

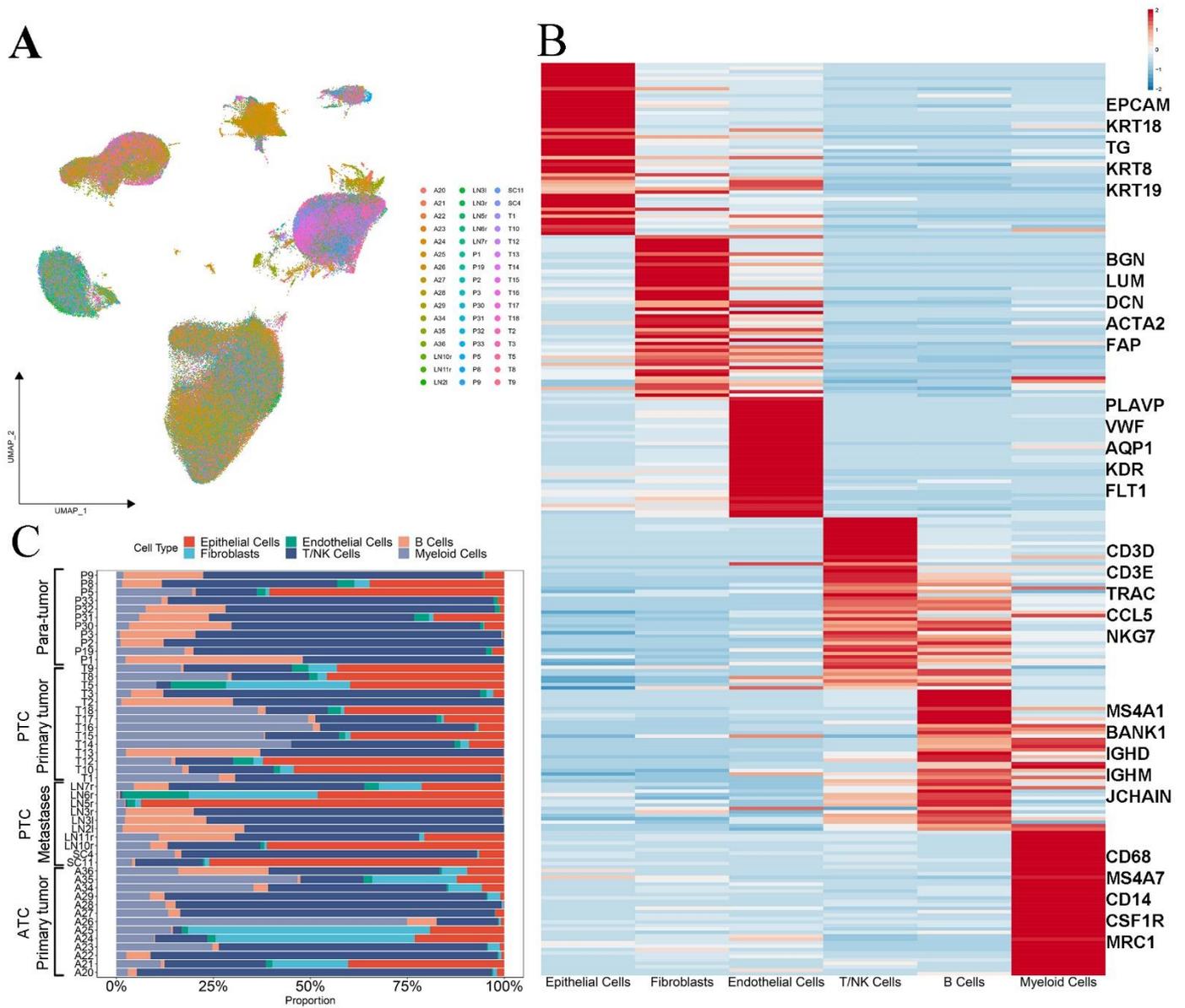
Supplemental Figures

Supplemental Figure 1. The cellular landscape of PTC and ATC.

