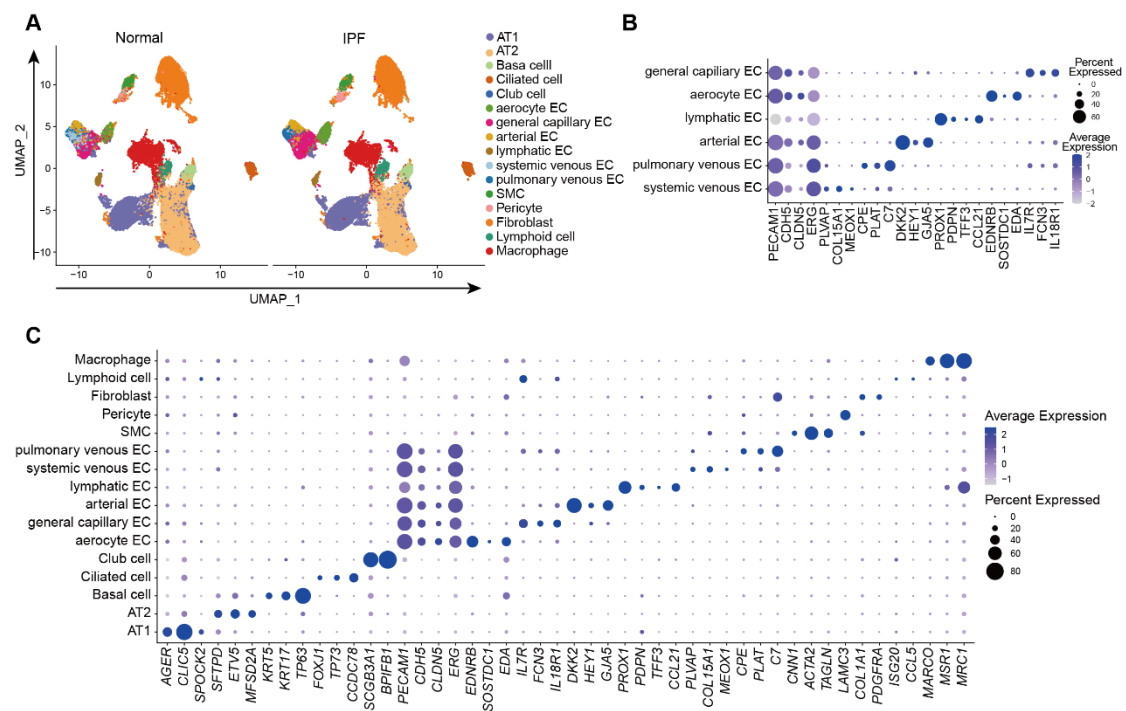
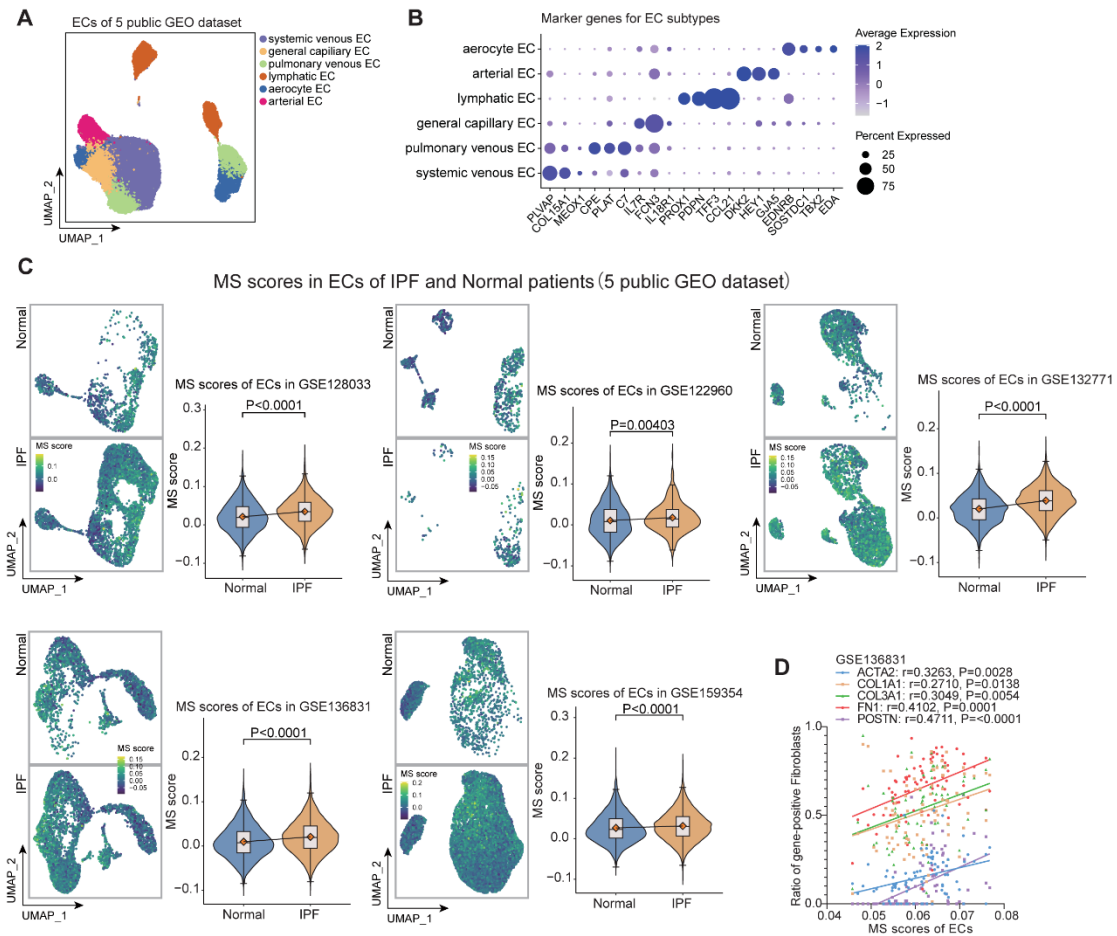




