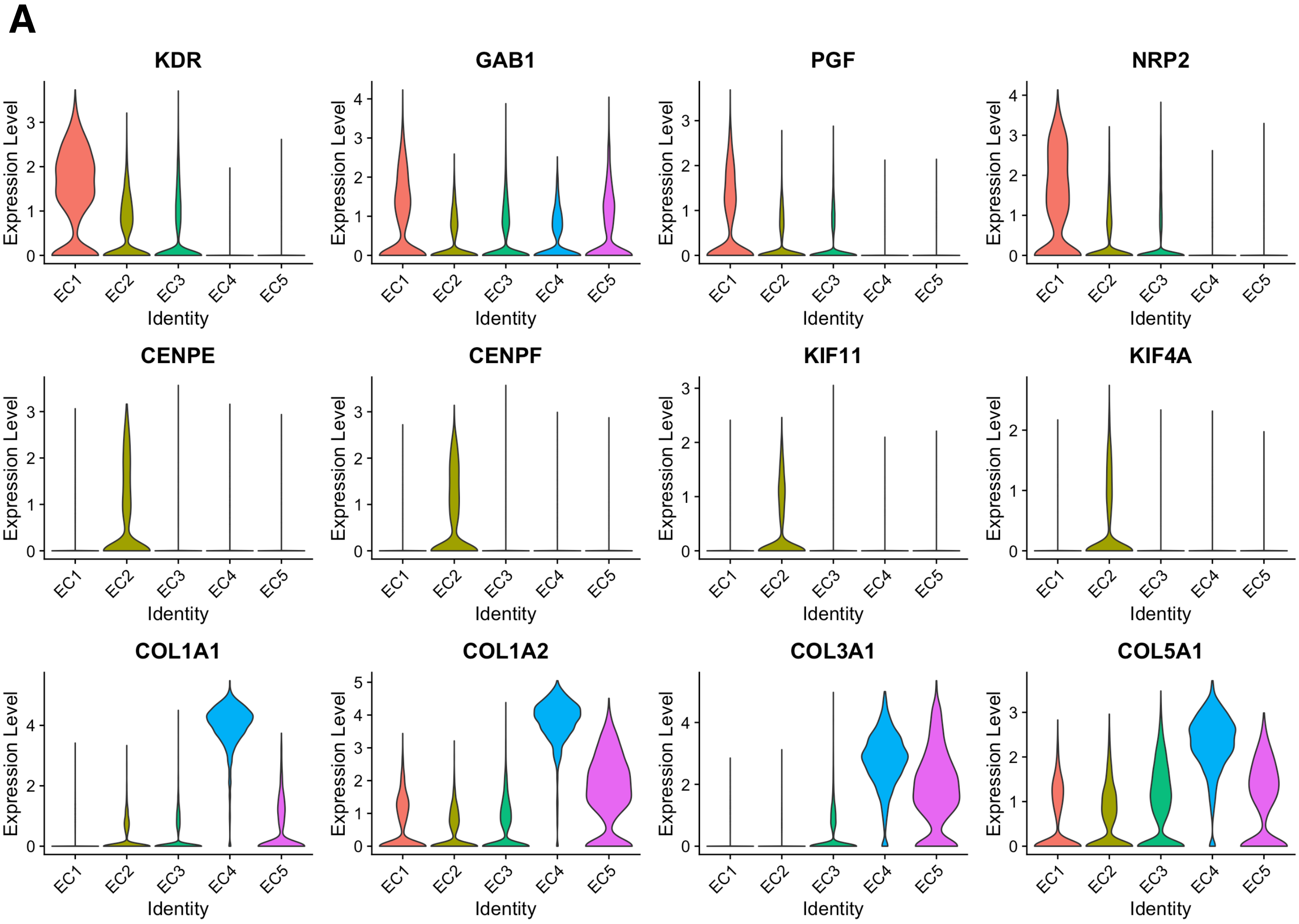
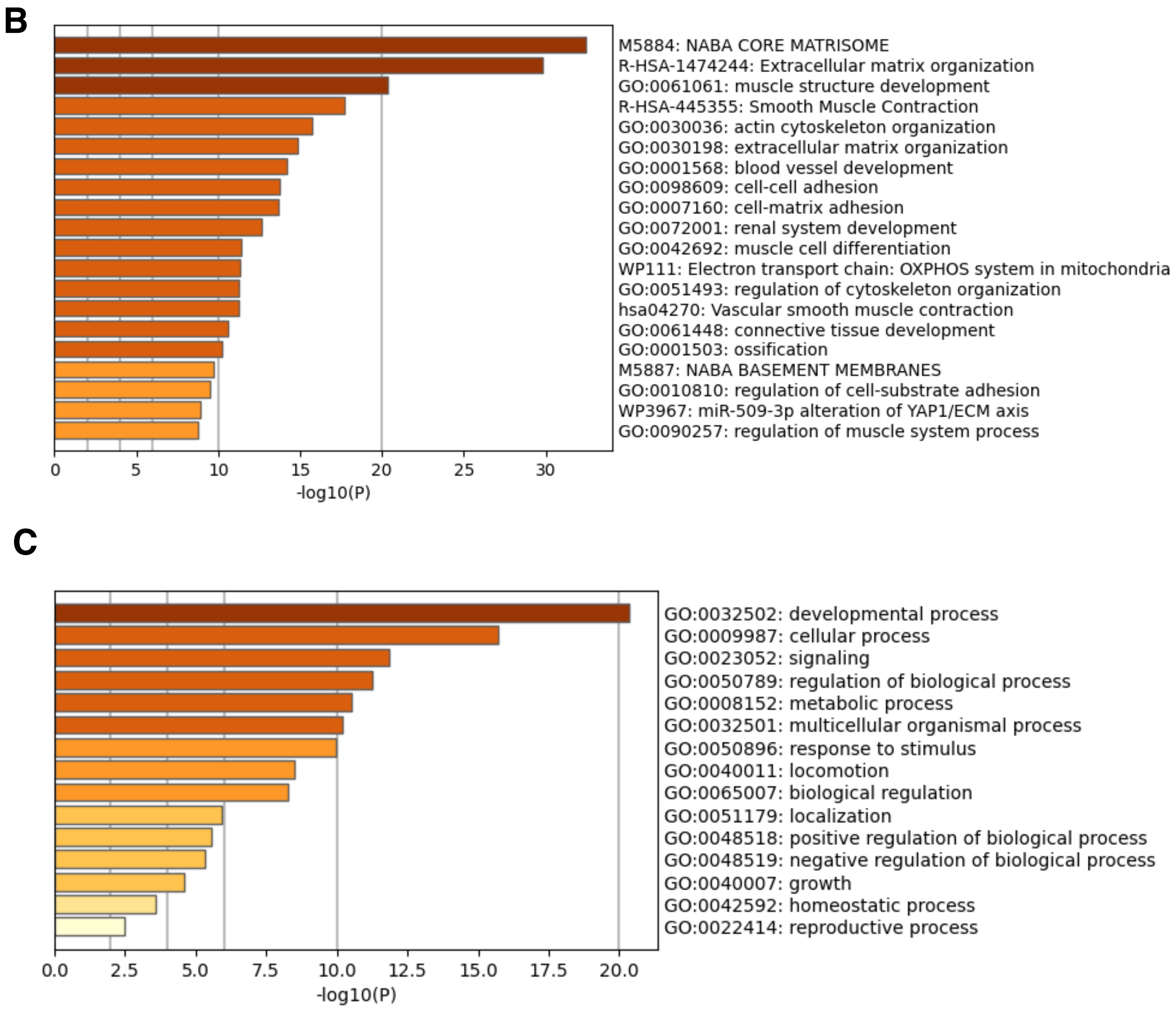