A. UMAP plot of qualified 226066 cells colored by sample names.

B. Normalized expression of top 50 upregulated genes for each major cell lineage.

C. Bar plot depicted the proportion of each major cell lineage in 48 samples.

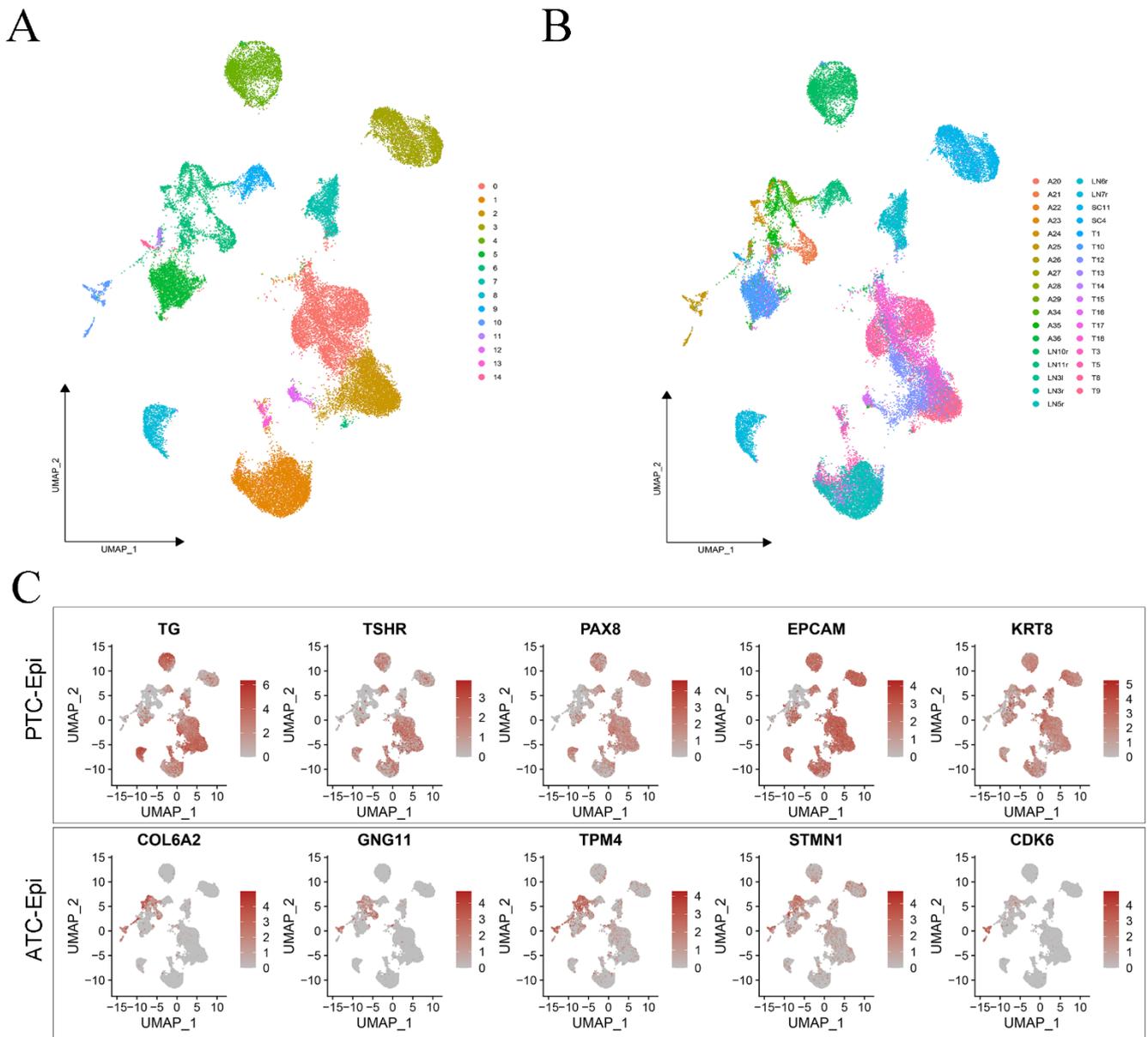


Supplemental Figure 2. Two major subgroups of epithelial cells from PTC and ATC primary tumor samples.