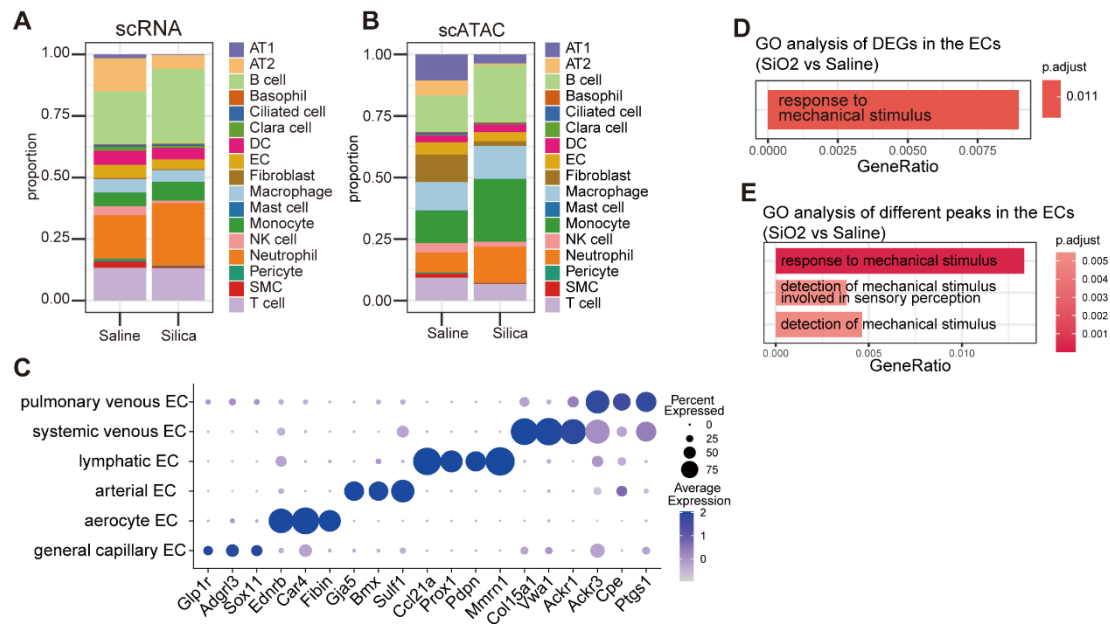
Supplementary Figure 1: Clustering Analysis of Lung Tissue Cells in IPF Patients and Normal Group

A UMAP plots of lung tissue cell clustering for Normal and IPF patients. **B** Dot plot showing the expression levels of marker genes for endothelial subpopulations. **C** Dot plot showing the expression levels of marker genes for each cell population.



