Supplementary Information

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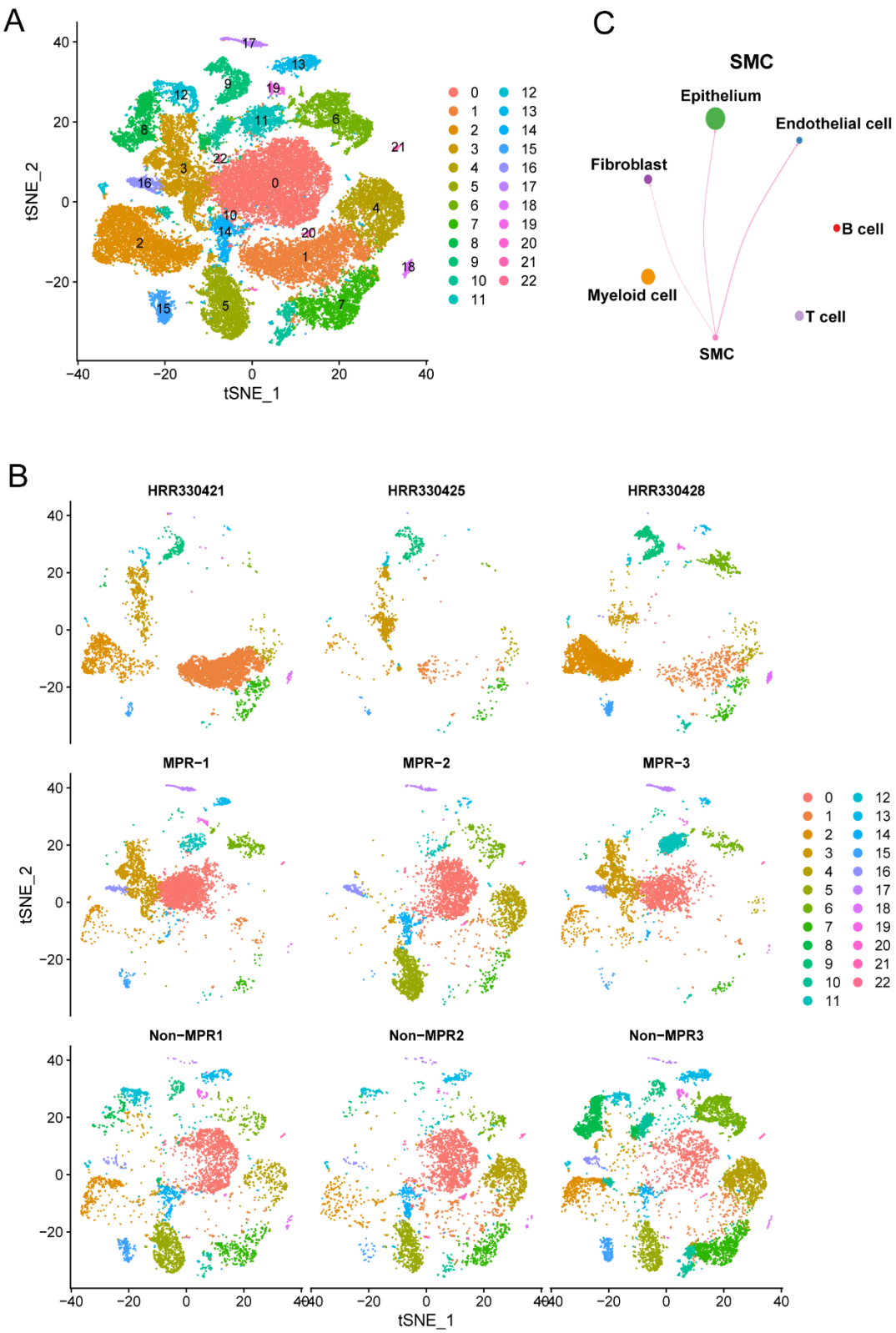

Figure S1. Single-cell clusters and interaction network.

(A) tSNE plot of all cells color-coded into 23 clusters.

(B) tSNE plot of all cells color-coded from TN, MPR and Non-MPR patients.

(C) Shell map of the interactions among SMC cells and other cell types.

