A

nCount_RNA

Myeloid
SMC
Fibroblast
Endothelial
B cells
T cells
Glia
Mast cells

Myeloid SMC Fibroblast Endothelial B cells T cells Glia Mast cells
Identity

nFeature_RNA

Myeloid
SMC
Fibroblast
Endothelial
B cells
T cells
Glia
Mast cells

Myeloid SMC Fibroblast Endothelial B cells T cells Glia Mast cells
Identity

B

Mast cells
Glia
T cells
B cells
Endothelial
Fibroblast
SMC
Myeloid

Identity

zrmyeloid zsmc zfibro zendo zbcell zttcell zglia zrmast
Features

C

Myeloid   SMC   Fibroblast

Endothelial   B cell   T cell

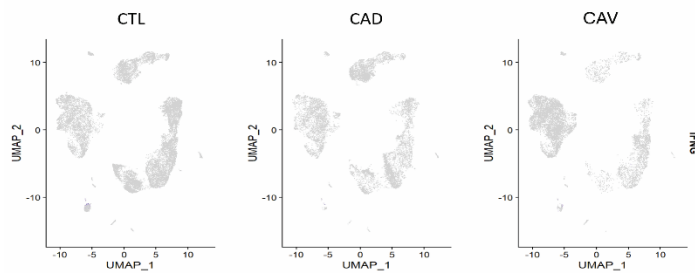Glia   Mast cell

D
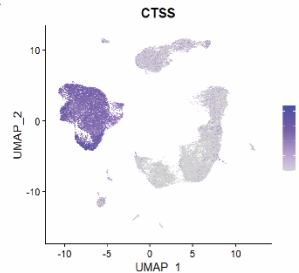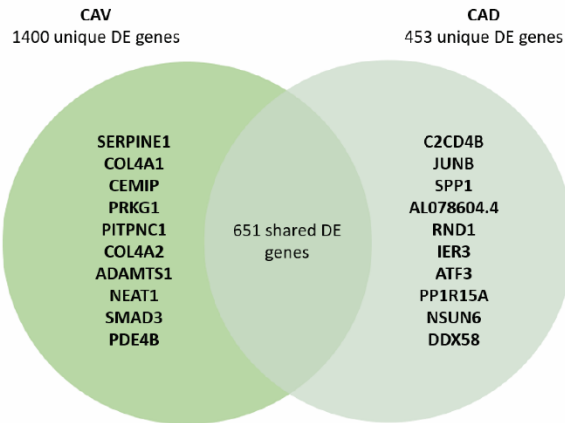
CTL   CAD   CAV   E   CTSS