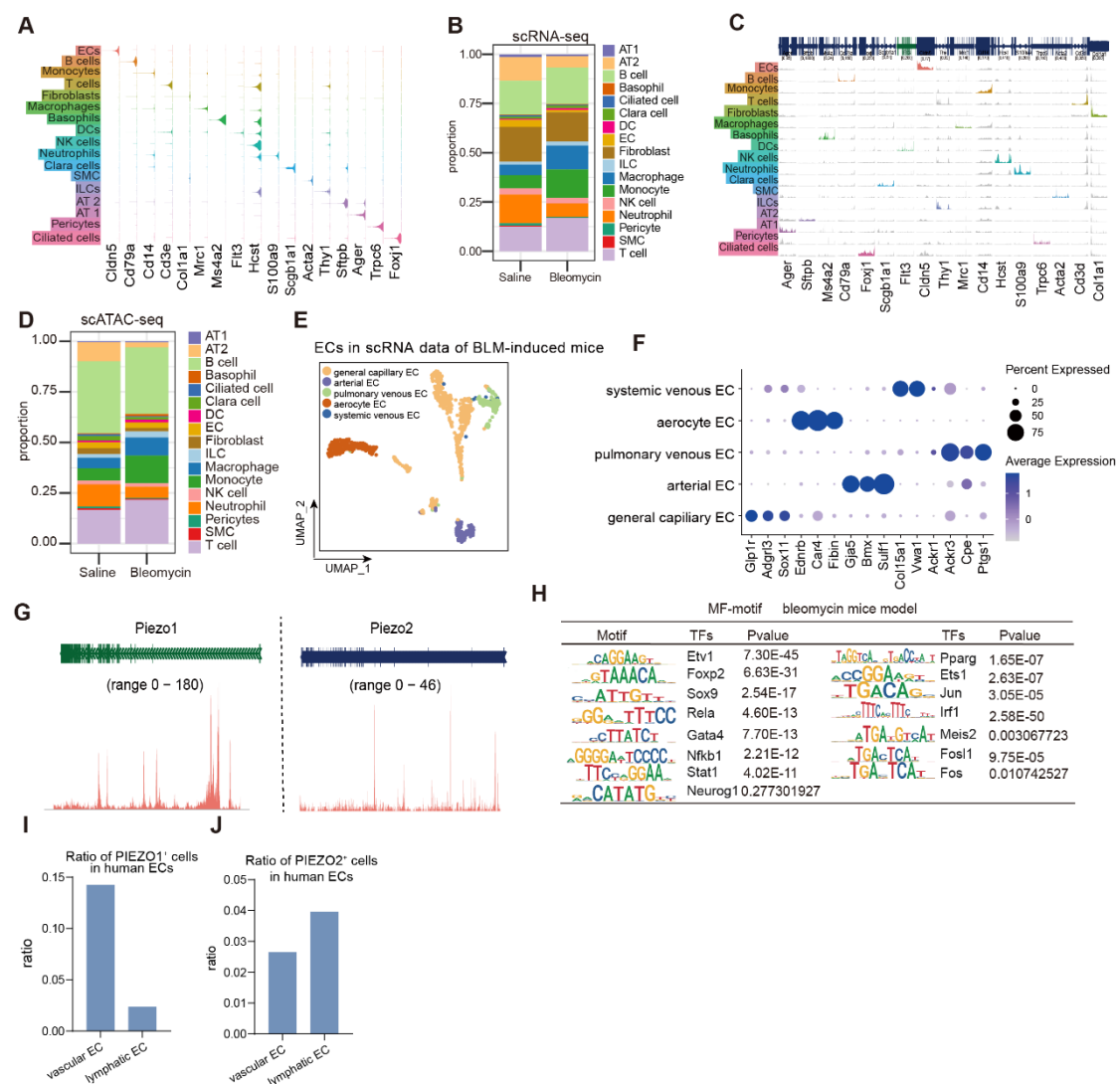
Supplementary Figure 2: IPF Patients Have Increased Mechanical Expression of Endothelial Cells

A UMAP plot of ECs of integrated 5 GEO datasets. **B** Dot plot showed the marker genes of ECs of integrated 5 GEO datasets. **C** Analysis of mechanical stress (MS) signaling in ECs using data from the GEO database (GSE122960: 969 Normal ECs, 284 IPF ECs, GSE128033: 1187 Normal ECs, 4479 IPF ECs, GSE132771: 2025 Normal ECs, 3868 IPF ECs, GSE136831: 3038 Normal ECs, 5139 IPF ECs, GSE159345: 2730 Normal ECs, 13855 IPF ECs). Violin plots displayed the mean (yellow diamond) the median (center line), the interquartile range, and the whiskers ($1.5 \times$ interquartile range). P values were calculated using the two-tailed unpaired t-test. **D** Person correlation analysis of MS scores and fibroblast-related genes.