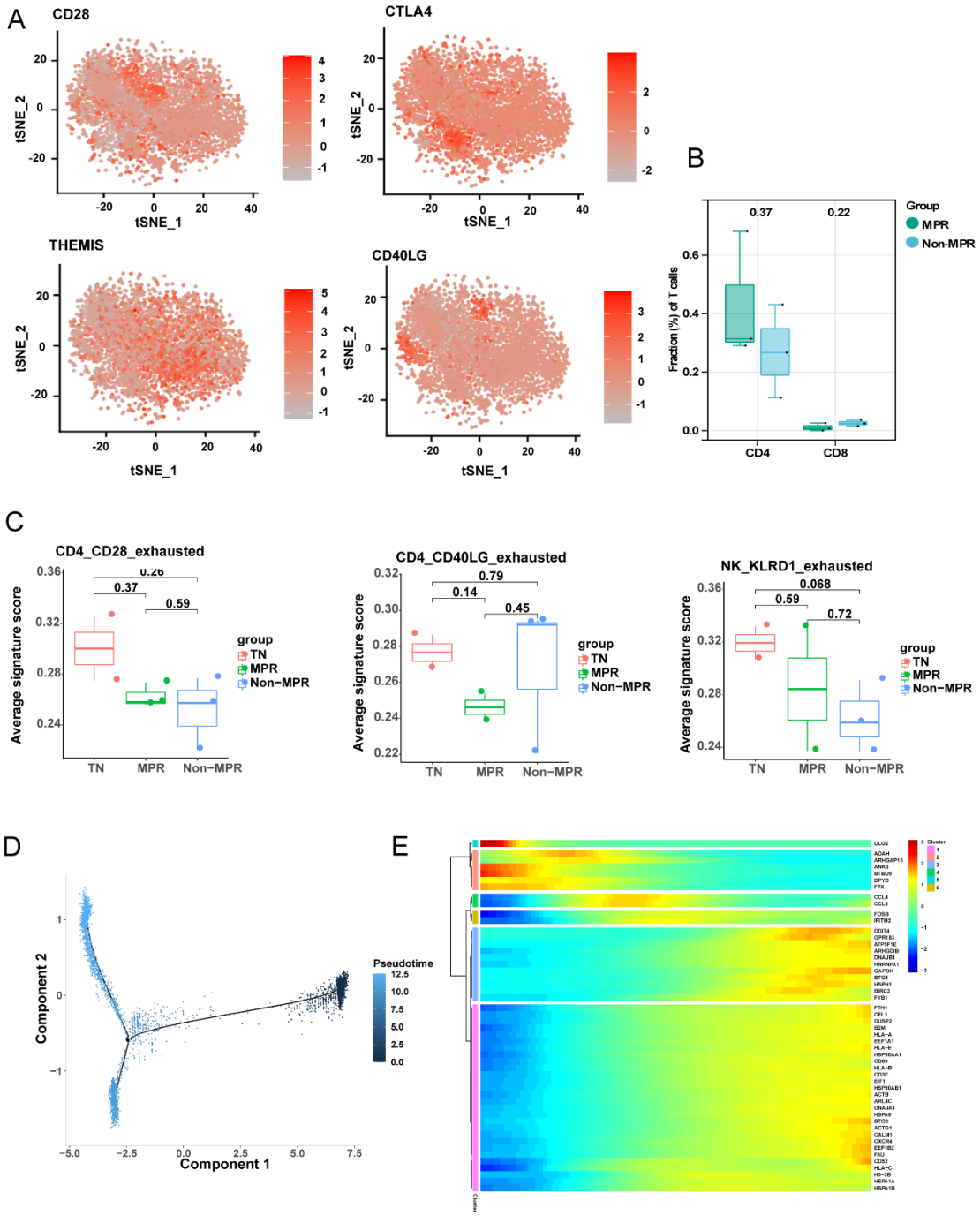

Figure S2. Marker genes of T cells and trajectory analysis.

(A) tSNE plot of normalized expression of T cells marker genes among clusters.

(B) Box plot of fractions of $CD4^+$ T and $CD8^+$ T cells in TN (n = 3), MPR (n = 3), and Non-MPR (n = 3) patients. The middle line represents the median, the lower and upper lines represent the 25th and 75th percentiles, respectively, with each point corresponding to one sample. t test was used for data analysis.

(C) Box plots of the average exhausted signature scores for CD4_CD28, CD4_CD40LG, and NK_KLRD1 cells in TN (n = 3), MPR (n =3), and Non-MPR (n =

3) patients.

(D) The developmental trajectory of T cells inferred by Monocle2. The right cells were the roots of trajectory, and differentiated into left cells.

(E) Heat map of the top50 differential genes in T_THEMIS cells along the pseudo-time.