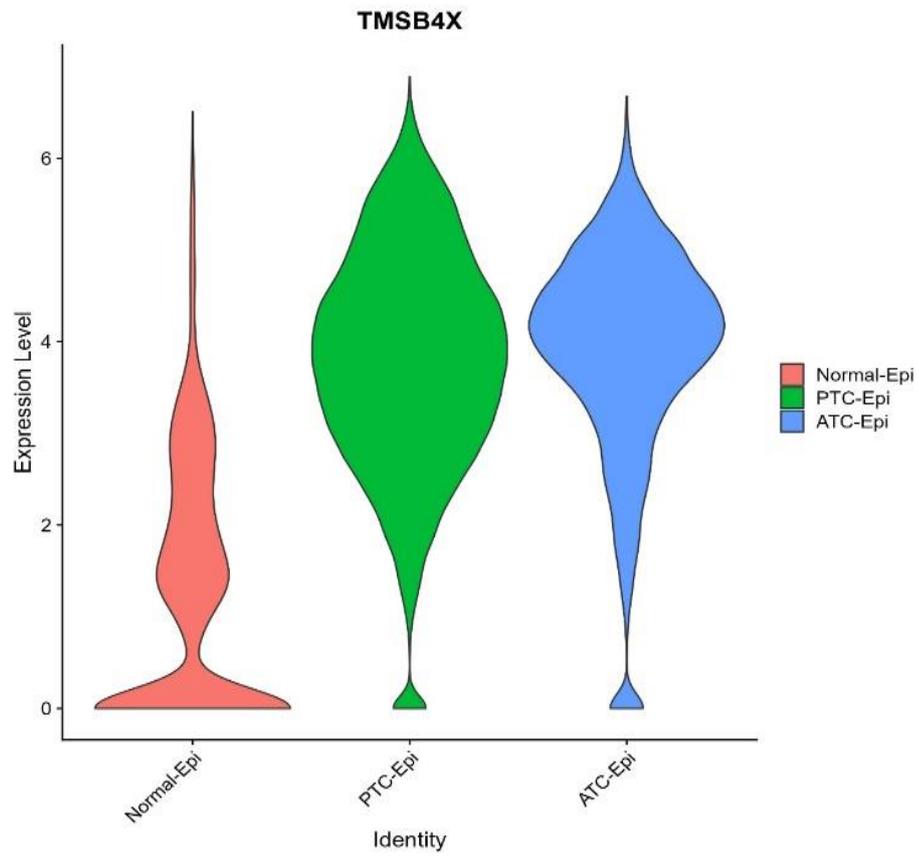
A. Unsupervised clustering analysis revealed 15 clusters of epithelial cells.