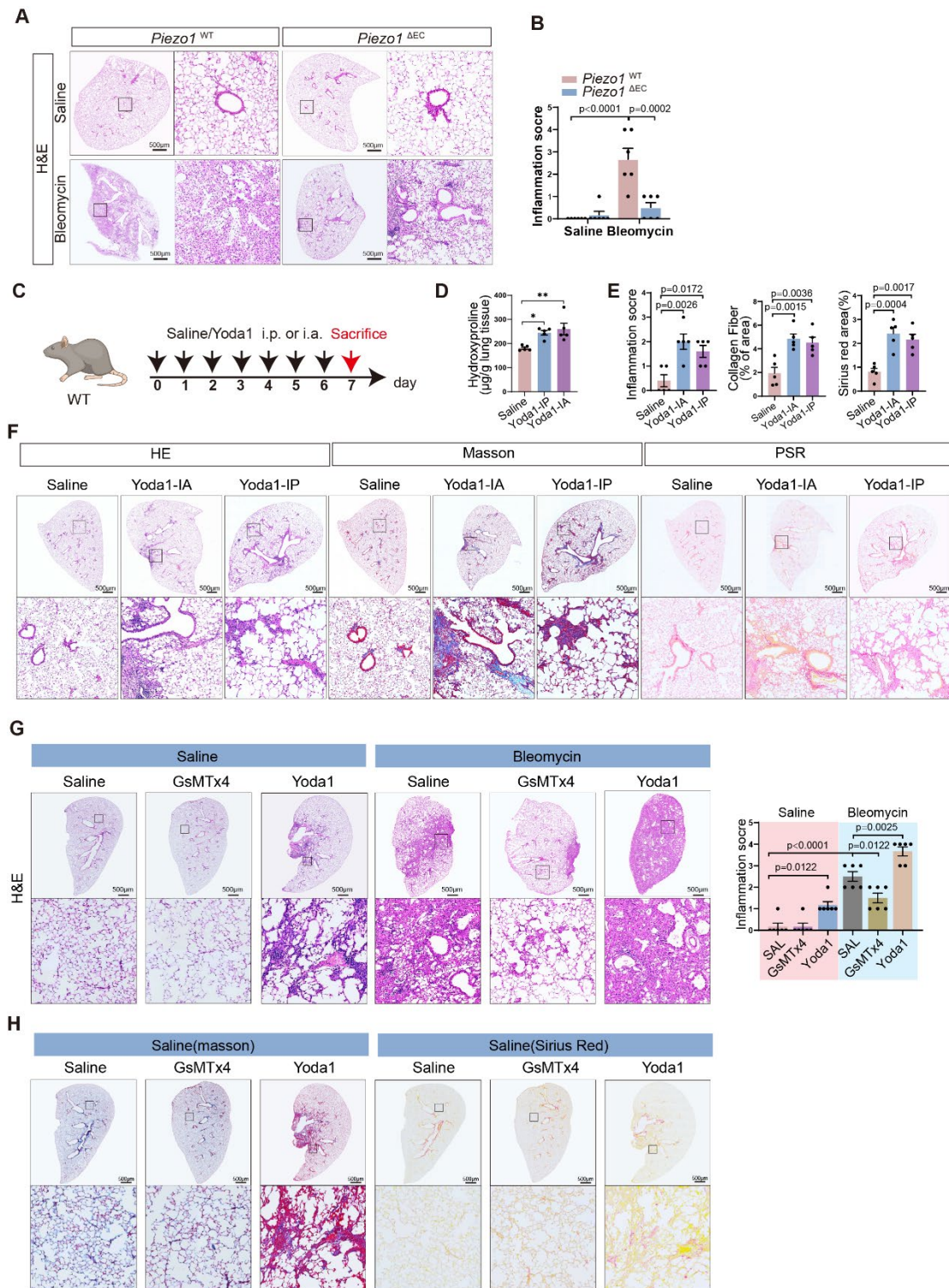
Supplementary Figure 3: Characterization of SiO₂-Induced Mouse Model for Pulmonary Fibrosis

