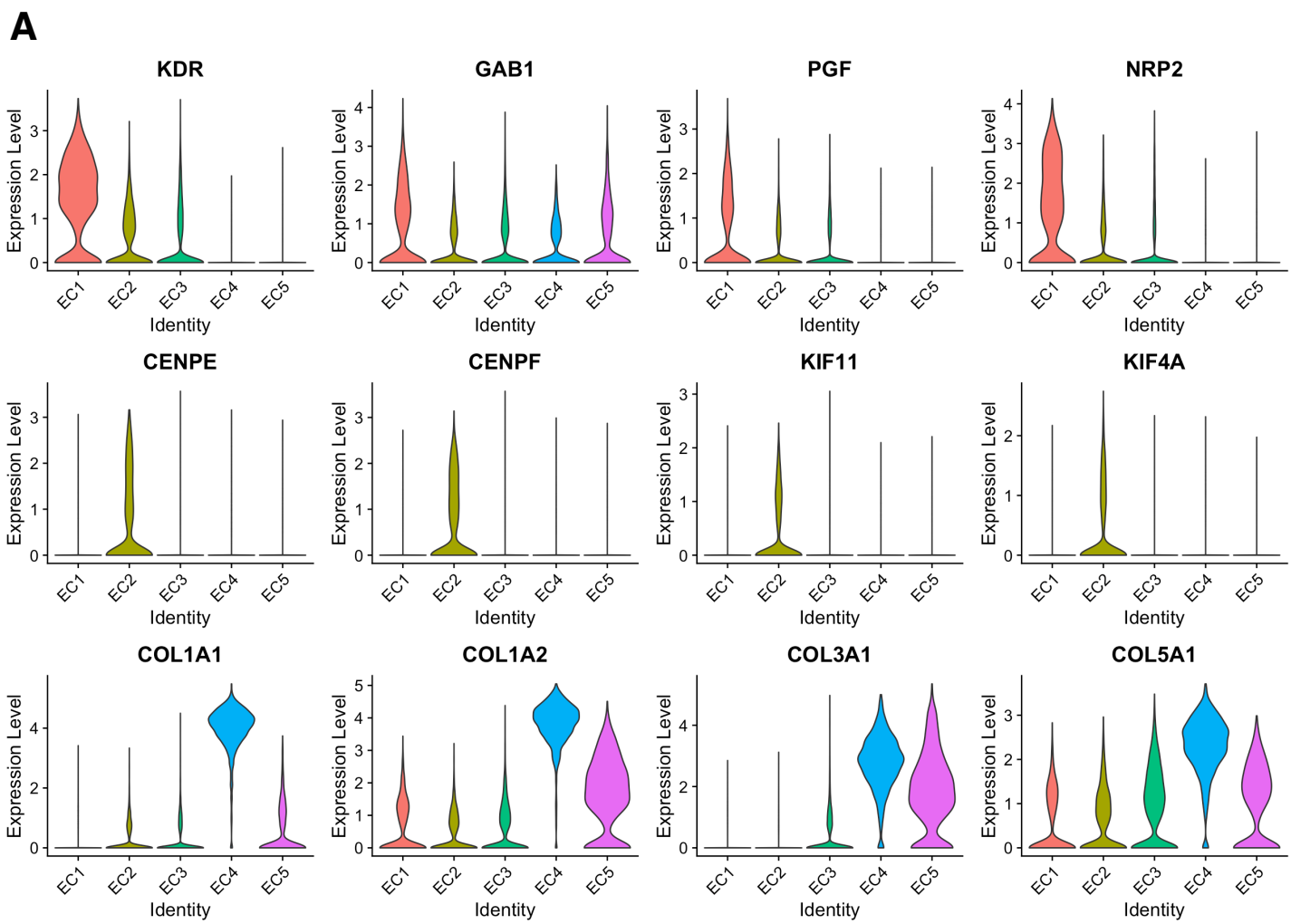
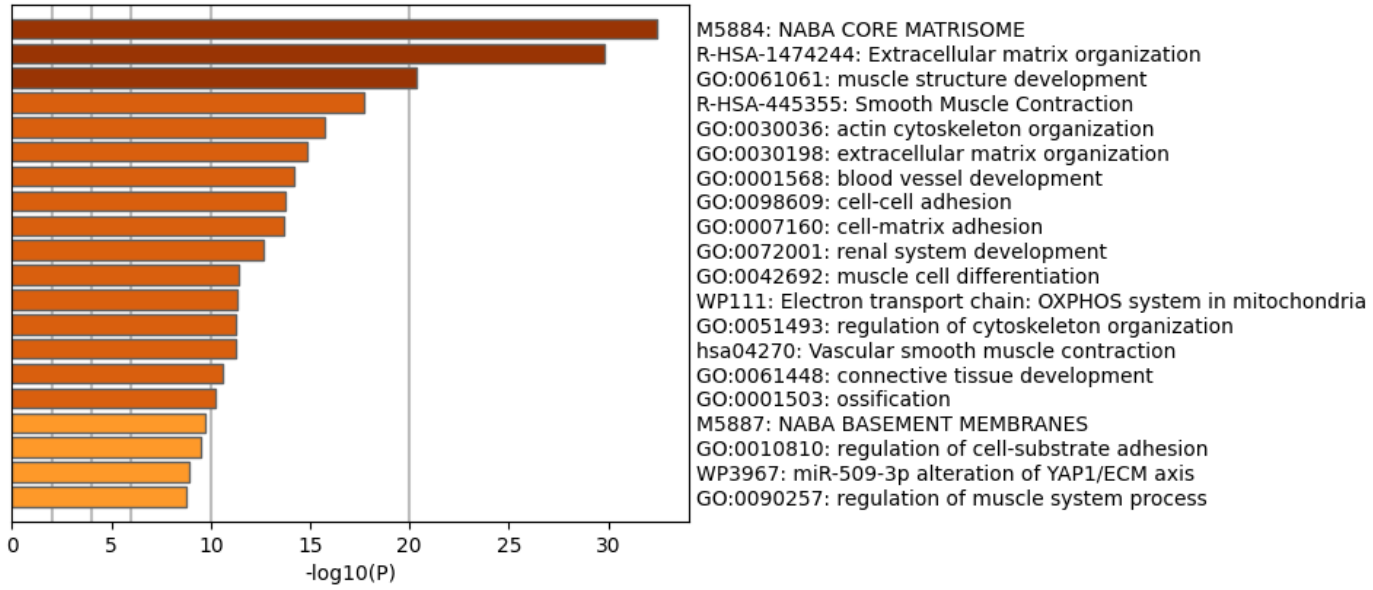
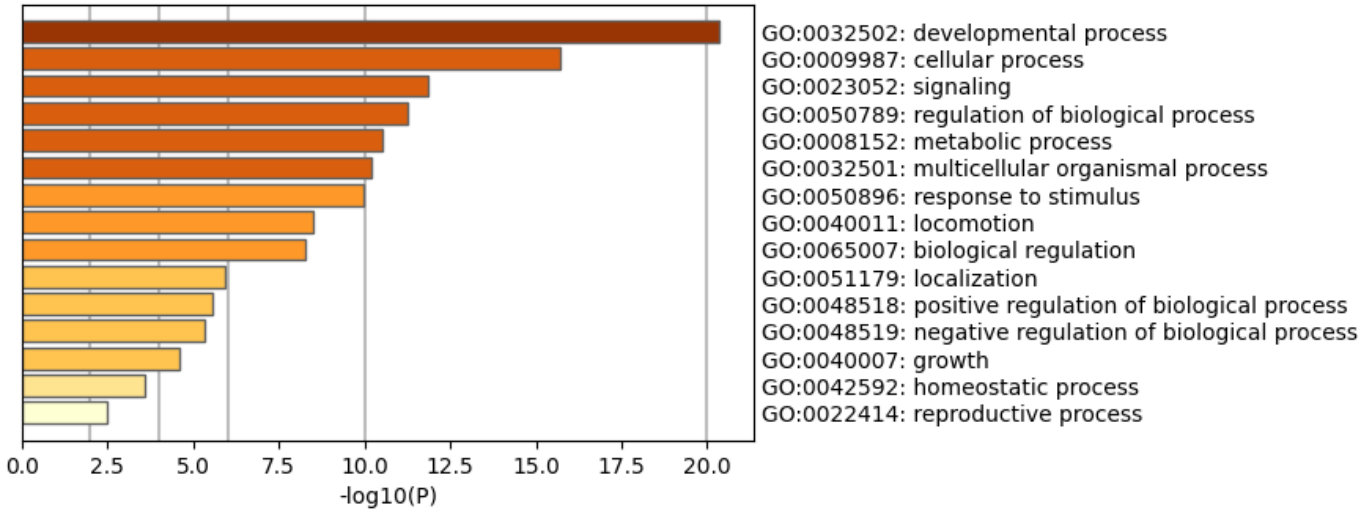

