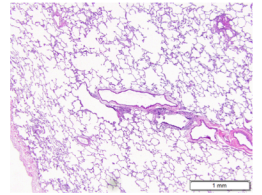


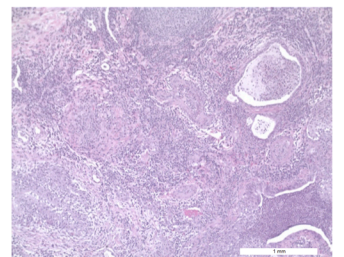
### **Supplemental Figure Legends**

**Supplemental Figure 1.** H&E stained histopathology of adjacent lung tissue sections from the explanted lungs, identified by sample id. Scale bar=1mm. IPF, idiopathic pulmonary fibrosis; SSc, systemic sclerosis.

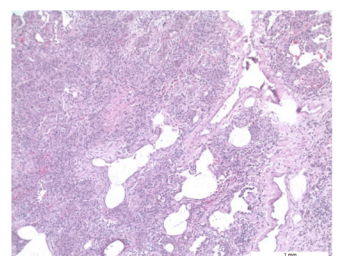
## Control 5



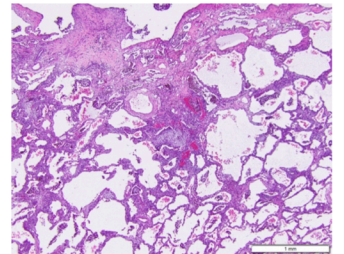
## IPF 7



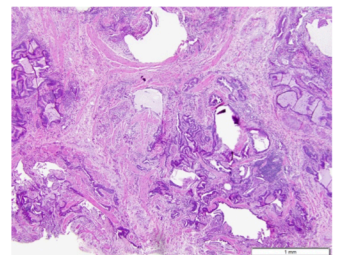
## IPF 8



## SSC 7

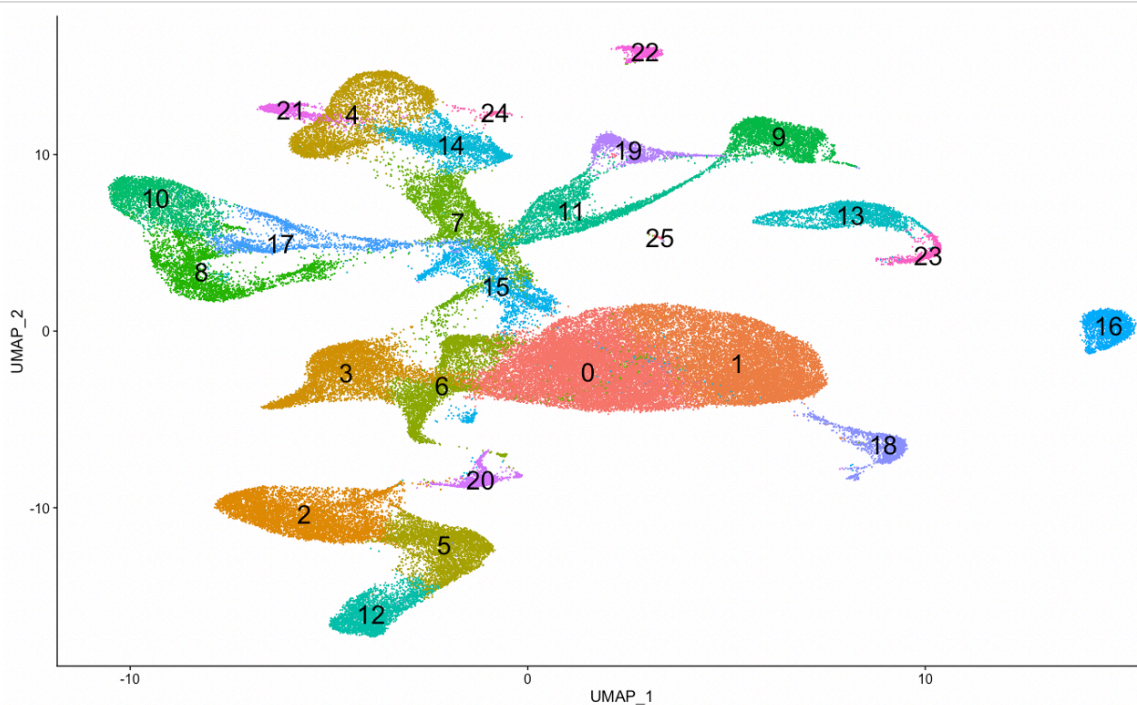


## SSC 8

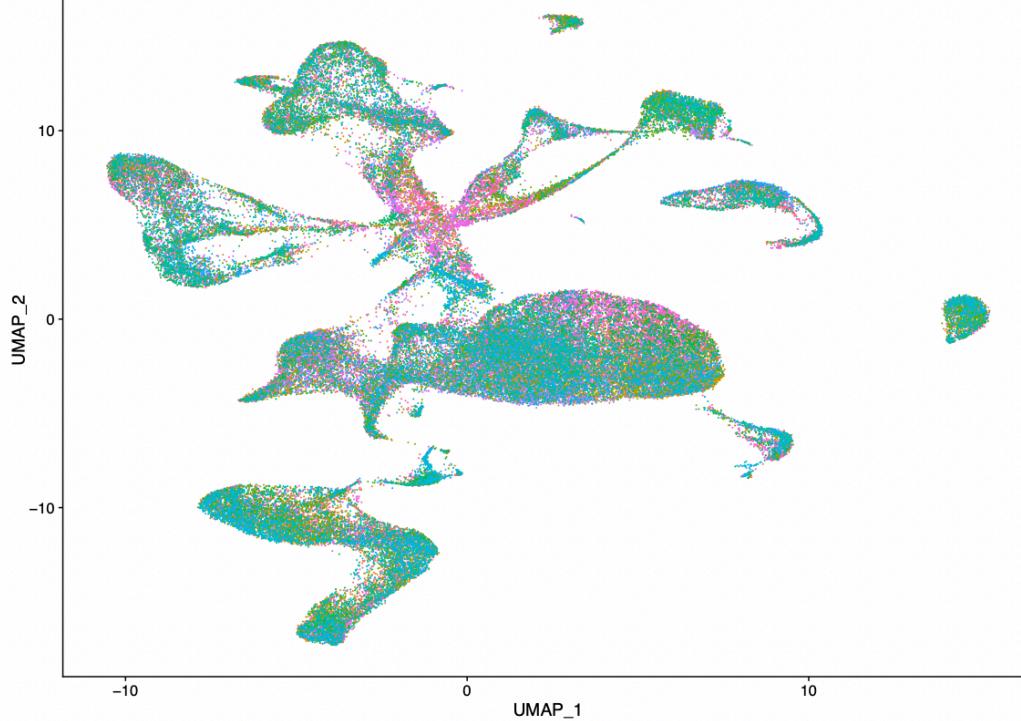


**Supplemental Figure 2.** ScRNA-seq analysis of 8 IPF, 8 SSc-ILD, and 5 organ donor control lung samples. (A) UMAP plot of all 21 integrated samples, with original 26 clusters, prior to aggregation by cell type. (B) UMAP plots of all samples, labeled by individual sample. scRNA-seq, single-cell RNA-sequencing; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease; UMAP, uniform manifold approximation and projection.



**a**

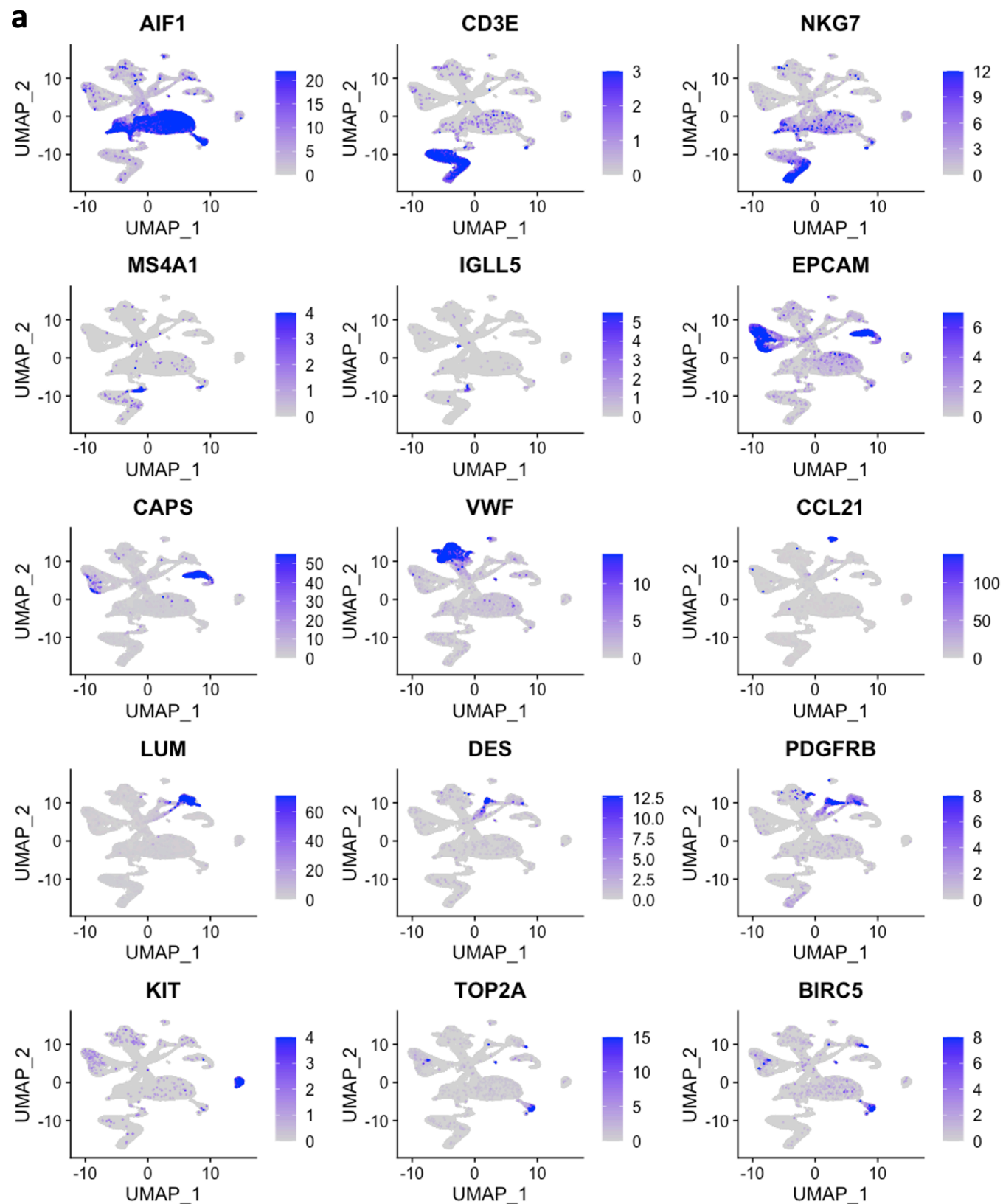
- |                                 |                                 |                             |
|---------------------------------|---------------------------------|-----------------------------|
| ● 0 -Macrophage                 | ● 11 -Fibroblast/Pericyte       | ● 22 -Lymphatic Endothelial |
| ● 1 -Macrophage                 | ● 12 -Natural Killer            | ● 23 -Ciliated              |
| ● 2 -T Lymphocyte               | ● 13 -Ciliated                  | ● 24 -Endothelial           |
| ● 3 -Monocytes                  | ● 14 -Endothelial               | ● 25 -Proliferating Cells   |
| ● 4 -Endothelial                | ● 15 -Low quality cells         |                             |
| ● 5 -T Lymphocyte               | ● 16 -Mast                      |                             |
| ● 6 -Macrophage/Dendritic       | ● 17 -Mixed Alveolar Epithelial |                             |
| ● 7 -Low quality cells          | ● 18 -Proliferating Macrophage  |                             |
| ● 8 -Mixed Bronchial Epithelial | ● 19 -Pericyte/Smooth Muscle    |                             |
| ● 9 -Fibroblasts                | ● 20 -B Lymphocyte/Plasma       |                             |
| ● 10 -Mixed Alveolar Epithelial | ● 21 -Endothelial               |                             |

