reader (Inifinte 200Pro, 30050303) was used to collect data on 5-mc level and cell viability; CFX96 Real-Time PCR Detection System was utilized for measuring mRNA expression; JPK Nanowizard 4a system was used for measuring cell modulus; TC-20 system for measuring cell diameter; Quantity One 4.6.3 software (Bio-Rad) used to perform blotting imaging; Nikon Eclipse Ti inverted microscope equipped with a cooled charge-coupled device (CCD) camera was utilized FRET imaging
Data analysis	Data analysis was performed by free or commercial software platforms, including ImageJ for measuring the cell percentage, nuclear size and winkling, and histone condensation. Origin 2018 was used to generate bar charts or box charts and perform statistical analysis. MetaFluor 7.8 was utilized to calculate and visualize the ECFP/FRET ratio. Nano Scope Analysis was utilized to record force-distance curves and calculate the elastic modulus of cells using the Hertz model.

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 authors declare that all data supporting the findings of this study are available within the paper, source data, and supplementary information files.

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	A minimum of three independent experiments were carried out for all in vitro studies. The sample size necessary to detect a significant effect was estimated by using data from pilot studies with the following information: minimum significant effect to be detected, data variation, power (0.8) and Type-I error rate (0.05). The significance between two groups was analyzed by two-tailed Student's t-test. For multiple comparisons, one-way analysis of variance (ANOVA) with Tukey's post hoc test was used. Statistical analysis was performed using Origin 2018 software. A p-value < 0.05 was considered significant.
Data exclusions	No data exclusion in this research
Replication	In all experiments, either replicate or triplicate of samples were processed in parallel. All experiments were performed independently 3 times or more and consistent results were evident across independent experiments.
Randomization	For our experiments, all fibroblasts were derived from 4-week old C57BL/6 mice. Cells isolated from the same batch were used in a given experiment and cells were randomly chosen for the control or experimental groups. Experiments were also performed with different batches of cells to confirm the findings.
Blinding	One of the co-authors (Tyler) assisted in quantifying the reprogramming efficiency and histone intensity (Fig. 2, Fig. 3, Fig. 4 and Supplemental figures) but he remained blinded as to which samples were the control versus experimental groups.

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

Tuj1, Biolegend, Cat# 801202, mouse, 1: 1000 (IF)
H3K4me1, Abcam, Cat# ab32356, Rabbit, 1: 300 (IF)
H3K9me3, Abcam, Cat# ab8898, Rabbit, 1: 500 (IF), 1: 1000 (WB)
H4K20me3, Abcam, Cat# ab9053, Rabbit, 1: 300 (IF)
H3K27me3, Abcam, Cat# ab192985, Rabbit, 1: 300 (IF), 1: 1000 (WB)
AcH3, Millipore, Cat# 06-599, Rabbit, 1: 300 (IF), 1: 1000 (WB)
H3K9ac, Abcam, Cat# ab4441, Rabbit, 1: 300 (IF)
5-mC, Cell Signaling, Cat# 28692, Rabbit, 1: 500 (IF)
Synapsin, Abcam, Cat# ab64581, Rabbit, 1: 100 (IF)
MAP-2, Sigma, Cat# M9942, Mouse, 1: 200 (IF)
Lamin A/C, Santa Cruz, Cat# sc-376248, Mouse, 1: 50 (IF), 1: 1000 (WB)
Histone H3, Abcam, Cat# ab1791 , Rabbit, 1: 2000 (WB)
Nanog, Abcam, Cat# ab214549 , Rabbit, 1: 300 (IF)
Lamin B1, Santa Cruz, Cat# sc-374015, Mouse, 1: 50 (IF)
Lamin B1, Abcam, Cat# ab133741, Rabbit, 1: 1000 (WB)
YAP-1, Santa Cruz, Cat# sc-376830, Mouse, 1: 100 (IF)
Piezo-1, ThermoFisher, Cat# 15939-1-AP, Rabbit, 1: 200 (IF), 1: 1000 (WB)

Phospho-Lamin A/C, ThermoFisher, Cat# PA5-17113, Rabbit, 1: 200 (IF), 1: 1000 (WB)
Ki67, Abcam, Cat# ab16667, Rabbit, 1: 200 (IF)
Anti-mouse IgG HRP-linked Antibody, Cell Signaling, Cat# 7076S, 1: 2000 (WB)
Anti-rabbit IgG HRP-linked Antibody, Cell Signaling, Cat# 7074S, 1: 2000 (WB)
Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488, ThermoFisher, Cat# A-21202, 1: 300 (IF)
Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 546, ThermoFisher, Cat# A-10036, 1: 300 (IF)
Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488, ThermoFisher, Cat# A-21206, 1: 300 (IF)
Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 546, ThermoFisher, Cat# A-10040, 1: 300 (IF)

Validation

We used standard antibodies validated by the manufacturers, and previous studies in many laboratories, including our own experiments. In our experiments immunofluorescence staining was used to validate antibodies (i.e. localization of antibody staining was correct). All antibodies were purchased from commercial vendors.
Primary antibodies:

Tuj1: On product website (https://www.biolegend.com/en-us/products/purified-anti-tubulin-beta-3-tubb3-antibody-11580?GroupID=GROUP686)
H3K4me1: On product website (https://www.abcam.com/histone-h3-di-methyl-k4-antibody-y47-chip-grade-ab32356.html)
H3K9me3: On product website (https://www.abcam.com/histone-h3-tri-methyl-k9-antibody-chip-grade-ab8898.html)
H4K20me3: On product website (https://www.abcam.com/histone-h4-tri-methyl-k20-antibody-chip-grade-ab9053.html)
H3K27me3: On product website (https://www.abcam.com/histone-h3-tri-methyl-k27-antibody-epr18607-chip-grade-ab192985.html)
Histone H3: On product website (https://www.abcam.com/histone-h3-antibody-nuclear-marker-and-chip-grade-ab1791.html)
AcH3: On product website (https://www.sigmaaldrich.com/catalog/product/mm/06599 lang=en&region=US&gclid=Cj0KCQjwnueFBhChARIsAPu3YkSx-tby5fJwXQ7omLVCZ7uozJrqIE5KW0fPc39p_C0GvAazzmx9BVcaAm_4EALw_wcB)
H3K9ac: On product website (https://www.abcam.com/histone-h3-acetyl-k9-antibody-chip-grade-ab4441.html)
5-mc: On product website (https://www.cellsignal.com/products/primary-antibodies/5-methylcytosine-5-mc-d3s2z-rabbit-mab/28692)
Synapsin: On product website (https://www.abcam.com/synapsin-i-antibody-synaptic-marker-ab64581.html)
MAP-2: On product website (https://www.sigmaaldrich.com/catalog/product/sigma/m9942?lang=en&region=US&gclid=Cj0KCQjwnueFBhChARIsAPu3YkTGH6FAD61BYtjtZspA_KWpvXUrKCOPL6nnjgS7b4WXW95SQDylM6saApDVEALw_wcB)
Nanog: On product website (https://www.abcam.com/nanog-antibody-epr20694-chip-grade-ab214549.html)
Lamin A/C: On product website (https://www.scbt.com/p/lamin-a-c-antibody-e-1?gclid=Cj0KCQjwnueFBhChARIsAPu3YkTrrTUbG7Wnr2Envwvfzaxj8V4C_d0-F5FRTiTWvEsm6OeLK1IwYgUaAnW6EALw_wcB)
Lamin B1: On product website (https://www.scbt.com/p/lamin-b1-antibody-b-10?requestFrom=search)
Lamin B1: On product website (https://www.abcam.com/lamin-b1-antibody-epr8985b-ab133741.html)
YAP-1: On product website (https://www.scbt.com/p/yap-antibody-g-6?requestFrom=search)
Piezo-1: On product website (https://www.thermofisher.com/antibody/product/Piezo1-Antibody-Polyclonal/15939-1-AP)
Phospho-Lamin A/C: On product website(https://www.thermofisher.com/antibody/product/Phospho-Lamin-A-C-Ser22-Antibody-Polyclonal/PA5-17113)
Ki67: On product website (https://www.abcam.com/ki67-antibody-sp6-ab16667.html)
Anti-mouse IgG, HRP-linked Antibody: On product website (https://www.cellsignal.com/products/secondary-antibodies/anti-mouse-igg-hrp-linked-antibody/7076?site-search-type=Products&N=4294956287&Ntt=7076s&fromPage=plp&_requestid=5793580)
Anti-rabbit IgG, HRP-linked Antibody: On product website (https://www.cellsignal.com/products/secondary-antibodies/anti-rabbit-igg-hrp-linked-antibody/7074?site-search-type=Products&N=4294956287&Ntt=anti-rabbit+igg+hrp-linked+antibody&fromPage=plp&_requestid=5798267)
Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 546: on product website(https://www.thermofisher.com/antibody/product/Donkey-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A10040)
Donkey anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488: on product website(https://www.thermofisher.com/antibody/product/Donkey-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21206)
Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 546: on product website(https://www.thermofisher.com/antibody/product/Donkey-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A10036)
Donkey anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488: on product website(https://www.thermofisher.com/antibody/product/Donkey-anti-Mouse-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-21202)

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Lenti-X HEK293T (Clontech Laboratories, Cat # 632180)
Lenti-X 293T cells (#632180, Clontech Laboratories) were purchased from Takara Bio USA, Inc.

Authentication

This cell line was validated by the manufacturer.

Mycoplasma contamination	The cell line tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	*Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

Animals and other organisms

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

Laboratory animals	C57BL/6 mice (Jackson Laboratory, 002052), 1 month old, male and female; Tau-EGFP reporter mice (Jackson Laboratory, 004779), 1 month old, male and female; R26-M2rtTA;Col1a1-tetO-H2B-GFP compound mutant mice (Jackson Laboratory, 016836), 1 month old, male and female
Wild animals	*Provide details on animals observed in or captured in the field; report species, sex and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*
Field-collected samples	*For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*
Ethics oversight	UCLA Institutional Animal Care and Use Committee (Protocol # ARC-2016-036 and ARC-2016-101).

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