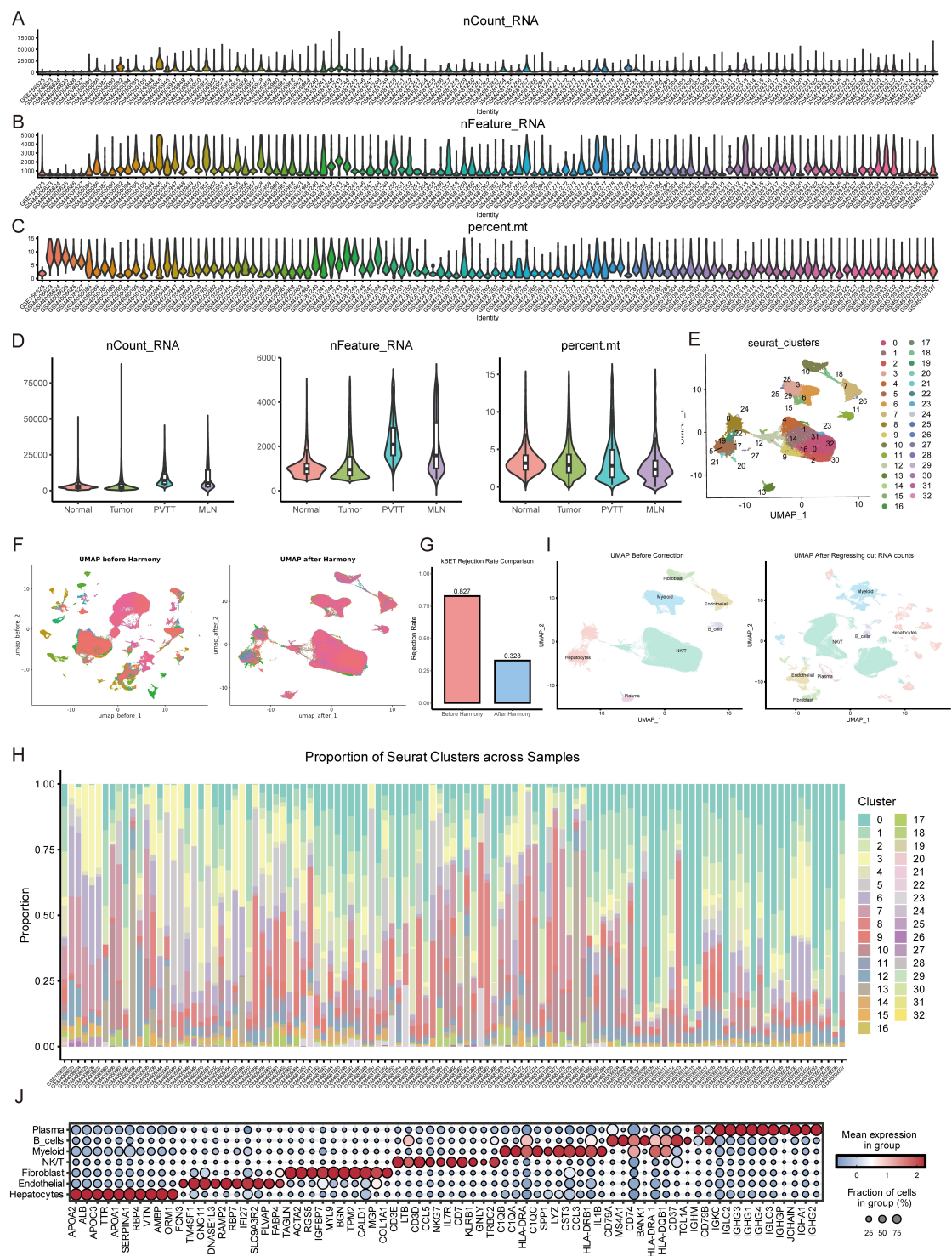


Supplementary Figures



Supplementary Figure 1. Quality control and batch correction of scRNA-seq data

(A–C) Quality control metrics showing distribution of nCount_RNA, nFeature_RNA, and percent.mt across individual samples, colored by sample identity.

(D) Violin plots comparing nCount_RNA, nFeature_RNA, and percent.mt distributions across tissue groups (Normal, Tumor, PVTT, MLN).

(E) UMAP visualization of 33 distinct clusters.