**b**

- |             |         |
|-------------|---------|
| ● CONTROL 1 | ● IPF 7 |
| ● CONTROL 2 | ● IPF 8 |
| ● CONTROL 3 | ● SSC 1 |
| ● CONTROL 4 | ● SSC 2 |
| ● CONTROL 5 | ● SSC 3 |
| ● IPF 1     | ● SSC 4 |
| ● IPF 2     | ● SSC 5 |
| ● IPF 3     | ● SSC 6 |
| ● IPF 4     | ● SSC 7 |
| ● IPF 5     | ● SSC 8 |
| ● IPF 6     |         |

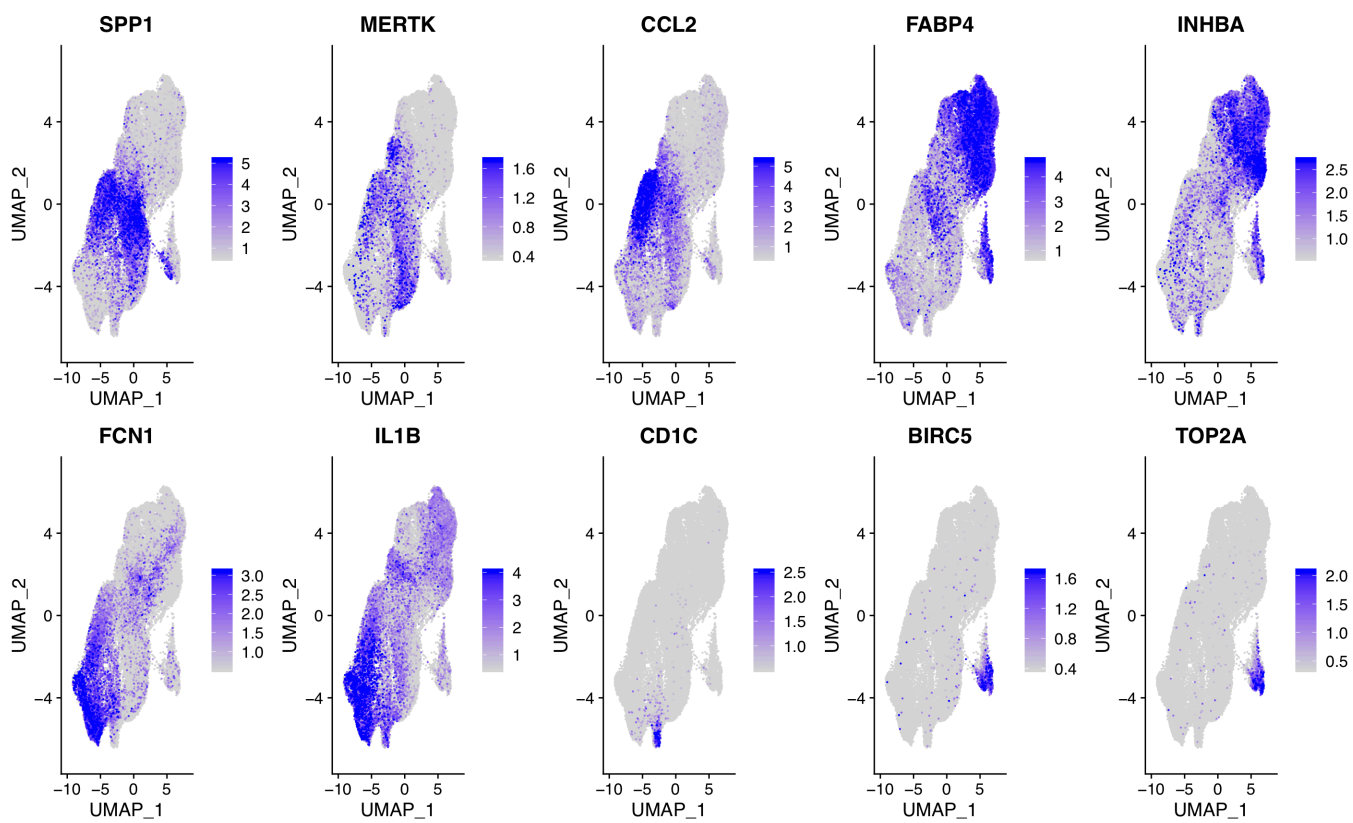


**Supplemental Figure 3.** ScRNA-seq analysis of IPF, SSc-ILD, and control cells with expression of selected cell type markers. *AIF1*- macrophages; *CD3E*-lymphoid cells; *NKG7*- natural killer cells; *MS4A1*- B lymphocytes; *IGLL5*- plasma cells; *EPCAM*-epithelial cells; *CAPS*- ciliated cells; *VWF*- endothelial cells; *CCL21*-lymphatic endothelial cells; *LUM*-fibroblasts; *DES*- smooth muscle cells; *PDGFRB*- pericytes; *KIT*-mast cells; *TOP2A*- proliferating cells; *BIRC5*-proliferating cells. scRNA-seq, single-cell RNA-sequencing; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

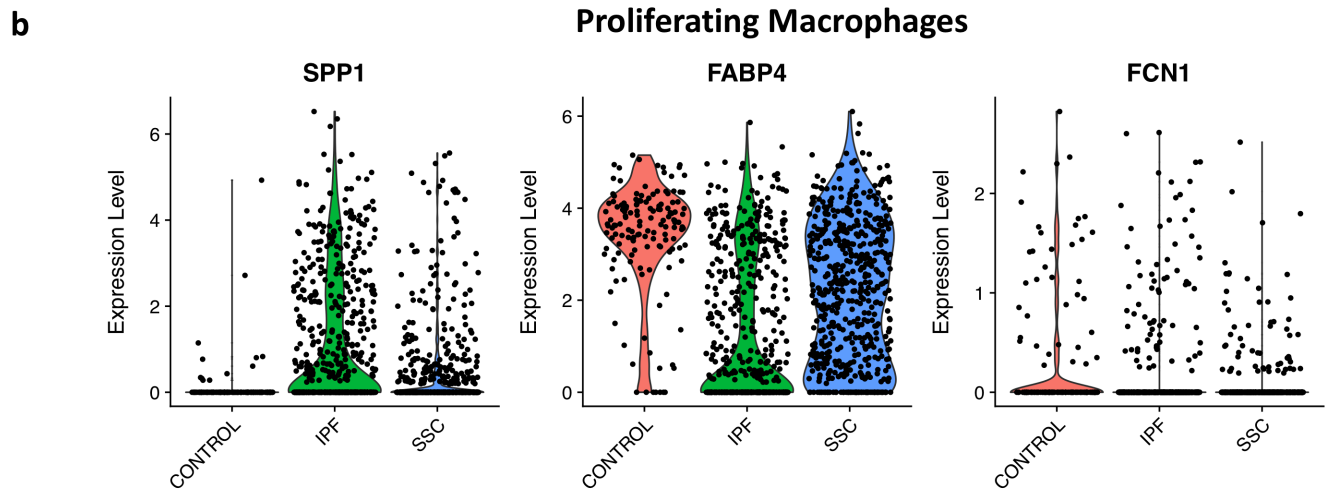
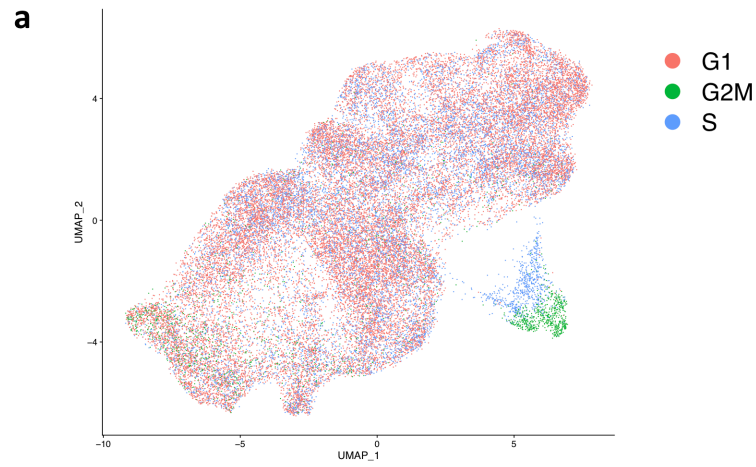


**Supplemental Figure 4.** ScRNA-seq analysis of IPF, SSc-ILD, and control myeloid populations. Expression of *SPP1*, *MERTK*, and *CCL2* indicate *SPP1*<sup>hi</sup> macrophages. Expression of *FABP4* and *INHBA* indicate *FABP4*<sup>hi</sup> macrophages. Expression of *FCN1* and *IL1B* indicate *FCN1*<sup>hi</sup> macrophages. Expression of *CD1C* indicates dendritic cells. Expression of *BIRC5* and *TOP2A* indicate proliferating macrophages. scRNA-seq, single-cell RNA-sequencing; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.





**Supplemental Figure 5.** ScRNA-seq analysis of IPF, SSc-ILD, and control myeloid populations. (A) UMAP plot of myeloid populations, identified by predicted cell phase. (B) Expression of macrophage subpopulation markers *SPPI*, *FABP4*, and *FCN1* in the proliferating macrophage cluster only, separated by disease status. scRNA-seq, single-cell RNA-sequencing; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease; UMAP, uniform manifold approximation and projection.

