

Reporting Summary

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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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ 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	ZEN (v3.1), NIS-Elements AR (v5.21.00, v5.20.02, v5.40.00), Metamorph (v7.8.12.0), Kronos HT (v5.23.190924), NovaSeq 6000 Control Software (v1.7.0, v1.7.5), MATLAB R2021a (v9.10), https://github.com/Alev-Lab/Axioloids-manuscript.git
Data analysis	Fiji (v2.3.0/1.53f), Excel (v16.59), Cutadapt (v3.4), Bowtie2 (v2.2.4), Samtools (v1.12), Picard (v2.25.2), bedtools (v2.30), deepTools (v3.5), IGV (v2.12.2), Cell Ranger (v6.0.1), Scrublet (v0.2.3), Seurat (v4.0.3, v4.0.6), Enrichr (v3.0), Kallisto (v0.46.0), loompy (v3.0.6), scVelo (v0.2.3), python (v3.8.8), JupyterLab (v3.0.14), R (v4.0.5), 3D Slicer (v4.11.202100226), Fusion (v2.3)

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

scRNA-seq and CUT&Tag data that support the findings in this study have been deposited to NCBI GEO with the accession number GSE199576. <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE199576>

Databases used in this study

- For CUT&Tag Human genome reference GRCh38/hg38, <https://hgdownload.soe.ucsc.edu/goldenPath/hg38/bigZips/analysisSet/>
- For single-cell analysis, we used refdata-gex-GRCh38-2020-A provided from 10X, which is based on hg38. https://support.10xgenomics.com/single-cell-gene-expression/software/release-notes/build#GRCh38_2020A
- The gene annotation file http://ftp.ebi.ac.uk/pub/databases/gencode/Gencode_human/release_32/gencode.v32.primary_assembly.annotation.gtf.gz

Source data for all Main Figures (Fig. 1-6) and Extended Data Figures 1-10 & 13-15 and Supplemental Data Figs. 2, 3 and 5 are available in the online version of the paper.

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	Sample sizes were chosen based on previous publications and to obtain sufficient number to reach statistical significance. No statistical test was performed to predetermine sample size.
Data exclusions	IX83 and Kronos oscillation data were not processed when the global signal intensity was too low.
Replication	Each experiment was reproduced and performed at least two times (N= number of independent experiments), with multiple biological and/or technical replicates (n= number of axioids or other samples) if not otherwise stated, by 2 or more operators. See figure legends and methods section for details.
Randomization	Axioids from specific morphologically categories were randomly chosen for each experiment.
Blinding	Morphogenetic differences between the axioids in different culture conditions or from different genetic background are too obvious, as a consequence blinding was not performed in this study.

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

All antibodies used in this study are commercially available antibodies, which were validated by suppliers and other researchers in the field. Details on used antibodies are listed in Supplementary Table 4.

Primary antibodies used for immunocytochemistry

β-catenin, BD Bioscience, #610153, Lot: 8240536, Monoclonal Mouse IgG1, Dilution 1:100
 ETV2, abcam, #ab181847, Lot: GR3357579-1, Monoclonal Rabbit IgG, Dilution 1:500
 Fibronectin, DSHB, #III-15-s, Lot: 11/19/15, Monoclonal Mouse IgG1, Dilution 1:10
 KDR, R&D Systems, #:AF357, Lot: CUE0621081, Polyclonal Goat IgG, Dilution 1:20
 MEOX1, ATLAS ANTIBODIES, #HPA045214, Lot: A115362, Polyclonal Rabbit IgG, Dilution 1:500
 MEOX1, ORIGENE, #TA804716, Lot: F001, Monoclonal Mouse IgG1, Dilution 1:500
 Phospho-p44/42 MAPK (Erk1/2), Cell Signaling, #4370, Lot: 28, Monoclonal Rabbit IgG, Dilution 1:200
 PKCζ, Santa Cruz, #SC-17781, Lot: F2520, Monoclonal Mouse IgG2, Dilution 1:100
 SOX2, Cell Signaling, #3579, Lot: 8, Monoclonal Rabbit IgG, Dilution 1:400
 TBX6, R&D Systems, #:AF4744, Lot: CAPT0217111, Polyclonal Goat IgG, Dilution 1:100
 TBXT(BRACHYURY), R&D Systems, #:AF2085, Lot: KQP0618021, Polyclonal Goat IgG, Dilution 1:100