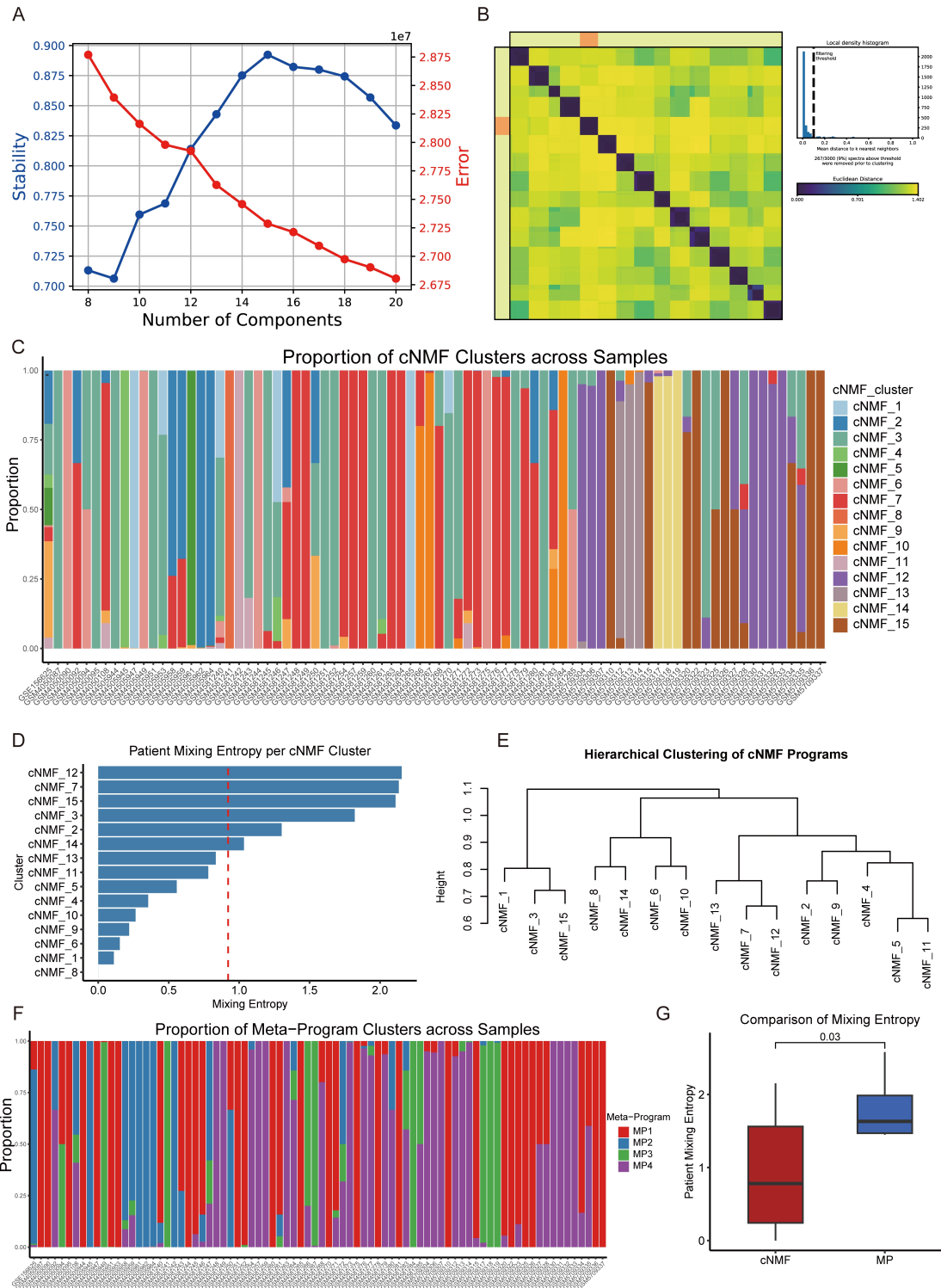
(F) UMAP projections before and after Harmony batch correction, demonstrating effective integration of samples across batches.

(G) k-nearest neighbour batch effect test (kBET) rejection rates before (0.827) and after (0.328) Harmony correction, quantifying batch integration efficacy.

(H) Stacked bar plot illustrating the proportional distribution of the 33 identified Seurat clusters across all samples.

(I) UMAP projections of seven major cell populations before and after regressing out RNA counts, showing that technical variation does not affect cell type clustering.

(J) Dot plot heatmap of differentially expressed marker genes validating the annotation of seven major cell populations across samples.

