

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 (<i>n</i>) 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> 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 <i>d</i> , Pearson's <i>r</i>), 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 Black or Zen Blue 3.3 (Zeiss) FACSDiva software Software 8.0.1 NovaSeq 6000 System (Illumina)
Data analysis	All statistical analyzes were carried out using R (version 4.4.1) or or Python (v3.12.3). For the scRNA-seq, Sequencing reads were aligned and annotated with the mm10-2020-A reference dataset as provided by 10X Genomics and demultiplexed using CellRanger (v.7.0.0) with default parameters. Quality control and downstream analysis were performed using the Seurat R package (v.5.1.0). Doublets are detected with both DoubletFinder (v.2.0.6) and scds (v.1.26.1), by default parameters. 3D manifold construction and analysis were done using the python packages Pegasus (v1.9.0) and Scanpy (v1.9.8). The python package scvelo (v.0.3.2) was used to run single cell velocity analysis. The python package dynamo (v1.4.1) was used to estimate both the speed and acceleration of cellular transcriptomic dynamics. The R package SCENIC (v1.3.1) was used to infer regulons, based on co-expression and DNA motif enrichment, following the standard SCENIC workflow. For the bulkRNA-seq, quality of each raw data was checked with FastQC (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/). The adaptor sequences and low-quality regions were trimmed by TrimmomaticPE (v.0.39). Trimmed reads were mapped against the mouse reference genome (Grcm38/mm10) using STAR aligner (v.2.7.11b). Duplicate reads were removed by Picard MarkDuplicates module (http://broadinstitute.github.io/picard/). After transcript assembling, gene-level counts were obtained using HTseq (v.0.11.1) and normalized to 20 million aligned reads per count. Differential expression analysis was then performed using the DESeq R package (v1.46.0). In parallel, differential expression analysis was independently performed using the edgeR package (v4.4.2) to validate the robustness of the results.

Codes for numerical simulations of the one- and two-proliferative compartment models have been deposited on Zenodo (ID: XXX).

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](#)

All of the raw sequencing data have been deposited in the Gene Expression Omnibus (GEO) with the accession number for bulk RNAseq: GSE294042 and scRNAseq: GSE294426.

For bulk RNA-seq, the mouse reference genome assembly GRCm38/mm10 was used throughout this study. Genome sequence and gene annotation files were obtained from Ensembl release 87 (<https://ftp.ensembl.org/pub/release-87/>), including the mouse genome FASTA files (https://ftp.ensembl.org/pub/release-87/fasta/mus_musculus/dna/) and GTF annotation files (https://ftp.ensembl.org/pub/release-87/gtf/mus_musculus/). For single-cell RNA-seq, reads were aligned and gene expression was quantified using the 10x Genomics pre-built Cell Ranger reference package refdata-gex-mm10-2020-A. The reference package and its build specifications are available from 10x genomics (<https://www.10xgenomics.com/support/software/cell-ranger/downloads/cr-ref-build-steps>).

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	Patient sex was recorded. No information regarding gender was collected.
Reporting on race, ethnicity, or other socially relevant groupings	No data was collected
Population characteristics	No data was collected
Recruitment	Skin samples were collected during elective facial plastic surgery
Ethics oversight	Ethical approval for cultures of human skin samples was obtained from the Commissie voor Medische Ethiek U(Z) Gent (ONZ-2025-0531) and Ethics Committee of Area Vasta Emilia Nord, approval number 178/09.

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

Life sciences study design

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

Sample size	Samples size for each experiment is indicated in corresponding figure legends. The sample size was chosen based on previous experience in the laboratory for each experiment to yield high power to detect specific effects. Previous experiments referes to Mascré 2012 Nature, Dekoninck 2020 Cell, Aragona 2020 Nature, Sarate 2024 Cell. No statistical methods were used to predetermine sample size.
Data exclusions	No data were excluded from the analysis
Replication	All the experiments were performed in at least 3 biologically independent replicates per condition. Except from Bulk RNA and sc RNA seq that was done on 2 biologically independent replicates per group. All replicates reported in the manuscript and on which statistics are based are biological replicates. No technical replicates were used to calculate statistics. All replication attempts have been successful.
Randomization	Randomization was not applicable for most analyses due to the inability to assign sex. For experimental procedures (castration, ovariectomy, or hormonal replacement), mice were randomly selected from the same litter and allocated to experimental groups to minimize litter-specific confounding effects.

Sex could not be blinded during experimental procedures due to inherent biological differences. However, all downstream data collection and analysis were performed in a blinded manner to prevent observer bias.

