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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.

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	scRNA-seq data (FASTQ files) were downloaded from the ENA (study IDs PRJNA153427, PRJEB11202 and PRJNA277181), mapped to the hg19 reference genome with STAR v2.7.0e and summarised to the gene level with Subread's featureCounts v1.6.2. Pre-processing and normalisation was carried out with the following packages under version 3.5.2 of the R environment for statistical computing and graphics: readr v1.3.1, dplyr v0.8.0.1, SummarizedExperiment v1.12.0, SingleCellExperiment v1.4.1, scran v1.10.2, scater v1.10.1 and DrImpute v1.1. For more details see https://github.com/galanisl/TE_differentiation. Chromatin accessibility profiles were downloaded from the ENA (study ID PRJNA494280) and pre-processed with version 1.1.0 of the nf-core pipeline for ATAC-seq data (https://nf-co.re/atacseq). Briefly, adapters and low quality reads were removed with Trim Galore! v0.6.5, trimmed FASTQ files were mapped to the GRCh38 human genome with BWA v0.7.17 and narrow peaks were called with MACS2 v2.2.7.1.
Data analysis	Analysis of the pre-processed and normalised scRNA-seq data was performed with the following packages under version 3.5.2 of R: SummarizedExperiment v1.12.0, SingleCellExperiment v1.4.1, scran v1.10.2, scater v1.10.1, MGFR v1.8.1, dplyr v0.8.0.1, readr v1.3.1, cowplot v0.9.4, ggplot2 v3.1.1, ggrepel v0.8.0, DrImpute v1.1, Seurat 3.1.1, griph v0.1.1 and enrichR v1.0. For more details see https://github.com/galanisl/TE_differentiation. Analysis of the pre-processed chromatin accessibility data was performed with the HINT and MotifAnalysis tools in version 0.13.0 of the Regulatory Genomics Toolbox. Genome browser tracks for scRNA-seq data were generated with SAMtools v1.3.1 and BAMscale v0.0.5-1.

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

The datasets analyzed in this study were previously published and are available at the GEO repositories GSE36552 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE36552) and GSE66507 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE66507), at EMBL-EBI ArrayExpress: E-MTAB-3929 (https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-3929/) and at EMBL-EBI ENA: PRJNA494280 (https://www.ebi.ac.uk/ena/browser/view/PRJNA494280). Source data behind Figures 1-3 and Extended Data Figures 1, 2, 5, 6, 8-11 are available within the manuscript 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	Sample size was determined based on our previous experience and experience from other groups' work. For human embryos: Fogarty et al., Nature, 2017 Blakeley et al., Development, 2015 Niakan et al., Developmental Biology, 2013 For mouse embryos: Hirate et al., Current Biology, 2013 Frum et al., Elife, 2018 For cow embryos: Berg et al., Developmental Cell, 2011 Fouladi-Nashta et al., Reproductive Biomedicine Online, 2005
Data exclusions	No data were excluded from the study design.
Replication	Experiment were replicated at least three times and the data were reproducible in the different attempts of replication. GATA3 and YAP1 immunofluorescence analysis was independently performed in three different laboratories: Niakan, David and Van de Velde Labs.
Randomization	Samples were allocated randomly into experimental groups
Blinding	The investigators were not blinded to group allocation during experiments and outcome assessment due to the experimental design in which embryos had to undergo specific treatments.