IFNG

Supplemental Fig. 1. **A** Violin plots of normalized RNA counts and features in scRNA-seq dataset. **B** Dot plot of zscores generated for scRNA-seq cell type clusters. **C** Feature plots of zscores for cell type clusters, generated by FindAllMarkers, using top 5 statistically significant (avg. logFC >0.5, adjusted P value <0.05, Bonferroni correction) genes per cell type. **D** Feature plot of IFNG expression split by disease state. **E** Feature plot of CTSS expression.
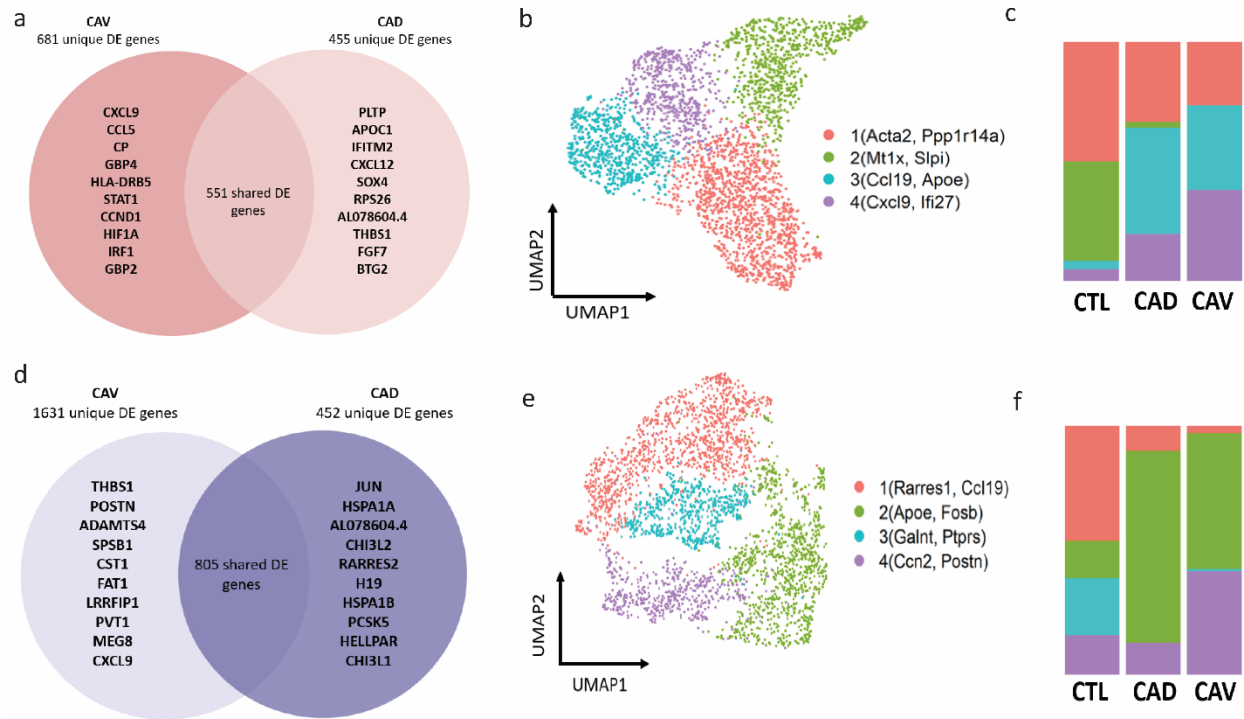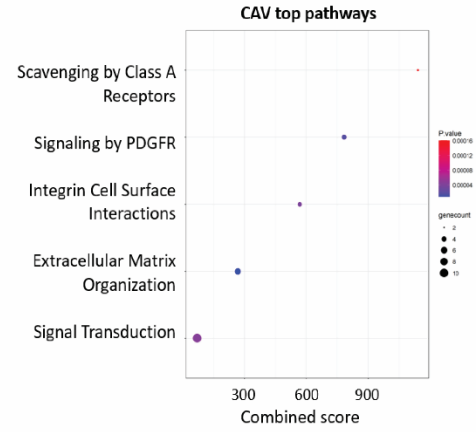
Supplemental Fig. 2. A Top unique and shared statistically significant (avg. logFC >0.5, adjusted P value <0.05, Bonferroni correction) DE genes in modulated smooth muscle cells in CAV and CAD relative to control samples. **B** UMAP embedding plot of subclustered modulated smooth muscle cells and **C** the respective composition plot. **D** Pathway analysis performed using top 25 statistically significant DE genes from CAV and CAD samples. **E** Top unique and shared statistically significant DE genes in fibroblasts in CAV and CAD relative to control samples. **F** UMAP embedding plot of subclustered fibroblasts and **F** the respective composition plot.
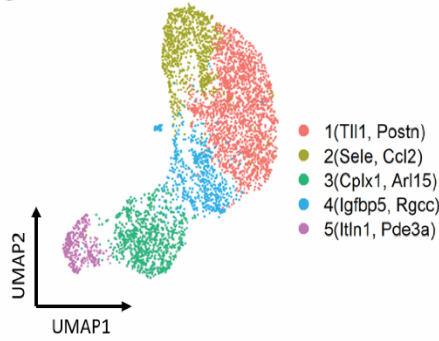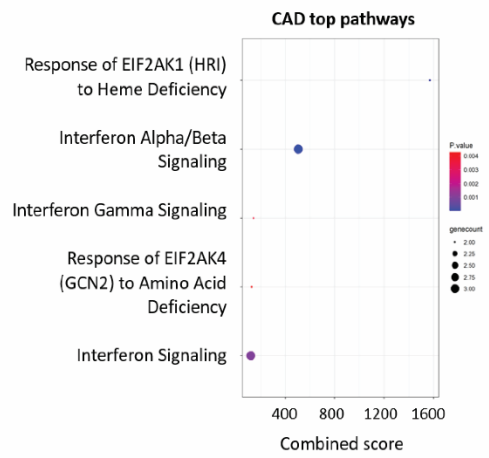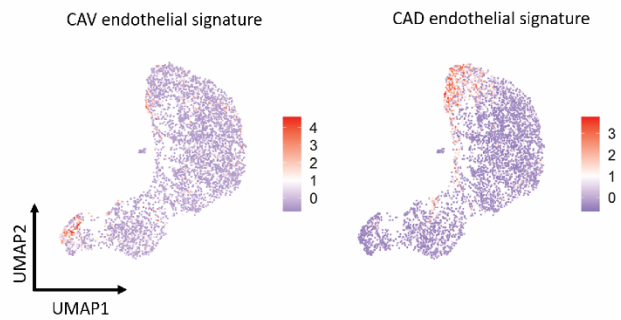
A