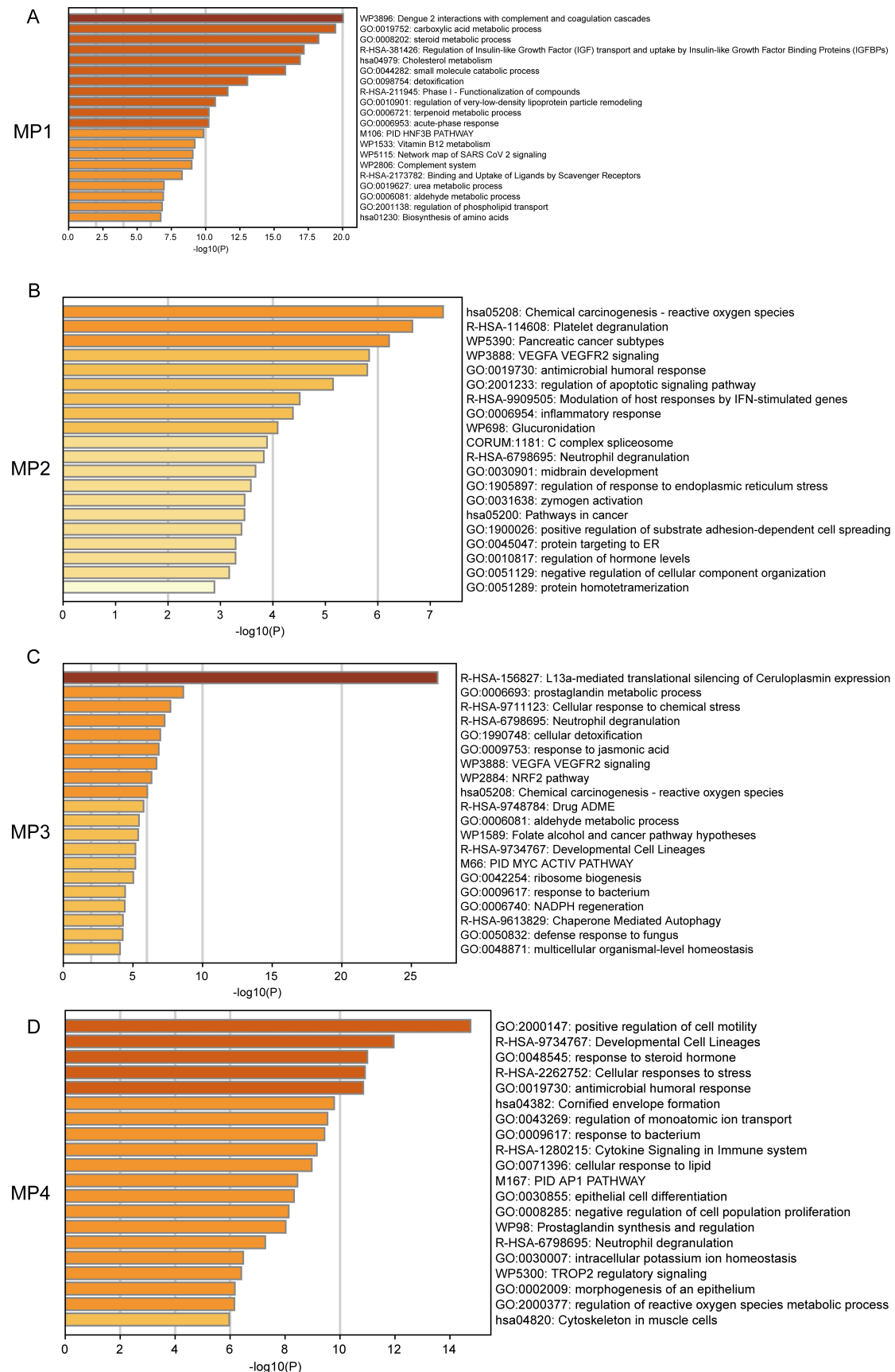


Supplementary Figure 3. Gene expression programs and meta-program derivation in HCC malignant cells

(A) cNMF parameter optimization showing model stability and reconstruction error across different component numbers ($k=8-20$).

(B) Euclidean distance matrix between 15 identified GEPs demonstrating program distinctiveness.

- (C) Proportional distribution of 15 GEPs across individual samples.
- (D) Patient mixing entropy for each GEP, demonstrating cross-patient sharing of transcriptional programs.
- (E) Hierarchical clustering of 15 GEPs revealing four overarching MPs.
- (F) Proportional distribution of four meta-programs across samples.
- (G) Comparison of patient mixing entropy between individual GEPs and MPs, showing significantly higher entropy for MPs ($p=0.03$).



Supplementary Figure 4. Functional enrichment analysis of meta-program signatures

(A) Metascape enrichment of MP1 showing hepatocyte-specific metabolic pathways including carboxylic acid, steroid, and cholesterol metabolism, and amino acid biosynthesis.

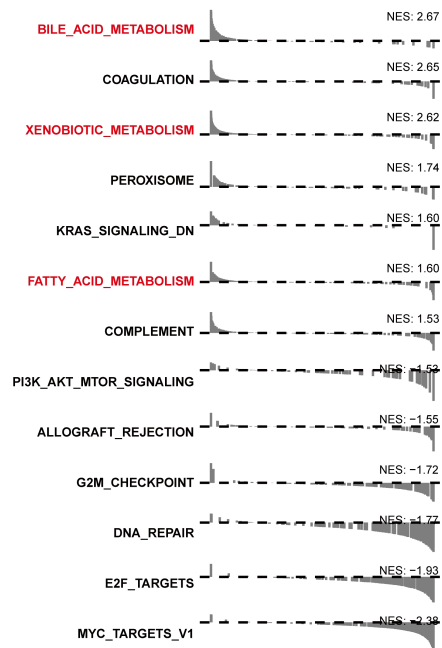
(B) Metascape enrichment of MP2 showing stress response pathways including ROS response, ER stress, apoptotic signaling, and inflammatory response.

(C) Metascape enrichment of MP3 showing MYC pathway activation, ribosome biogenesis, translational regulation, and innate immune processes.

(D) Metascape enrichment of MP4 showing cell motility, epithelial differentiation, cytokine signaling, and AP1 pathway activation.