B. UMAP plot of identified epithelial cells colored by sample names.

C. Feature plots showed maker genes for PTC-Epi and ATC-Epi.



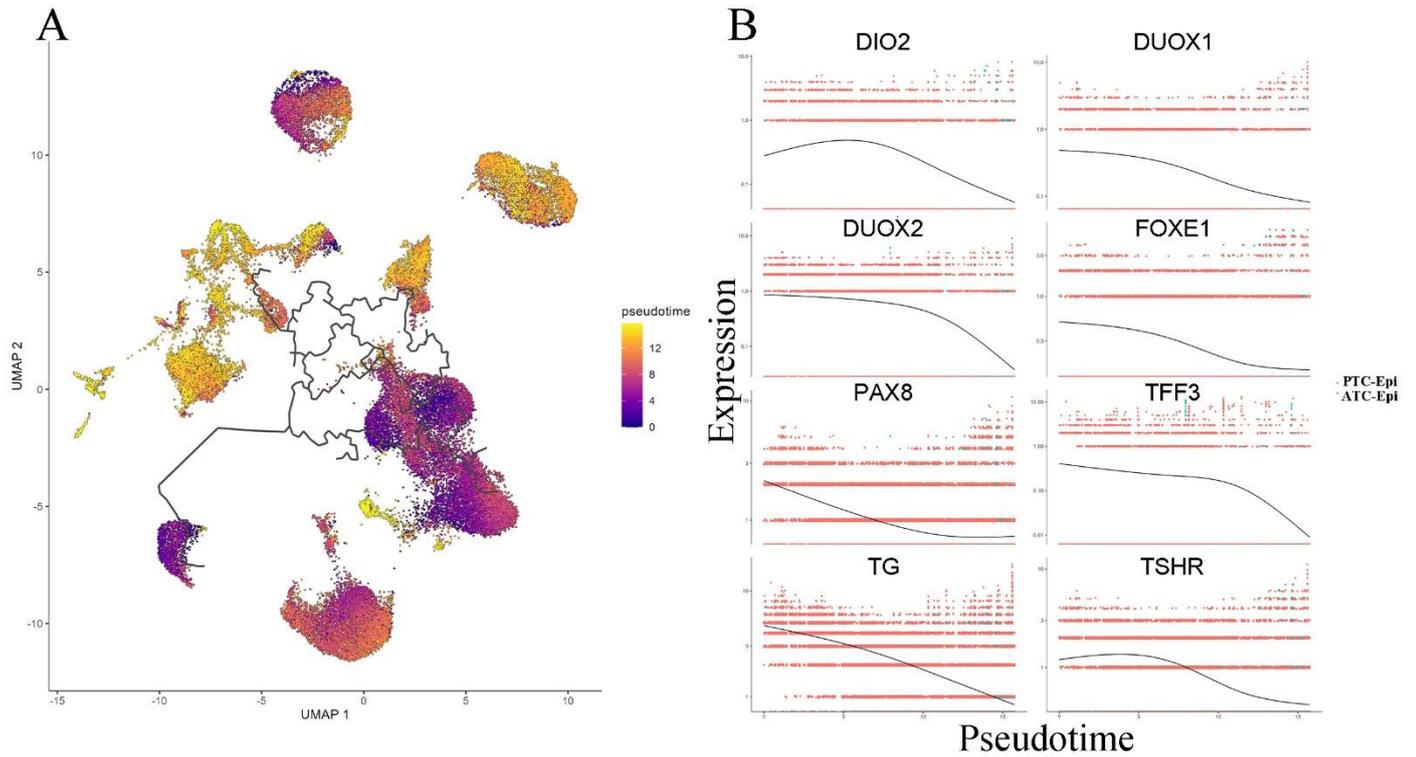
Supplemental Figure 3. TMSB4X, a potential shared biomarker for ATC-Epis and PTC-Epis.



Supplemental Figure 4. Trajectory analysis of the epithelial lineage.

