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Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work we publish. This form is published with all life science papers and is intended to promote consistency and transparency in reporting. All life sciences submissions use this form; while some list items might not apply to an individual manuscript, all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

   Describe how sample size was determined.

   No statistical method was used to predetermine sample size. The sample size was determined on the basis of our prior knowledge of the variability of experimental output and on initial results or pilot experiments for each line of in vitro or in vivo experiments reported.

2. Data exclusions

   Describe any data exclusions.

   No data were excluded from analyses.

3. Replication

   Describe whether the experimental findings were reliably reproduced.

   All attempts at replication were successful.

4. Randomization

   Describe how samples/organisms/participants were allocated into experimental groups.

   The experiment were not randomized.

5. Blinding

   Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

   The investigators were not blinded to group allocation during data collection and/or analysis.

   Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

   For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or the Methods section if additional space is needed).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒	A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly.
☐	☒	A statement indicating how many times each experiment was replicated
☐	☒	The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒	A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒	The test results (e.g. *p* values) given as exact values whenever possible and with confidence intervals noted
☐	☒	A summary of the descriptive statistics, including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒	Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	Only commercially available or free software was used for data analysis. This includes Graphpad Prism, Fluidigm Singular, FlowJo, and Microsoft Excel.

For all studies, we encourage code deposition in a community repository (e.g. GitHub). Authors must make computer code available to editors and reviewers upon request. The *Nature Methods* guidance for providing algorithms and software for publication may be useful for any submission.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	Goat anti-CC10 antibody was a gift from Dr. Barry Stripp and HTII-280 antibody was a gift from Dr. Leland Dobbs.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	IF: rabbit anti-pro-SPC (1:3000; Millipore, #AB3786), goat anti-pro-SPC (1:2000; Santa Cruz, #SC-7706), rabbit anti-Krt5 (1:1000; Covance, #PRB-160P), chicken anti-Krt5 (1:1000; Covance, #SIG-3475), rabbit anti-ΔNp63 (1:100; Cell Signaling, #13109), rat anti-mouse integrin β4 (1:200; BD, #555721), goat anti-CC10 (1:10,000, a gift from Dr. B. Stripp), mouse anti-acetylated tubulin (1:500, Sigma, 6-11B-1), rat anti-E-cadherin (1:500, Invitrogen, #13-1900), rabbit anti-Hes1 (1:1000; Cell Signaling, #11988), goat anti-Scgb3a2 (1:100, R&D, AF3465). Western blots: HIF1α (1:500, R&D systems, #AF1935), pro-SPC (1:500, Millipore, #AB3786), Krt5 (1:1000, Covance, #PRB-160P), Cleaved Notch1 (1:1000, Cell signaling, #4147), E-cadherin (1:2000, BD, #610181), ?-actin (1:10000, Sigma-Aldrich, #A5441). To detect influenza A virus, unboiled lysates in 1mM DTT and 2% SDS were blotted with anti-Influenza A antibody (1:1000, Millipore, #AB1074). FACS: rat anti-mouse CD45 (1:200, BD, #553078), rat anti-mouse CD16/CD32 (1:200, BD, #553143), rat anti-mouse CD31 (1:200, BD, #553371), then incubated for 1 hr at 4°C with the following primary antibodies or viability dye diluted in DMEM (without phenol red) plus 2% FBS (Gibco): phycoerythrin (PE) or BV421-conjugated rat anti-mouse EpCAM (1:500; Biolegend, #563477, #563214), Alexa Fluor® 647 or PE-conjugated rat anti-mouse integrin β4 (1:75; BD, #553745), fixable viability dye eFluor® 780 (1:2000, eBioscience), Goat anti-pro-SPC (1:500; Santa Cruz, #SC-7706), BV421 rat anti-mouse EpCAM, Alexa Fluor® 488 donkey anti-goat IgG (1:2000, ThermoFisher, #A-11055). Validation for species and application was from manufacturer website.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	No eukaryotic cell line was used.
b. Describe the method of cell line authentication used.	No eukaryotic cell line was used.
c. Report whether the cell lines were tested for mycoplasma contamination.	No eukaryotic cell line was used.
d. If any of the cell lines used in the paper are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	No commonly misidentified cell lines were used.

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

HIF1αfl/fl, Shh-Cre, Krt5-CreERT2, Sox2-CreERT2, β-cateninloxEx3, CC10-CreERT, FoxJ1-CreERT2, p63-CreERT2, Ub-GFP, SPC-CreERT2, and Ai14-tdTomato mice were used in the study and they were all previously described. For all experiments, 6–8 week old animals of both sexes were used in equal proportions.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

The study did not involved human research participants. All human samples are non-identified, otherwise discarded tissues.

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Date: Jun 6, 2017

Flow Cytometry Reporting Summary

Form fields will expand as needed. Please do not leave fields blank.

Data presentation

For all flow cytometry data, confirm that:

☒ 1. The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ 2. 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).

☒ 3. All plots are contour plots with outliers or pseudocolor plots.

☒ 4. A numerical value for number of cells or percentage (with statistics) is provided.

Methodological details

5. Describe the sample preparation.	Lung epithelial cells were obtained by Dispase digestion of primary tissue, exactly as described in Methods.
6. Identify the instrument used for data collection.	All data was collected on either FACSAria II or LSR II.
7. Describe the software used to collect and analyze the flow cytometry data.	Analysis was performed using FlowJo.
8. Describe the abundance of the relevant cell populations within post-sort fractions.	Purity checks were routinely performed by re-running ~100-500 sorted cells back through the sorter and ensuring they fell within appropriate gates.
9. Describe the gating strategy used.	As a general rule cells were gated on forward and side scatter corresponding to the known scatter profile of lung epithelial cells. Next they were gated as singlets, and then gated as live (viability dye negative) and CD45 negative. All positive gates were based off of the background fluorescence signal obtained by staining with an isotype antibody conjugated to the same fluorophore as the primary antibody.

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