CAV
1400 unique DE genes

CAD
453 unique DE genes

SERPINE1
COL4A1
CEMIP
PRKG1
PITPNC1
COL4A2
ADAMTS1
NEAT1
SMAD3
PDE4B

651 shared DE genes

C2CD4B
JUNB
SPP1
AL078604.4
RND1
IER3
ATF3
PP1R15A
NSUN6
DDX58

B

CAV top pathways

Scavenging by Class A Receptors

Signaling by PDGFR

Integrin Cell Surface Interactions

Extracellular Matrix Organization

Signal Transduction

P.value
0.00016
0.00012
0.00008
0.00004

genecount
2
4
6
8
10

Combined score
300   600   900

CAD top pathways

Response of EIF2AK1 (HRI) to Heme Deficiency

Interferon Alpha/Beta Signaling

Interferon Gamma Signaling

Response of EIF2AK4 (GCN2) to Amino Acid Deficiency

Interferon Signaling

P.value
0.004
0.003
0.002
0.001

genecount
2.00
2.25
2.50
2.75
3.00

Combined score
400   800   1200   1600

C

UMAP2
UMAP1

1(Tll1, Postn)
2(Sele, Ccl2)
3(Cplx1, Arl15)
4(Igfbp5, Rgcc)
5(Itln1, Pde3a)

D

CTL   CAD   CAV

E

CAV endothelial signature

CAD endothelial signature

UMAP2
UMAP1

4
3
2
1
0

3
2
1
0

F

5(Itln1, Pde3a)

4(Igfbp5, Rgcc)

3(Cplx1, Arl15)

2(Sele, Ccl2)

1(Tll1, Postn)