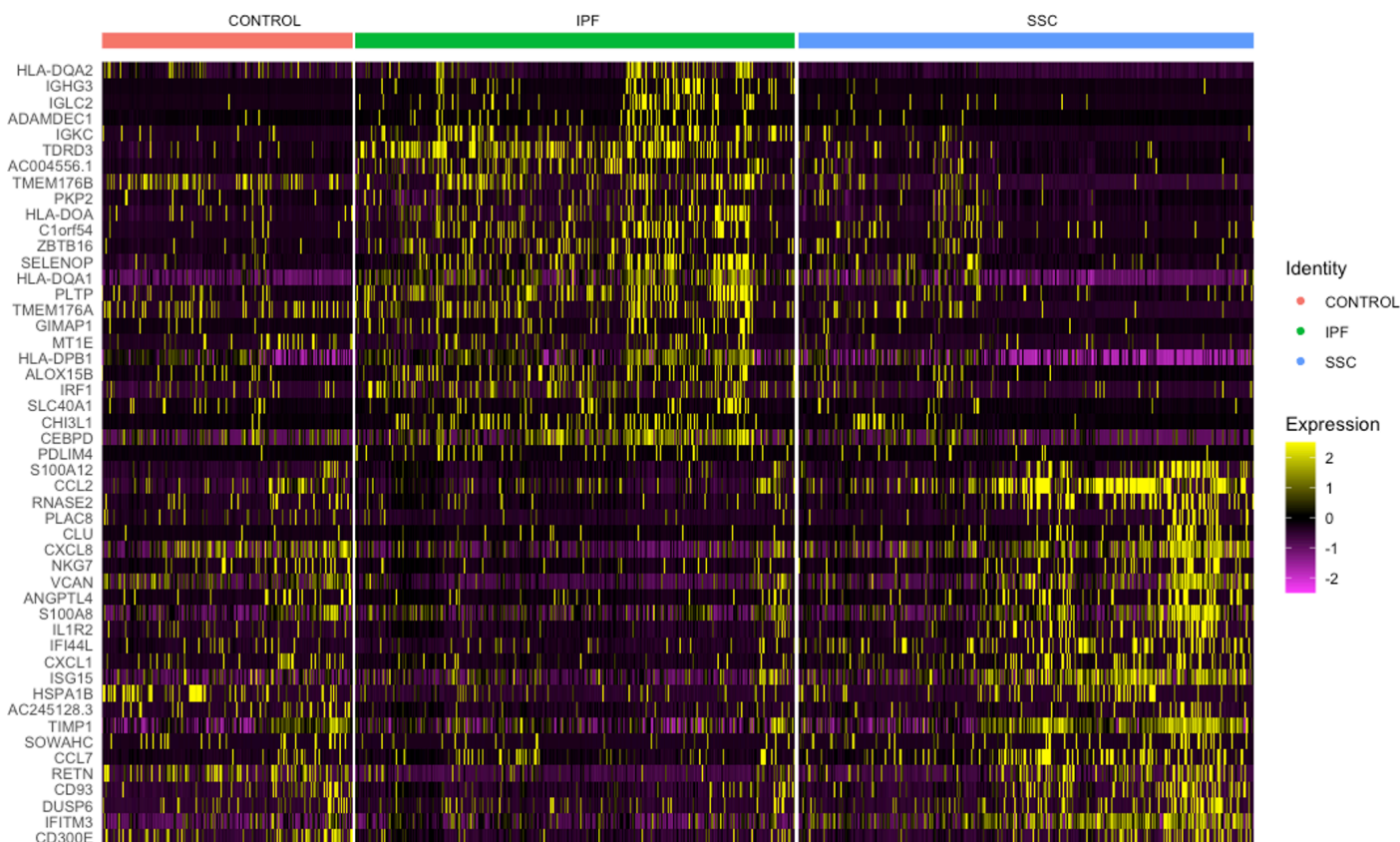




**Supplemental Figure 6.** (A) Heat map of *SPP1*<sup>hi</sup> macrophages, labeled by disease status, displaying 50 differentially expressed genes for the comparison of IPF and SSc-ILD cells. (B) Heat map of *FABP4*<sup>hi</sup> macrophages, labeled by disease status, displaying 50 differentially expressed genes for the comparison of IPF and SSc-ILD cells.

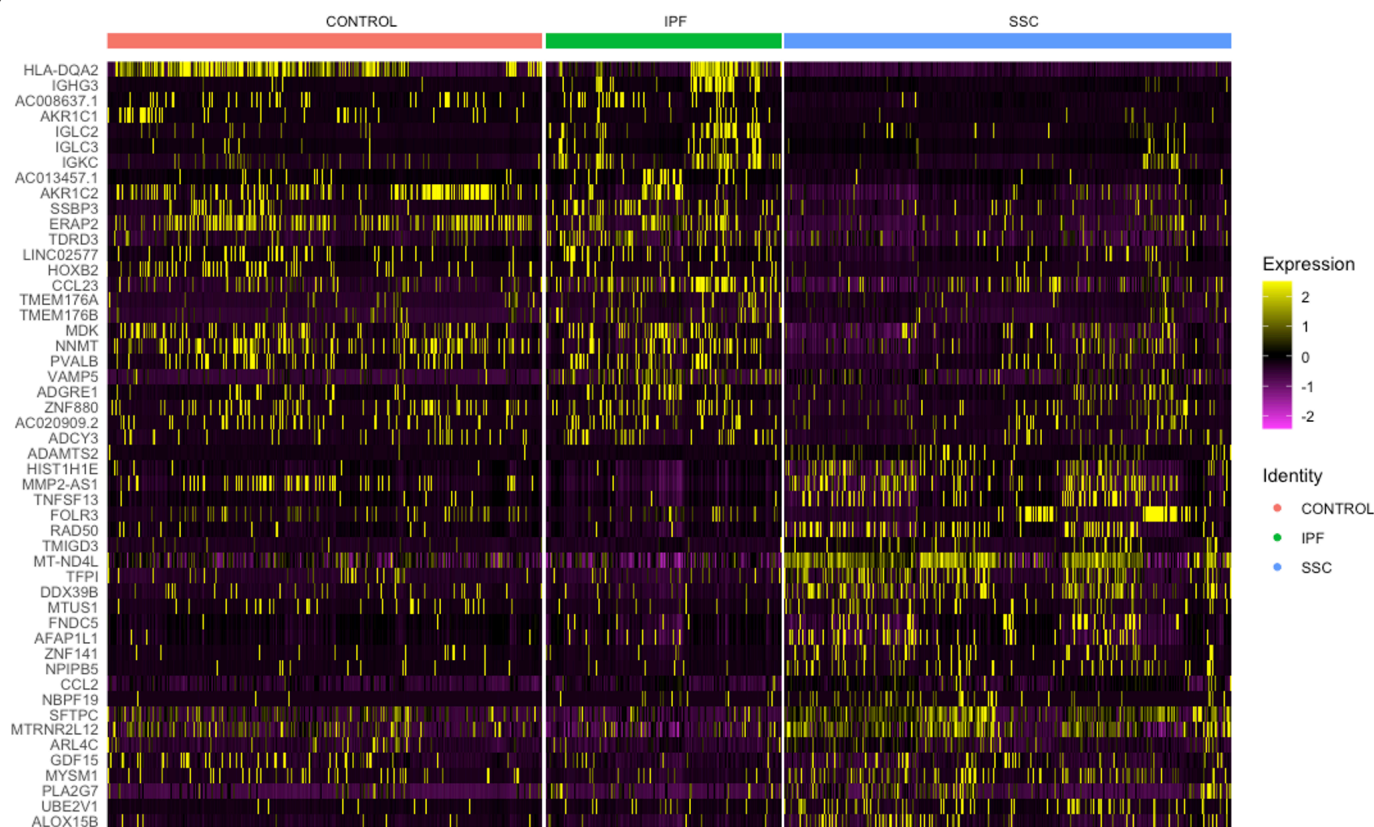
## Differentially expressed genes *SPP1*<sup>hi</sup> macrophages

**a**



## Differentially expressed genes *FABP4*<sup>hi</sup> macrophages

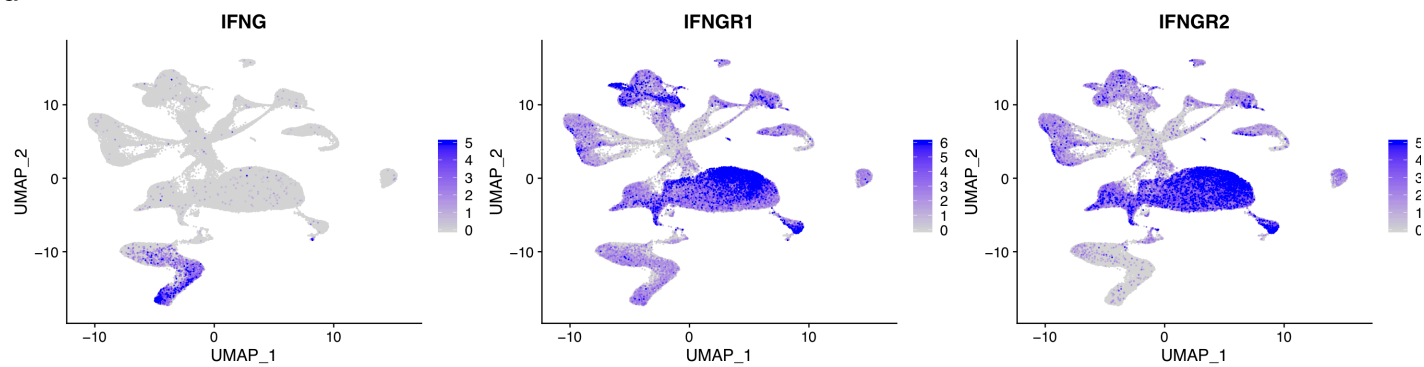
**b**



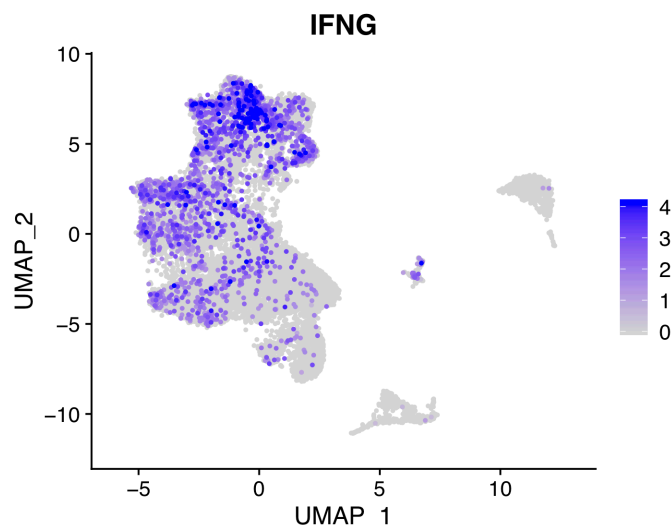
**Supplemental Figure 7.** (A) UMAP plot of all cell type populations with expression of *IFNG* highest in the natural killer cells, and expression of *IFNGR1* and *IFNGR2* highest in the macrophages. (B) UMAP plot of the lymphoid populations indicating expression of *IFNG* is highest in the natural killer cells, and also expressed in the T lymphocytes. UMAP, uniform manifold approximation and projection.