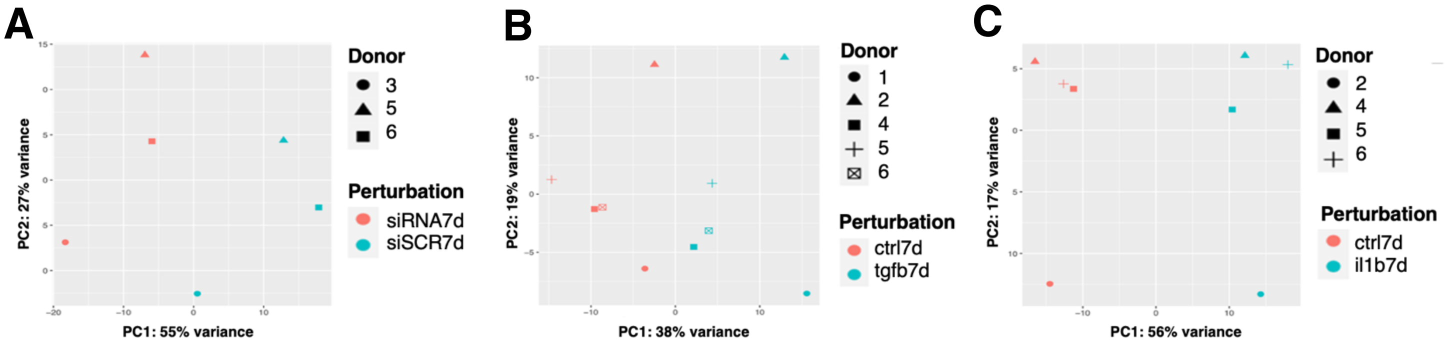
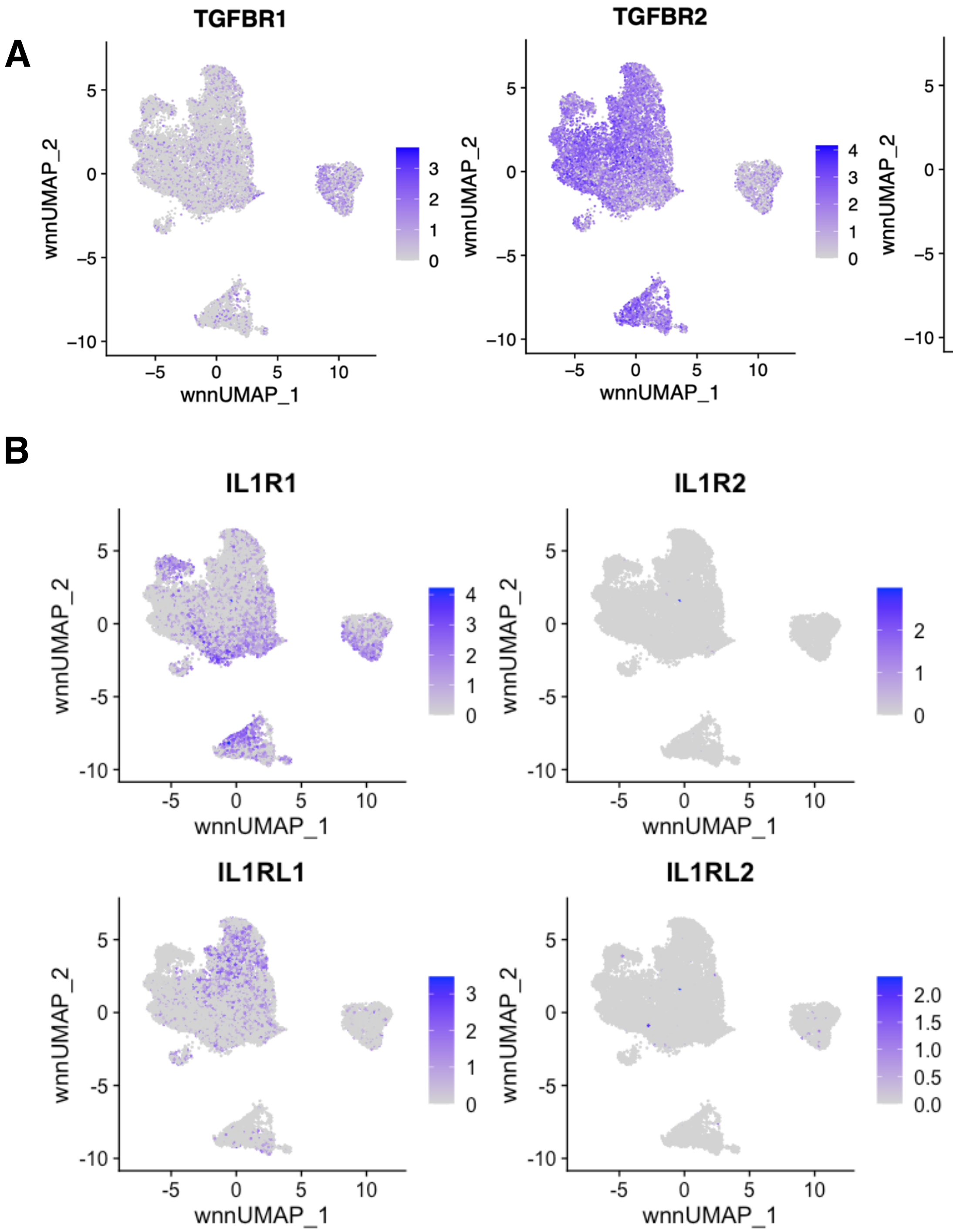