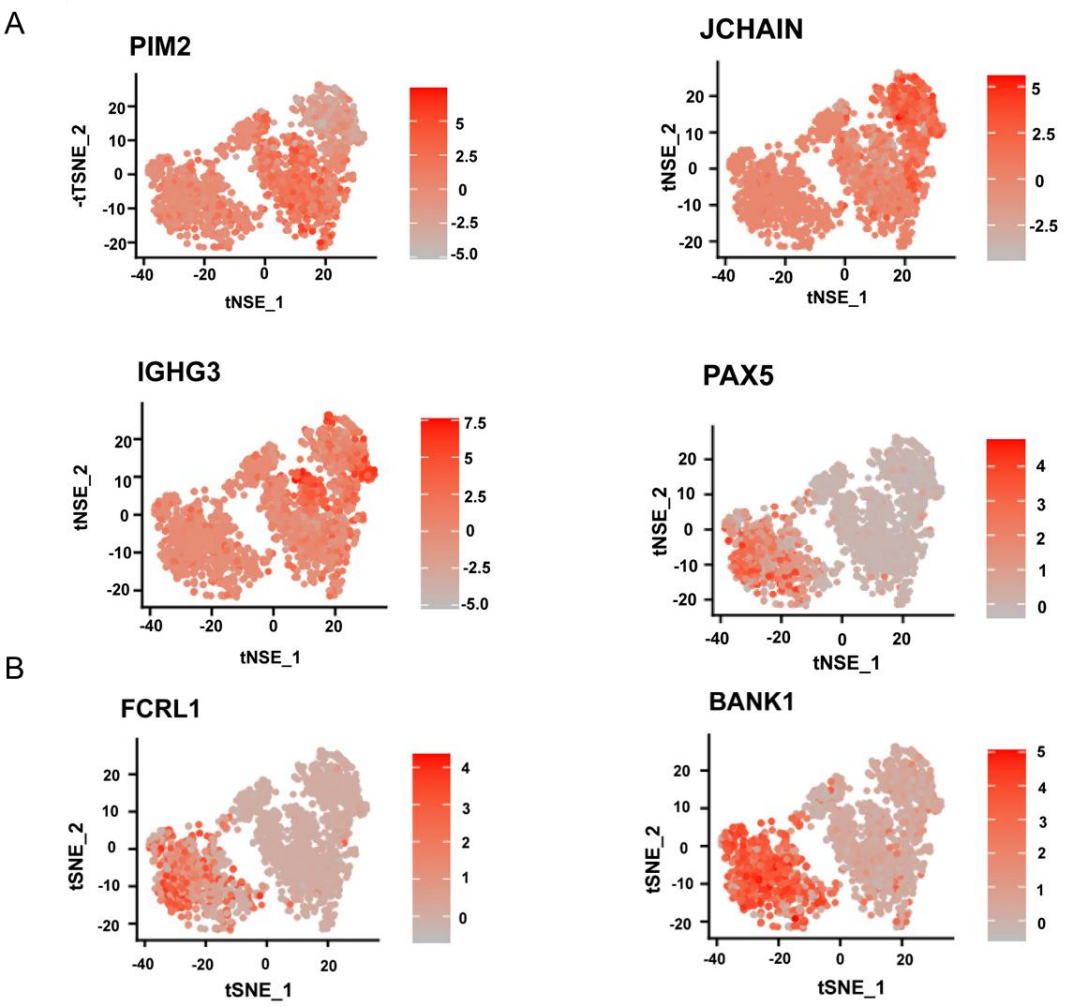

Figure S3. Marker genes of B cells.

(A) tSNE plot of marker genes of B cells among clusters.

(B) tSNE plot of normalized expression of marker genes of B4_PAX5 memory B cells.