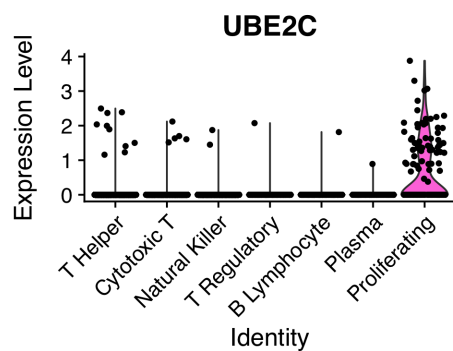
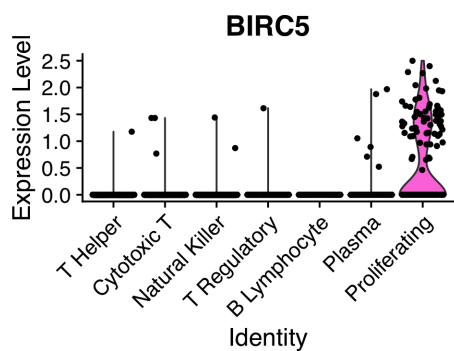
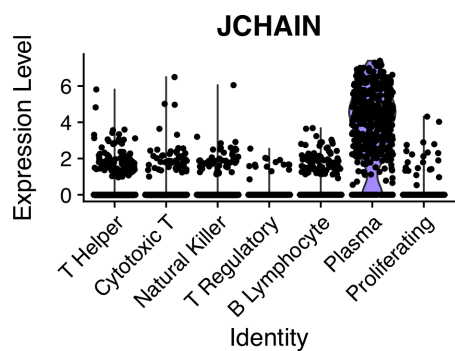
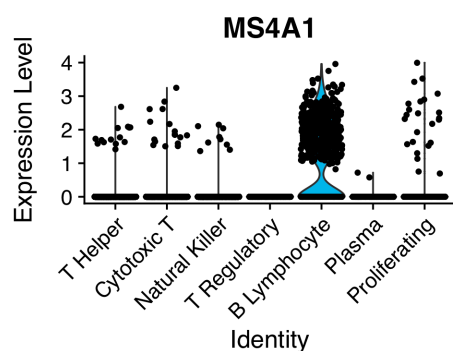
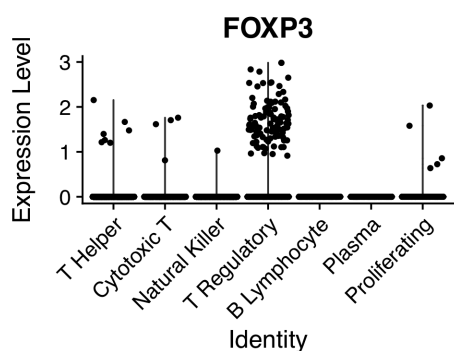
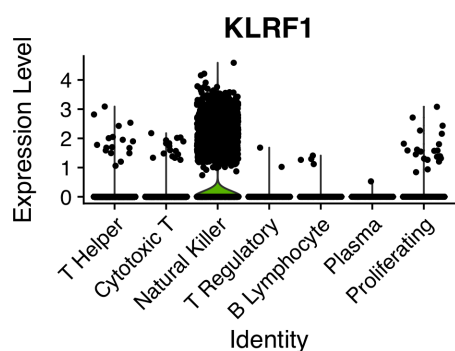
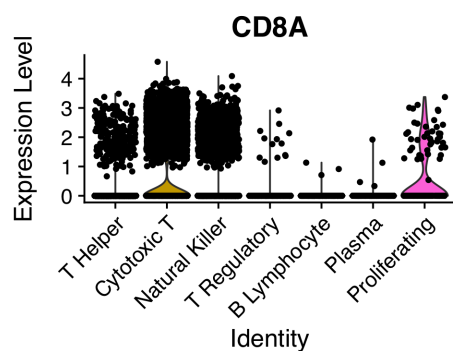
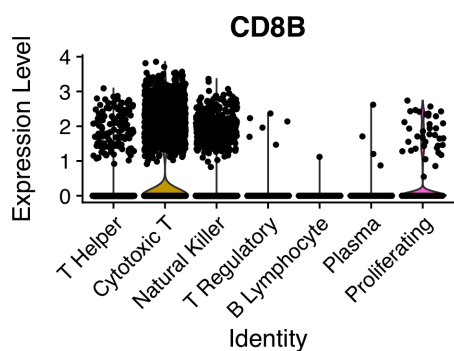
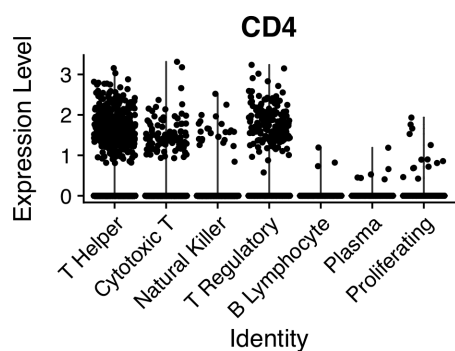
**a**



**b**



**Supplemental Figure 8.** Violin plots demonstrating expression of selected marker genes for the lymphoid populations clustering.