A
KDR
GAB1
PGF
NRP2
CENPE
CENPF
KIF11
KIF4A
COL1A1
COL1A2
COL3A1
COL5A1
Expression Level
Identity
EC1
EC2
EC3
EC4
EC5
0
1
2
3
4
5



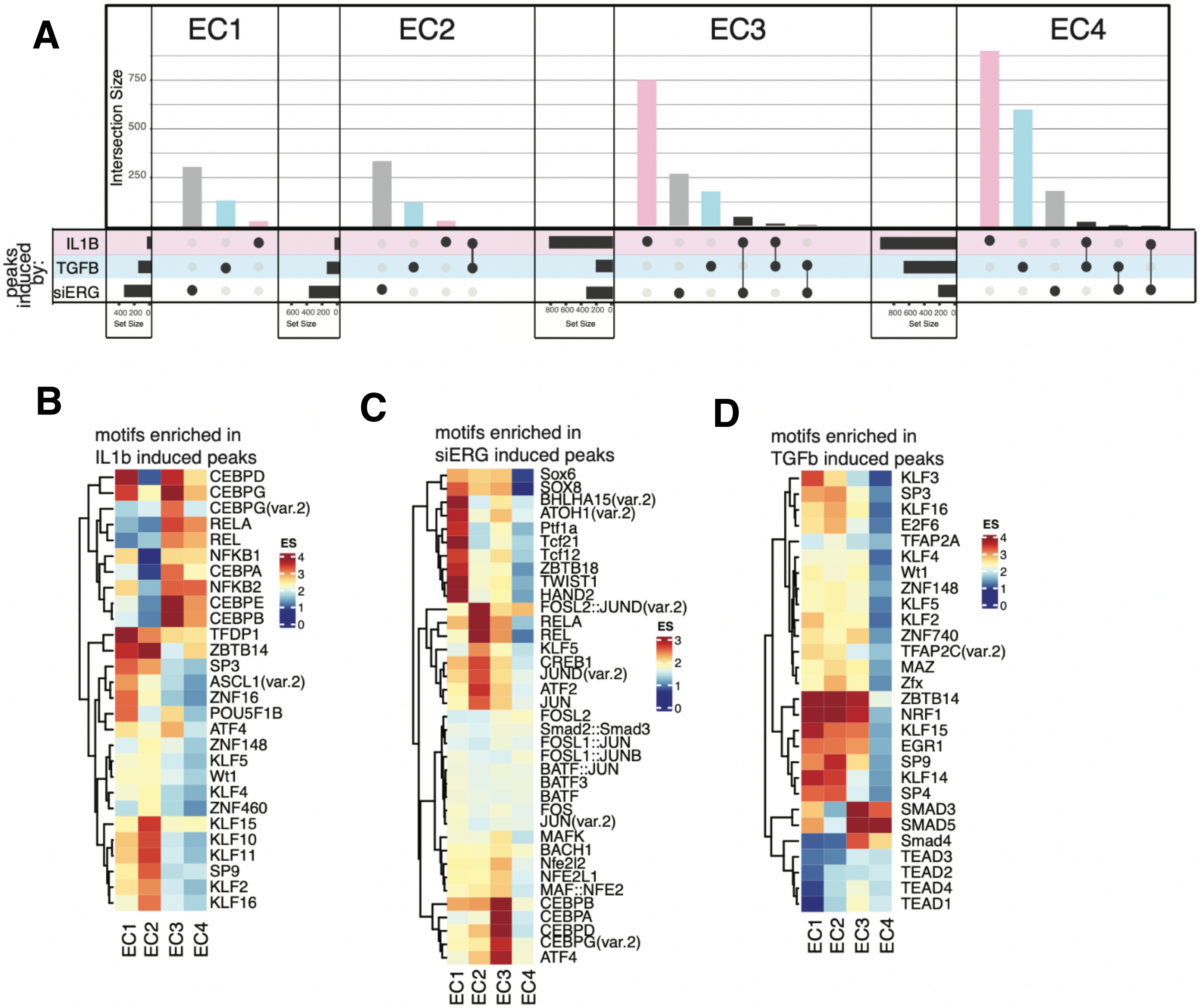
Supplementary Figure 1 (Figure S1) – Related to Figure 1 | (A), Violin plots of representative marker genes for angiogenic EC1 (*KDR*, *GAB1*, *PGF*, *NRP1*), proliferative EC2 (*CENPE*, *CENPF*, *KIF11*, *KIF4A*), and mesenchymal EC4 (*COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*) sub-phenotypes. **(B)**, 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.