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		Methods	
n/a	Involved in the study	n/a	Involved in the study
☐	☒ Antibodies	☒	☐ ChIP-seq
☒	☐ Eukaryotic cell lines	☐	☒ Flow cytometry
☒	☐ Palaeontology and archaeology	☒	☐ MRI-based neuroimaging
☐	☒ Animals and other organisms		
☒	☐ Clinical data		
☒	☐ Dual use research of concern		
☒	☐ Plants		

Antibodies

Antibodies used	For whole-mount immunostaining : For primary antibody staining, samples were incubated with the primary antibodies Krt14 (chicken, Thermo Fisher Scientific, Custom batch, 1:2 000), Krt10 (rabbit, Biolegend 905404, 1:1 000), GFP (goat, Abcam, ab6673, 1:3000) and mCherry (rat, Invitrogen, M11217, 1:3000) . The following secondary antibodies were used (dilution 1:400): anti-rabbit and anti-chicken conjugated either to Alexa Fluor 488 (Molecular Probes) or Rhodamine Red-X (Jackson ImmunoResearch) or cyanine 5 (Cy5) (Jackson ImmunoResearch). For IHC : AR was performed using a rabbit monoclonal antibody (rabbit, Abcam, ab108341, 1:500) and ER was performed using a rabbit monoclonal antibody (rabbit, Cell Signaling, 13258, 1:200). For FACS : a biotinylated anti-CD34 primary antibody (clone RAM34, eBiosciences, 13-0341-82, 1:50) with streptavidin–APC secondary antibody (BD Biosciences, 554067, 1:100) and CD49f (Integrin alpha 6) PE-Cyanine7 conjugated antibody (clone eBioGoH3 (GoH3), Thermo Fisher Scientific, 25-0495-82, 1:250)
Validation	Antibodies used are commercially available and were validated by the provider. We used protocols and recommendations of the manufacturer on validated species. We used positive and negative control tissues to validate the specificity of the stainings. The following antibodies were tested for immunofluorescence and/or IHC in murine samples according to the manufacturers information: Krt10, AR, GFP, mCherry, CD34 and CD49f. Krt14 antibody was validated for immunofluorescence in murine samples in previous publications: Bansaccal et al, Nature, 2023; Sarate et al, Cell, 2024. ER antibody was validated for immunofluorescence in murine samples in previous publications such as: Ciwinska et al, Nature, 2024

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	K14CreER transgenic mice were provided by E. Fuchs (Rockefeller University). (Vasioukhin et al, 1999). iChr-Control-Mosaic transgenic mice were provided by R. Benedito (Centro Nacional de Investigaciones Cardiovasculares Carlos III) (Pontes-Quero et al., 2017). Notch1CreER (N1-CreERT2SAT) were kindly provided by S. Fre (Institut Curie). Lgr6-GFP-CreER were obtain from The Jackson Laboratory (JAX). Tissues from Four Core Genotypes (FCG) mice were provided by the Schwartz laboratory (USC); the original FCG mice were obtained from Dr. Arthur Arnold (UCLA) under a material transfer agreement. CD1 mice were obtained from Janvier-Labs. Mice were induced around P60, and mice used for sequencing were also P60.
Wild animals	No wild animals were used in the study
Reporting on sex	All experiments were performed on female and male mice at the same time. The experiments were designed accordingly to highlight potential variations between males and females.
Field-collected samples	No field collected samples were used in the study
Ethics oversight	The experiments were approved by the local ethical committee (Commission d’Ethique et du Bien Être Animal (CEBEA), Faculty of Medicine, Université Libre de Bruxelles) under protocols 794N, 851N and 912N. CEBEA follows the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes. The FCG mouse colonies were maintained at the University of Southern California (Department of Animal Resources, BCC facility) in accordance with institutional guidelines. All

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Plants

Seed stocks	NA
Novel plant genotypes	NA
Authentication	NA

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	To isolate skin epidermal cells, ears were dissected, opened in two along the cartilage with forceps. Fat tissue and cartilage were removed and skin was floated on 0.25% trypsin + EDTA 1mM (Gibco, Thermo Fisher Scientific) in DMEM (Gibco, Thermo Fisher Scientific) overnight at 4°C. The day after, the epidermis was carefully separated from the dermis by using forceps and then floated on a rocking plate (100 rpm) at 37°C for 10min on the trypsin mix. Tissue was cut into pieces, and epidermal cells were mechanically dissociated by pipetting with a 5ml pipette. Trypsin was neutralized by adding DMEM supplemented with 5% Chelex-treated fetal calf serum (CFCS), and samples were filtrated on a 70-µm filter then on a 40-µm filter and washed in PBS supplemented with 2% CFCS (FACS buffer). Single cells were incubated with a biotinylated anti-CD34 primary antibody (clone RAM34, BD Biosciences, 1:50) diluted in FACS buffer, incubated for 30 min on ice, and protected from light. Cells were washed with FACS buffer, incubated for 30 min on ice, with streptavidin-APC secondary antibody (BD Biosciences, 1:100) and CD49f (Integrin alpha 6) PE-Cyanine7 conjugated antibody (clone eBioGoH3 (GoH3), Thermo Fisher Scientific, 1:250). Then the cells were washed again and finally resuspended in a Hoechst (10 mg/ml) solution diluted at 1:4 000 in FACS buffer.
Instrument	Cell sorting was performed on a BD FACSARIA III using the FACSDiva software (BD Bioscience) at the ULB Flow Cytometry Platform
Software	We used FACSDiva software.
Cell population abundance	Viability was around 80% for all samples. Basal cells (Itga6+/CD34-) represent around 35%-40% of living cells.
Gating strategy	Living epidermal cells were gated by forward scatter, side scatter and negative for Hoechst. Bulge (hair follicle) cells were excluded by CD34 staining. Only basal cells (integrin alpha6 positive) cells were sorted.

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