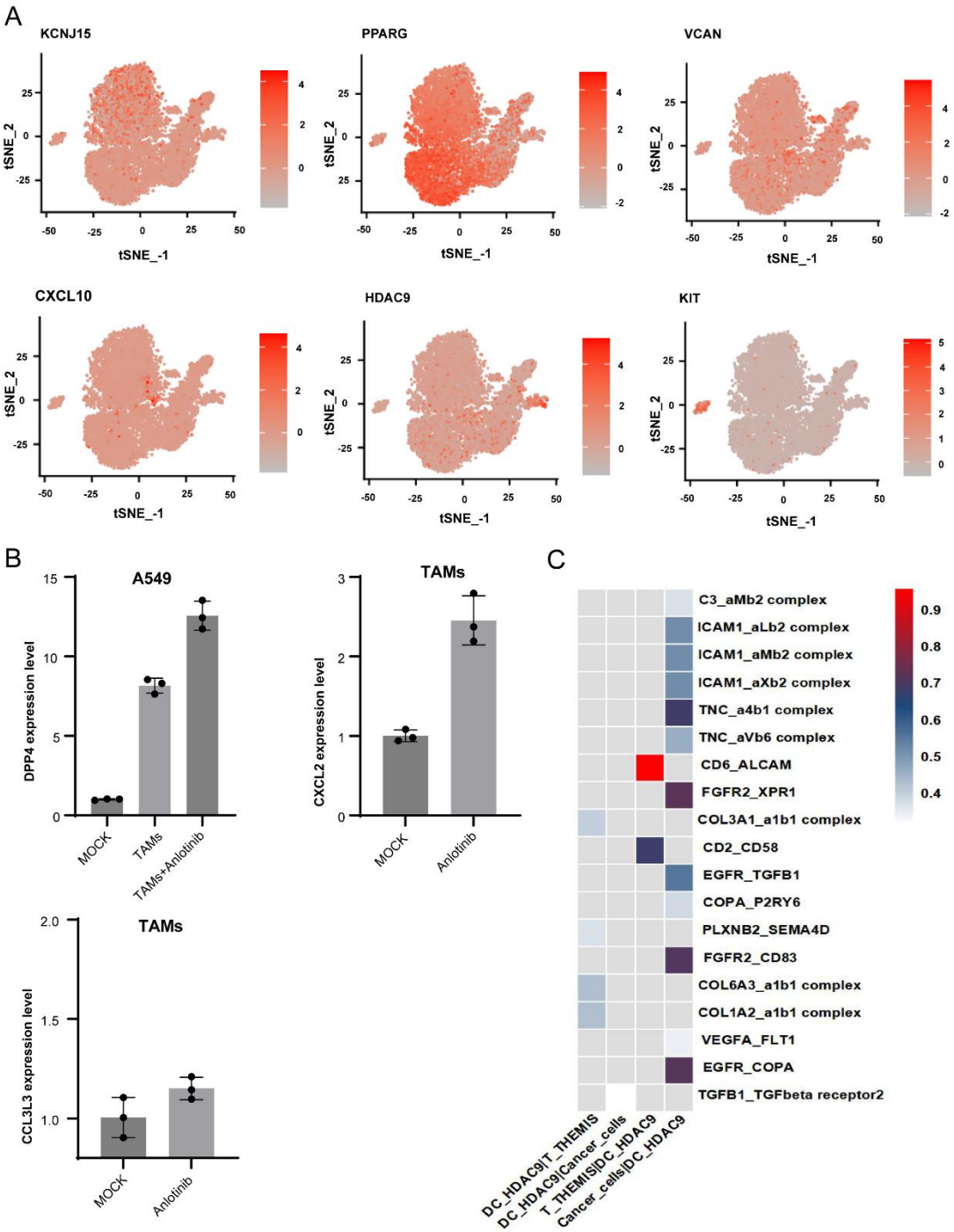

Figure S4. Marker genes of myeloid cells and cell-interaction analysis.

(A) tSNE plot of normalized expression of myeloid marker genes among clusters.

(B) qPCR was used to detect the expression of DPP4 in A549 cells and CXCL2 and CCL3L3 in TAMs in the co-culture system treated with anlotinib (20 μM).

(C) Heat map of the interactions between DC_HDAC9 and T_THEMIS cells.