A
KDR
GAB1
PGF
NRP2
CENPE
CENPF
KIF11
KIF4A
COL1A1
COL1A2
COL3A1
COL5A1
Expression Level
Identity
EC1
EC2
EC3
EC4
EC5

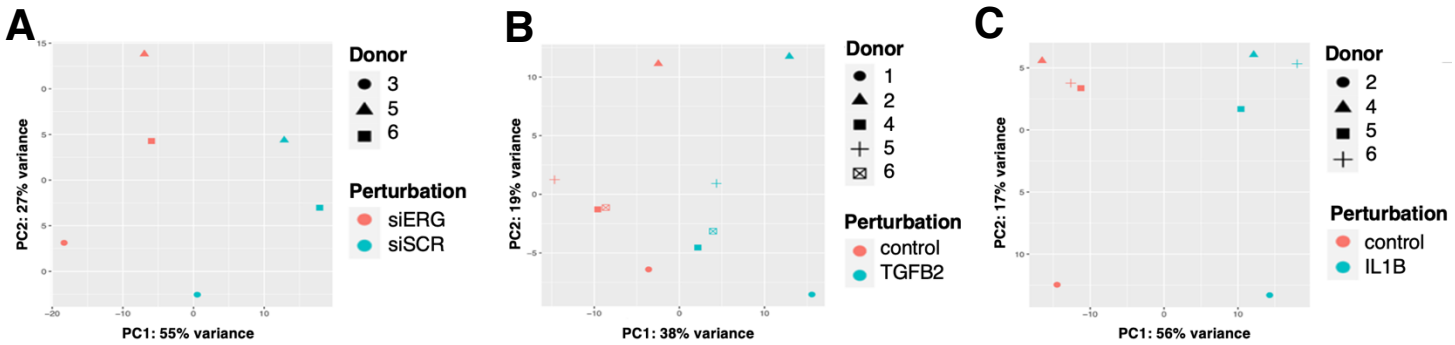
B



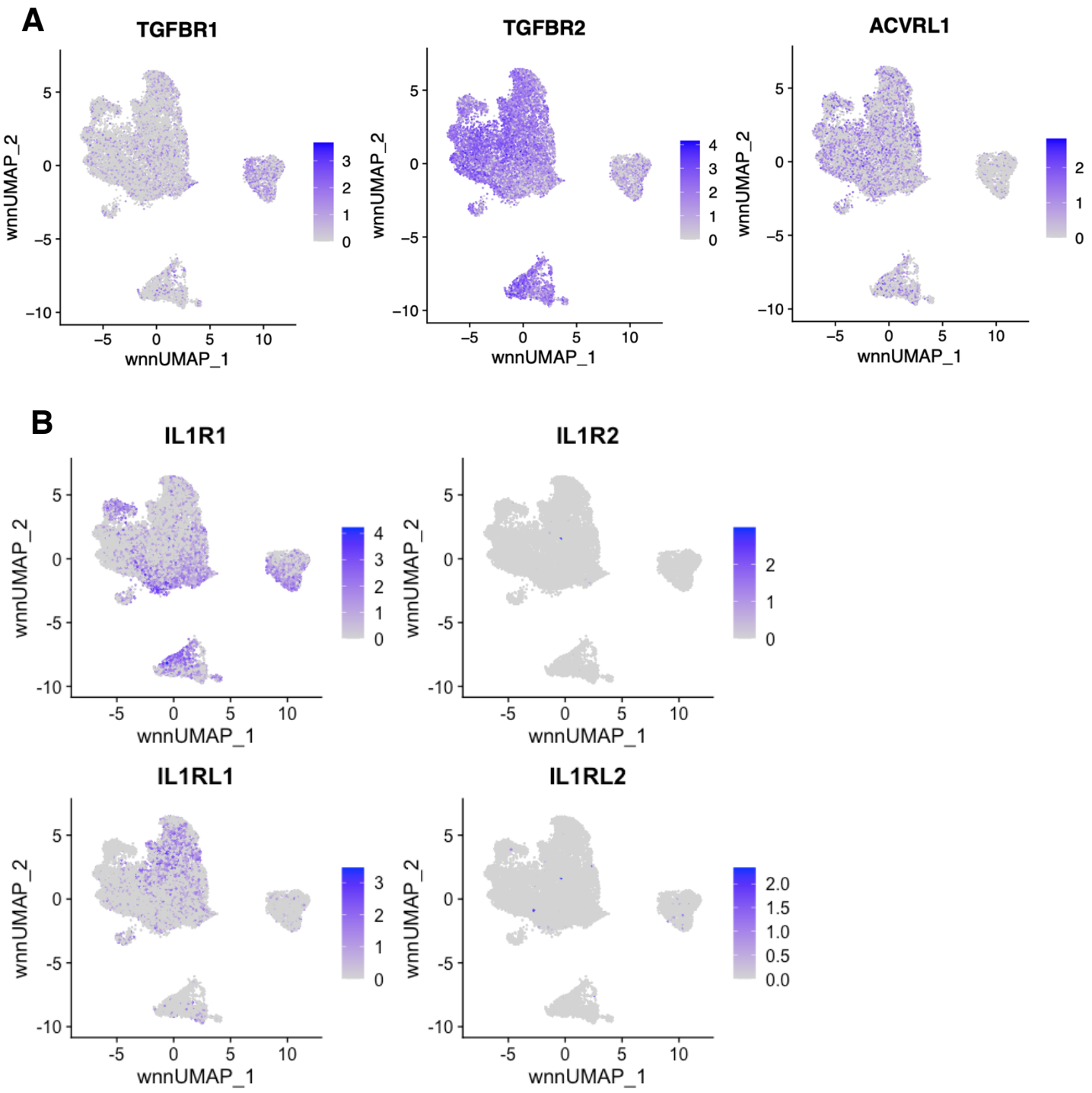
C



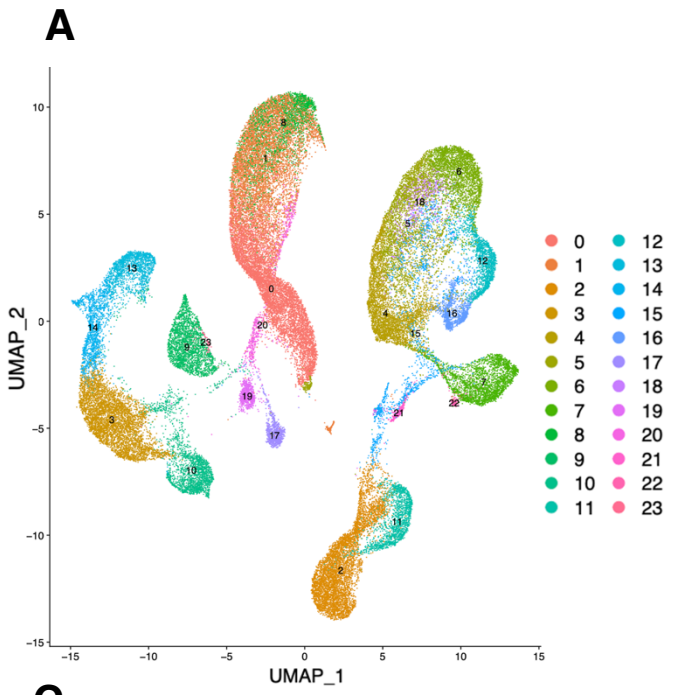
Supplementary Figure 1 (Figure S1) – Related to Figure 1 I (A), Violin plots of representative marker genes for angiogenic EC1 (*KDR*, *GAB1*, *PGF*, *NRP1*), proliferative EC2 (*CENPE*, *CENPF*, *KIF11*, *KIF4A*), and mesenchymal EC4 (*COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*) sub-phenotypes. **(B)**, Top 20 pathway enrichment analysis (PEA) results from submitting top 200 differentially expressed genes (DEGs; by ascending p-value) regulated in EC3 versus EC1-2 and EC4-5. **(C)**, Top 20 Gene Ontology (GO) PEA results from submitting top 200 DEGs (by ascending p-value) regulated in EC3 versus EC1-2 and EC4-5.

