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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 (*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	Public data used in this study were obtained from GEO database and the corresponding GEO accessions have been listed in the manuscript.
Data analysis	All the bioinformatic and statistical analyses were accomplished using R (4.4.0) and GraphPad Prism 9. R packages and versions: Scissor_2.0.0, Signac_1.14.0, Seurat_5.2.1, SeuratObject_5.0.2, ggplot2_4.0.0, CellChat_1.6.1. All the bioinformatic analyses were performed according to the official recommended workflow. Codes used in this study could be found at https://github.com/houruijiejerry/RuijieHou-Code, DOI: 10.5281/zenodo.17960326.

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

The snRNA-seq data of human lung tissue used in this study are available in the GEO database under accession number GSE314709 (https://www.ncbi.nlm.nih.gov/

geo/query/acc.cgi?acc=GSE314709). The scRNA-seq data of mice used in this study are available in the GEO database under accession number GSE314943 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE314943). The data supporting the findings from this study are available within the manuscript and its supplementary information. Source data are provided with this paper. In this study, public datasets used for analysis including GSE47460 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE47460), GSE136831 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE136831), GSE132771 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE132771), GSE128033 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE128033), GSE159354 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE159354) and GSE122960 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE122960).

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	In this study, we enrolled four patients (male: 3; female: 1) with idiopathic pulmonary fibrosis (IPF) and five normal individuals (male: 3; female: 2) .
Reporting on race, ethnicity, or other socially relevant groupings	Detailed demographic and clinical characteristics of the patients are shown in Supplementary Table S1.
Population characteristics	Detailed demographic and clinical characteristics of the patients are shown in Supplementary Table S1.
Recruitment	We enrolled four patients with idiopathic pulmonary fibrosis (IPF) who underwent lung transplantation surgery and five normal individuals whose lung tissue specimens were obtained from surgical resections for other indications.
Ethics oversight	This study was approved by the Medical Ethics Committees of West China Hospital, Sichuan University and Shenzhen People's Hospital. All participants (or their legal guardians) provided written informed consent for participation in this study, the publication of indirect identifiers mentioned in Supplementary Table S1 and future related research.

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	This study includes 5 snRNA-deq data of normal human lungs, 4 IPF snRNA-deq data of IPF human lungs, 3 scRNA-seq data and 3 scATAC-seq data of silica-induced mice, 3 scRNA-seq data and 3 scATAC-seq data of bleomycin-induced mice, 3 scRNA-seq data and 3 scATAC-seq data of saline-induced control mice, scRNA-seq data of 5 GEO datasets and RNA-seq data of 1 GEO dataset for bioinformatic analyses. For animal experiments, there are 3-6 mice in each group, considered sufficient for the downstream analyses based on the previous study.
Data exclusions	No participant-level data were manually excluded.
Replication	Key findings were validated across multiple independent human datasets, and results were consistent. Both animal and in vitro experiments were repeated at least three times with reproducible results.
Randomization	In animal experiments, mice were randomly assigned to treatment or control groups to minimize selection bias. In cell culture experiments, groups were divided based on treatment conditions and processed using standardized protocols without manual intervention.
Blinding	For all experiments, group allocation (genotype, drug treatment, etc.) had to be known to the investigator before tissue harvesting or drug administration, making blinding impossible during data collection. Data analysis was nevertheless performed by independent researchers using identical, automated scripts to minimize subjective bias. Because prior knowledge of treatment identity was essential for correct experimental execution, blinding was not applicable and is fully described in the Methods.