Secondary antibodies used for immunocytochemistry

Alexa Fluor® 405 Donkey Anti-Goat IgG H&L Abcam, #:ab175665, Lot: GR3267053-3, Dilution 1:500

Alexa Fluor® 405 Donkey Anti-Mouse IgG H&L Abcam, #:ab175658, Lot: GR3258168-7, Dilution 1:500
 Alexa Fluor® 488 Donkey Anti-Goat IgG (H+L), Invitrogen, #:A11055, Lot: 2059218, Dilution 1:500
 Alexa Fluor® 488 Donkey Anti-Mouse IgG (H+L) Invitrogen, #:A21202, Lot: 2018296, Dilution 1:500
 Alexa Fluor® 488 Donkey Anti-Rabbit IgG (H+L) Invitrogen, #:A21206, Lot: 2072687, Dilution 1:500
 Alexa Fluor® 555 Donkey Anti-Goat IgG (H+L) Invitrogen, #:A21432, Lot: 2026158, Dilution 1:500
 Alexa Fluor® 555 Donkey Anti-Mouse IgG (H+L) Invitrogen, #:A31570, Lot: 2045336, Dilution 1:500
 Alexa Fluor® 555 Donkey Anti-Rabbit IgG (H+L) Invitrogen, #:A31572, Lot: 2017396, Dilution 1:500
 Alexa Fluor® 647 Phalloidin Invitrogen, #:A-22287, Lot: 2101947, Dilution 1:200

Primary antibodies used for CUT&Tag library preparation

Anti-trimethyl Histone H3 (Lys4), mouse monoclonal antibody IgG1, MAB Institute, #MA304B, Lot:18032, Dilution 1:100
 Anti-trimethyl Histone H3 (Lys27), mouse monoclonal antibody IgG1, MAB Institute, #MA323B, Lot:19014, Dilution 1:100

Secondary antibodies used for CUT&Tag library preparation

Rabbit Anti-Mouse IgG HL Abcam, #ab46540, Lot: GR3286449-5, Dilution 1:100

Validation

Besides initial validation of utilized (commercial) primary antibodies by manufacturers/suppliers, antibodies were validated/ tested for possible signals at unrelated stages/controls; only antibodies with reproducible (differentiation stage) specific signals were used.

Primary antibodies used for immunocytochemistry

β-catenin, BD Bioscience, #610153 (<https://www.bdbiosciences.com/en-ca/products/reagents/microscopy-imaging-reagents/immunofluorescence-reagents/purified-mouse-anti-catenin.610153>)

Anti-β-catenin antibody was validated by the manufacturer by using the samples of human (A431 cell). There are 6 references.

ETV2, abcam, #ab181847 (<https://www.abcam.co.jp/etv2-antibody-epr52293-ab181847.html>)

Anti-ETV2 antibody was validated by the manufacturer by using HUVEC cell lysate of lent-virally expressed Human ETV2 and Human bone marrow stromal cell lysate lent-virally expressed mouse ETV2. There are 3 references.

Fibronectin 1, DSHB, #III-15-s (<https://dshb.biology.uiowa.edu/13G3B7-Fibronectin-III-15>)

Anti-Fibronectin antibody was validated by the manufacturer by using canine and human samples. There are 2 references.

KDR, R&D Systems, #:AF357 (https://www.rndsystems.com/products/human-vegfr2-kdr-flk-1-antibody_af357)

Anti-KDR antibody was validated by the manufacturer by using human placenta and human kidney. There are 31 references.

MEOX1, ATLAS ANTIBODIES (<https://www.atlasantibodies.com/products/antibodies/primary-antibodies/triple-a-polyclonals/meox1-antibody-hpa045214/>)

Anti-MEOX1 antibody was validated by the manufacturer by using the samples of 44 normal tissues and 20 cancers. There are 2 references.