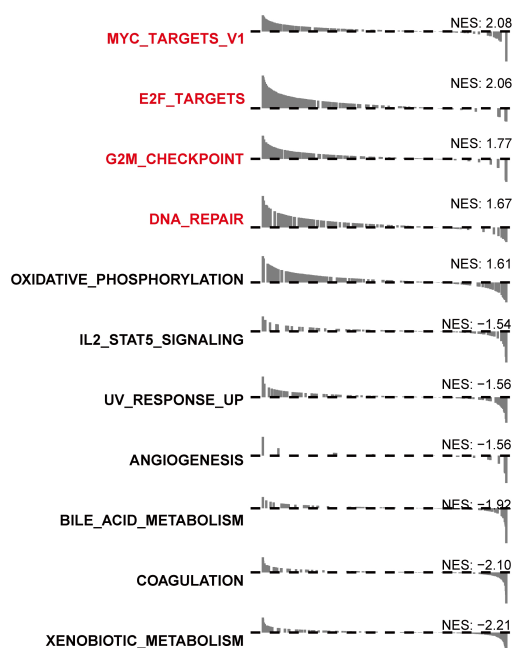
A

MP1



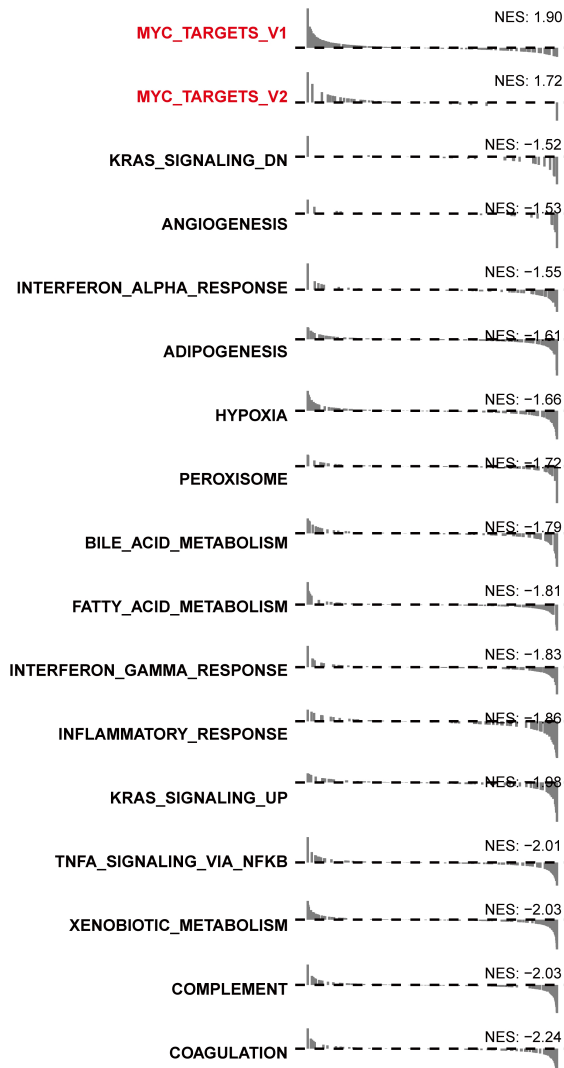
B

MP2



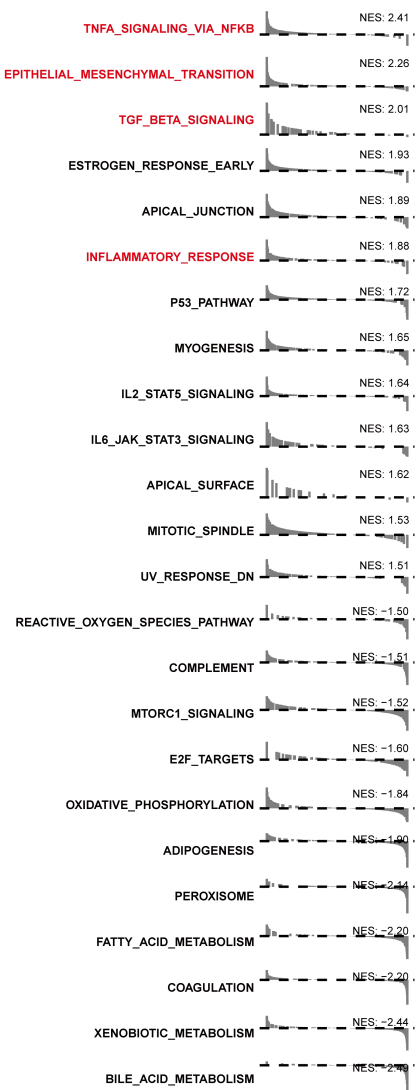
C

MP3



D

MP4



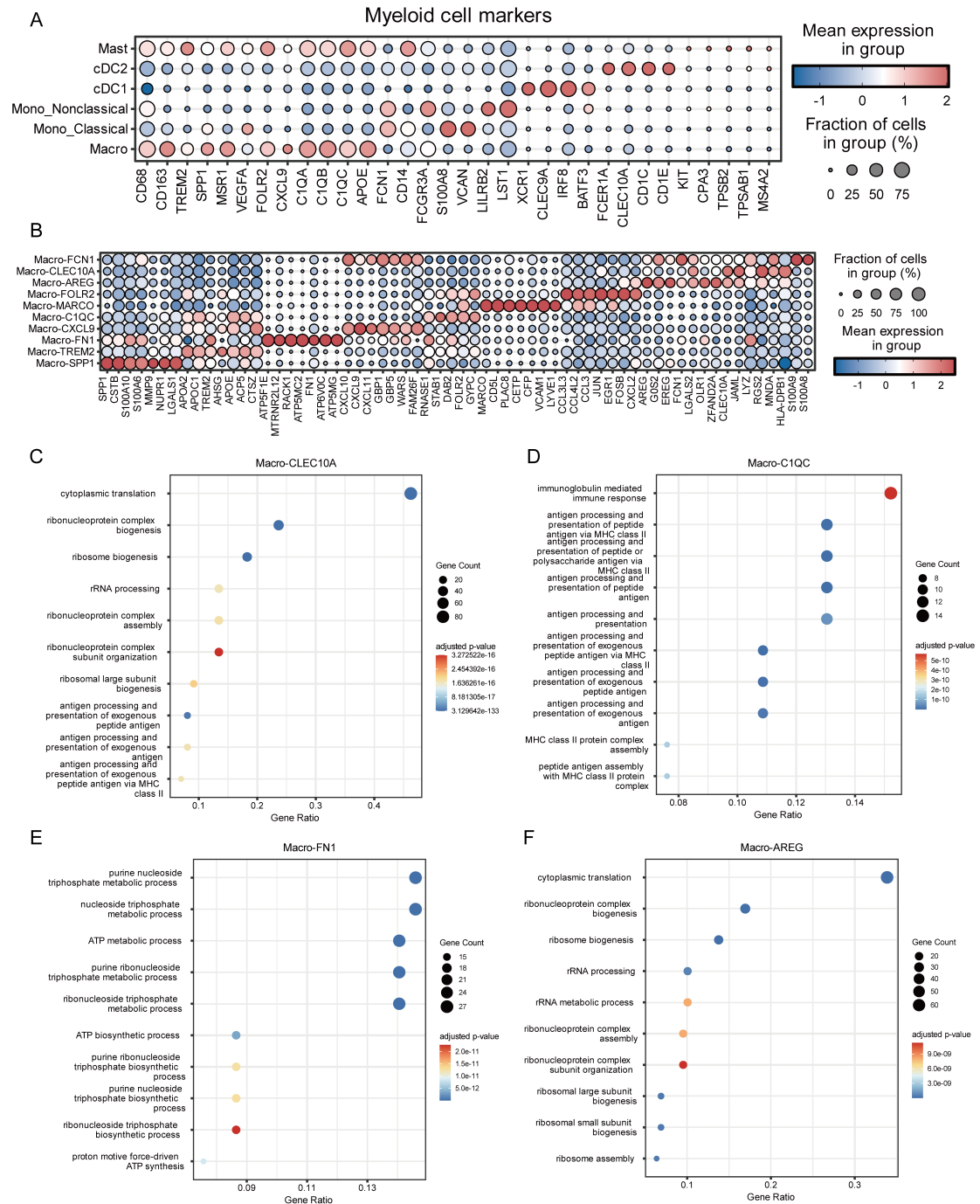
Supplementary Figure 5. GSEA hallmark pathway analysis of meta-programs