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

List of antibodies used available below and in Extended Data Table 11.
Anti-GATA3 antibody, catalogue number: AF2605, supplier: R&D, dilution: 1:200
Anti-GATA3 antibody, catalogue number: AB199428, supplier: Abcam, dilution: 2 µg/ml
Anti-E-CADHERIN antibody, catalogue number: 13-1900, supplier: ThermoFischer, dilution: 1:400 (mouse), 1:50 (human, cow)
Anti-YAP1 antibody, catalogue number: H00010413-M01, supplier: Abnova, dilution: 1:50
Anti-YAP1 antibody, catalogue number: 14074, supplier: Cell Signaling, dilution: 1:50
Anti-aPKC antibody, catalogue number: sc-17781, supplier: Santa Cruz, dilution: 1:50
Anti-aPKC antibody, catalogue number: LC-C354069, supplier: LSBio, dilution: 1:50
Anti-SOX2 antibody, catalogue number: 14-9811-82, supplier: eBioscience, dilution: 1:100
Anti-SOX2 antibody, catalogue number: MAB2018, supplier: R&D, dilution: 1:100
Anti-β-CATENIN antibody, catalogue number: 8814, supplier Cell Signaling, dilution: 1:100
Anti-AMOT antibody, catalogue number: sc-82493, supplier: Santa Cruz, dilution: 1:50 (cow, human)
Anti-AMOT antibody, specific for mouse, AMOT, gently provided by Hiroshi Sasaki's Lab, dilution: 1:200 (mouse)
Anti-KRT18 antibody, catalogue number: ab668, supplier: Abcam, dilution: 1:100
Anti-GATA2 antibody, catalogue number: sc-9008, supplier: Santa Cruz, dilution: 1:100
Anti-PARD6B antibody, catalogue number: BP1-87337, supplier: Novus Biologicals, dilution: 1:50
Anti-WWTR1, catalogue number: HPA007415, supplier: Sigma, dilution: 1:100
Anti-NANOG antibody, catalogue number: AF1997, supplier: R&D, dilution: 1:100
Anti-OCT3/4 antibody, catalogue number: sc-5279, supplier: Santa Cruz, dilution: 1:250
Anti-TEAD4 antibody, catalogue number: ab58310, supplier: Abcam, dilution: 1 µg/ml
Anti-GRHL2 antibody, catalogue number: HPA004820, supplier: Sigma, dilution: 1:200
Anti-mCHERRY antibody, catalogue number: ab167453, supplier: Abcam, dilution: 1:200
Alexa Fluor 594 Phalloidin, catalogue number A12381, supplier: ThermoFischer, dilution 1:250
Alexa Fluor 546 Phalloidin, catalogue number: A22283, supplier: ThermoFischer, dilution: 1:250
Also, Alexa Fluor secondary antibodies from ThermoFisher, dilution: 1:300