A Proportions of cell subpopulations in control and SiO₂-induced mouse models as analyzed by scRNA-seq. **B** Proportions of cell subpopulations in control and SiO₂-induced mouse models as analyzed by scATAC-seq. **C** Dot plot showing expression of marker genes for endothelial subpopulations in SiO₂-induced mice scRNA data. **D** GO enrichment analysis of differential genes in ECs from scRNA-seq data of SiO₂ and control mice, highlighting enrichment in the mechanical force signaling pathway. **E** GO enrichment analysis of differential peaks in ECs from scATAC-seq data of SiO₂ and control mice, revealing enrichment in the mechanical force signaling pathway.



Supplementary Figure 4: Analysis of BLM-Induced Mouse Model Using scRNA-seq and scATAC-seq

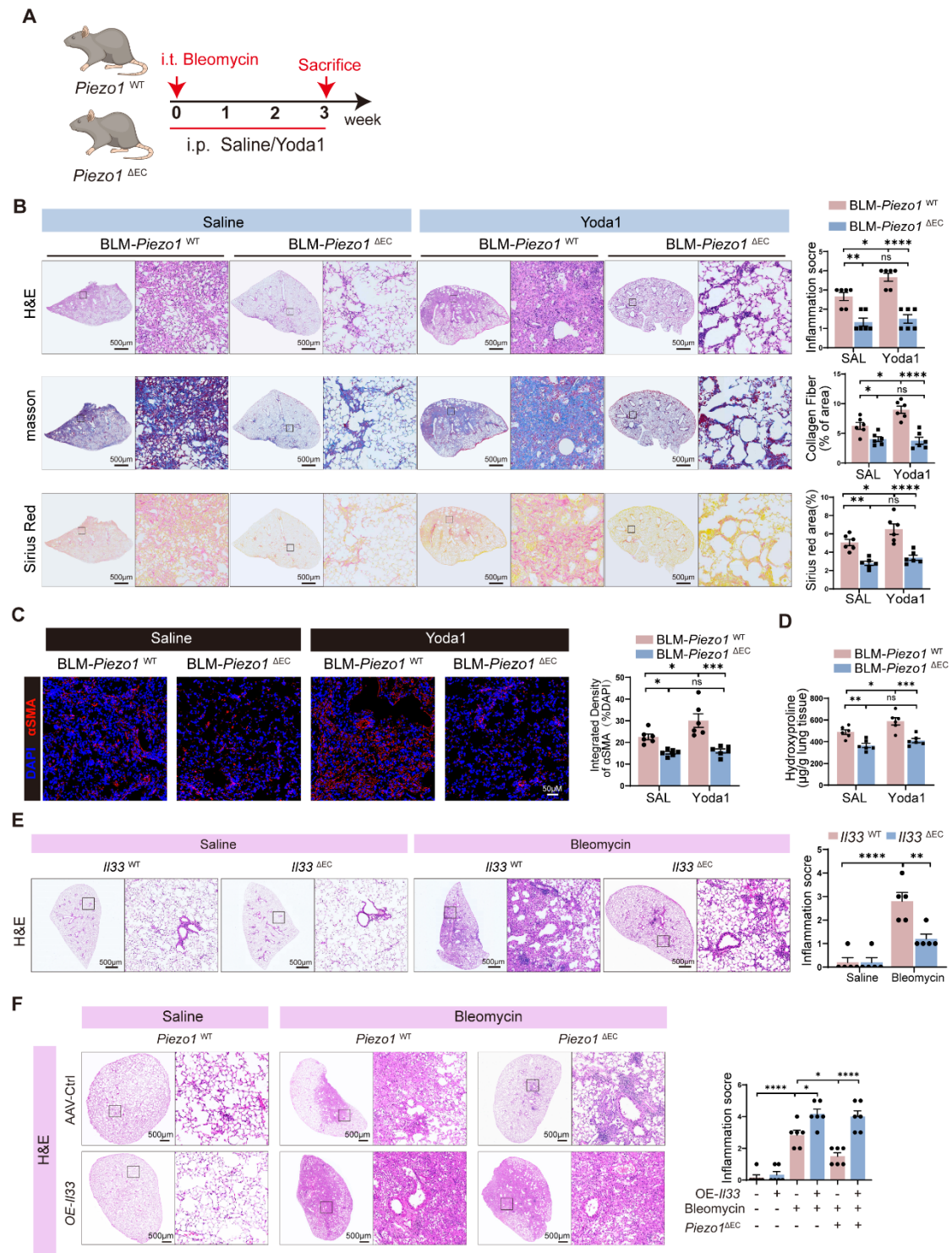
A Violin plot showing markers for various lung cell types in BLM-treated mice and control of scRNA-seq data. **B** Proportions of cell subpopulations in control and BLM-induced mouse models of scRNA-seq data. **C** The coverage plot illustrated the peak of marker genes for cellular subtypes in the lung tissue of BLM-treated mice and control of scATAC-seq data. **D** Proportions of cell subpopulations in control and BLM-induced mouse models of scATAC-seq data. **E** Subpopulation of ECs of scRNA-seq data from BLM model and control mice clustered using cellular marker genes. The UMAP plot showed the distribution of each endothelial subpopulation. **F** Dot plot showing expression of marker genes for endothelial subpopulations in BLM-induced mice scRNA-seq data. **G** Chromatin opening regions near *Piezo1* and *Piezo2*. **H** Table showing TF motifs of ECs enriched in mechanical stress-related pathways by scATAC-seq data of BLM-induced and saline-induced mice. Bar chart showed the distribution of *PIEZO1*-positive cells (**I**) and *PIEZO2*-positive cells (**J**) in endothelial cells.