Identity

Average Expression
1.00
0.75
0.50
0.25
0.00

Percent Expressed
0
25
50
75

Features:
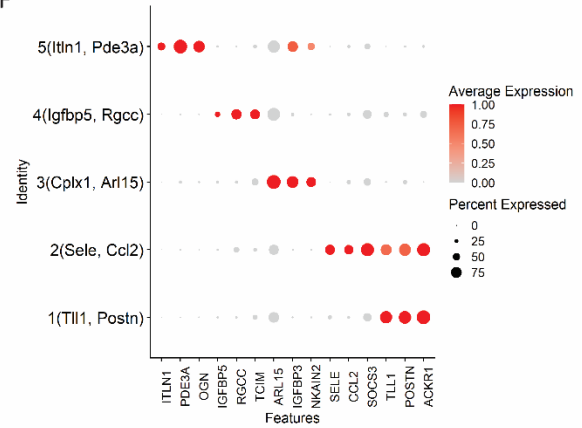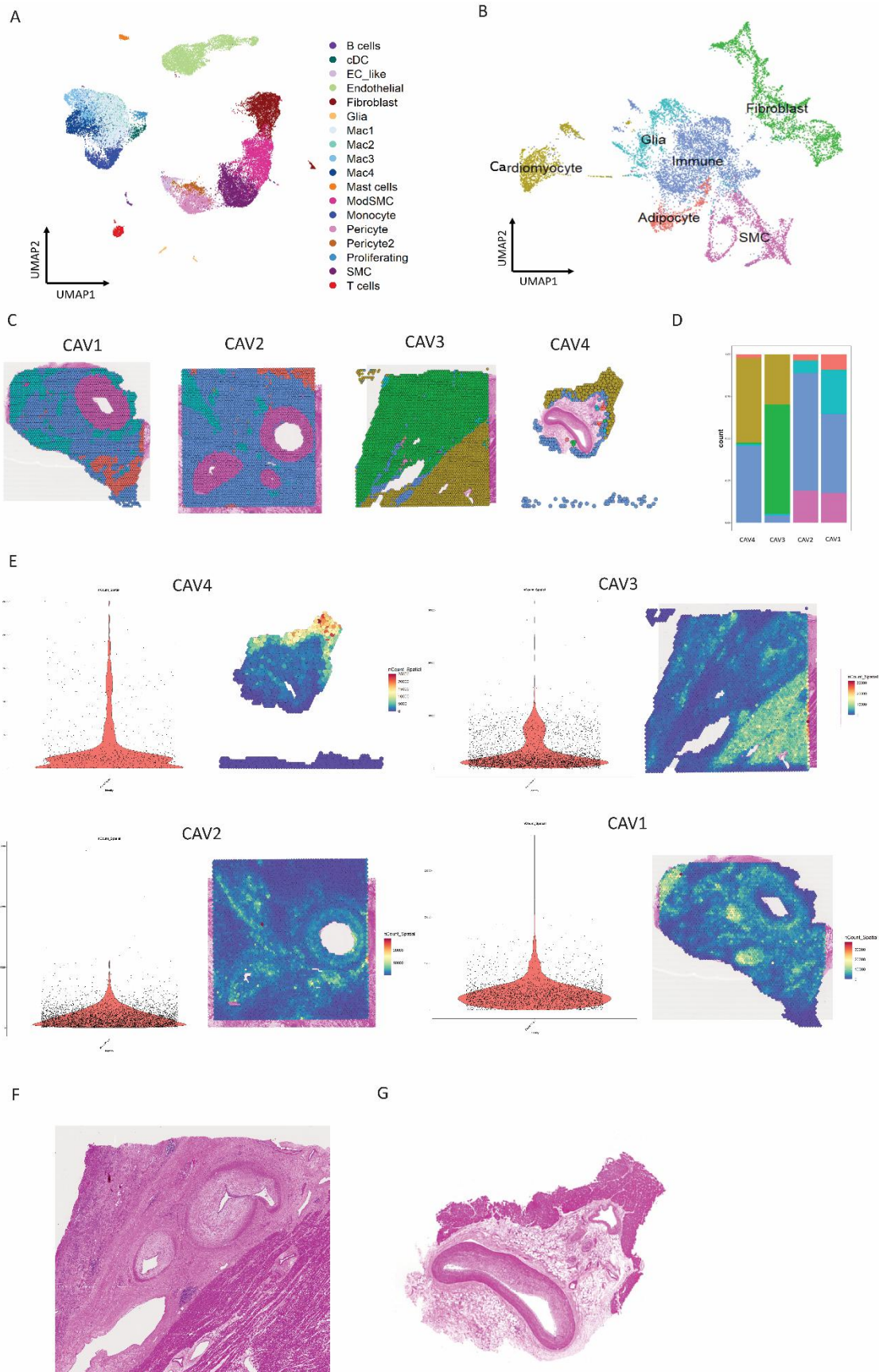ITLN1 PDE3A OGN IGFBP5 RGCC TCIM ARL15 IGFBP3 NKAIN2 SELE CCL2 SOCS3 TLL1 POSTN ACKR1
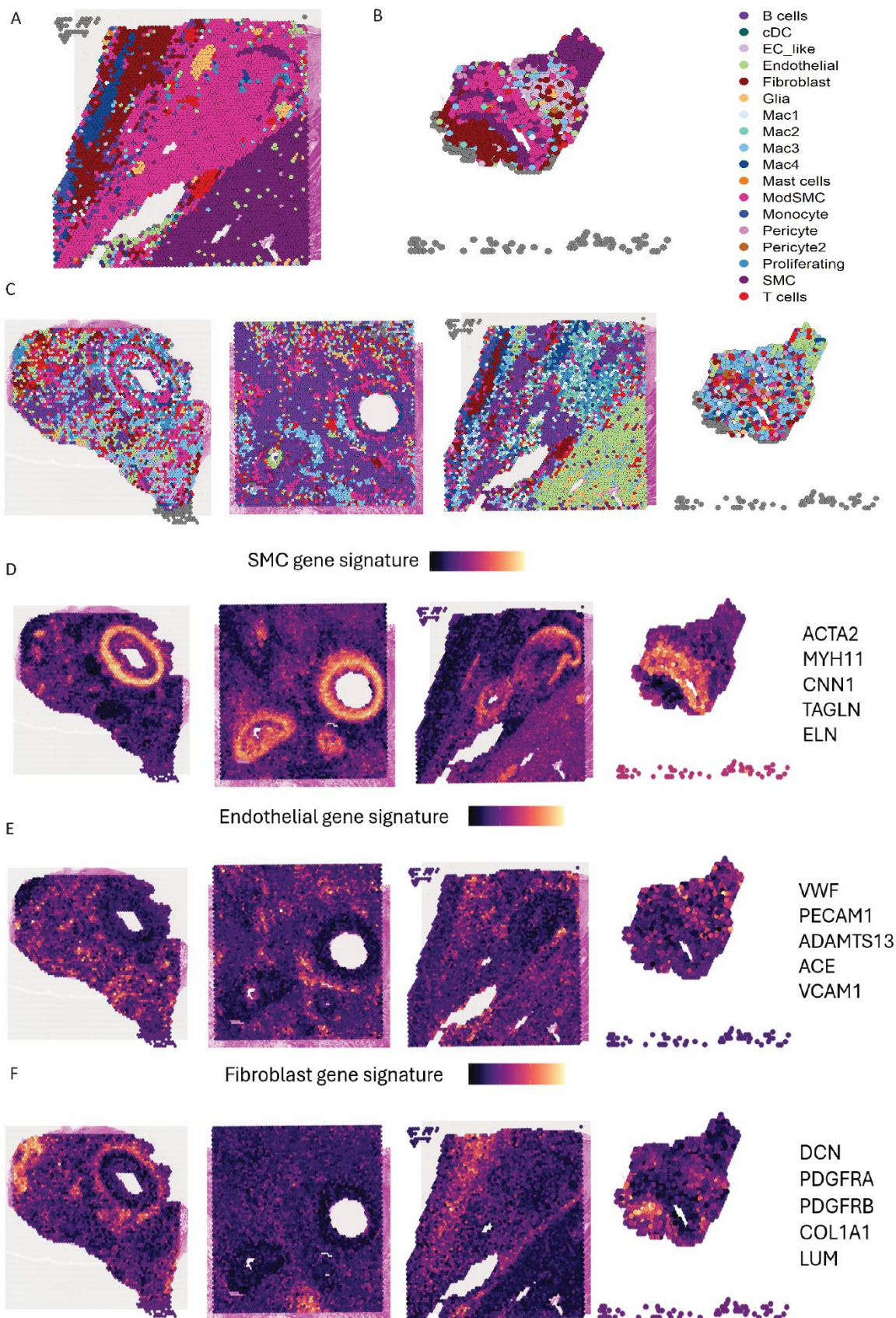
Supplemental Fig. 3. **A** Top unique and shared statistically significant (avg. logFC >0.5, adjusted P value <0.05, Bonferroni correction) DE genes in endothelial cells in CAV and CAD relative to