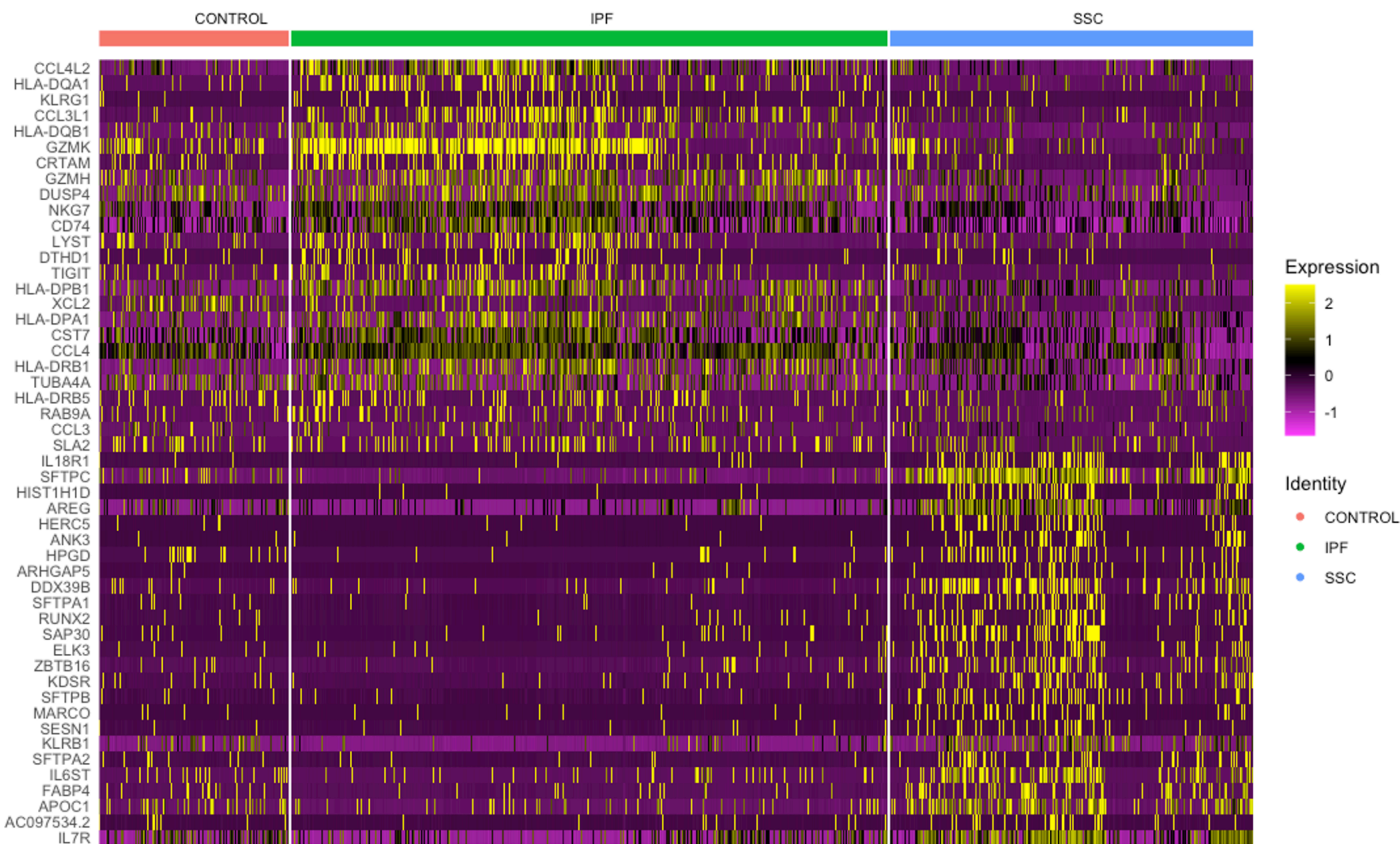




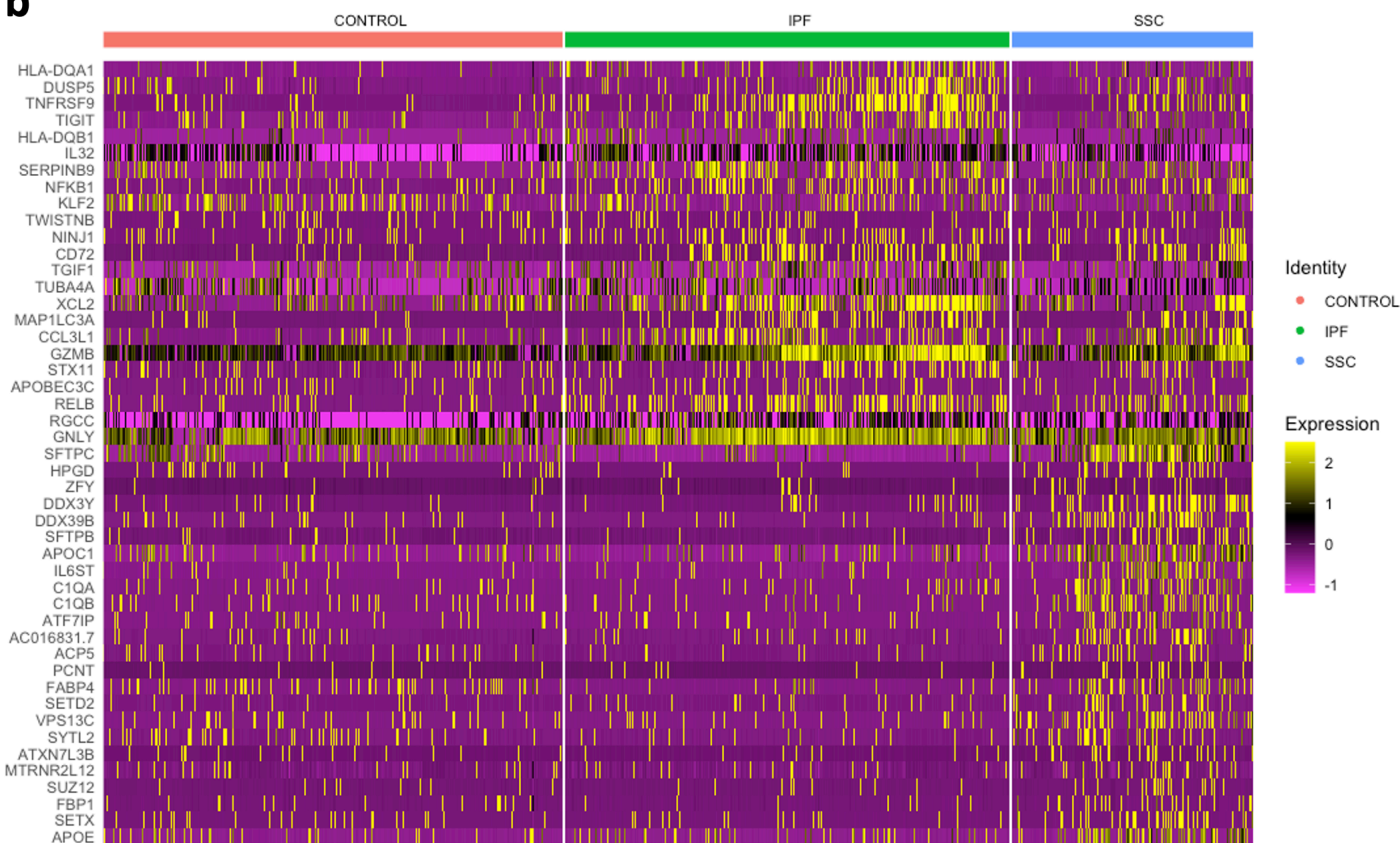
**Supplemental Figure 9.** (A) Heat map of cytotoxic T cells, labeled by disease status, displaying 50 differentially expressed genes for the comparison of IPF and SSc-ILD cells. (B) Heat map of natural killer cells, labeled by disease status, displaying 50 differentially expressed genes for the comparison of IPF and SSc-ILD cells.

**a**

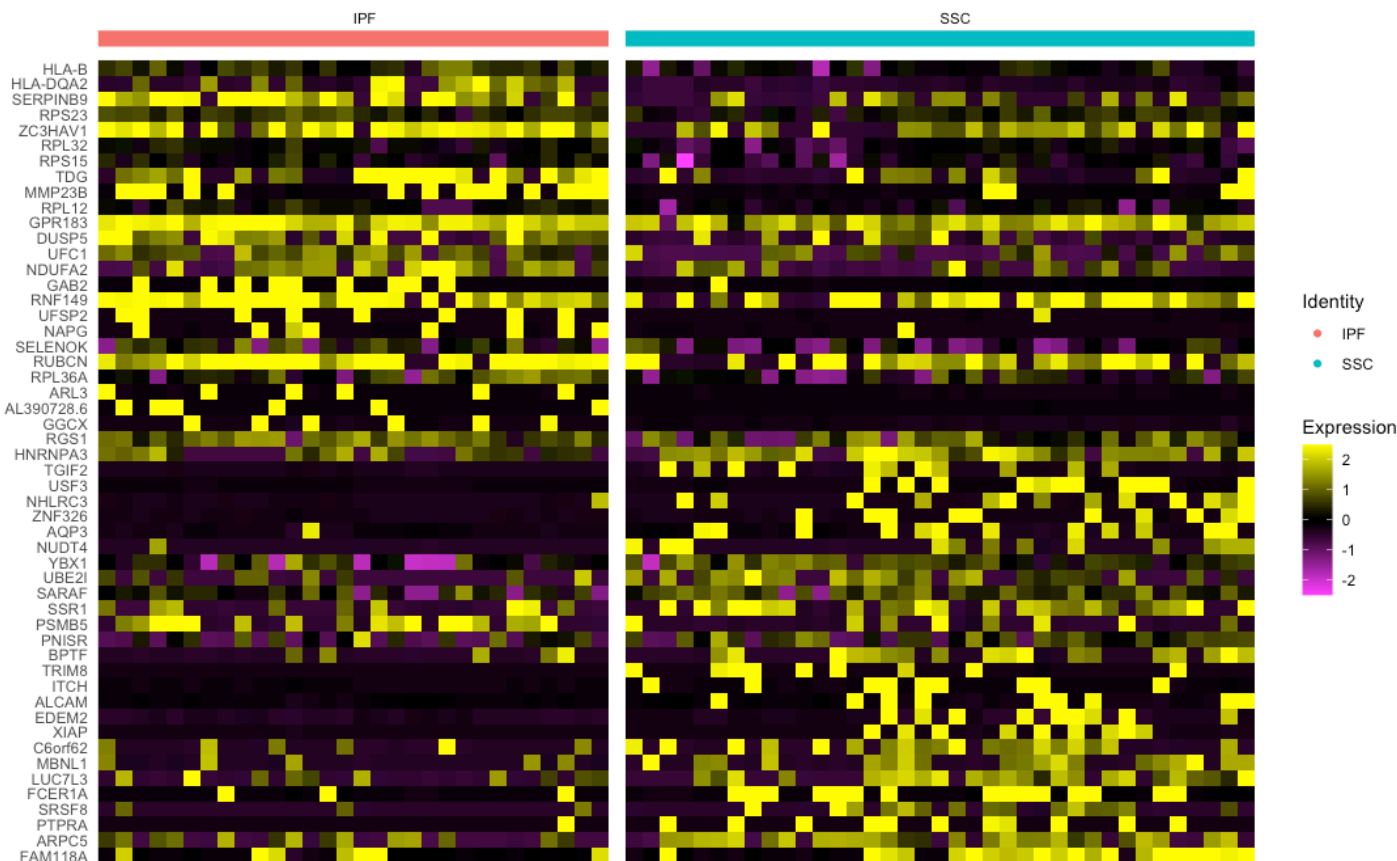
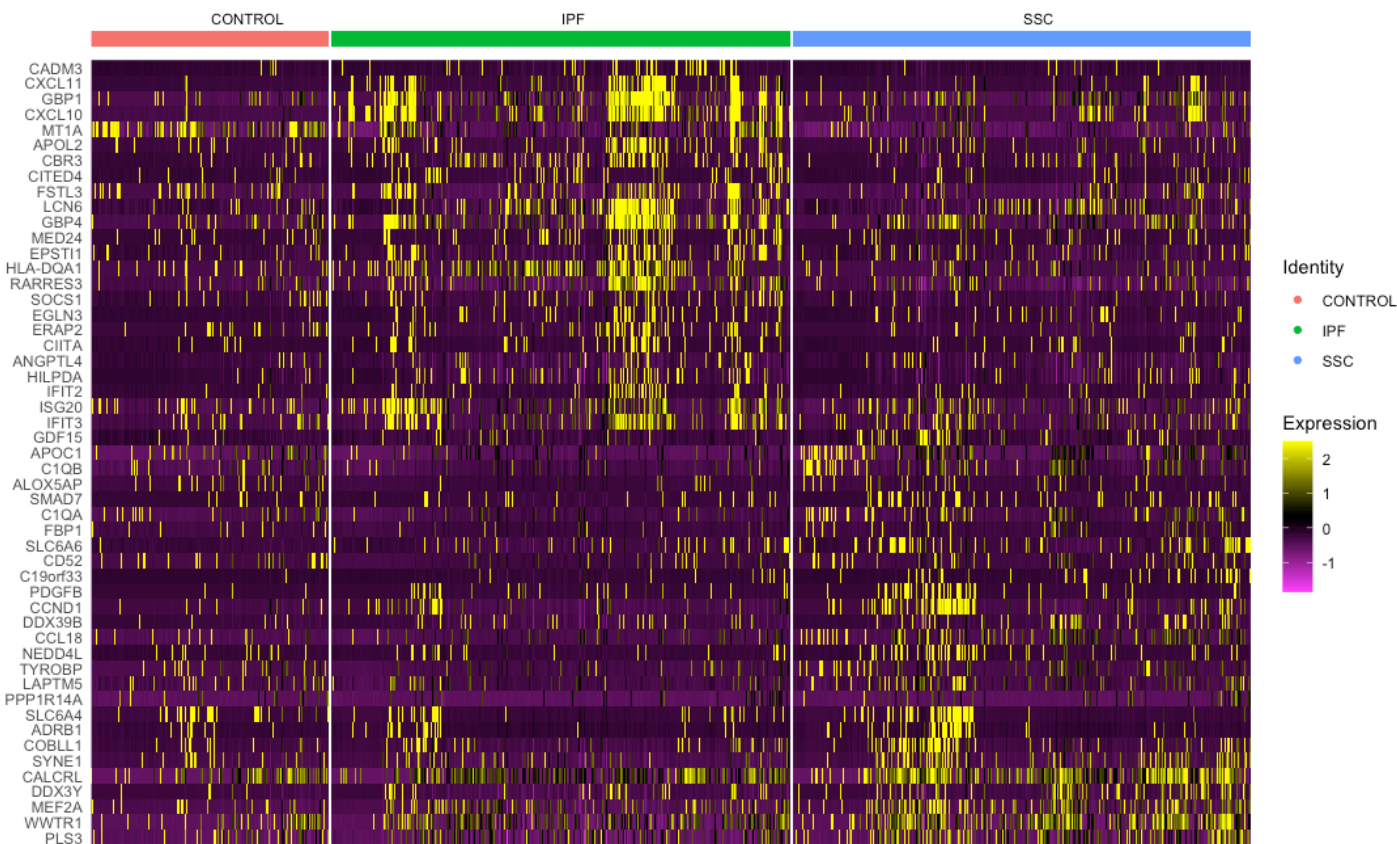
## Differentially expressed genes cytotoxic T lymphocytes