(A) GSEA of MP1 showing activation of bile acid, xenobiotic, and fatty acid metabolism, with suppression of MYC and E2F targets.

(B) GSEA of MP2 showing activation of MYC targets, E2F targets, and G2M checkpoint, with suppression of metabolic pathways.

(C) GSEA of MP3 showing MYC target activation with concurrent suppression of metabolic (bile acid, fatty acid, xenobiotic) and inflammatory pathways (TNF α , interferon signaling).

(D) GSEA of MP4 showing activation of TNF α -NF κ B signaling, EMT, TGF β signaling, and inflammatory response, with metabolic pathway suppression.

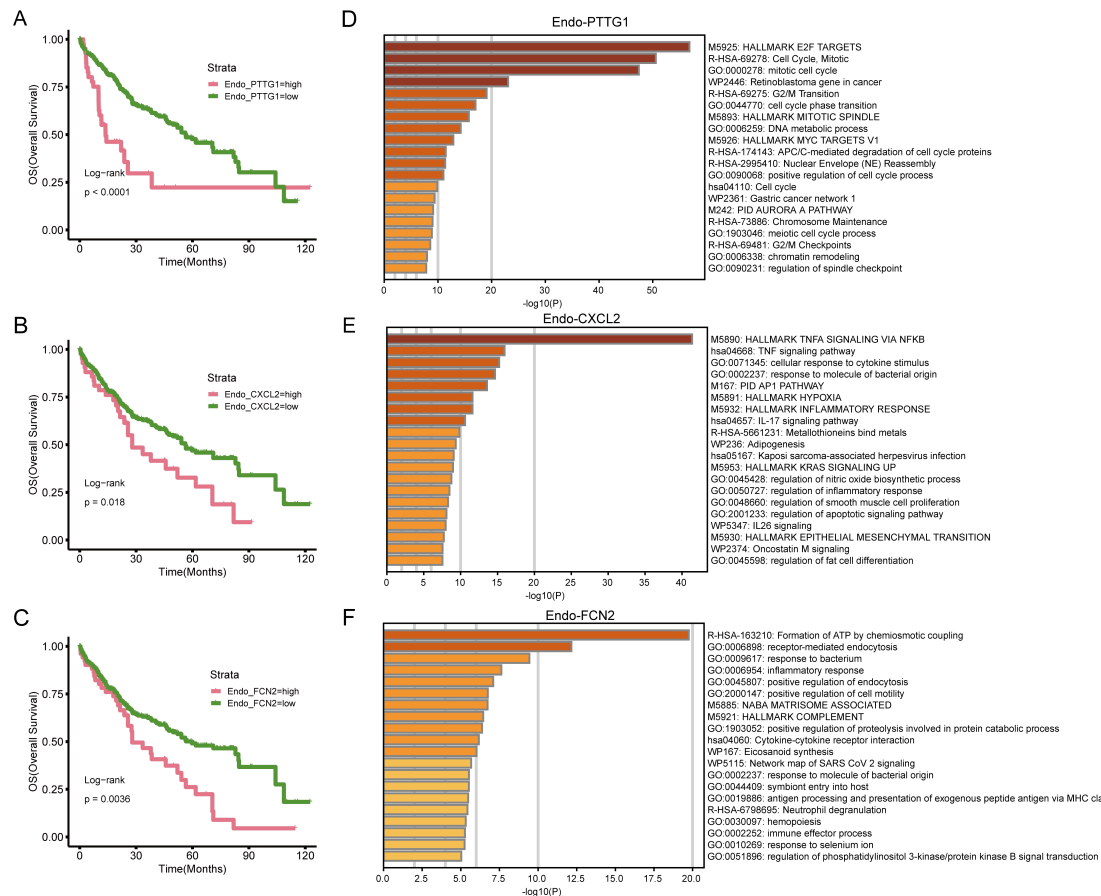


Supplementary Figure 6. Characterization of myeloid cell subsets and macrophage functional profiles

(A) Dot plot showing canonical marker expression across six major myeloid cell types (macrophages, classical and nonclassical monocytes, cDC1, cDC2, and mast cells).