Validation

Here we report the list of antibodies along with manufacturer's website link where validation was reported:
Anti-GATA3 antibody, AF2605, R&D = https://www.rndsystems.com/products/human-gata-3-antibody_af2605
Anti-GATA3 antibody, AB199428, Abcam = https://www.abcam.com/gata3-antibody-epr16651-chip-grade-ab199428.html
Anti-E-CADHERIN antibody, 13-1900, Life Technologies = https://www.thermofisher.com/antibody/product/13-1900.html?CID=AFLCA-13-1900
Anti-YAP1 antibody, H00010413-M01, Abnova = http://www.abnova.com/products/products_detail.asp?catalog_id=H00010413-M01
Anti-YAP1 antibody, 14074, Cell Signaling = https://www.cellsignal.com/products/primary-antibodies/yap-d8h1x-xp-rabbit-mab/14074
Anti-aPKC antibody, sc-17781, Santa Cruz = https://www.scbt.com/scbt/product/pkc-zeta-antibody-h-1
Anti-aPKC, LC-C354069, LSBio = https://www.lsbio.com/antibodies/prkcz-antibody-pkc-zeta-antibody-c-terminus-icc-if-immunofluorescence-ihc-ip-wb-western-ls-c354069/365190
Anti-SOX2 antibody, 14-9811-82, Ebioscience = https://www.thermofisher.com/antibody/product/SOX2-Antibody-clone-Btjce-Monoclonal/14-9811-82
Anti-SOX2 antibody, MAB2018, R&D = https://www.rndsystems.com/products/human-mouse-rat-sox2-antibody-245610_mab2018
Anti-β-CATENIN antibody, 8814, Cell Signalling = https://www.cellsignal.com/products/primary-antibodies/non-phospho-active-b-catenin-ser33-37-thr41-d13a1-rabbit-mab/8814
Anti-AMOT antibody, provided by Hiroshi Sasaki's Lab = https://pubmed.ncbi.nlm.nih.gov/23791731/
Anti-AMOT antibody, sc-82493, Santa Cruz = http://datasheets.scbt.com/sc-82493.pdf
Anti-KRT18 antibody, ab668, Abcam = https://www.abcam.com/cytokeratin-18-antibody-c-04-ab668.html
Anti-GATA2 antibody, sc-9008, Santa Cruz = https://www.scbt.com/scbt/product/gata-2-antibody-h-116
Anti-PARD6B antibody, NBP1-87337, Novus Biologicals = https://www.novusbio.com/products/pard6b-antibody_nbp1-87337
Anti-WWTR1 antibody, HPA007415, Sigma = https://www.sigmaaldrich.com/catalog/product/sigma/hpa007415?lang=en&region=GB
Anti-NANOG antibody, AF1997, R&D = https://www.rndsystems.com/products/human-nanog-antibody_af1997
Anti-OCT3/4 antibody, sc-5279, Santa Cruz = https://www.scbt.com/scbt/product/oct-3-4-antibody-c-10
Anti-TEAD4 antibody, ab58310, Abcam = https://www.abcam.com/tead4-antibody-chip-grade-ab58310.html
Anti-GRHL2 antibody, HPA004820, Sigma-Aldrich = https://www.sigmaaldrich.com/catalog/product/sigma/hpa004820?lang=en&region=GB
Anti-mCherry antibody, ab167453, Abcam = https://www.abcam.com/mcherry-antibody-ab167453.html
Alexa Fluor 594 Phalloidin, A12381, ThermoFischer = https://www.thermofisher.com/order/catalog/product/A12381?SID=srch-srp-A12381
Alexa Fluor 546 Phalloidin, A22283, ThermoFischer = https://www.thermofisher.com/order/catalog/product/A22283?SID=srch-srp-A22283

Animals and other organisms

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

Laboratory animals

Four- to eight-week-old (C57BL6×CBA) F1 female mice were super-ovulated using injection of 5 IU of pregnant mare serum gonadotrophin (PMSG; Sigma-Aldrich). Forty-eight hours after PMSG injection, 5 IU of human chorionic gonadotrophin (HCG; Sigma-Aldrich) was administered. Superovulated females were set up for mating with eight-week-old or older (C57BL6×CBA) F1 males. Mice were maintained on a 12h light–dark cycle, ambient temperature 19/22°C, and humidity 45/65%.

Wild animals	No wild animals were used in this study
Field-collected samples	Cow ovaries were obtained from the abattoir and transported to laboratory in PBS kept at 38°C.
Ethics oversight	This study was approved by the Animal Ethics Committee and by the UK Home Office Licence Number 70/8560 and followed all relevant institutional and national guidelines and regulations. The cow work was approved by the Ethics Committee at the Royal Veterinary College. All experiments followed all relevant institutional and national guidelines and regulations

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	This is not applicable as we used donated embryos surplus to IVF treatment.
Recruitment	Informed consent was obtained from all couples that donated spare embryos following IVF treatment.
Ethics oversight	All human embryo experiments followed all relevant institutional and national guidelines and regulations. For the work conducted in UK: This study was approved by the UK Human Fertilisation and Embryology Authority (HFEA): research licence number R0162, and the Health Research Authority's Research Ethics Committee (Cambridge Central reference number 19/EE/0297). For the work conducted in France: The use of human embryo donated to research as surplus of IVF treatment was allowed by the French embryo research oversight committee: Agence de la Biomédecine, under approval number RE13-010. For the work conducted in Belgium: The use of human embryos donated to research was allowed by the Local Ethical Committee of UZ Brussel (BUN 143201526417) and the Belgian Federal Committee for research on human embryos (AdV057).

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