control samples. **B** Pathway analysis performed using top 25 statistically significant DE genes in endothelial cells in CAV and CAD. **C** UMAP embedding plot of subclustered endothelial cell states and **D** the respective composition plot. **E** Feature plot of CAV and CAD endothelial module scores generated from top 25 statistically significant DE genes relative to control samples. **F** Dot plot of top DE gene expression in endothelial cell states.
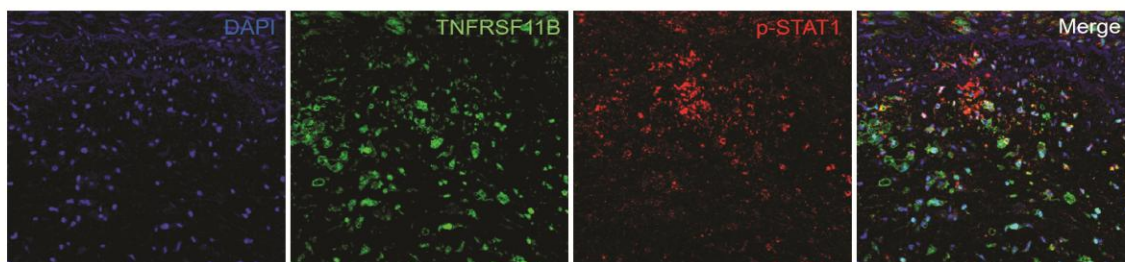
A

