nature research

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Last updated by author(s): Juuly 31, 2020

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 *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	Cell sorting data was collected using MoFlo Astrios software (Summit (v 6.3.0.16900)) from Beckman Coulter. Confocal Images were acquired with the aid of Leica software (LAS X, v 3.0.13). Brightfield images of H & E stained sections were obtained using Aperio software (ImageScope v. 12.4)
Data analysis	Flow cytometry data was analyzed using FlowJo (v. 10.6). scRNA-seq data was analyzed using Cell Ranger and the following R packages: CellRangerRkit(v. 2.0.0), Seurat (v. 3.0.2), Reshape2 (v. 1.4.3), Monocle (v2.4.0), and ggplot2 (v. 3.2.0) ATAC-seq data was analyzed using the following packages: Bowtie (v. 1.1.2), Samtools (v. 1.3), Homer (v. 4.9), Picard-tools (v. 1.119), Bedtools (v. 2.25.0), Attack (v. 0.1.6), Deeptools (v. 3.2.0), Macs2 (v. 2.1.1.20160309), IGV (v. 2.4.18), and R packages ggplot2 (v. 3.2.0) and DESeq2 (v. 1.22.2). Pathway analysis utilized Ingenuity Pathways Analysis (IPA) (Spring release 2018). Statistics were analyzed using Prism (v. 8.1). Analysis of images was performed using Fiji (Image J v. 2.0.0). Analysis of alveolar septal thickness and mean linear intercepts was performed using Metlab 2018a (RRID:SCR_001662).

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

Sequencing (ATAC-seq and scRNA-seq) data generated during this study has been deposited in the GEO database with the primary accession number GSE132535 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE132535).

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 sizes were not predetermined and were based on previous experience (footnotes 19 and 39) that resulted in generation of statistically-significant data.
Data exclusions	No data were excluded.
Replication	All data was reliably reproduced. The number of repeats is indicated in each figure legend.
Randomization	Mice were randomly assigned to groups consistent with genotype. Human samples were selected using predefined criteria which was having a pathology report that identified diffuse alveolar damage or normal lung parenchyma (control). Control lungs were age-matched to damaged lung.
Blinding	Histologic sections were coded and analyzed by a blinded observer. Once all images had been graded, blinding was reversed for analysis by another investigator. Similarly, we used coding to conceal the conditions from which BAL samples used for ELISAs and cDNA used for RT-PCR were obtained. The samples were subsequently decoded by the primary investigator only after the data was acquired and analyzed. The scientist performing ELISAs and RT-PCR was unaware of the conditions from which the samples were obtained. Furthermore, the scientist collecting the BAL and RNA specimens was also unaware of the treatment conditions. Determination of mortality in the influenza experiments did not involve blinding as it is necessary for us to accurately label our mouse cages and post relevant information on the experimental conditions on cage cards to allow for the mice to properly be cared for by our staff.

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	Please see Supplementary Table 2.
Validation	Other than the HT2-280 antibody from Dr. Dobbs, all of the other antibodies are commercially available and validated by the manufacturer for use in mice (flow cytometry) or humans (MACs sorting). Validation of HT2-280 for these purposes has been

deposited into the Nature Protocol Exchange (Zacharias, W. & Morrisey, E. Isolation and culture of human alveolar epithelial progenitor cells. Nature Protocol Exchange (2018)).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Primary AT2 cells from murine and human lungs were sorted and cultured with either primary lung fibroblasts (PDGFRA+) in the case of murine organoids, or MRC5 fibroblast cell line in the case of human organoids. The Human MRC5 fibroblast line was obtained from ATCC
Authentication	AT2 cells were defined as follows: Mouse: Epcam+;CD45-;CD31-;PDGFRA-;CD24-; Sca-1- Human: Positive for HT2-280 antibody Fibroblasts: Mouse PDGFRA+ Human MRC5 fibroblast line was obtained from ATCC and were not independently authenticated by our lab.
Mycoplasma contamination	Mycoplasma testing was performed on MRC5 fibroblast cell line and was negative. Mycoplasma testing was not performed on primary cells.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

Animals and other organisms

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

Laboratory animals	Mus musculus of both sexes were used. Experimental mice were 8-12 weeks of age. Donor mice for isolation of AT2 and lung fibroblasts were 4-6 weeks of age. SftpcCreERT2 mice were generously donated by Harold A. Chapman at the University of California San Francisco. TrkbEGFP mice were generously donated by David D. Ginty at Harvard University. TrkBLoxP mice were generated by Louis F. Parada, currently at Memorial Sloan Kettering Cancer Center, and were shared with us by James O. McNamera at Duke University. All other mice were obtained from the Jaxon Laboratory – C57BL/6 (stock #000664), BdnfCre (stock #030189), BdnfLoxP (stock #004339), Hopx3FlagGFP (stock #029271), PdgfraCreERT2 (stock #018280), R26RTdTomato (stock #007914), and Stat3LoxP/LoxP (stock #016923).
Wild animals	No wild animals were used in this study.
Field-collected samples	This study did not involved samples collected from the field.
Ethics oversight	The protocol was approved by the IACUC at the Children's Hospital of Philadelphia and University of Pennsylvania.

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	Donated and de-identified post-mortem lungs rejected for transplant were used.
Recruitment	Samples of uninjured, de-identified human lungs were obtained from non-utilized lungs donated for organ transplantation via an established protocol for the Prospective Registry of Outcomes in Patients Electing Lung Transplant study approved by University of Pennsylvania Institutional Review Board with informed consent in accordance with institutional procedures.
Ethics oversight	University of Pennsylvania Institutional Review Board

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

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	Murine lung tissue was digested into a single-cell suspension using dispase (Corning catalog #354235), collagenase (Roche catalog #10103578001), and DNase (Roche catalog #10104159001).
Instrument	MoFlo Astrios
Software	Summit (v 6.3.0.16900) by Beckman-Coulter was used for sorting.
Cell population abundance	Information on cell abundance is included in Extended Figure 1 and Extended Figure 8. Data on cell purity is in Figure 1B.
Gating strategy	For all flow experiments the initial sorting material was a single-cell suspension of murine lung tissue. The FSC/SSC gates were set to exclude debris. Boundaries between positive and negative cells were set using unstained samples. Extended Figure 1 and Extended Figure 8 show our gating strategies in detail.

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