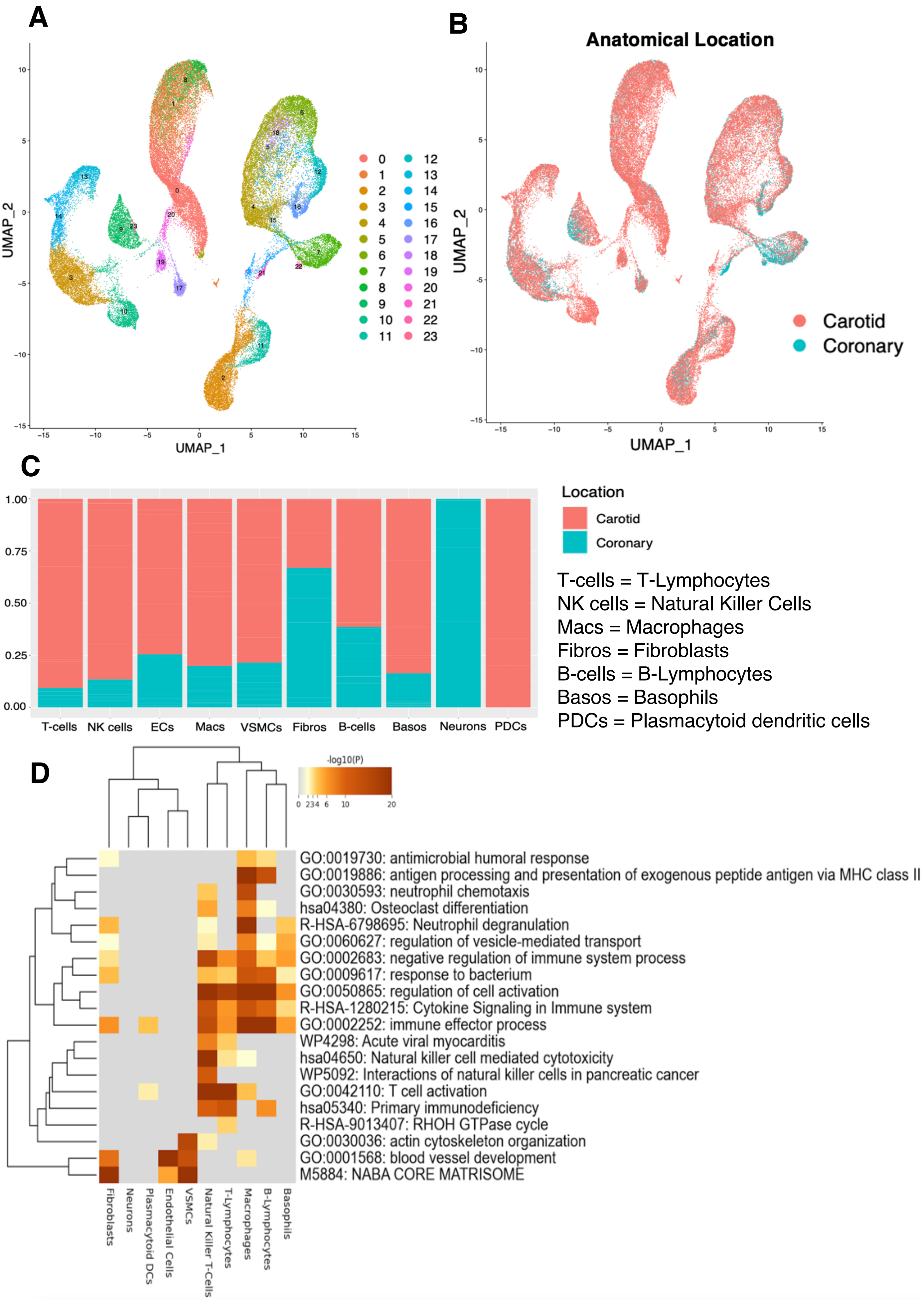
Supplementary Figure 2 (Figure S2) – Related to Figure 3 I (A), Principal component analysis (PCA) of EC1-4 snRNA-seq samples +/- siERG or control across donor replicates. **(B)**, PCA of EC1-4 snRNA-seq samples +/- TGFB2 or control across donor replicates. **(C)**, PCA of EC1-4 snRNA-seq samples +/-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



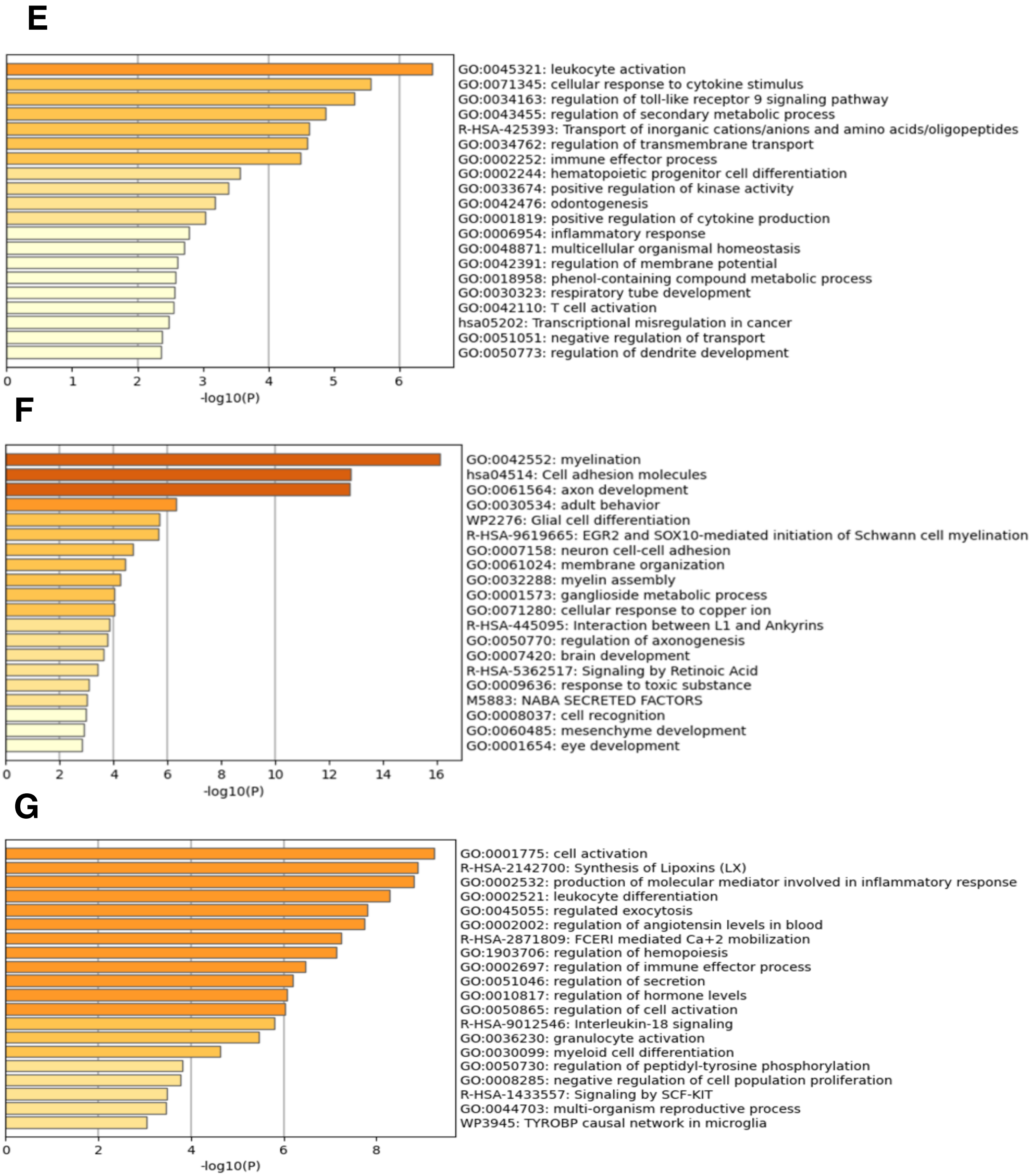
Supplementary Figure 3 (Figure S3) – Related to Figure 3 l (A), Feature plots of expression of TGFB pathway receptors: *TGFBR1*, *TGFBR2*, and *ACVRL1*. **(B)**, Feature plots of IL1B pathway receptors: *IL1R1*, *IL1R2*, *IL1RL1*, and *IL1RL2*.