MEOX1, ORIGENE, #TA804716 (<https://www.origene.com/catalog/antibodies/primary-antibodies/ta804716/mox1-meox1-mouse-monoclonal-antibody-clone-id-oti5d8>)

Anti-MEOX1 antibody was validated by the manufacturer by using human breast tissue, human endometrium tissue, human lymphoma tissue and human tonsil.

Phospho-p44/42 MAPK (Erk1/2), Cell Signaling, #4370 (<https://www.cellsignal.jp/products/primary-antibodies/phospho-p44-42-mapk-erk1-2-thr202-tyr204-d13-14-4e-xp-rabbit-mab/4370>)

Anti-Phospho-p44/42 MAPK (Erk1/2) antibody was validated by the manufacturer by using the samples of human (HT1080 cells). There are 6735 references.

PKCζ, Santa Cruz, #SC-17781 (<https://www.scbt.com/ja/p/pkc-zeta-antibody-h-1>)

Anti-PKCζ antibody was validated by the manufacturer by using the samples of human, mouse and rat. There are 124 references.

SOX2, Cell Signaling, #3579 (<https://www.cellsignal.jp/products/primary-antibodies/sox2-d6d9-xp-rabbit-mab/3579>)

Anti-SOX2 antibody was validated by the manufacturer by using the samples of human (HeLa cells). There are 369 references.

TBX6, R&D Systems, AF4744 (https://www.rndsystems.com/products/human-tbx6-antibody_af4744)

Anti-TBX6 antibody was validated by the manufacturer by using embryonic mouse mesoderm (E9.5) and JOY6 human induced pluripotent stem cells undifferentiated and differentiated into mesoderm. There are 5 references.

TBXT (BRACHYURY), R&D Systems, AF2085 (https://www.rndsystems.com/products/human-mouse-brachyury-antibody_af2085)

Anti-TBXT antibody was validated by the manufacturer by using human embryonic stem cells. There are 98 references.

Primary antibodies used for CUT&Tag library preparation

Anti-trimethyl Histone H3 (Lys4), MAB Institute, #MA304B (https://catalog.takara-bio.co.jp/PDFS/ma304b_ds_j.pdf)

Anti-trimethyl Histone H3 (Lys4) antibody was validated by the manufacturer. There is 1 reference.

Anti-trimethyl Histone H3 (Lys27), MAB Institute, #MA323B (https://catalog.takara-bio.co.jp/PDFS/ma323b_ds_j.pdf)

Anti-trimethyl Histone H3 (Lys27) antibody was validated by the manufacturer. There is 1 reference.

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)	Human induced pluripotent stem cell (iPSC) lines derived from healthy donors, i.e. 409B2 used for majority of experiments was obtained from the Riken BioResource Research Center (RIKEN BRC). 201B7 Luc cell line has been described previously [https://doi.org/10.1038/s41586-020-2144-9] and was established from the 201B7 iPSC line derived from a healthy donor, provided by the Center for iPS Cell Research and Application (CiRA).
Authentication	Patient-like iPSC lines (HES7 KO1 (c.128_137delCCCGGACCA p.(Thr43ArgfsTer21) in one allele & c.98_138+1del p.(Glu34ProfsTer123) in other allele), HES7 KO2 (c.55_56insC p.(Leu19ProfsTer152) in one allele combined with c.55_56insT p.(Val20CysfsTer151) in other allele), HES7 R25W Mt1 (homozygous mutation c.73C>T p.(Arg25Trp)), HES7 R25W Mt2 (homozygous mutation c.73C>T p.(Arg25Trp)), MESP2 KO1 (homozygous mutation c.335_336insT p.(Leu112PhefsTer255)) and MESP2 KO2 (homozygous mutation c.223_241del p.(Arg75AspfsTer39))) have been generated as part of our earlier manuscript [https://doi.org/10.1038/s41586-020-2144-9] and were used in this study for disease modeling with human axioids.
Mycoplasma contamination	All cell lines were tested negative for mycoplasma infection.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used.