(B) Dot plot showing specific marker gene expression across macrophage subsets.

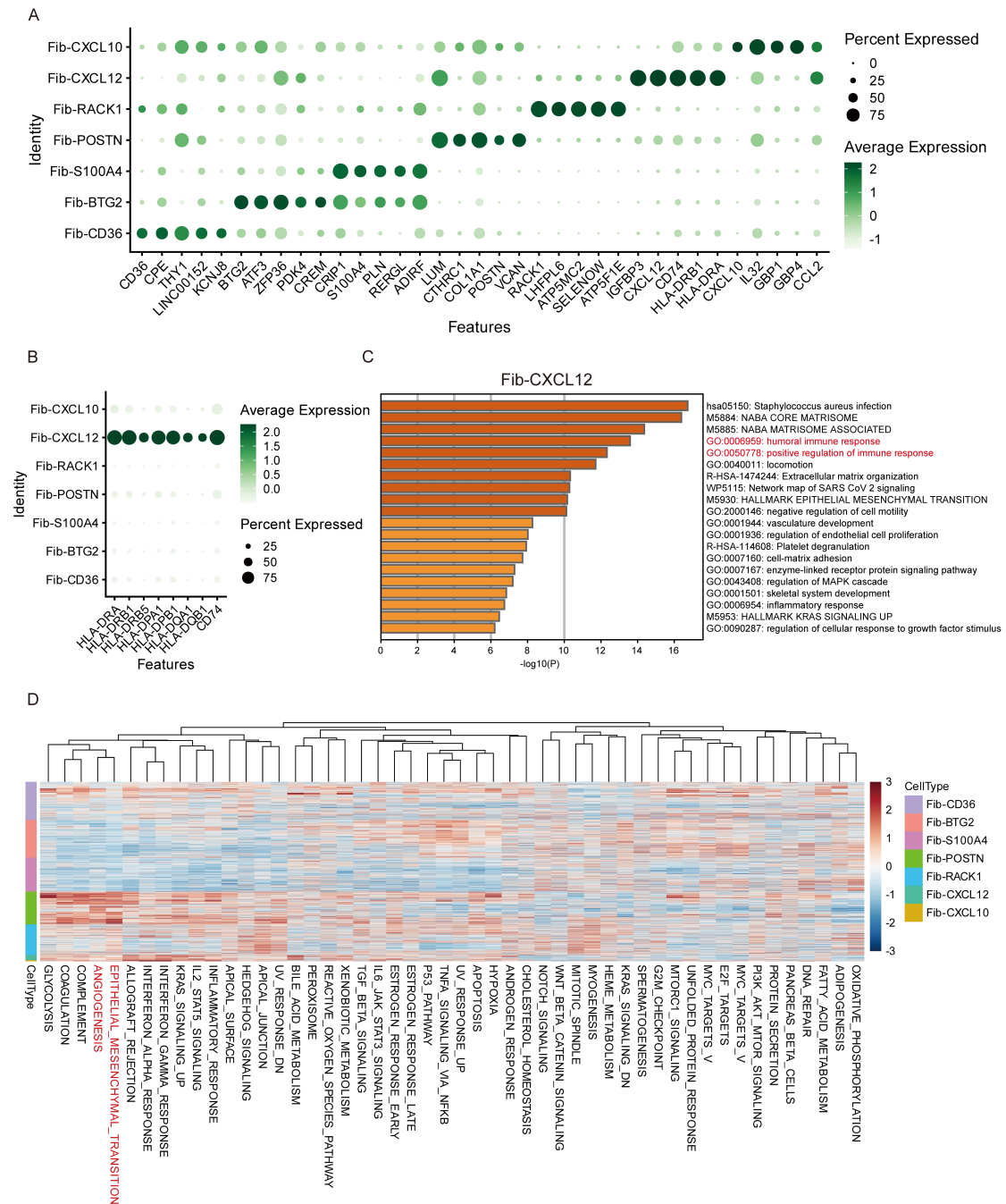
(C-F) GO enrichment analysis of macrophage subsets: (C) Macro-CLEC10A, (D) Macro-C1QC, (E) Macro-FN1, and (F) Macro-AREG.



Supplementary Figure 7. Prognostic endothelial subsets and their functional characterization

(A-C) Kaplan-Meier survival curves showing that high expression of risk-associated endothelial subsets correlates with poor overall survival in TCGA-LIHC cohort: Endo-PTTG1 (A), Endo-CXCL2 (B), Endo-FCN2 (C).

(D-F) Pathway enrichment analysis of risk-associated endothelial subsets: (D) Endo-PTTG1, (E) Endo-CXCL2, and Endo-FCN2 (F).



Supplementary Figure 8. Characterization of fibroblast subsets

(A) Dot plot showing representative marker gene expression across fibroblast subsets.

(B) Dot plot showing high expression of HLA family genes and CD74 in Fib-CXCL12, indicating antigen-presenting cancer-associated fibroblast characteristics.