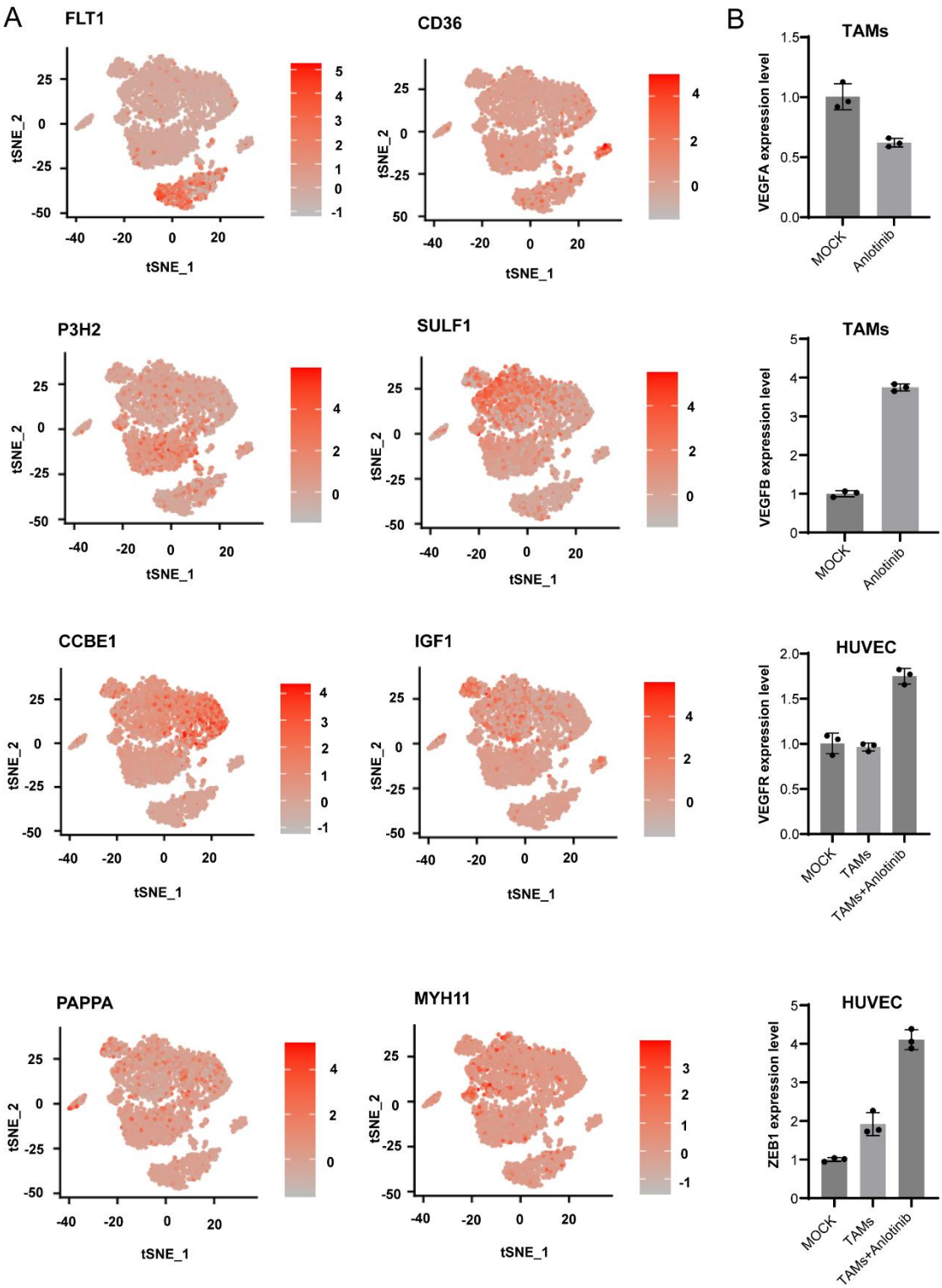

Figure S5. Marker genes of stromal cells.

(A) tSNE plot of normalized expression of marker genes of Endo1_FLT1, Endo2_CD36, Fib1_P3H2, Fib2_SULF1, Fib3_CCBE1, Fib4_IGF1, Fib5_PAPPA, and SMC_MYH11 cells.

(B) qPCR was used to detect the expression of VEGFA and VEGFB in TAMs and VEGFR and ZEB1 in HUVEC in the co-culture system treated with anlotinib (20 μM).