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 and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Anti-PIEZO1, for human Immunofluorescence, Novus Biologicals, Cat# NBP1-78446, Polyclonal; Anti-PIEZO1, Western Blot, Proteintech, Cat# 15939-1-AP, Polyclonal; Anti-αSMA, Immunofluorescence, abcam, Cat# ab7817, Monoclonal; Anti-mouse VE-CAD, Immunofluorescence, R&D system, Cat# AF1002, Polyclonal; Anti-CD31, Immunofluorescence, abcam, Cat# ab9498, Monoclonal; Anti-CD31, Immunofluorescence, Servicebio, Cat# GB13063 Polyclonal; Anti-Mouse CD31, Blocking, BD Pharmingen™, Cat# 553370, Monoclonal; Anti-GAPDH, Western Blot, Servicebio, Cat# GB12002-100, Monoclonal; Anti-pSTAT3(Ser727), Western Blot, Cell Signaling Technology, Cat# 9134s, Polyclonal; Anti-STAT3, Western Blot, abcam, Cat# ab68153, monoclonal [EPR787Y]; Anti-pSTAT1 (Tyr701), Western Blot, Cell Signaling Technology, Cat# 9171, Polyclonal; Anti-STAT1, Western Blot, Proteintech, Cat# 10144-2-AP, Polyclonal; Anti-CAPN2, Western Blot, Labome, Cat# A03492, Monoclonal; Anti-mouse IL-33, Western Blot and Immunofluorescence, R&D system, Cat# AF3626, Polyclonal; Anti-Mouse CD45, Blocking, BD Pharmingen™, Cat# 553076, Monoclonal

Validation

The immunofluorescence experiment for Anti-PIEZO1 (Cat# NBP1-78446, for human samples), Anti-mouse VE-CAD (Cat# AF1002, for mouse samples), Anti-CD31(Cat# ab9498, for human samples), Anti-CD31(Cat# GB13063, for mouse samples) and Anti-mouse IL-33(Cat# AF3626, for human and mouse samples) has been validated.
The Western Blot experiment for Anti-PIEZO1 (Cat# 15939-1-AP, for human and mouse samples), Anti-GAPDH(Cat# GB12002-100, for human samples), Anti-pSTAT3(Ser727)(Cat# 9134s, for human samples), Anti-STAT3(Cat# ab68153, for human samples), Anti-pSTAT1 (Tyr701)(Cat# 9171 for human samples), Anti-STAT1(Cat# 10144-2-AP, for human samples), Anti-CAPN2(Cat# A03492, for human samples) and Anti-mouse IL-33(Cat# AF3626, for human and mouse samples) has been validated.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

HEK293T (CRL-3216, ATCC) cells were purchased from the American Tissue Collection Center (ATCC, Manassas, VA); Human umbilical vein endothelial cells (HUVEC) were isolated from neonatal umbilical cord

Authentication

HEK293T cells were purchased from the ATCC official website and were not authenticated. Human umbilical vein endothelial cells (HUVECs) were validated by flow cytometry using CD31 as a marker, with a purity of 98%.

Mycoplasma contamination

All cell experiments were conducted in a biosafety cabinet under negative pressure to ensure a sterile environment, and no mycoplasma contamination was detected.

Commonly misidentified lines
(See ICLAC register)

Name any commonly misidentified cell lines used in the study and provide a rationale for their use.

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

C57BL/6J mice were obtained from the Model Animal Research Center of Nanjing University. Piezo1loxP/loxP (STOCK Piezo1tm2.1Apat/J; 029213) and Il33 loxP/loxP(B6(129S4)-Il-33tm1.1Bryc/J; 030619) mice were obtained from GemPharmatech, Nanjing, China. Mice expressing ECspecific Cdh5-(PAC)-CreERT2 were provided by R. H. Adam.All experiments used 8 - 10-week-old male specific pathogen-free (SPF) mice. The animals were housed in a temperature-controlled (22 ± 2°C), humidity-regulated (50% ± 10% relative humidity) environment under a standard 12-hour light/dark cycle at the Experimental Center of West China Second University Hospital, Sichuan University.

Wild animals

This section was not involved.

Reporting on sex

All experiments used 8 - 10-week-old male specific pathogen-free (SPF) mice housed and maintained under pathogen-free facility at the Experimental Center of West China Second University Hospital and fed ad libitum on a standard 12-hour light/dark cycle.

Field-collected samples

This section was not involved.

Ethics oversight

All animal experimental protocols were approved by the Laboratory Animal Ethics Committee of West China Second University

Ethics oversight	Hospital, Sichuan University (approval number: 20220303070), and conducted in strict accordance with the institutional guidelines for the care and use of laboratory animals.

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

Plants

Seed stocks	This section was not involved.
Novel plant genotypes	This section was not involved.
Authentication	This section was not involved.