Supplementary Figure 5: Gene Deletion and Pharmacological Intervention of PIEZO1 Affect PF Development

Representative H&E staining (A) and quantification (B) of lungs from BLM-induced fibrotic *Piezo1*^{WT} and *Piezo1*^{ΔEC} mice. C The schematic illustrated the administration of the PIEZO1 agonist Yoda1 to mice via tracheal or intraperitoneal injection. The mice were euthanized one week later. D The plot showed hydroxyproline amounts in lung tissues from mice in Yoda1-induced via tracheal or intraperitoneal injection (n = 5). Representative images of H&E, Masson,

PSR staining (**F**) and quantification (**E**) in lungs of mice in Yoda1-induced via tracheal or intraperitoneal injection (n = 5). **G** Representative images of H&E staining in fibrotic lungs of mice in Yoda1 or GsMTx4-induced via intraperitoneal. Quantification was shown at right (n = 6). **H** Representative images of Masson and PSR staining in saline control lungs of mice in Yoda1 or GsMTx4-induced via intraperitoneal. Error bars represent mean $\pm$ SEM. A: two-tailed unpaired *t*-test, B: two-way ANOVA followed Tukey's multiple comparisons test, one-way ANOVA followed Šídák's multiple comparisons test was used in D-E and Tukey's multiple comparisons test was used in G. All n denote biologically independent samples. Source data are provided as a Source Data file.



Supplementary Figure 6: Genetic ablation of endothelial Piezo1 abrogates the pro-fibrotic effect of Yoda1

A Schematic of intraperitoneal Yoda1 injection for 3 weeks in BLM-induced pulmonary fibrosis models in *Piezo1*^{WT} and *Piezo1*^{ΔEC} mice. **B** Representative H&E, Masson, and Sirius red staining and quantification of lungs from *Piezo1*^{WT} and *Piezo1*^{ΔEC} mice treated with Yoda1 or saline in BLM fibrosis model (n=6). **C** Immunofluorescent staining and quantification of αSMA in lungs of *Piezo1*^{WT} and *Piezo1*^{ΔEC} mice with Yoda1 or saline treatment (n=6). **D** Hydroxyproline content in lung tissues from BLM- and saline-induced fibrosis models treated

with Yoda1 or GsMTx4 intraperitoneally (n=6). **E** H&E staining and quantification of lungs from *Il33*^{wt} and *Il33*^{ΔEC} mice in BLM-induced fibrosis (n=5). **F** H&E staining and quantification of fibrotic lungs from *Piezo1*^{WT} and *Piezo1*^{ΔEC} mice injected with AAV-control (AAV-NC) or AAV-OE-*Il33* (n=5). Error bars represent mean ± SEM. B-E: two-way ANOVA followed Tukey's multiple comparisons test, F: one-way ANOVA followed Tukey's multiple comparisons test. All n denote biologically independent samples. Source data are provided as a Source Data file.