B cells
cDC
EC_like
Endothelial
Fibroblast
Glia
Mac1
Mac2
Mac3
Mac4
Mast cells
ModSMC
Monocyte
Pericyte
Pericyte2
Proliferating
SMC
T cells

UMAP2
UMAP1

B

Cardiomyocyte
Glia
Immune
Fibroblast
Adipocyte
SMC

UMAP2
UMAP1

C

CAV1   CAV2   CAV3   CAV4

D

count

CAV4 CAV3 CAV2 CAV1

E

CAV4   CAV3

CAV2   CAV1

F

G

Supplemental Fig. 4. A UMAP embedding plot of scRNA-seq object containing high-resolution, subclustered myeloid and stromal cell states. **B** UMAP embedding plot of merged spatial object with annotated spatial niches. **C** DimPlot of annotated spatial niches on tissue slices and **D** composition plot of spatial niches in CAV1, CAV2, CAV3 and CAV4. **E** Normalized RNA counts in spatial samples. **F** Histopathology (H&E) of CAV3 and **G** CAV4.
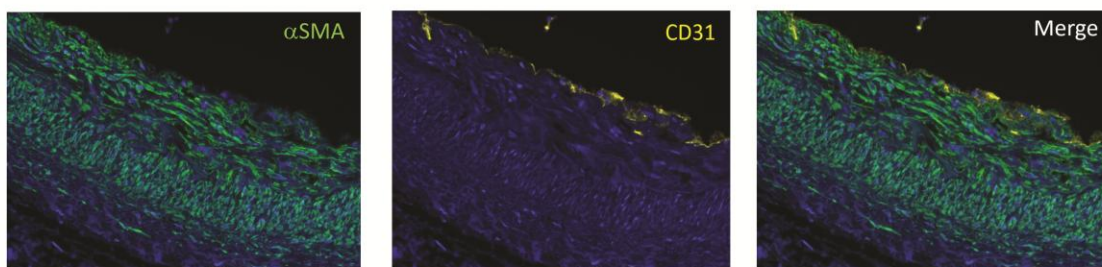
A

B

Legend:
- B cells
- cDC
- EC_like
- Endothelial
- Fibroblast
- Glia
- Mac1
- Mac2
- Mac3
- Mac4
- Mast cells
- ModSMC
- Monocyte
- Pericyte
- Pericyte2
- Proliferating
- SMC
- T cells

C

SMC gene signature

D

ACTA2
MYH11
CNN1
TAGLN
ELN

Endothelial gene signature

E

VWF
PECAM1
ADAMTS13
ACE
VCAM1

Fibroblast gene signature

F

DCN
PDGFRA
PDGFRB
COL1A1
LUM

Supplemental Fig. 5. A First-type Seurat deconvolution results for CAV3 and **B** CAV4.
C Second-type Seurat deconvolution results for CAV1, CAV2, CAV3, and CAV4. **D**
Spatial feature plot of SMC, **E** endothelial, and **F** fibroblast gene signatures to validate
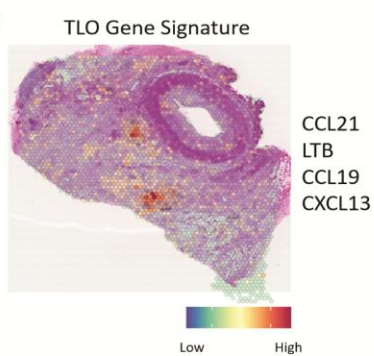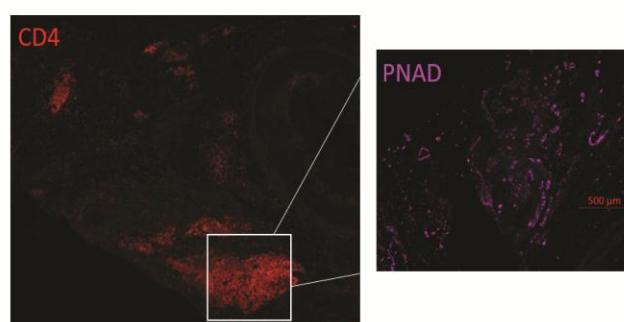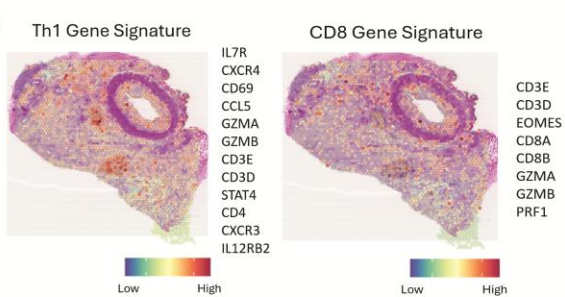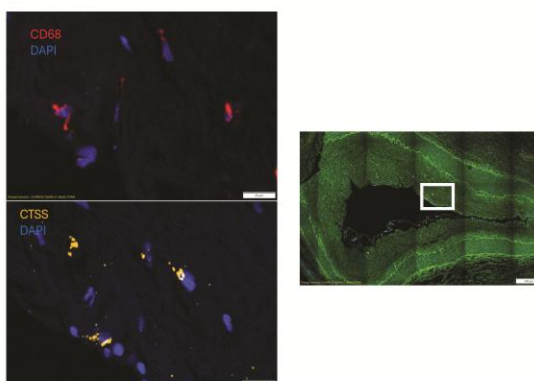spatial deconvolution results