**b**

## Differentially expressed genes natural killer cells

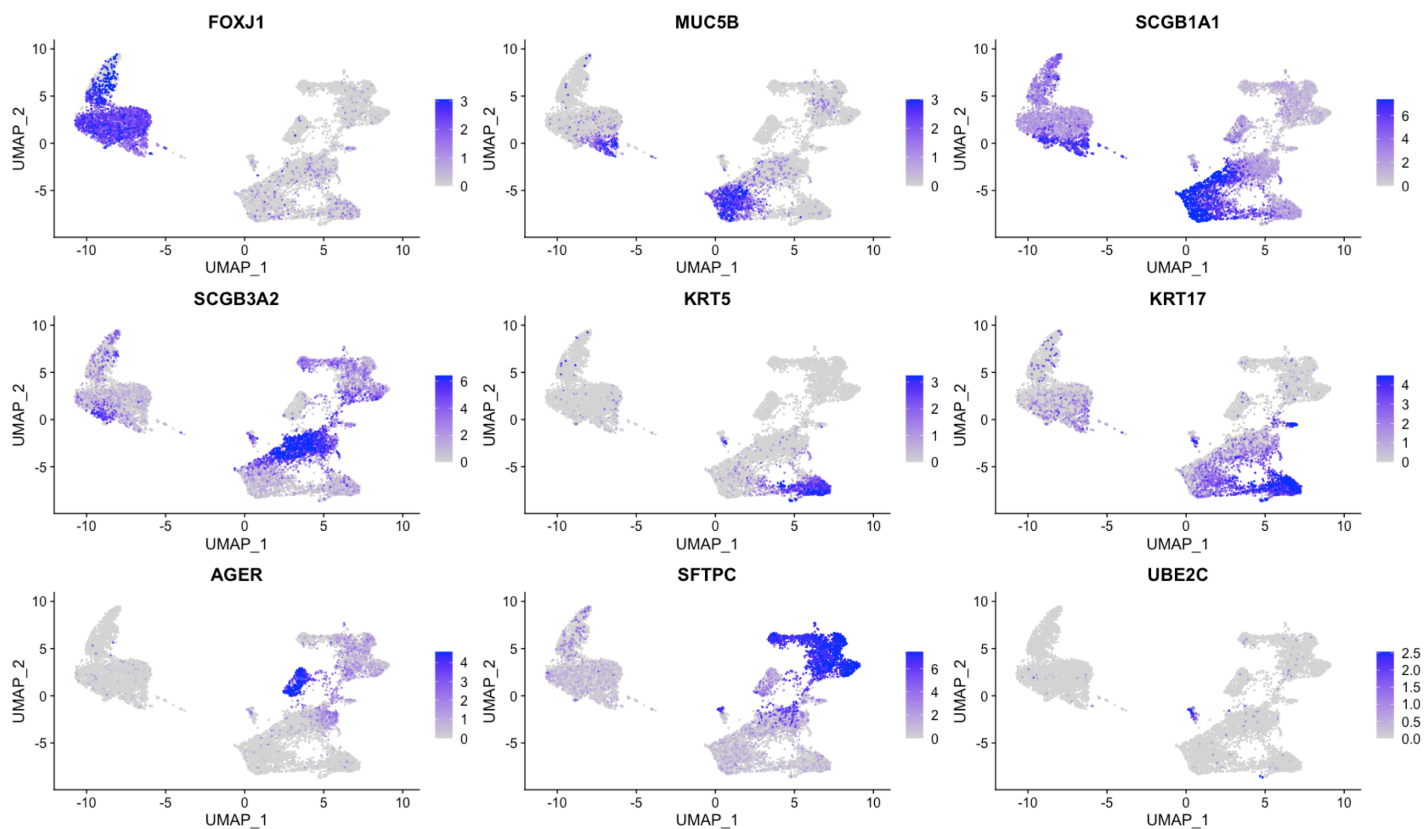


**Supplemental Figure 10.** (A) Heat map of plasmacytoid dendritic cells labeled by disease status, displaying 50 differentially expressed genes for the comparison of IPF and SSc-ILD cells. (B) Heat map of non-lymphatic endothelial cells, labeled by disease status, displaying 50 differentially expressed genes for the comparison of IPF and SSc-ILD cells.

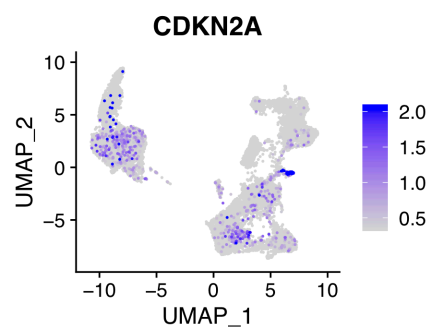
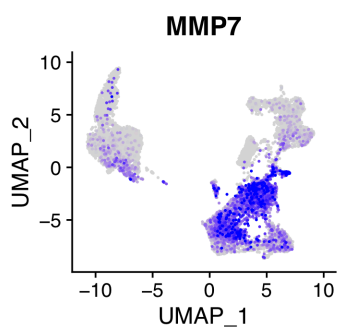
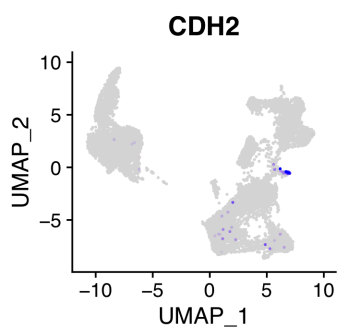
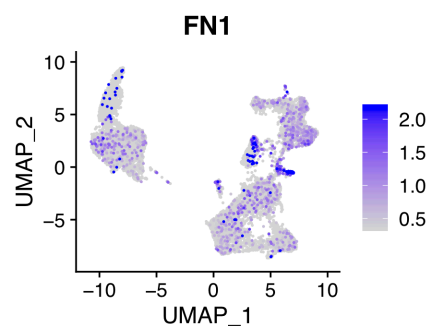
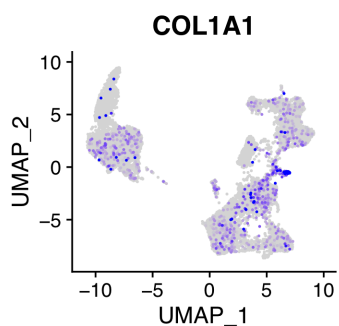
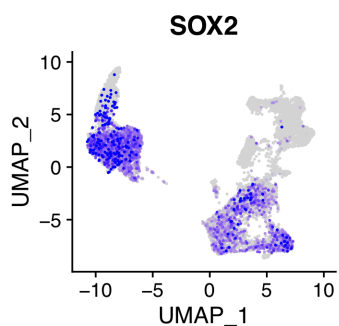
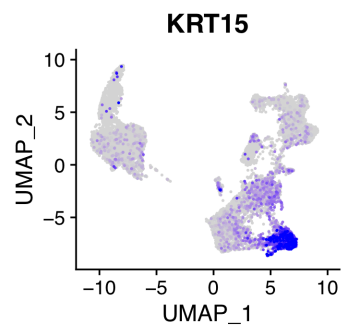
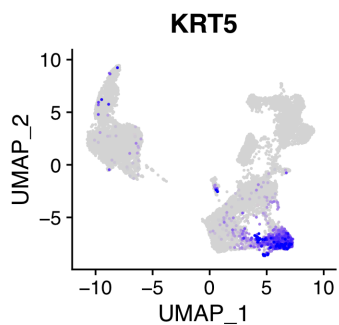
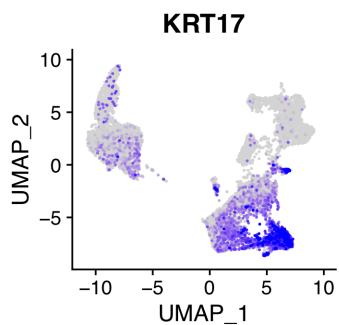
**a****Differentially expressed genes plasmacytoid dendritic cells****b****Differentially expressed genes endothelial cells**