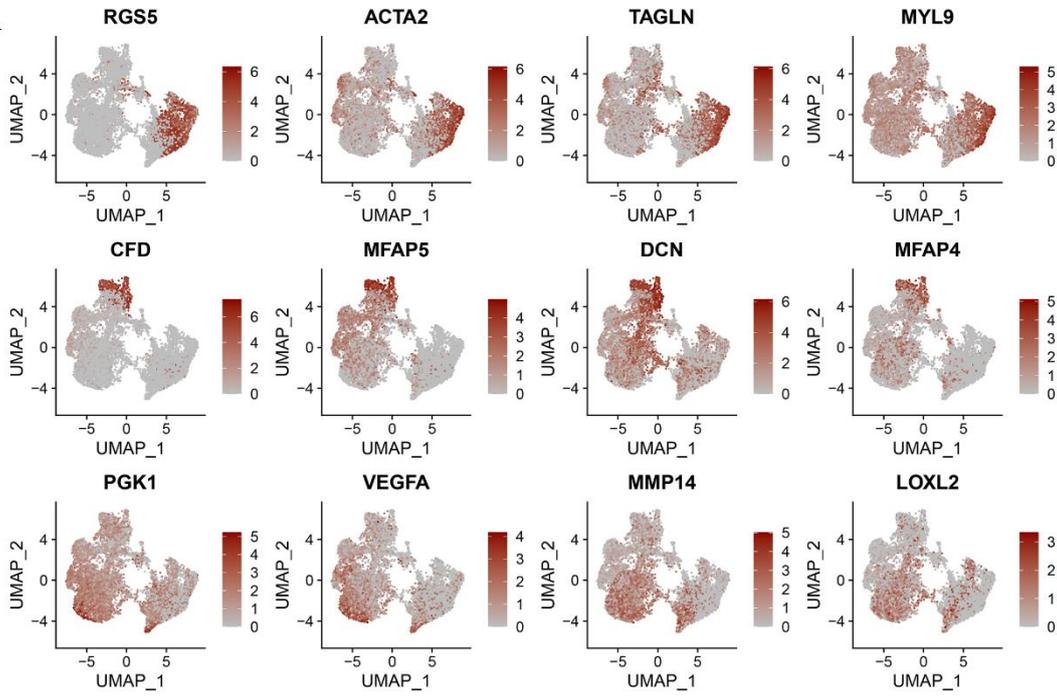
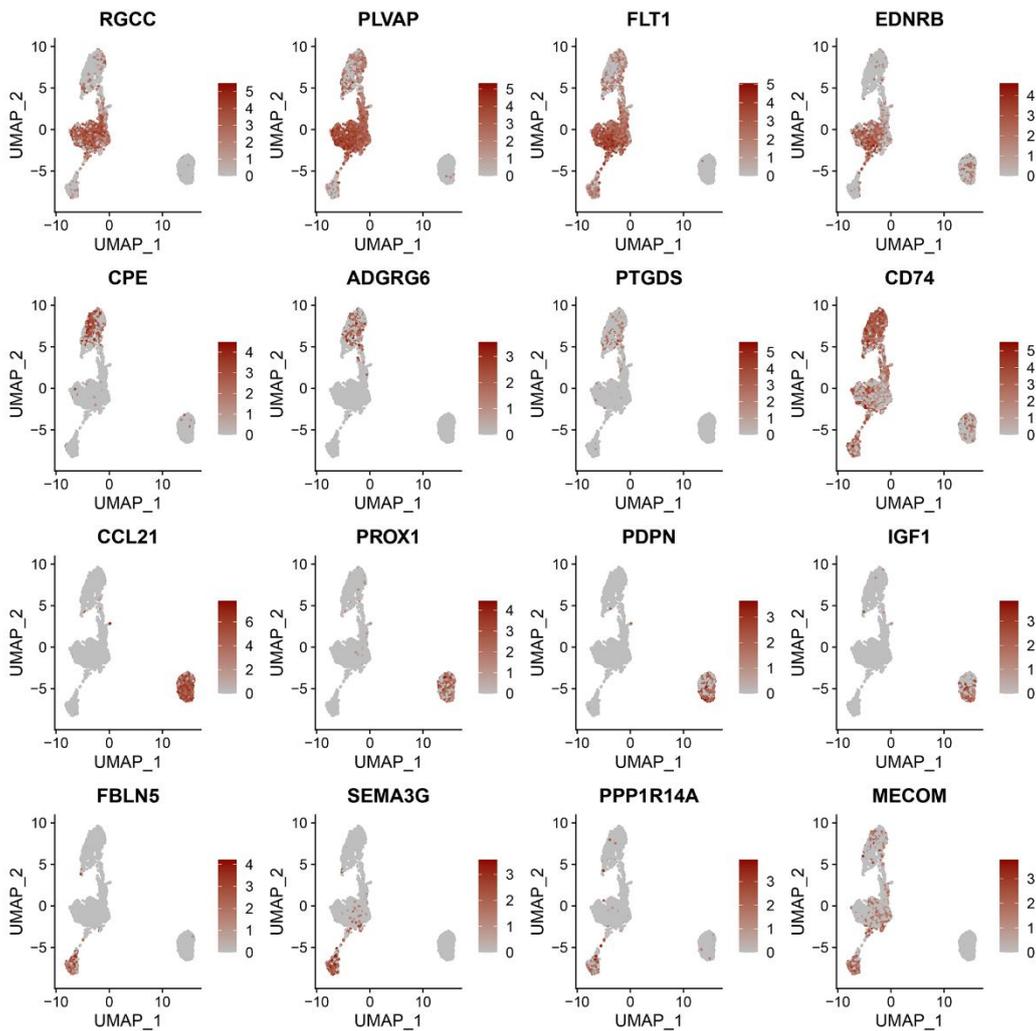
A. UMAP plot of epithelial cells colored by pseudotime with potential trajectory.

B. Negative correlation between the level of thyroid differentiated markers expression and pseudotime.



Supplemental Figure 5. Feature plots of markers genes for each subcluster of CAFs(A)

and ECs(B).

A**B**

Supplemental Figure 7. Different pattern of T/NK cells between ATC and PTC.