A

DAPI | TNFRSF11B | p-STAT1 | Merge

B

αSMA | CD31 | Merge

C

TLO Gene Signature

CCL21
LTB
CCL19
CXCL13

Low   High

D

CD4

PNAD

500 μm

E

Th1 Gene Signature

IL7R
CXCR4
CD69
CCL5
GZMA
GZMB
CD3E
CD3D
STAT4
CD4
CXCR3
IL12RB2

Low   High

CD8 Gene Signature

CD3E
CD3D
EOMES
CD8A
CD8B
GZMA
GZMB
PRF1

Low   High

F

CD68
DAPI

CTSS
DAPI

G

CAV2

Mac1Glia
Mac2   Fibroblast
Mac3   Endothelial
Mac4   EC.like
Mast.cells   B.cells
ModSMC   cDC
Monocyte   T.cells
Pericyte   SMC
Proliferating

CAV3

Mac1Glia
Mac2   Fibroblast
Mac3   Endothelial
Mac4   EC.like
Mast.cells   B.cells
ModSMC   cDC
Monocyte   T.cells
Pericyte   SMC
Proliferating

CAV4

Mac1Glia
Mac2   Fibroblast
Mac3   Endothelial
Mac4   EC.like
Mast.cells   B.cells
ModSMC   cDC
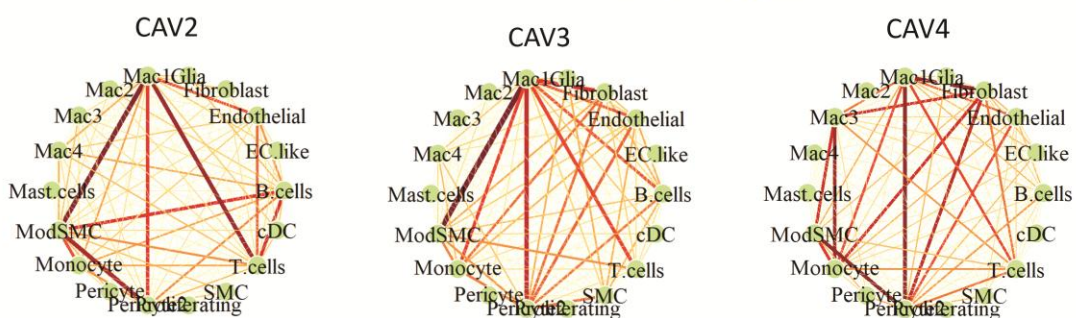Monocyte   T.cells
Pericyte   SMC
Proliferating