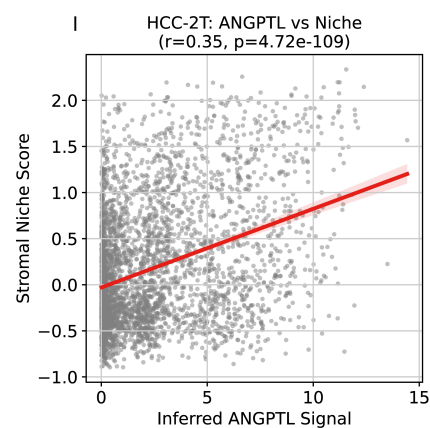
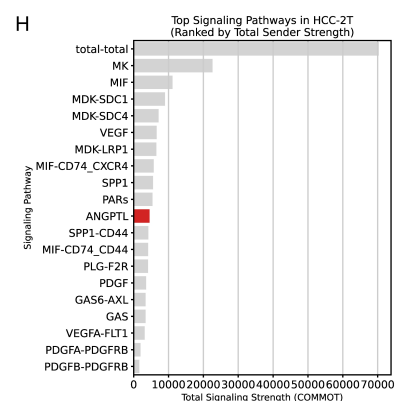
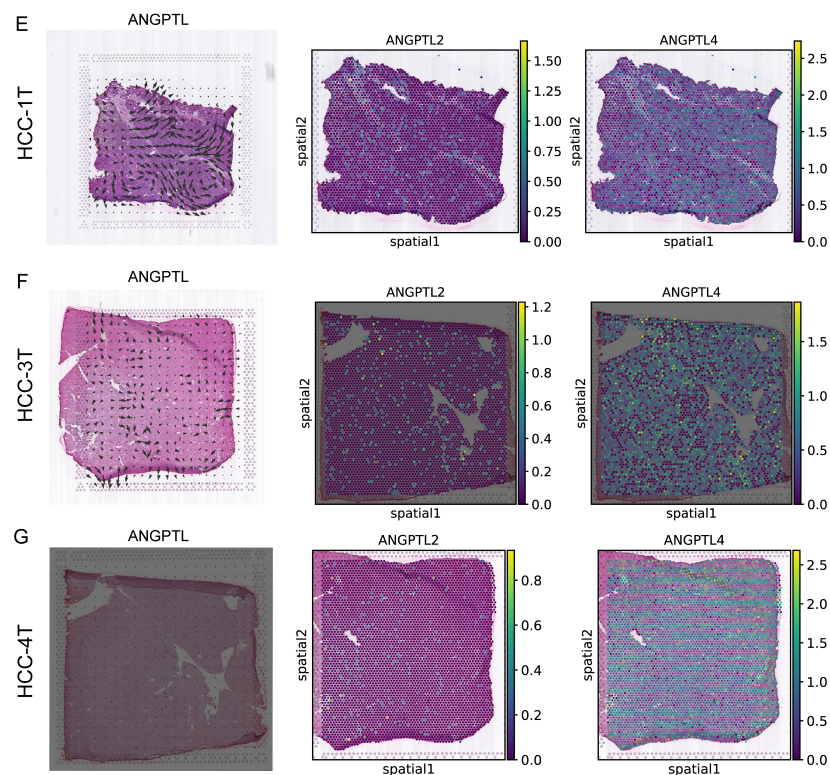
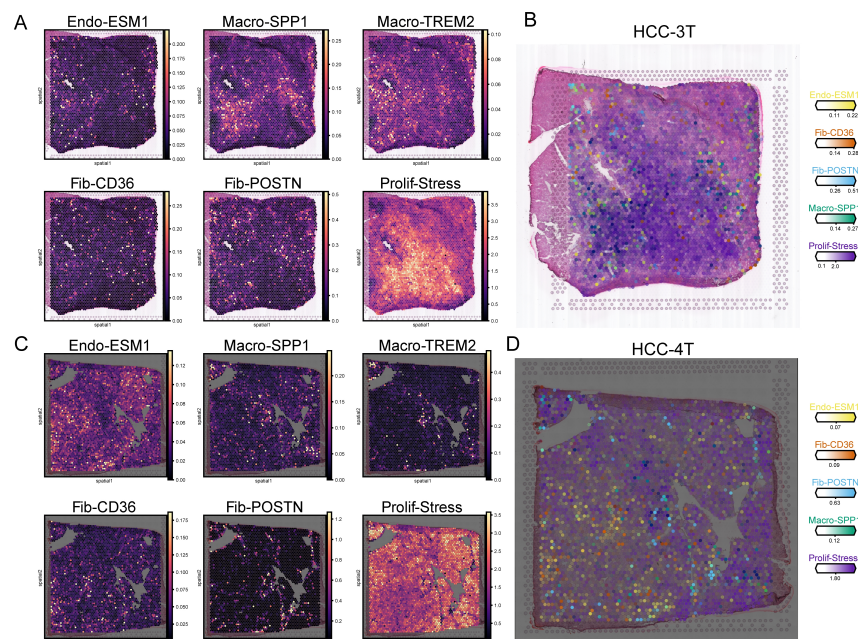
(C) Pathway enrichment analysis of Fib-CXCL12 showing enrichment in humoral immune response and positive regulation of immune response.

(D) Heatmap showing Hallmark gene set scores across fibroblast subsets.

(A-B) Global interaction mapping between major cell types in primary tumor and PVTT/MLN: (A) interaction strength (weight); (B) interaction number.

(C) Heatmaps displaying subset-level interaction numbers in primary tumor (left) and PVTT/MLN (right).