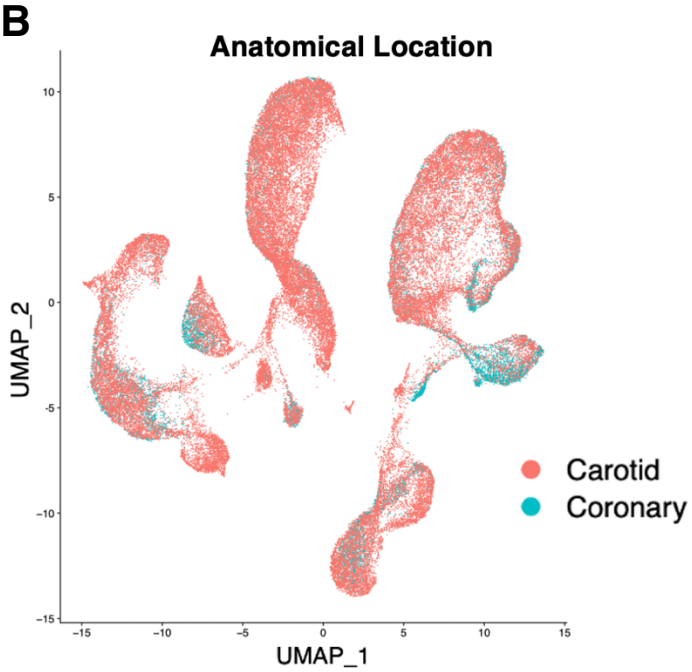


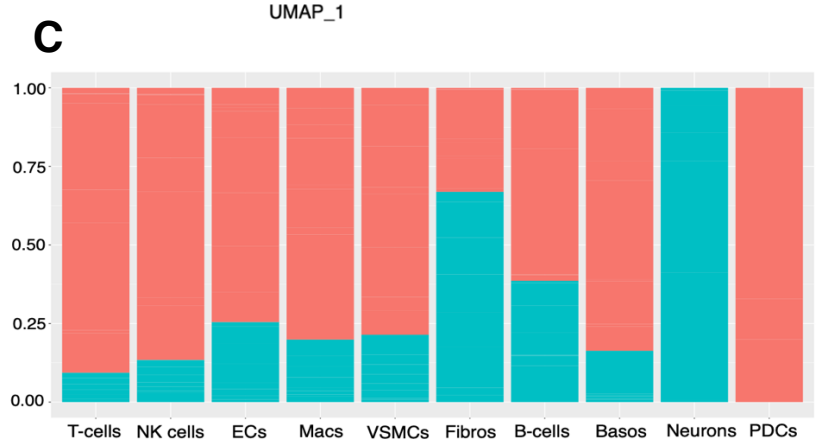
Supplementary Figure 2 (Figure S2) – Related to Figure 3 l (A), Principal component analysis (PCA) of EC1-4 snRNA-seq samples +/- siERG or scramble (siSCR) across donor replicates. **(B)**, PCA of EC1-4 snRNA-seq samples +/- TGFB2 or control across donor replicates. **(C)**, PCA of EC1-4 snRNA-seq samples +/- IL1B or control across donor replicates.



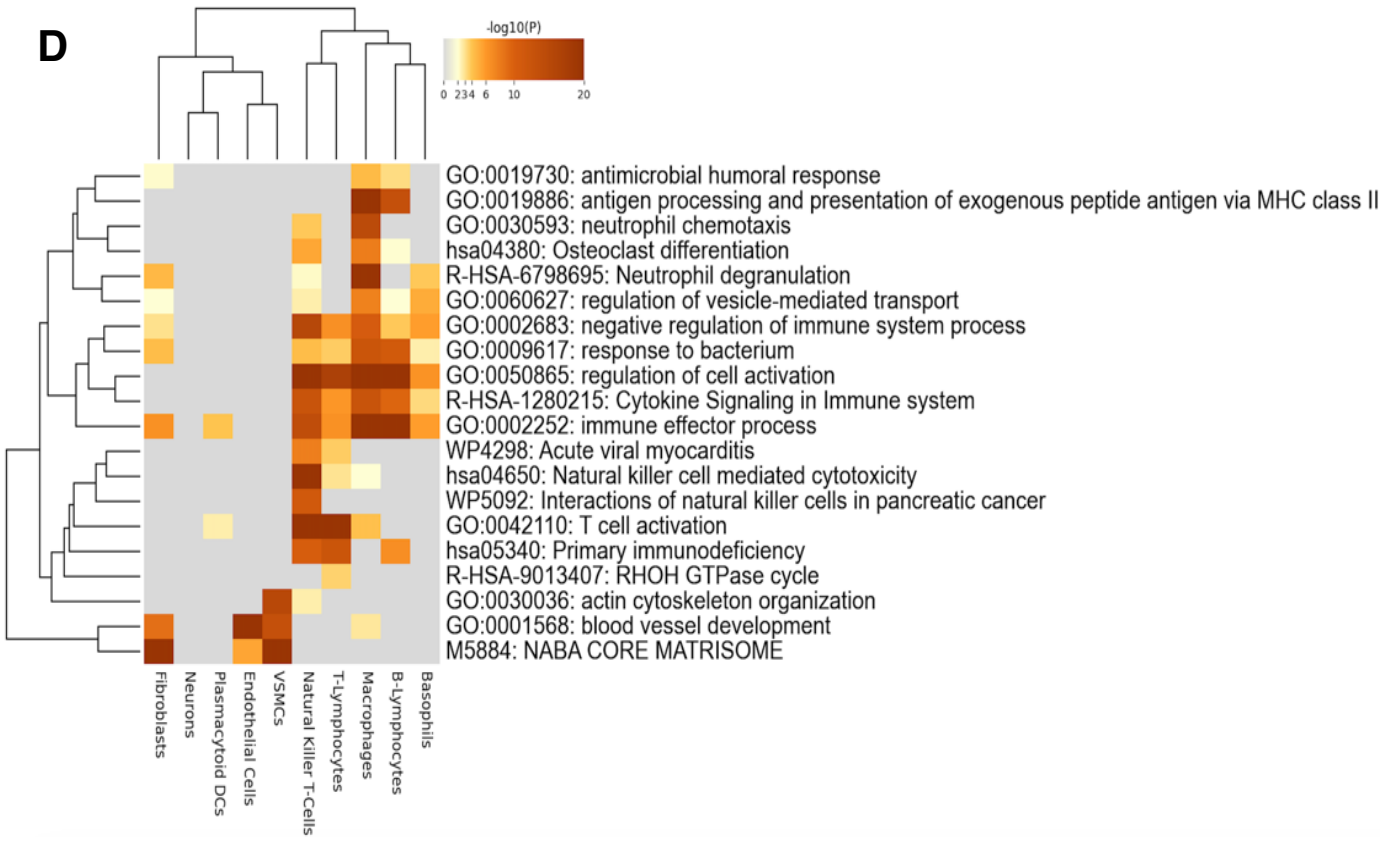
Supplementary Figure 3 (Figure S3) – Related to Figure 4 I (A), Feature plots of expression of TGFB pathway receptors: *TGFBR1*, *TGFBR2*, and *ACVRL1*. **(B)**, Feature plots of IL1B pathway receptors: *IL1R1*, *IL1R2*, *IL1RL1*, and *IL1RL2*.