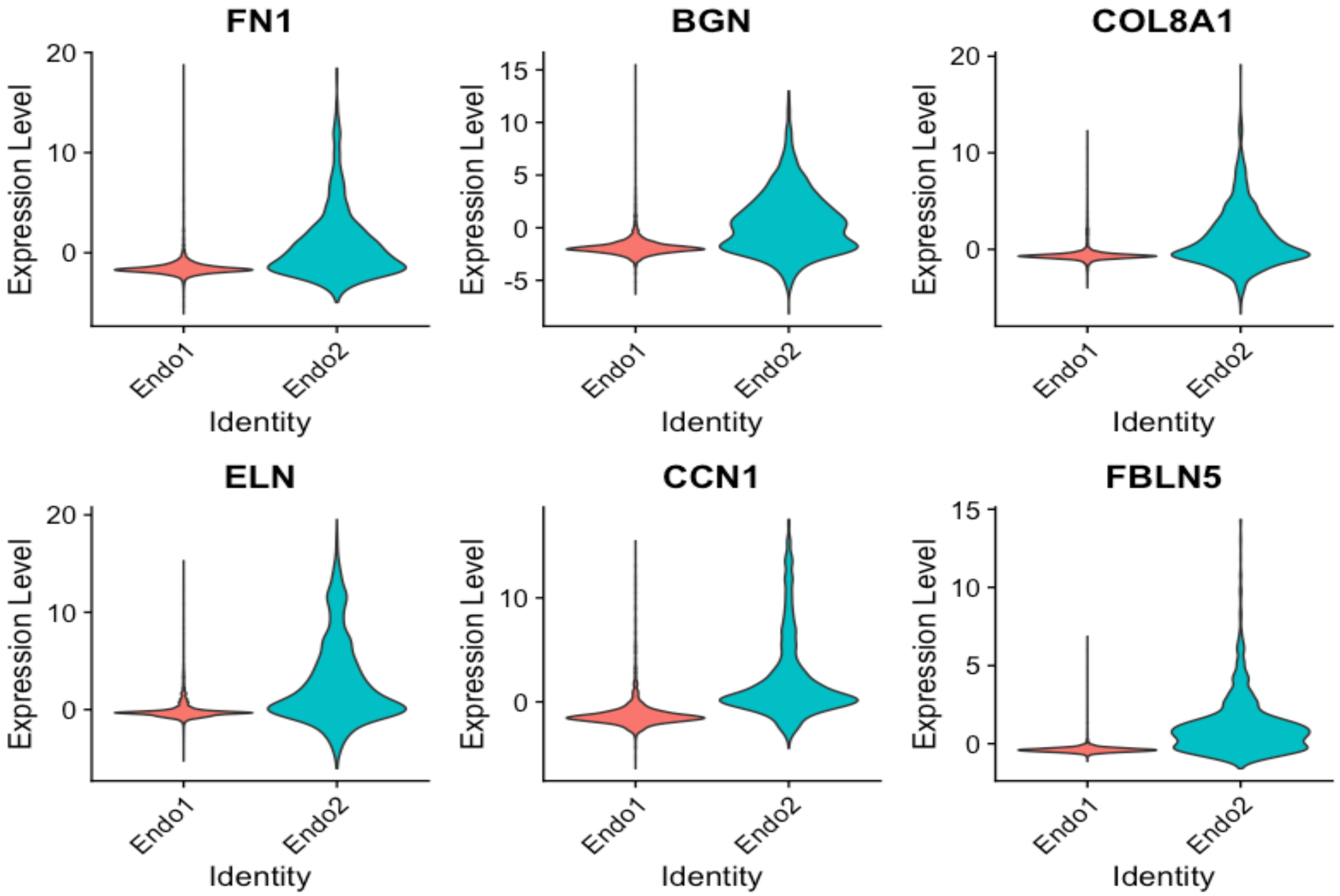
Supplementary Figure 4 (Figure S4) I (A), Upset plot of induced peaks for siERG (grey), IL1B (pink), and TGFB2 (blue) across EC1, EC2, EC3, and EC4. Upset plots visualize intersections between sets in a matrix, where the columns of the matrix correspond to the sets, and the rows correspond to the intersections. Intersection size represents the number of genes at each intersection. **(B)**, Heatmap of top motifs enriched in IL1B-induced peaks. Top TFs for each EC subtype are selected based on ascending p-value. Rows (TFs) and columns (EC subtype) are clustered based on enrichment score (ES). **(C)**, Heatmap of top motifs enriched in siERG-induced peaks. **(D)**, Heatmap of top motifs enriched in TGFB2-induced peaks.



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 5 (Figure S5) – Related to Figure 5 | (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 6 (Figure S6) – 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*.