(D) Heatmaps displaying subset-level interaction strengths in primary tumor (left) and PVTT/MLN (right).



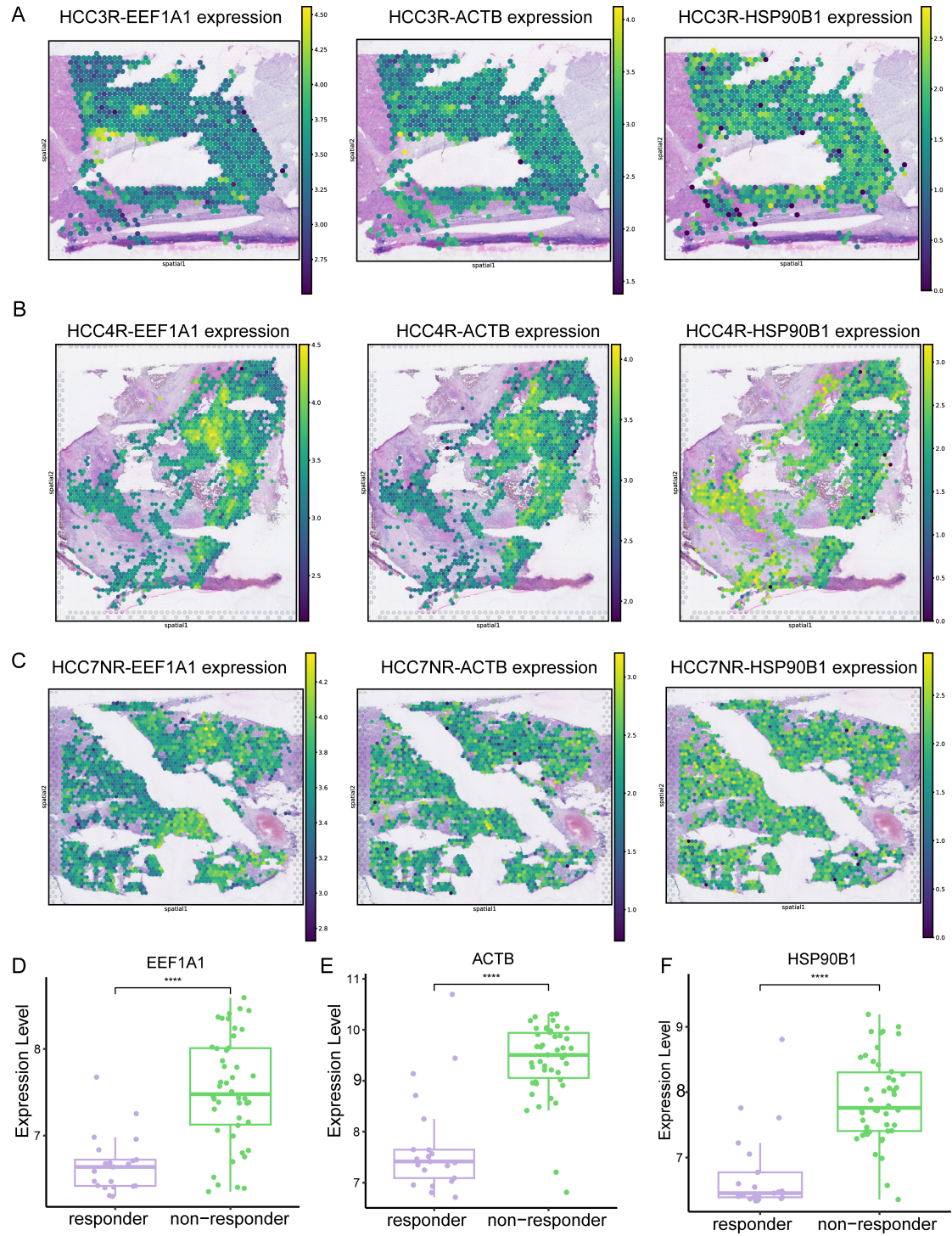
Supplementary Figure 10. Spatial transcriptomics analysis of HCC samples and ANGPTL signaling

(A-D) Cell2location spatial deconvolution of HCC-3T and HCC-4T samples: (A, C) individual spatial distribution of Endo-ESM1, Macro-SPP1, Macro-TREM2, Fib-CD36, Fib-POSTN, and Prolif-Stress populations; (B, D) composite spatial maps showing co-localization patterns.

(E-G) Spatial expression of ANGPTL signaling ligands in HCC-1T (E), HCC-3T (F), and HCC-4T (G). Left panels show ANGPTL signals; right panels display spatial expression of ANGPTL2 and ANGPTL4.

(H) Ranking of top signaling pathways in HCC-2T based on total sender strength inferred by COMMOT, identifying ANGPTL as a prominent signaling axis within the tumor microenvironment.

(I) Quantitative spot-level correlation analysis confirming a significant positive association between the inferred ANGPTL signaling activity and the stromal niche score in HCC-2T.



Supplementary Figure 11. Spatial expression patterns and differential expression analysis of candidate genes

(A-C) Spatial expression of EEF1A1, ACTB, and HSP90B1 in cabozantinib and nivolumab-treated HCC samples: (A) HCC3R, (B) HCC4R, and (C) HCC7NR.

(D-F) Differential expression analysis in the sorafenib-treated cohort: (D) EEF1A1, (E) ACTB, and (F) HSP90B1 expression levels comparing responders and non-responders.