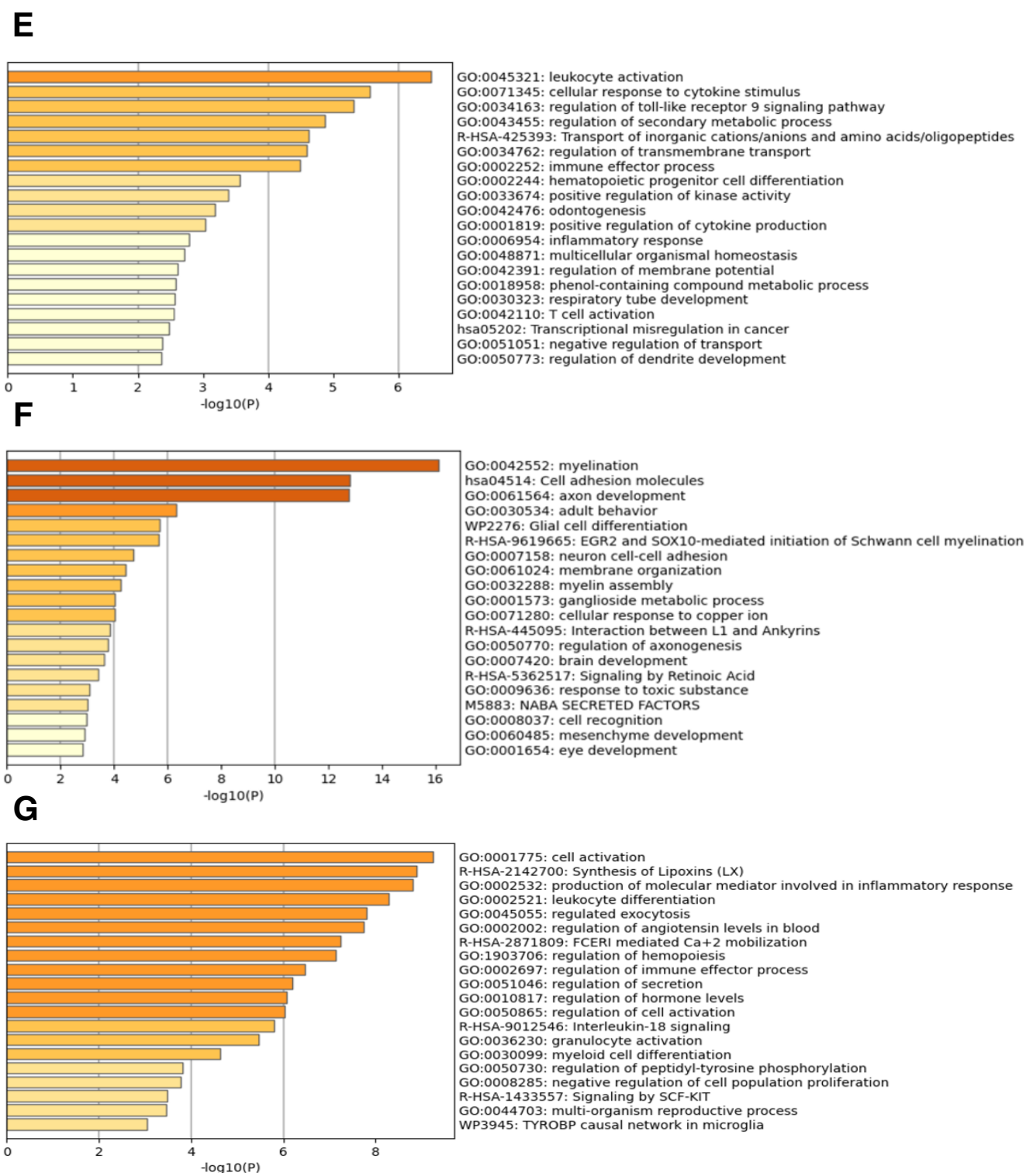




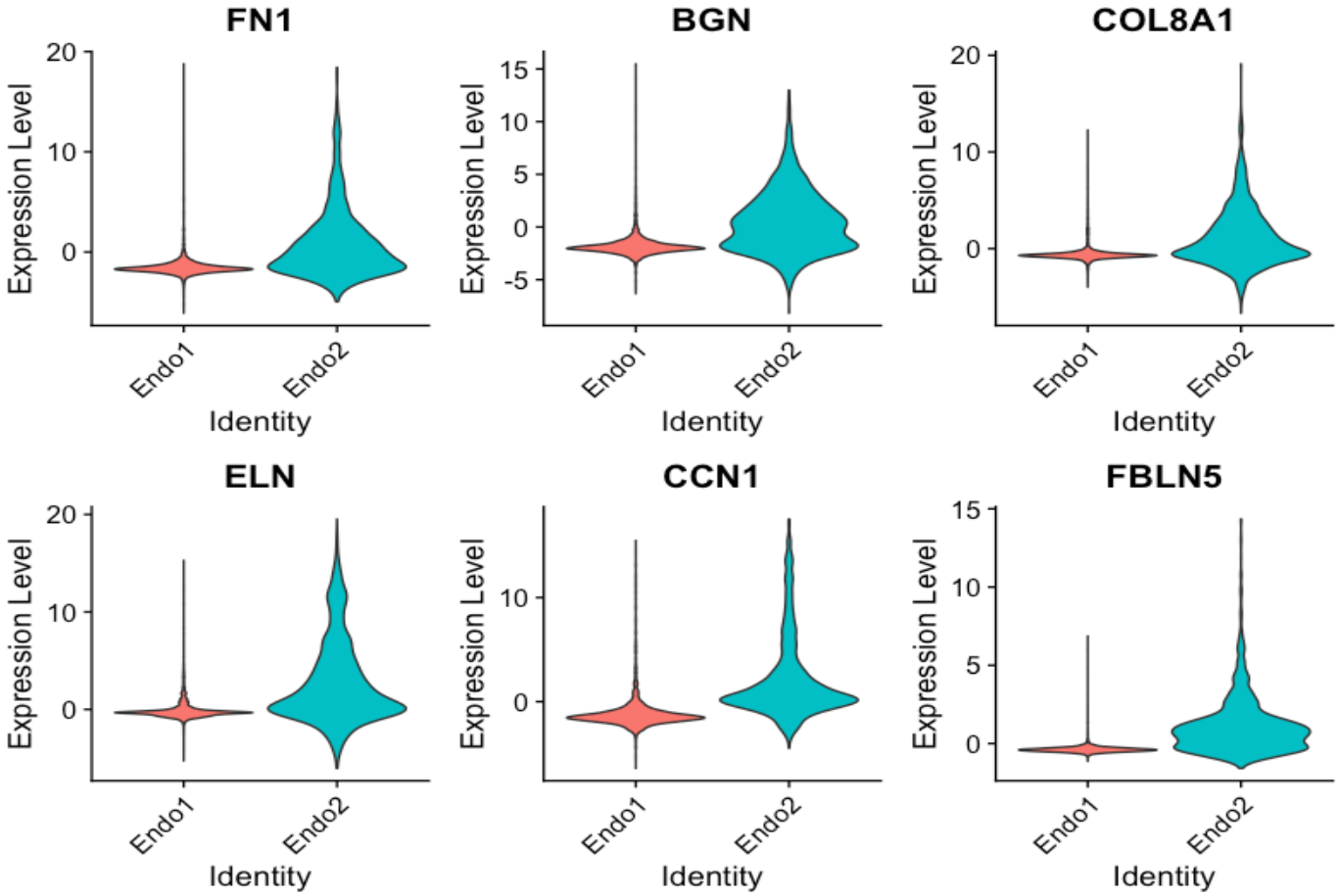


T-cells = T-Lymphocytes
NK cells = Natural Killer Cells
Macs = Macrophages
Fibros = Fibroblasts
B-cells = B-Lymphocytes
Basos = Basophils
PDCs = Plasmacytoid dendritic cells





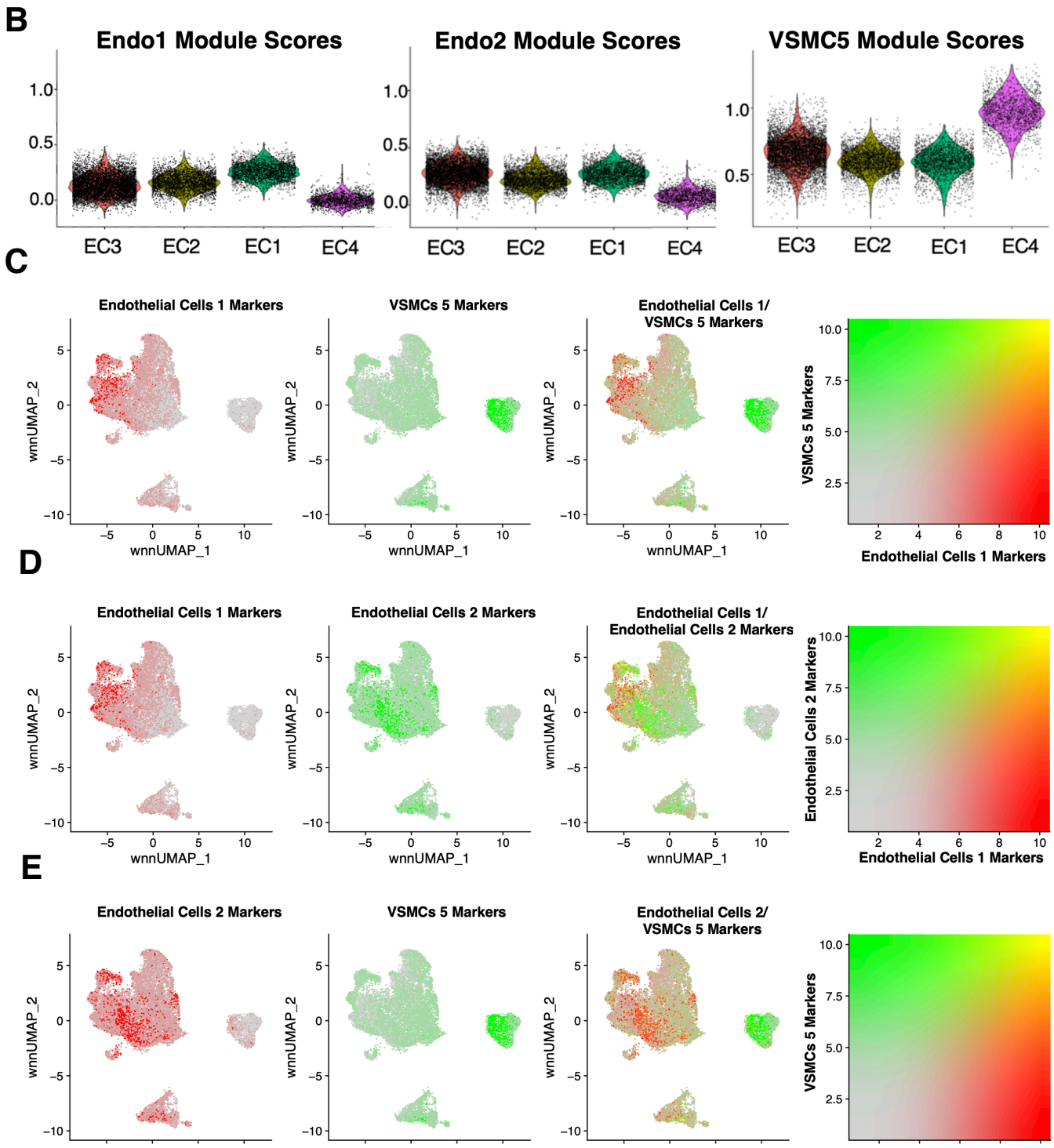
Supplementary Figure 4 (Figure S4) – Related to Figure 5 I (A), UMAP displaying original clusters formed from scRNA-seq data taken from 17 samples across 4 studies of human *ex vivo* atherosclerotic plaques. Colors denote different clusters. **(B)**, UMAP from (A). Colors denote anatomical location from which cells derived. **(C)**, Stacked bar graph showing the distribution of anatomic location (red denoting carotid, blue denoting coronary arteries) from which cells derived. **(D)**, Heatmap of PEA results from submitting top 100 DEGs (by ascending p-value) between *ex vivo* cell types. Rows (pathways) and columns (cell subtypes) are clustered based on -Log_{10}(P)**. (E)**, PEA of the top 100 DEGs (by ascending p-value) for PDCs. **(F)**, PEA of the top 100 DEGs (by ascending p-value) for neurons. **(G)**, PEA of the top 100 DEGs (by ascending p-value) for basophils. Adjusted p-value < 0.05 for DEGs submitted in D-G.