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

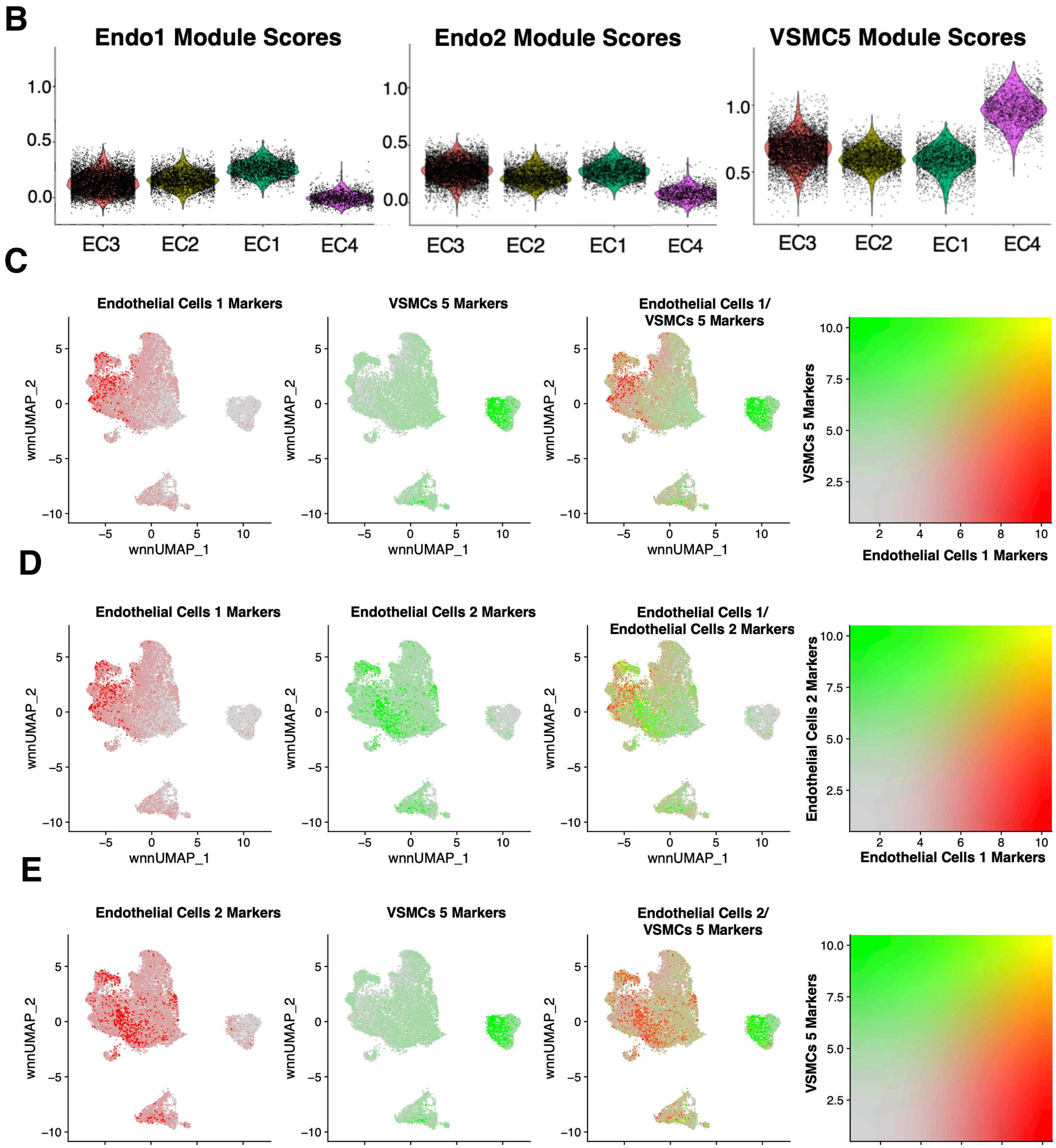
VSMCs 3 Markers

VSMCs 4 Markers

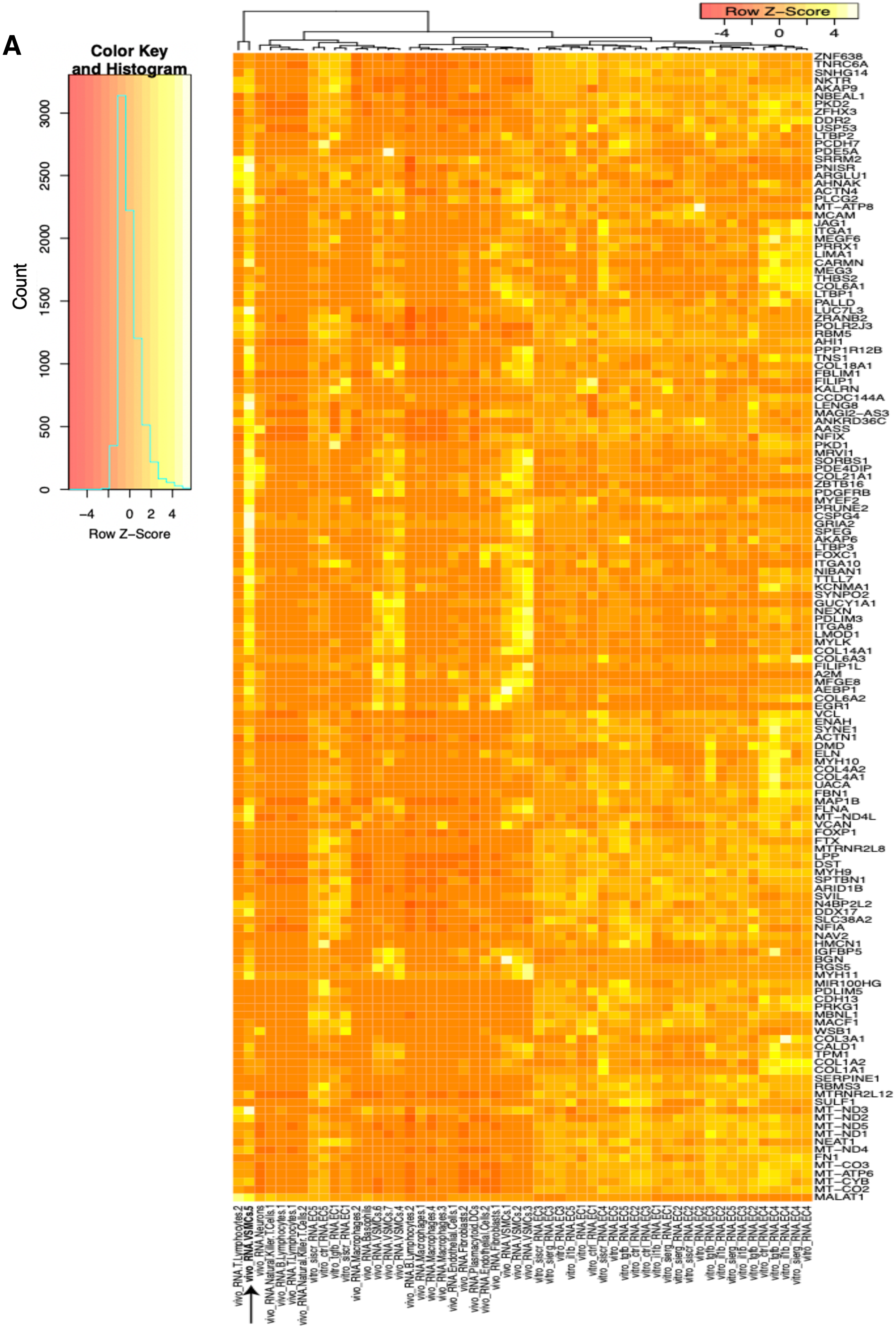
VSMCs 5 Markers

VSMCs 6 Markers

VSMCs 7 Markers



Supplementary Figure 7 (Figure S7) – 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. The 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
Count
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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
POLR2J3
RBM5
AHI1
PPP1R12B
TNS1
COL18A1
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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ENAH
SYNE1
ACTN1
DMD
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MYH10
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COL4A1
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MAP1B
FLNA
MT−ND4L