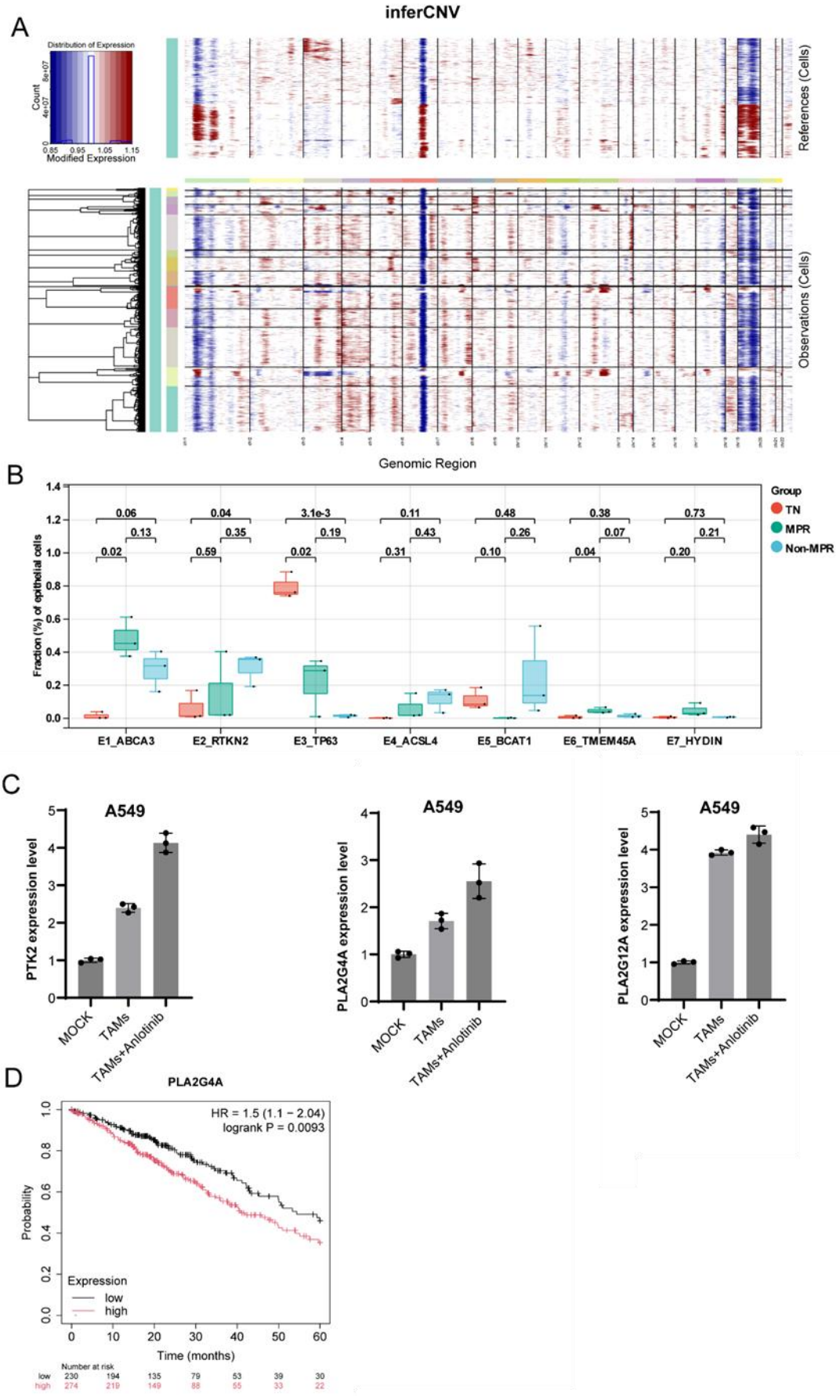
A
inferCNV
Distribution of Expression
Count
Modified Expression
References (Cells)
Observations (Cells)
Genomic Region
B
Fraction (%) of epithelial cells
Group
TN
MPR
Non-MPR
0.06
0.13
0.02
0.04
0.35
0.59
3.1e-3
0.19
0.02
0.11
0.43
0.31
0.48
0.26
0.10
0.38
0.07
0.04
0.73
0.21
0.20
E1_ABCA3
E2_RTKN2
E3_TP63
E4_ACSL4
E5_BCAT1
E6_TMEM45A
E7_HYDIN
C
A549
PTK2 expression level
PLA2G4A expression level
PLA2G12A expression level
MOCK
TAMs
TAMs+Anlotinib
D
PLA2G4A
HR = 1.5 (1.1 − 2.04)
logrank P = 0.0093
Probability
Expression
low
high
Time (months)
Number at risk
low 230 194 135 79 53 39 30
high 274 219 149 88 55 33 22

Figure S6. InferCNV analysis and fractions of epithelial cells.

(A) Heat map of identification of malignant cells with myeloid cells as control group by inferCNV.

(B) Box plot of fractions of epithelial cells in TN (n = 3), MPR (n = 3), and Non-MPR (n = 3) patients. The middle line represents the median, the lower and upper lines represent the 25th and 75th percentiles, respectively, with each point corresponding to one sample. t test was used for data analysis.

(C) qPCR was used to detect the expression of PTK2, PLA2G4A and PLA2G12A in A549 cells in the co-culture system treated with anlotinib (20 μM).

(D) Overall survival according to PLA2G4A expression level by Kaplan–Meier in TCGA database.