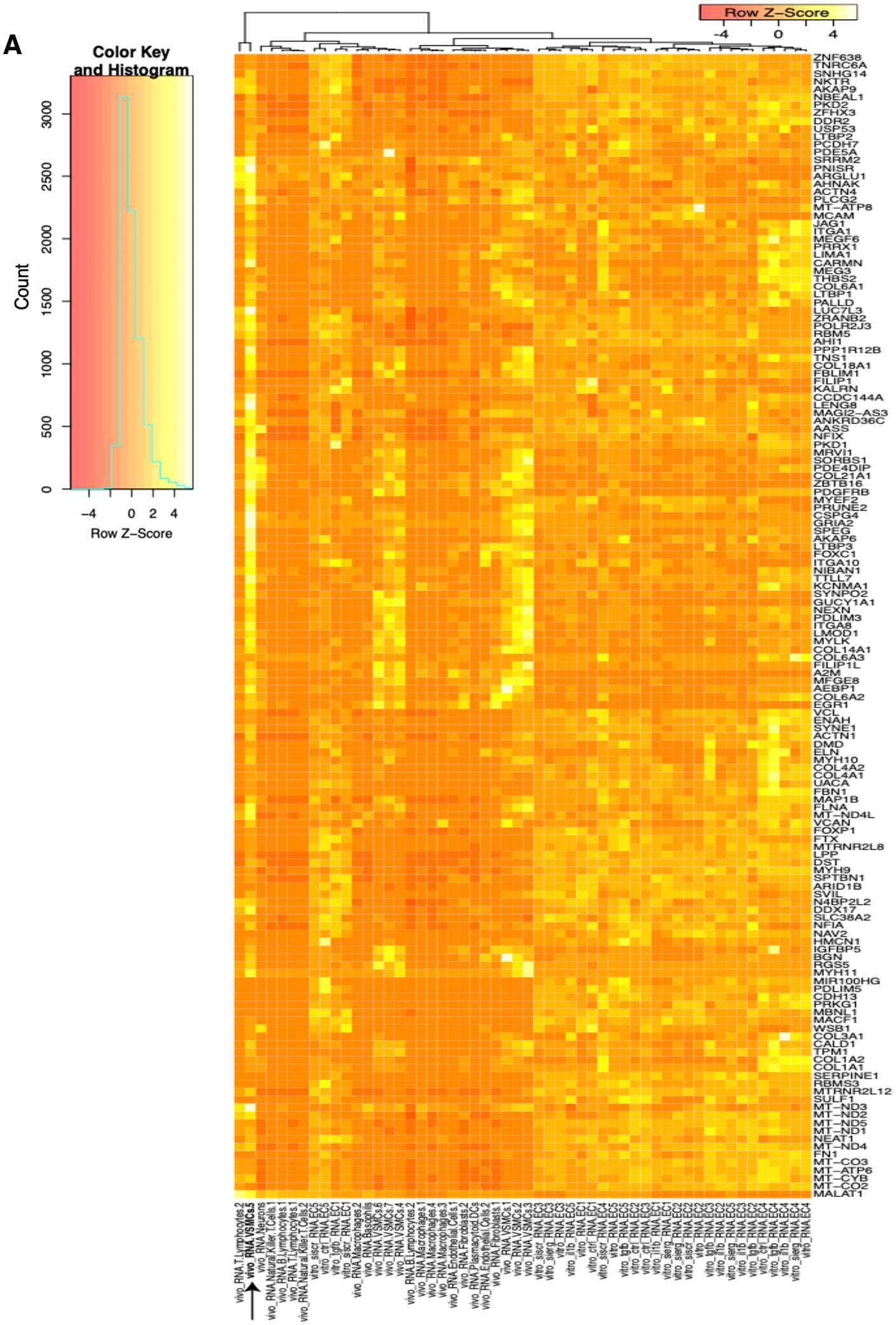
Supplementary Figure 5 (Figure S5) – Related to Figure 5 I Violin plots displaying upregulation of several EndMT markers in Endo2, compared to Endo1, including: *FN1*, *BGN*, *COL8A1*, *ELN*, *CCN1*, *FBLN5*.

A


Basophils Markers
Endothelial Cells 1 Markers
Endothelial Cells 2 Markers
Fibroblasts 1 Markers
Fibroblasts 2 Markers
Macrophages 1 Markers
Macrophages 2 Markers
Macrophages 3 Markers
Macrophages 4 Markers
Neurons Markers
Plasmacytoid DCs Markers
VSMCs 1 Markers
VSMCs 2 Markers
VSMCs 3 Markers
VSMCs 4 Markers
VSMCs 5 Markers
VSMCs 6 Markers
VSMCs 7 Markers
wnnUMAP_1
wnnUMAP_2



Supplementary Figure 6 (Figure S6) – Related to Figure 5 | **(A)**, Feature plots for each *ex vivo* module score across *in vitro* cells. Briefly, *ex vivo* module scores are generated using top marker genes for each *ex vivo* cell subtype. Seurat function AddModuleScore is used to score each cell for visualization. **(B)**, Violin plots displaying Endothelial Cells 1 (Endo1), Endothelial Cells 2 (Endo2), and VSMCs 5 (VSMC5) module scores for each perturbation across *in vitro* EC1-4. **(C)**, Feature plots displaying distribution of Endo1 (red) versus Endo2 (green) module scores across *in vitro* cells. **(D)**, Feature plots displaying distribution of Endo1 (red) versus VSMC5 (green) module scores across *in vitro* cells. **(E)**, Feature plots displaying distribution of Endo2 (red) versus VSMC5 (green) modules scores across *in vitro* cells.