VCAN
FOXP1
FTX
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LPP
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SPTBN1
ARID1B
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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
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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_RNA.EC3
vitro_il1b_RNA.EC5
vitro_RNA.EC1
vitro_ctrl_RNA.EC1
vitro_siscr_RNA.EC4
vitro_RNA.EC5
vitro_tgfb_RNA.EC5
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_RNA.EC2
vitro_tgfb_RNA.EC3
vitro_il1b_RNA.EC2
vitro_sierg_RNA.EC5
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vitro_tgfb_RNA.EC2
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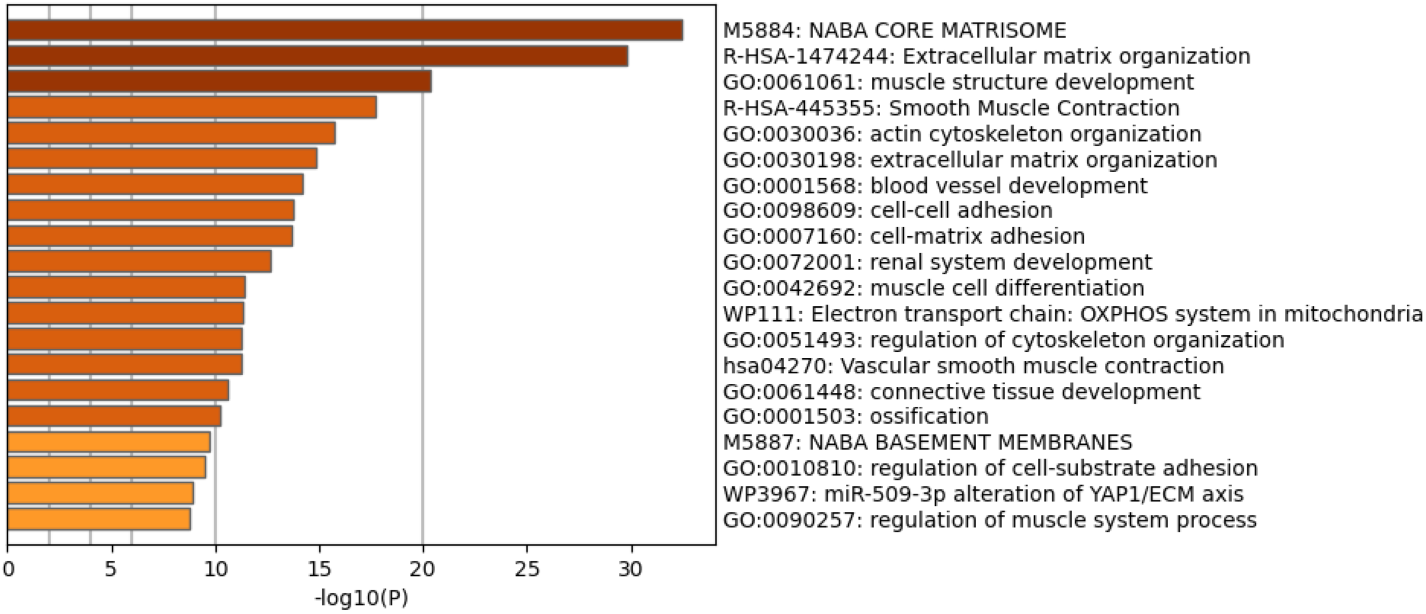
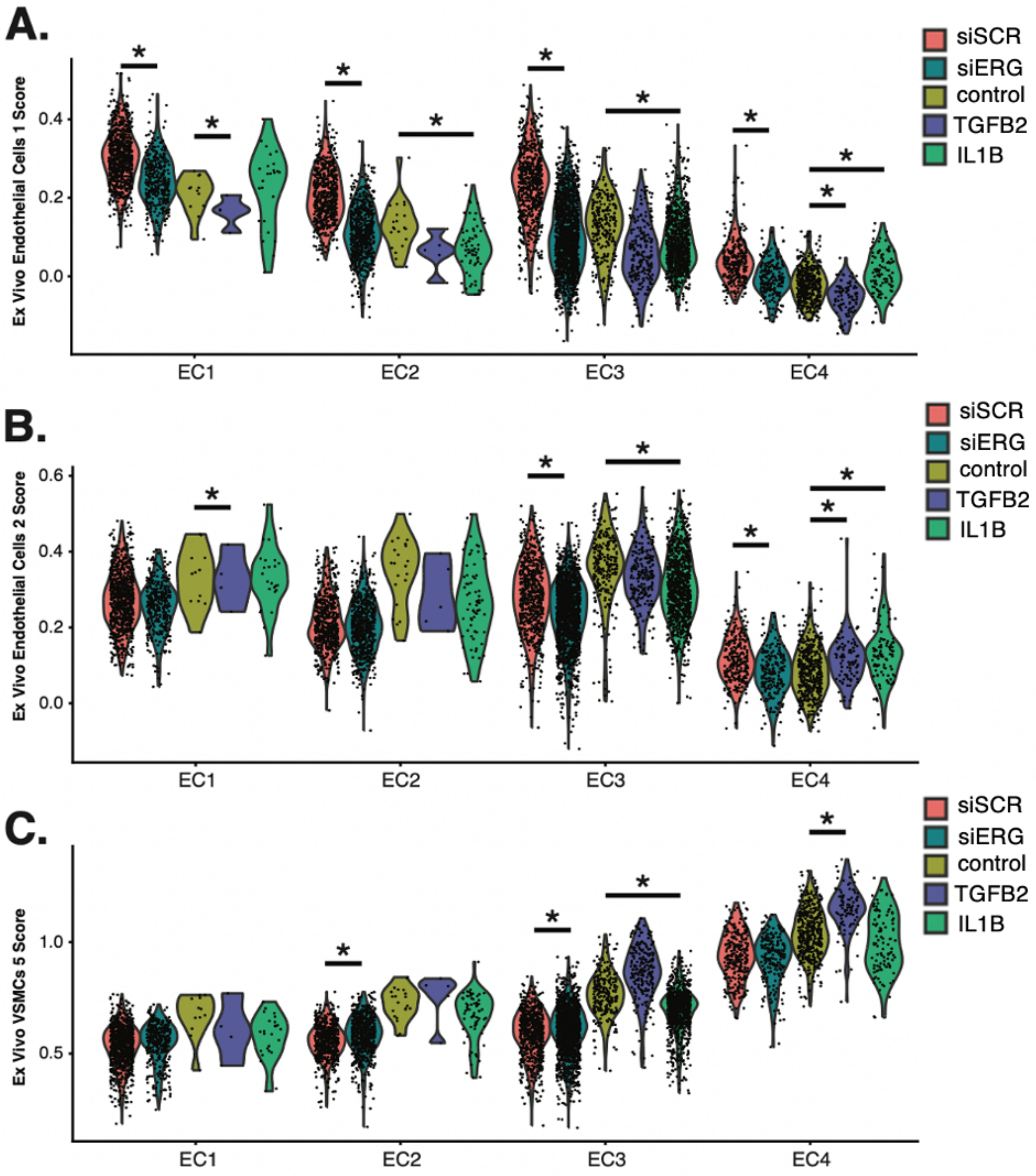
vitro_il1b_RNA.EC4
vitro_sierg_RNA.EC4
vitro_RNA.EC4