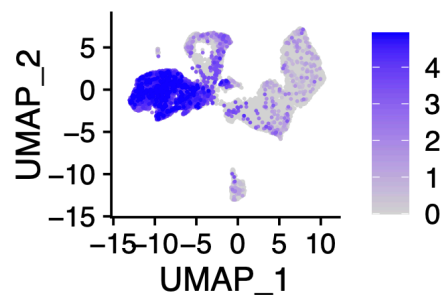
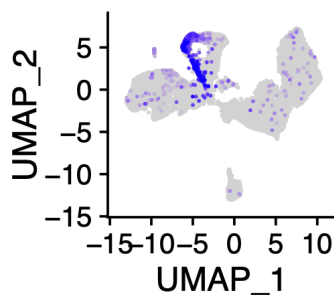
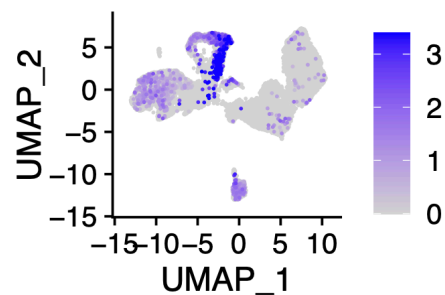
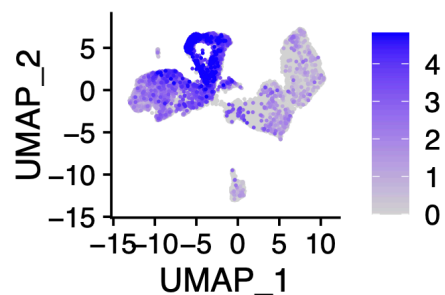
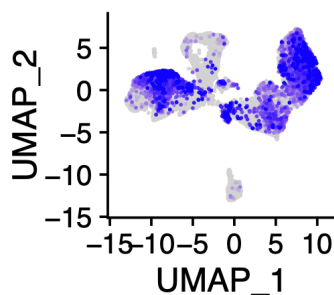
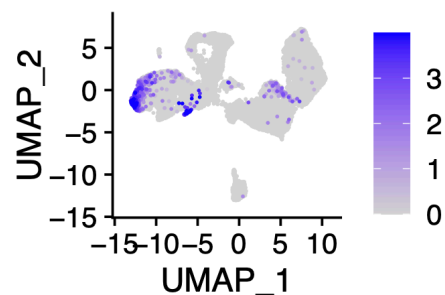
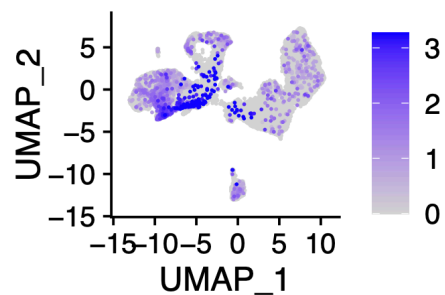
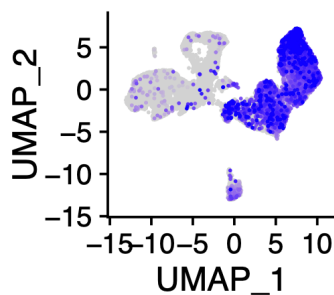
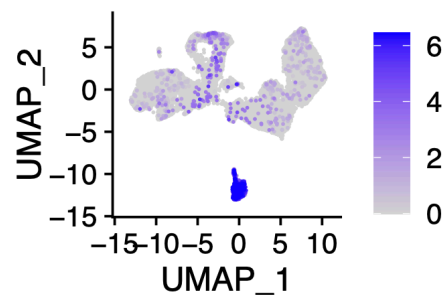
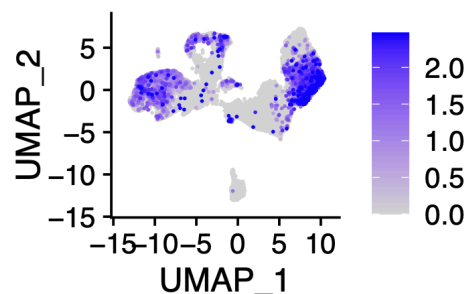
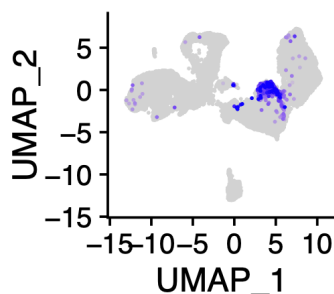
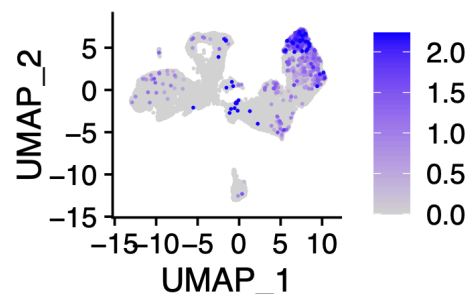
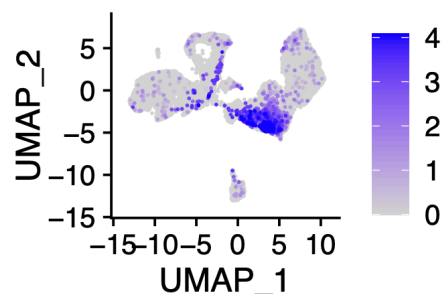
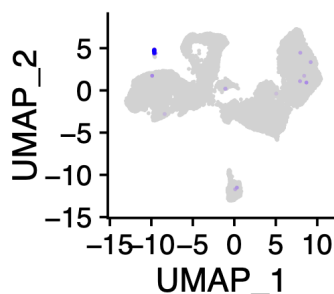
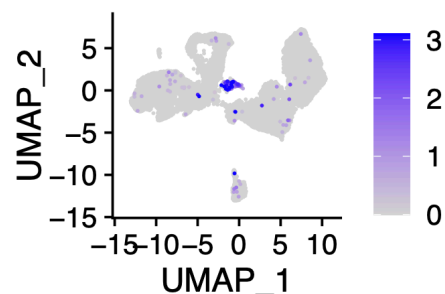
**Supplemental Figure 11.** ScRNA-seq analysis of IPF, SSc-ILD, and control epithelial populations with expression of selected cell type markers. Expression of *FOXJ1* indicates ciliated cells. Co-expression of *FOXJ1*, *MUC5B*, and *SCGB1A1* indicate secretory cells. Co-expression of *MUC5B* and *SCGB1A1* indicates goblet cells. Expression of *SCGB3A2* indicates club cells. Coexpression of *KRT5* and *KRT17* indicates basal cells. Expression of *KRT17* only indicates aberrant basaloid cells. Expression of *AGER* indicates AT1 cells. Expression of *SFTPC* indicates alveolar type 2 cells. Expression of *UBE2C* indicates proliferating cells. scRNA-seq, single-cell RNA-sequencing; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.



**Supplemental Figure 12.** ScRNA-seq analysis of IPF, SSc-ILD, and control epithelial populations with expression of highlighted genes (or lack thereof in the case of *KRT5*, *KRT15*, and *SOX9*) in the aberrant basaloid cells. scRNA-seq, single-cell RNA-sequencing; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

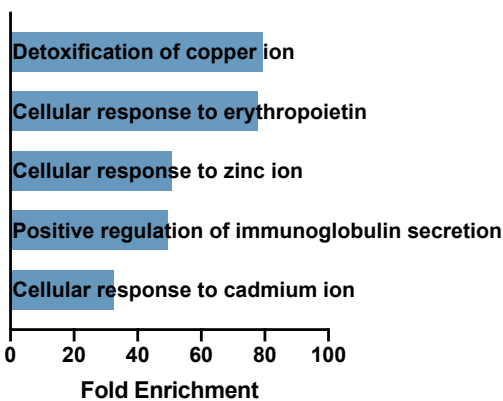
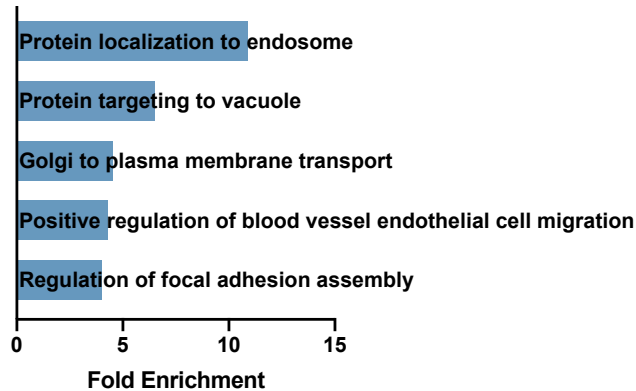
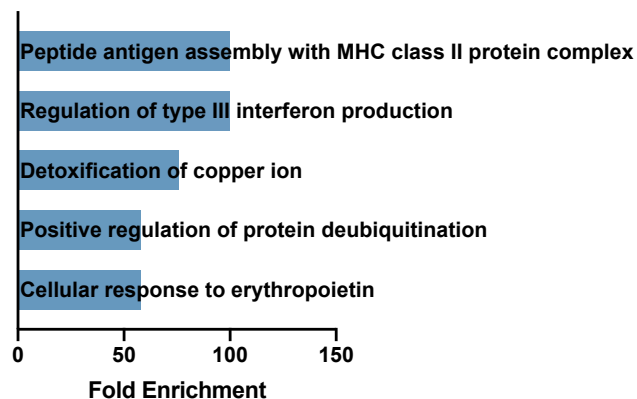
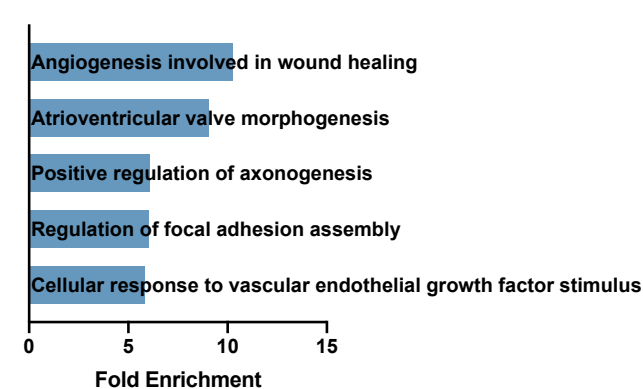
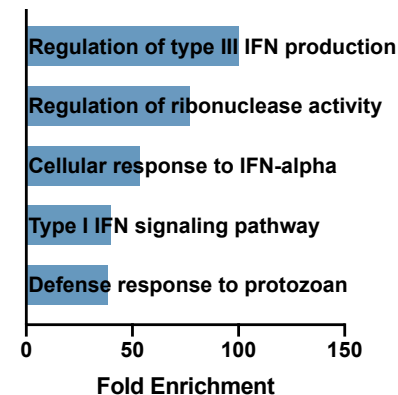
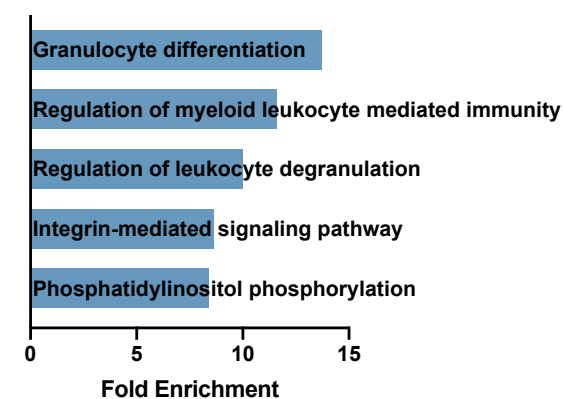
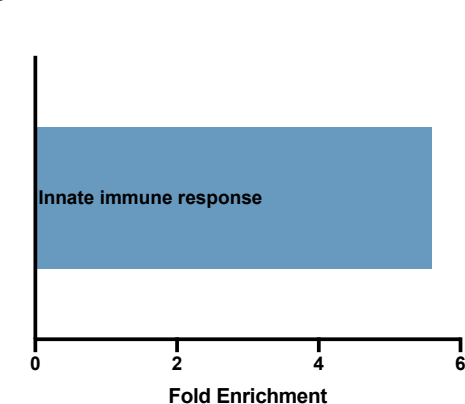
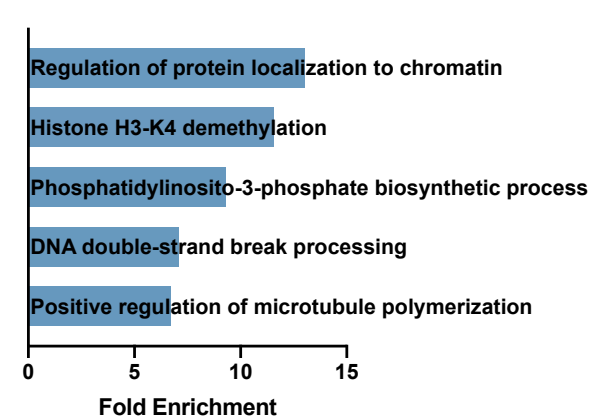