A
Color Key and Histogram
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500
1000
1500
2000
2500
3000
−4
0
2
4
Row Z−Score
Row Z−Score
-4
0
4
ZNF638
TNRC6A
SNHG14
NKTR
AKAP9
NBEAL1
PKD2
ZFHX3
DDR2
USP53
LTBP2
PCDH7
PDE5A
SRRM2
PNISR
ARGLU1
AHNAK
ACTN4
PLCG2
MT−ATP8
MCAM
JAG1
ITGA1
MEGF6
PRRX1
LIMA1
CARMN
MEG3
THBS2
COL6A1
LTBP1
PALLD
LUC7L3
ZRANB2
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AHI1
PPP1R12B
TNS1
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FBLIM1
FILIP1
KALRN
CCDC144A
LENG8
MAGI2−AS3
ANKRD36C
AASS
NFIX
PKD1
MRVI1
SORBS1
PDE4DIP
COL21A1
ZBTB16
PDGFRB
MYEF2
PRUNE2
CSPG4
GRIA2
SPEG
AKAP6
LTBP3
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TTLL7
KCNMA1
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ITGA8
LMOD1
MYLK
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COL6A3
FILIP1L
A2M
MFGE8
AEBP1
COL6A2
EGFR1
VCL
ENAH
SYNE1
ACTN1
DMD
ELN
MYH10
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COL4A1
UACA
FBN1
MAP1B
FLNA
MT−ND4L
VCAN
FOXP1
FTX
MTRNR2L8
LPP
DST
MYH9
SPTBN1
ARID1B
SVIL
N4BP2L2
DDX17
SLC38A2
NFIA
NAV2
HMCN1
IGFBP5
BGN
RGS5
MYH11
MIR100HG
PDLIM5
CDH13
PRKG1
MBNL1
MACF1
WSB1
COL3A1
CALD1
TPM1
COL1A2
COL1A1
SERPINE1
RBMS3
MTRNR2L12
SULF1
MT−ND3
MT−ND2
MT−ND5
MT−ND1
NEAT1
MT−ND4
FN1
MT−CO3
MT−ATP6
MT−CYB
MT−CO2
MALAT1
vivo_RNA.T.Lymphocytes.2
vivo_RNA.VSMCs.5
vivo_RNA.Neurons
vivo_RNA.Natural.Killer.T.Cells.1
vivo_RNA.B.Lymphocytes.1
vivo_RNA.T.Lymphocytes.1
vivo_RNA.Natural.Killer.T.Cells.2
vitro_siscr_RNA.EC5
vitro_ctrl_RNA.EC5
vitro_tgfb_RNA.EC1
vitro_siscr_RNA.EC1
vivo_RNA.Macrophages.2
vivo_RNA.Basophils
vivo_RNA.VSMCs.6
vivo_RNA.VSMCs.7
vivo_RNA.VSMCs.4
vivo_RNA.B.Lymphocytes.2
vivo_RNA.Macrophages.1
vivo_RNA.Macrophages.4
vivo_RNA.Macrophages.3
vivo_RNA.Endothelial.Cells.1
vivo_RNA.Fibroblasts.2
vivo_RNA.Plasmacytoid.DCs
vivo_RNA.Endothelial.Cells.2
vivo_RNA.Fibroblasts.1
vivo_RNA.VSMCs.1
vivo_RNA.VSMCs.2
vivo_RNA.VSMCs.3
vitro_siscr_RNA.EC3
vitro_sierg_RNA.EC3
vitro_il1b_RNA.EC5
vitro_il1b_RNA.EC1
vitro_ctrl_RNA.EC1
vitro_siscr_RNA.EC4
vitro_siscr_RNA.EC5
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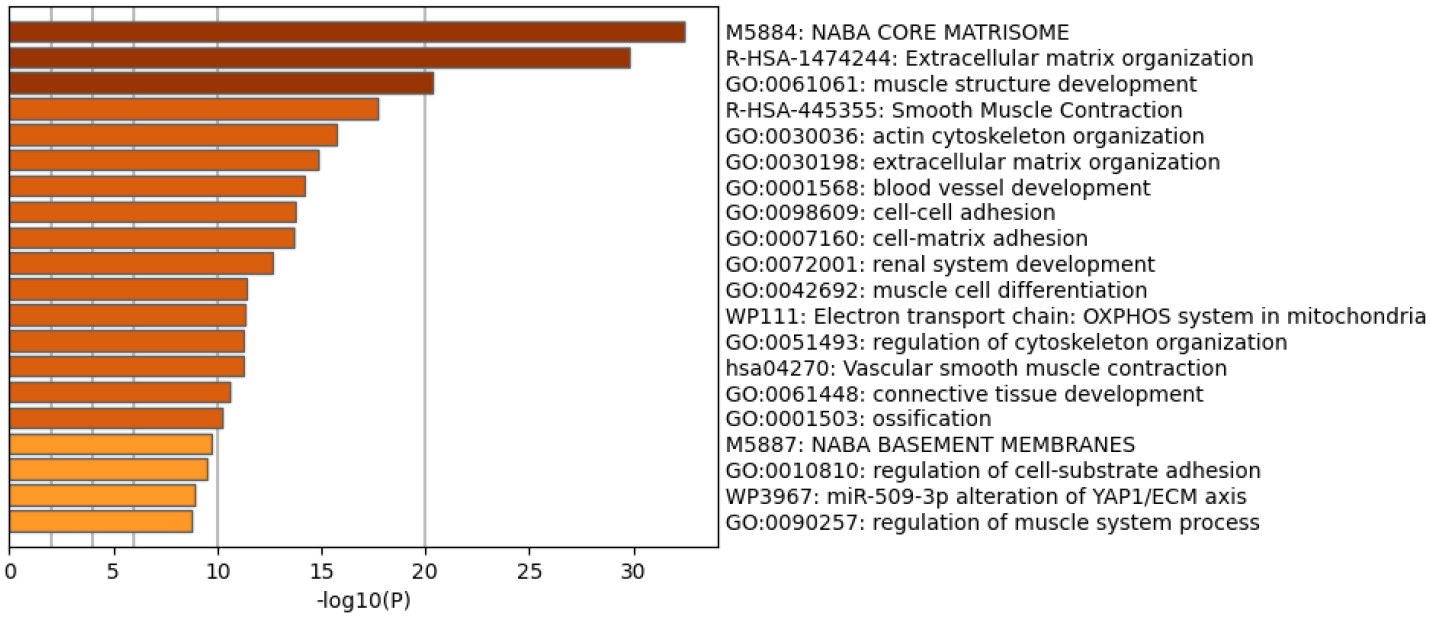
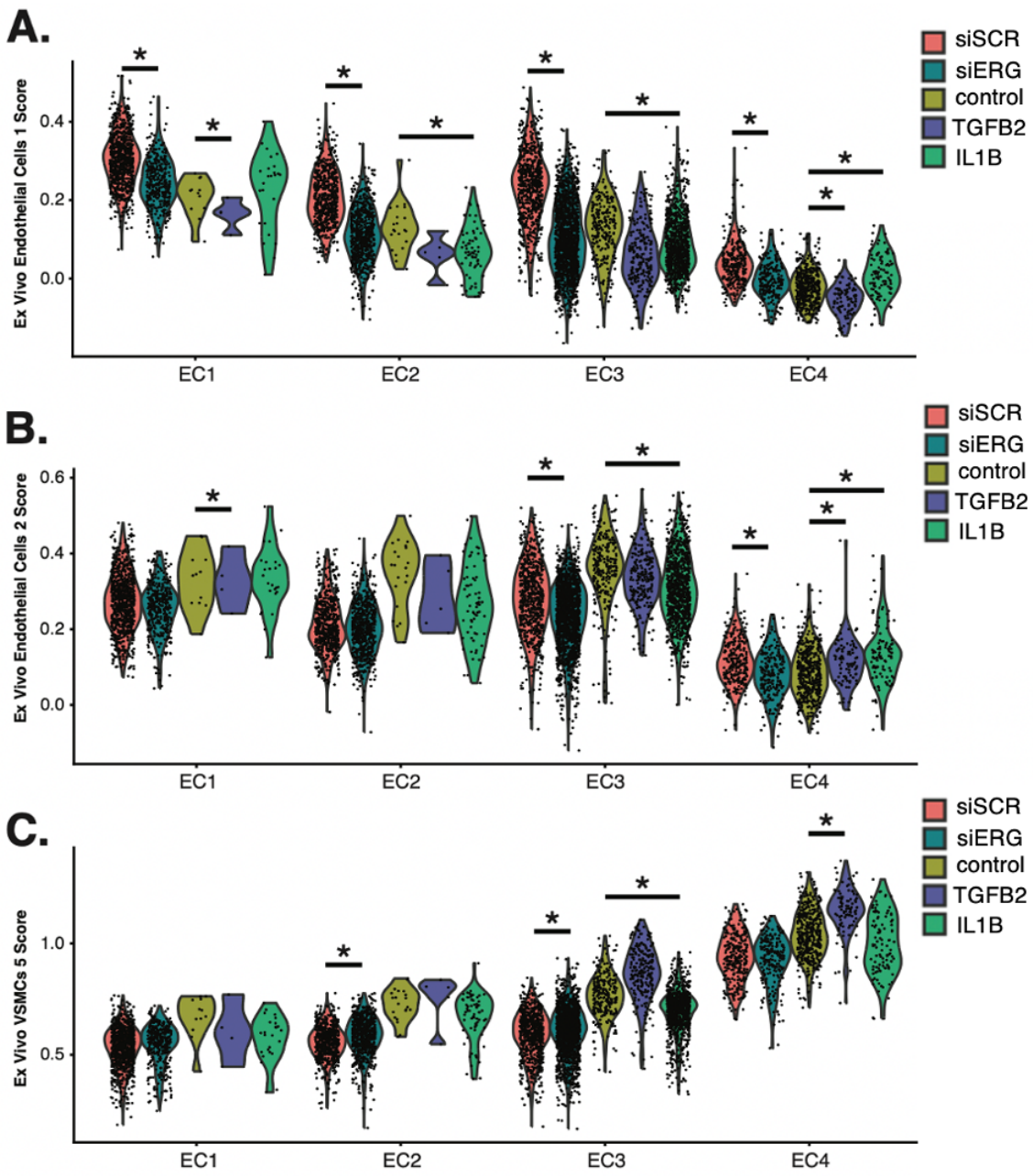
vitro_ctrl_RNA.EC2
vitro_ctrl_RNA.EC3
vitro_il1b_RNA.EC1
vitro_sierg_RNA.EC1
vitro_sierg_RNA.EC2
vitro_siscr_RNA.EC2
vitro_il1b_RNA.EC2
vitro_tgfb_RNA.EC3
vitro_il1b_RNA.EC3
vitro_sierg_RNA.EC5
vitro_il1b_RNA.EC4
vitro_tgfb_RNA.EC5
vitro_ctrl_RNA.EC4
vitro_tgfb_RNA.EC4
vitro_sierg_RNA.EC4
vitro_