Supplemental Fig. 6. A Immunostaining of TNFRSF11B (modulated SMC) and Phospho-Stat1 (IFN signaling) within the neointima of CAV1. **B** Immunostaining of aSMA (SMC) and CD31 (endothelial cell) within the neointima. **C** Spatial feature plot of tertiary lymphoid organ genes and **D** immunofluorescence staining for CD4 (CD4+ T cell) and PNAd (peripheral node addressin) in CAV1 **E** Spatial feature plot of T helper 1 (Th1) and CD8 (CD8+ T cell) gene signature scores in CAV1 **F** Immunofluorescence staining for CD68 and CTSS (Cathepsin S) within the neointima of a CAV sample. **E** SPOTlight spatial interaction plots for CAV2, CAV3, and CAV4 samples.
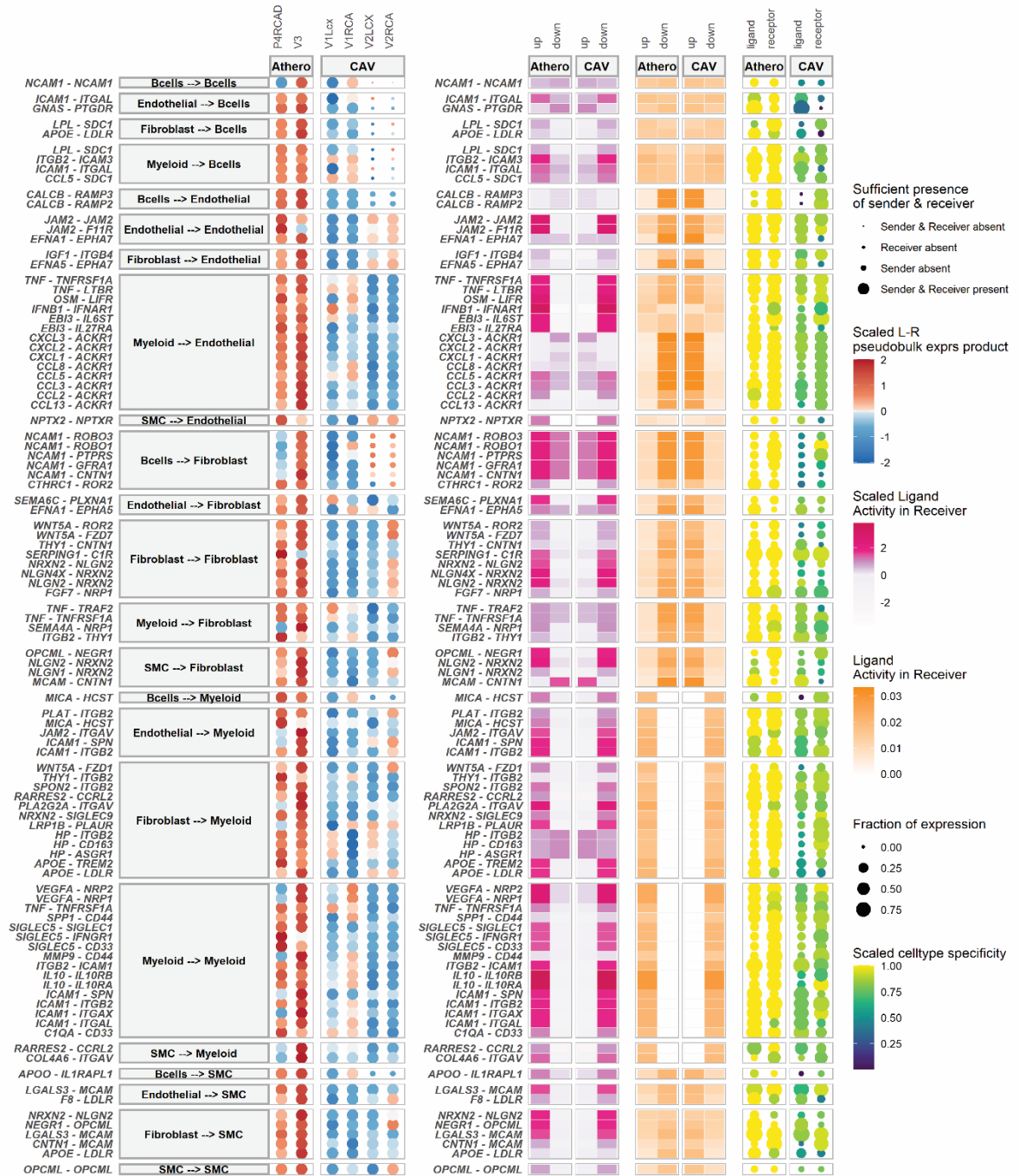
Supplemental Fig. 7. A MultiNicheNetr top 50 predicted ligand:receptor interactions in CAD scRNA-seq samples.