**Supplemental Figure 13.** ScRNA-seq analysis of IPF, SSc-ILD, and control mesenchymal populations with expression of selected cell type markers. *LUM*- fibroblasts; *DES*- smooth muscle cells; *FAM162B*- pericytes; *ACTA2*-smooth muscle, pericyte, and myofibroblasts; *POSTN*-myofibroblasts and endothelial cells; *MFAP5*-*MFAP5*<sup>hi</sup> fibroblasts; *SPINT2*-*SPINT2*<sup>hi</sup> fibroblasts; *VWF*-endothelial cells; *CCL21*-lymphatic endothelial cells; *COL15A1*-peribronchial endothelial cells; *DKK2*-arterial endothelial cells; *HDAC9*-venous endothelial cells; *HPGD*-capillary endothelial cells; *UPK3B*-mesothelial cells; *TOP2A*-proliferating cells.  
scRNA-seq, single-cell RNA-sequencing; IPF, idiopathic pulmonary fibrosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

**a****LUM****DES****FAM162B****ACTA2****POSTN****MFAP5****SPINT2****VWF****CCL21****COL15A1****DKK2****HDAC9****HPGD****UPK3B****TOP2A**

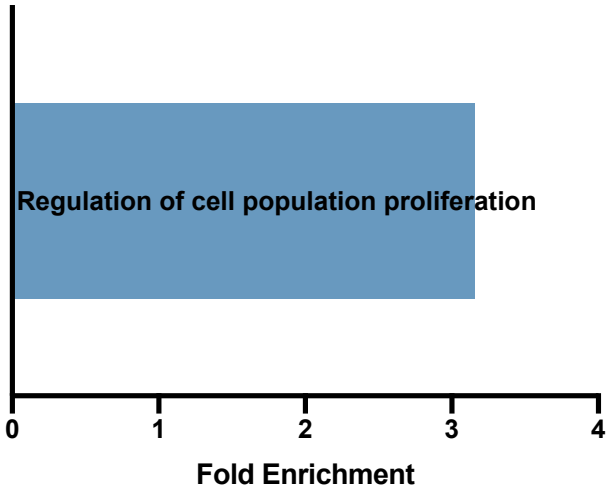
**Supplemental Figure 14.** Gene ontology pathway analysis of endothelial cell subpopulations. (A) Pathways upregulated in IPF arterial endothelial cells compared to SSc-ILD arterial endothelial cells, and pathways upregulated in SSc-ILD arterial endothelial cells compared to IPF arterial endothelial cells. (B) Pathways upregulated in IPF capillary endothelial cells compared to SSc-ILD capillary endothelial cells, and pathways upregulated in SSc-ILD capillary endothelial cells compared to IPF capillary endothelial cells. (C) Pathways upregulated in IPF peribronchial endothelial cells compared to SSc-ILD peribronchial endothelial cells, and pathways upregulated in SSc-ILD peribronchial endothelial cells compared to IPF peribronchial endothelial cells. (D) Pathways upregulated in IPF venous endothelial cells compared to SSc-ILD venous endothelial cells, and pathways upregulated in SSc-ILD venous endothelial cells compared to IPF venous endothelial cells. If fold enrichment was calculated as  $>100$  it is depicted as 100 for visualization.



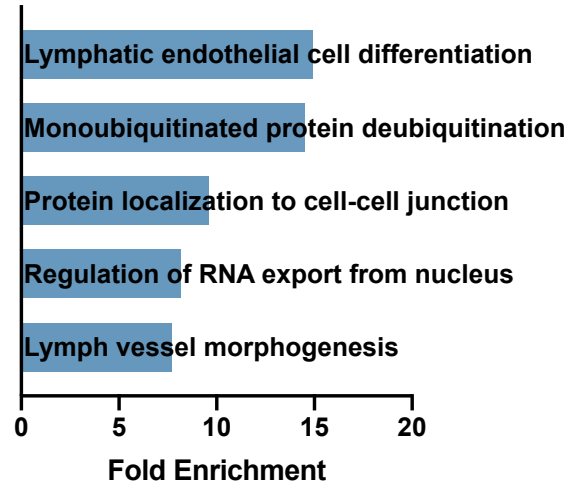
**a****Arterial Endothelial Upregulated in IPF****Arterial Endothelial Upregulated in SSC****b****Capillary Endothelial Upregulated in IPF****Capillary Endothelial Upregulated in SSC****c****Peribronchial Endothelial Upregulated in IPF****Peribronchial Endothelial Upregulated in SSC****d****Venous Endothelial Upregulated in IPF****Venous Endothelial Upregulated in SSC**

**Supplemental Figure 15.** Gene ontology pathway analysis of lymphatic endothelial cell subpopulation. (A) Pathways upregulated in IPF lymphatic endothelial cells compared to SSc-ILD lymphatic endothelial cells. (B) Pathways upregulated in SSc-ILD lymphatic endothelial cells compared to IPF lymphatic endothelial cells.

**a**     Lymphatic Endothelial Upregulated in IPF



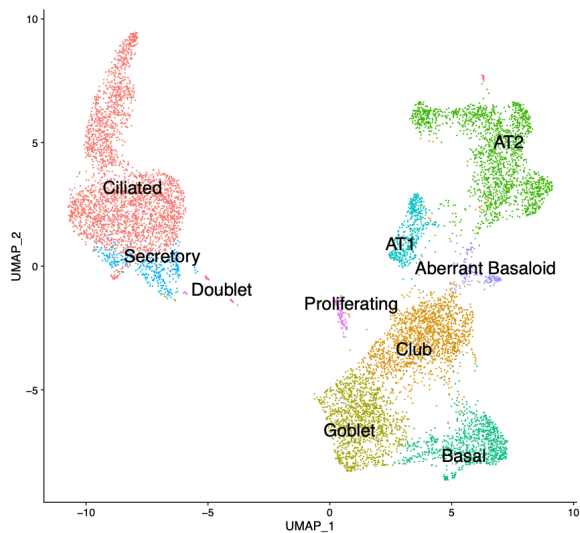
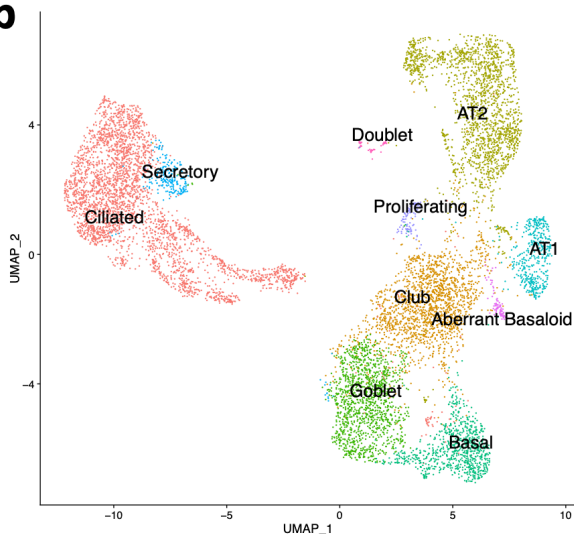
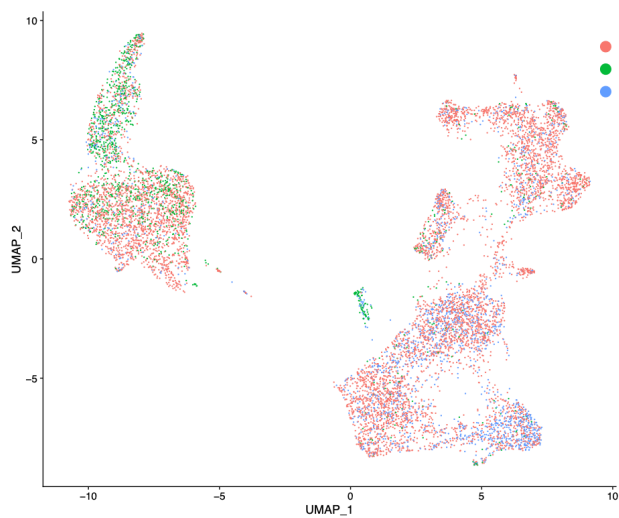
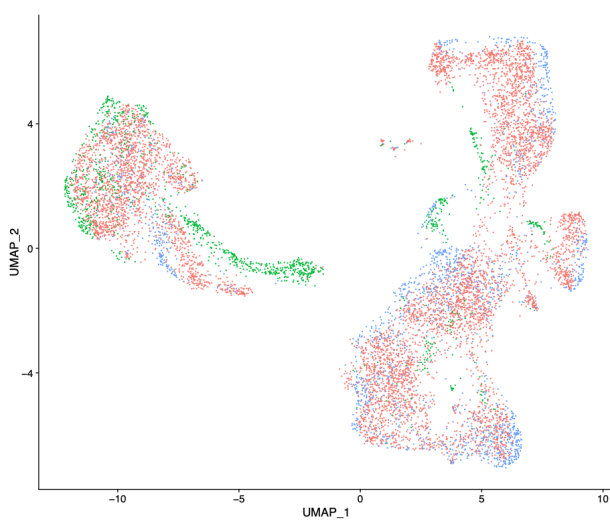
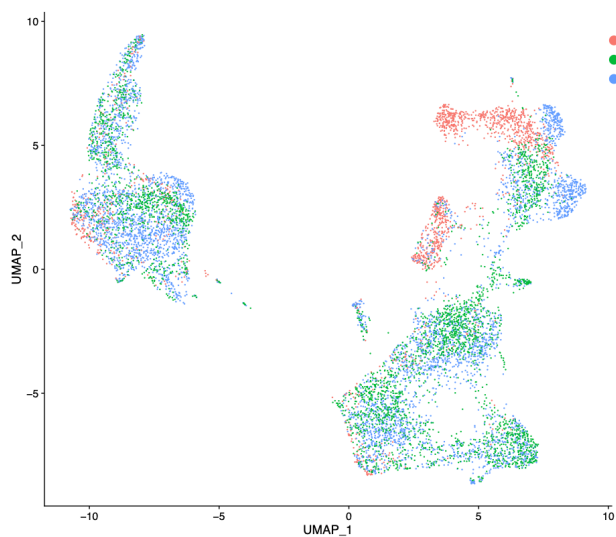
**b**     Lymphatic Endothelial Upregulated in SSC



**Supplemental Figure 16.** ScRNA-seq analysis of epithelial cell subpopulations with and without regression of cell phase when scaling data, demonstrating that controlling for cell phase does not alter the overall data's architecture. (A) UMAP plot of epithelial cells without (B) and with correction for cell phase labeled by cell type. (C) UMAP plot of epithelial cells without (D) and with correction for cell phase labeled by predicted cell phase. (E) UMAP plot of epithelial cells without (F) and with correction for cell phase labeled by disease status.

## Without cell phase regression

## With cell phase regression

**a****b****c****d****e****f**