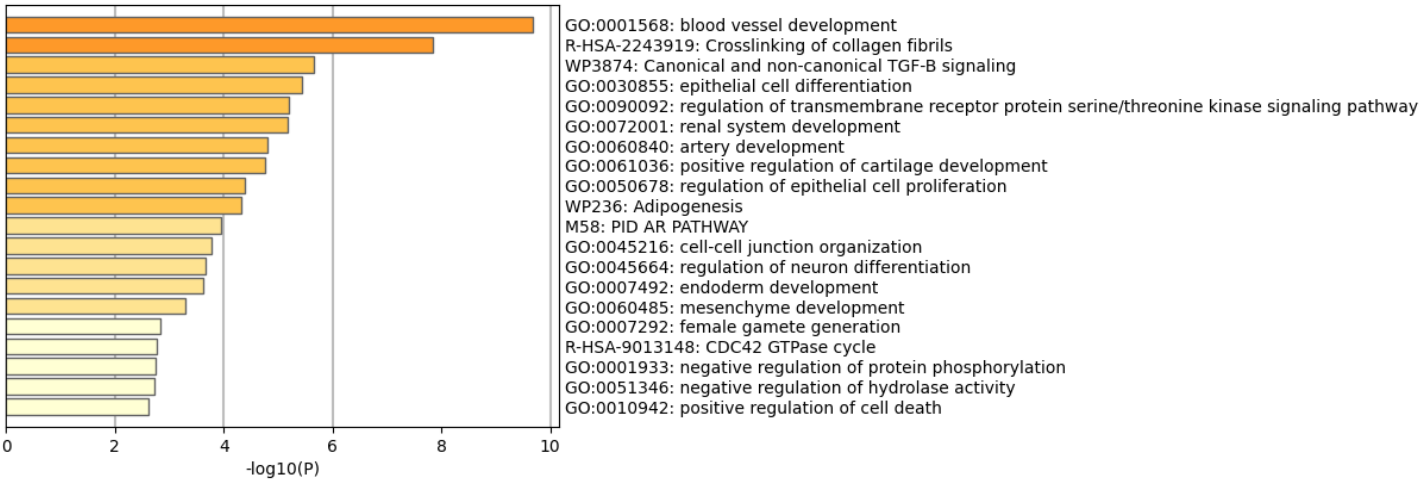
B



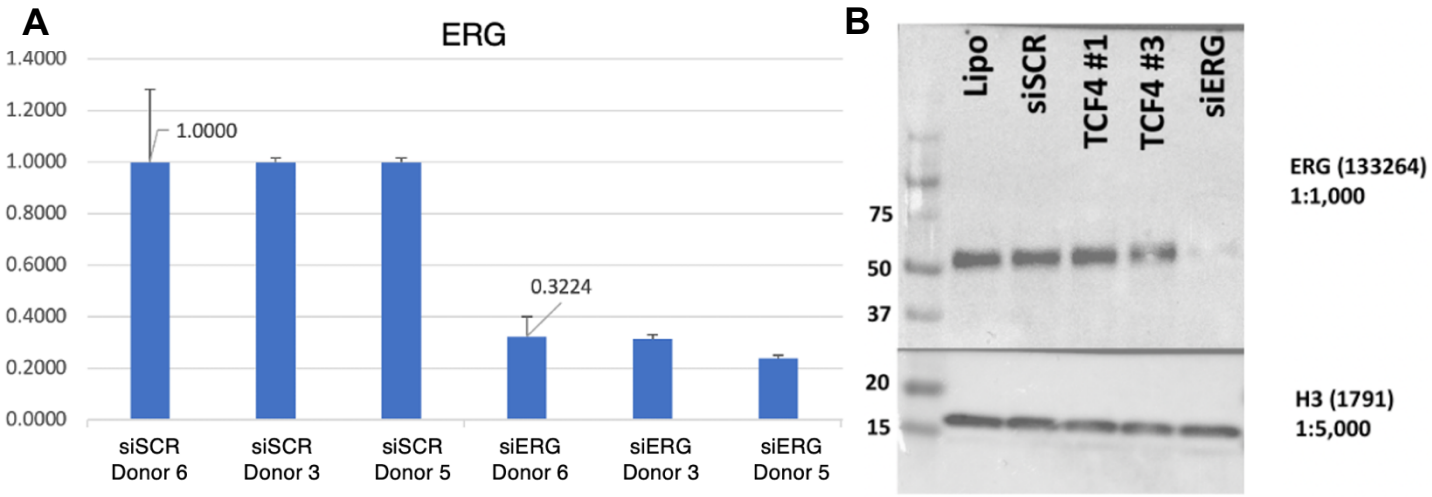
Supplementary Figure 7 (Figure S7) – Related to Figure 5 l (A), Heatmap displaying average expression of VSMC5 maker genes (black arrow) across *in vitro* and *ex vivo* datasets. Rows (genes) and columns (cell subtypes) are clustered based on average expression for each given gene. **(B)**, PEA of the top 200 genes for VSMC5 (adjusted p-value < 0.05).



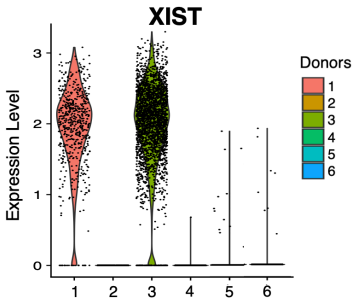
Supplementary Figure 8 (Figure S8) – Related to Figure 5 I (A), Violin plots of *ex vivo* Endo1 module scores across EC1-4. **(B)**, Violin plots of *ex vivo* Endo2 module scores across EC1-4. **(C)**, Violin plots of *ex vivo* VSMC5 module scores across EC1-4. Adjusted p-value for A-C generated using Wilcoxon rank sum test with continuity correction by setting the alternative hypothesis to "two.sided".



Supplementary Figure 9 (Figure S9) – Related to Figure 6 l PEA of significant (p-value < 0.05) EC4 linked genes which overlap with significant (p-value < 10^{-8}) CAD-associated SNPs.



Supplementary Figure 10 (Figure S10) – Related to Methods l (A), qPCR results for ERG knockdown across donors. **(B)**, Western Blot representing a typical knockdown of siERG with the siRNA pools used in this study. TCF4 samples are irrelevant for the purposes of this study.



Supplementary Figure 11 (Figure S11) – Related to Methods l Violin plot of *XIST* showing expected expression in female *in vitro* donor cells (1 and 3) and lack of expression in male *in vitro* donor cells (2, 4, 5, and 6).