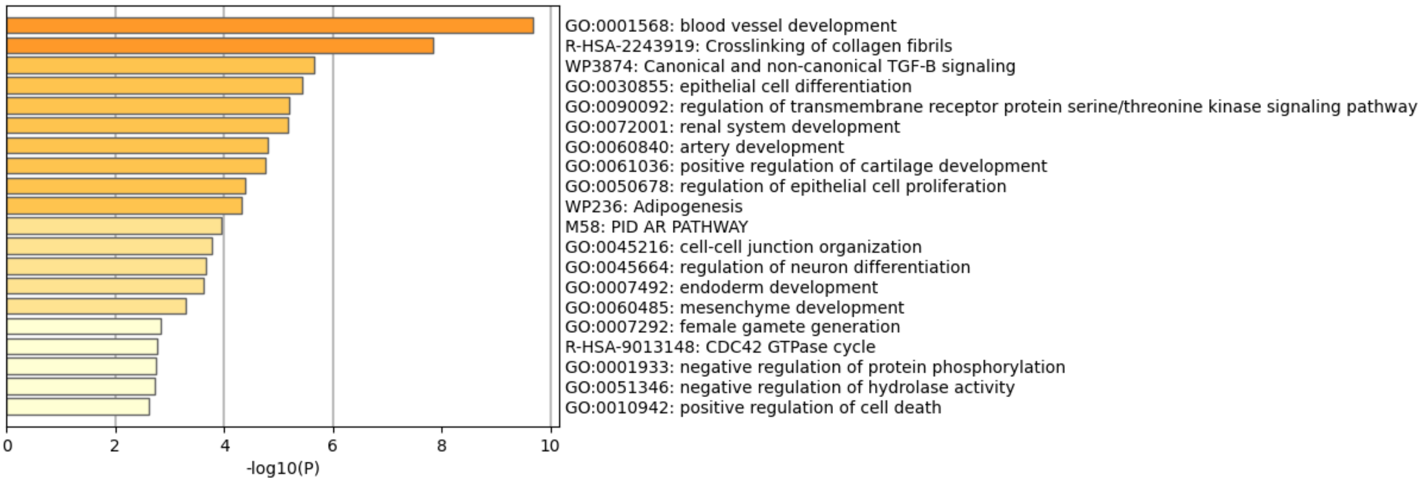
B



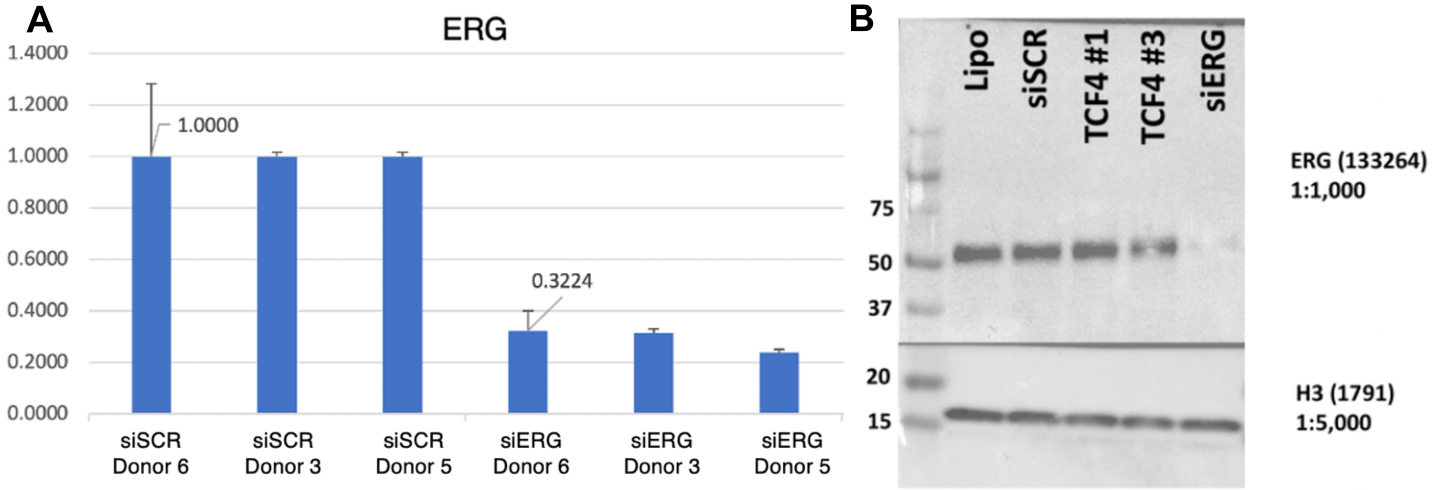
Supplementary Figure 8 (Figure S8) – Related to Figure 5 I (A), Heatmap displaying average expression of VSMC5 maker genes (black arrow) across *in vitro* and *ex vivo* datasets. Rows (genes) and columns (cell subtypes) are clustered based on average expression for each given gene. **(B)**, PEA of the top 200 genes for VSMC5 (adjusted p-value < 0.05).



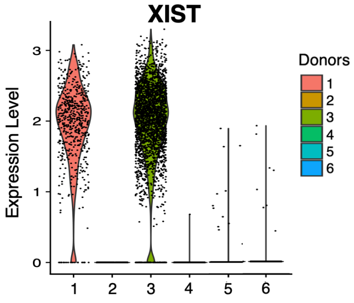
Supplementary Figure 9 (Figure S9) – Related to Figure 5 | (A), Violin plots of *ex vivo* Endo1 module scores across EC1-4. **(B)**, Violin plots of *ex vivo* Endo2 module scores across EC1-4. **(C)**, Violin plots of *ex vivo* VSMC5 module scores across EC1-4. Adjusted p-value for A-C generated using Wilcoxon rank sum test with continuity correction by setting the alternative hypothesis to "two.sided".



Supplementary Figure 10 (Figure S10) – 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 11 (Figure S11) – 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 12 (Figure S12) – 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).