A. Heatmap of the top biomarkers for each subcluster of T/NK cells.

B. Bar plots demonstrated the percentage of twelve T/NK cell subclusters in different tissues.

C. Boxplots compared the percentage of each T/NK cell subcluster between ATC and PTC primary tumors. Wilcoxon test: *: $p < 0.05$; **: $p < 0.01$, ***: $p < 0.001$; ns: $p > 0.05$

D. Potential evolutionary trajectory of CD8 T cells colored by pseudotime (left) and cell identities (right).

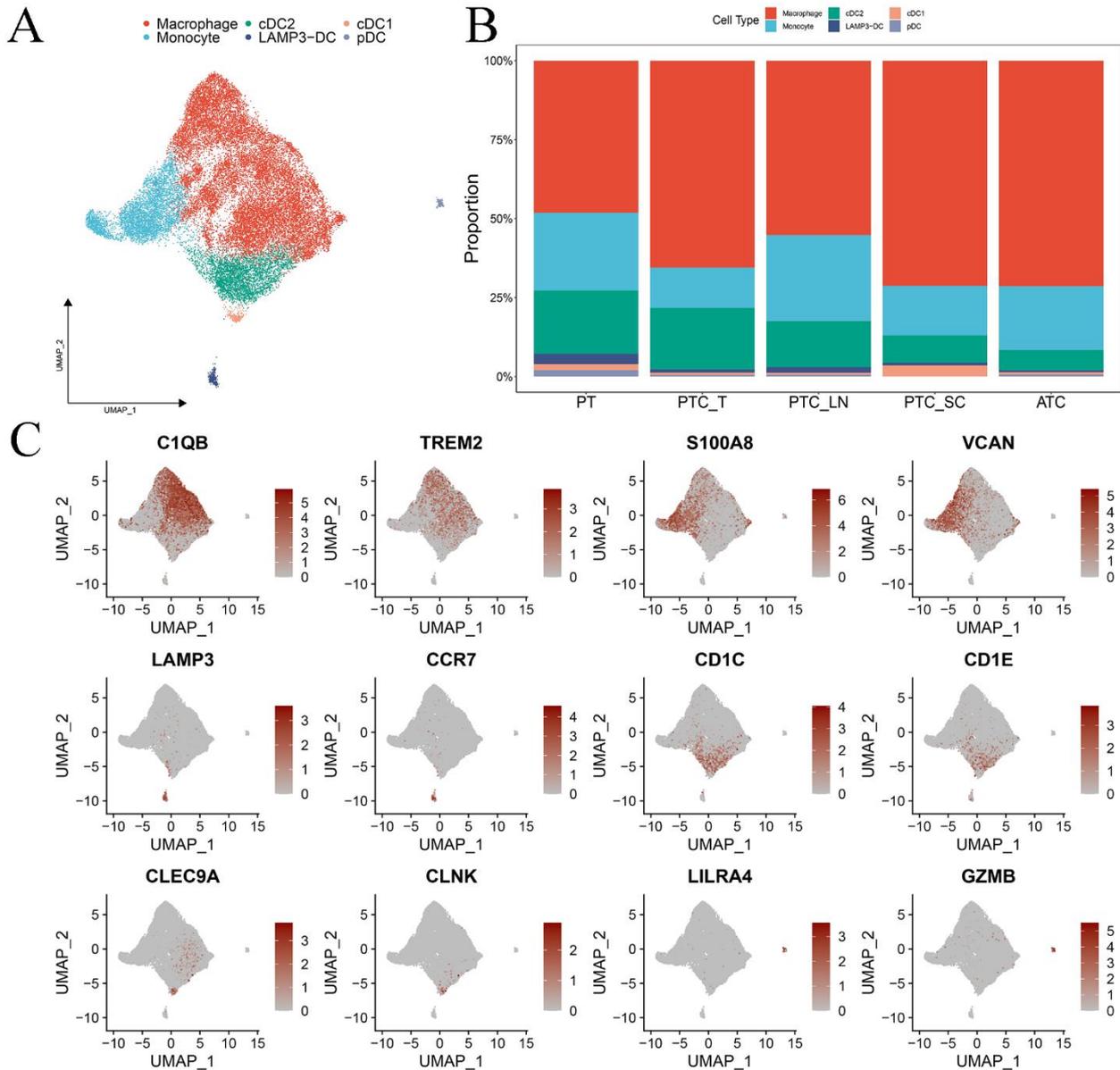
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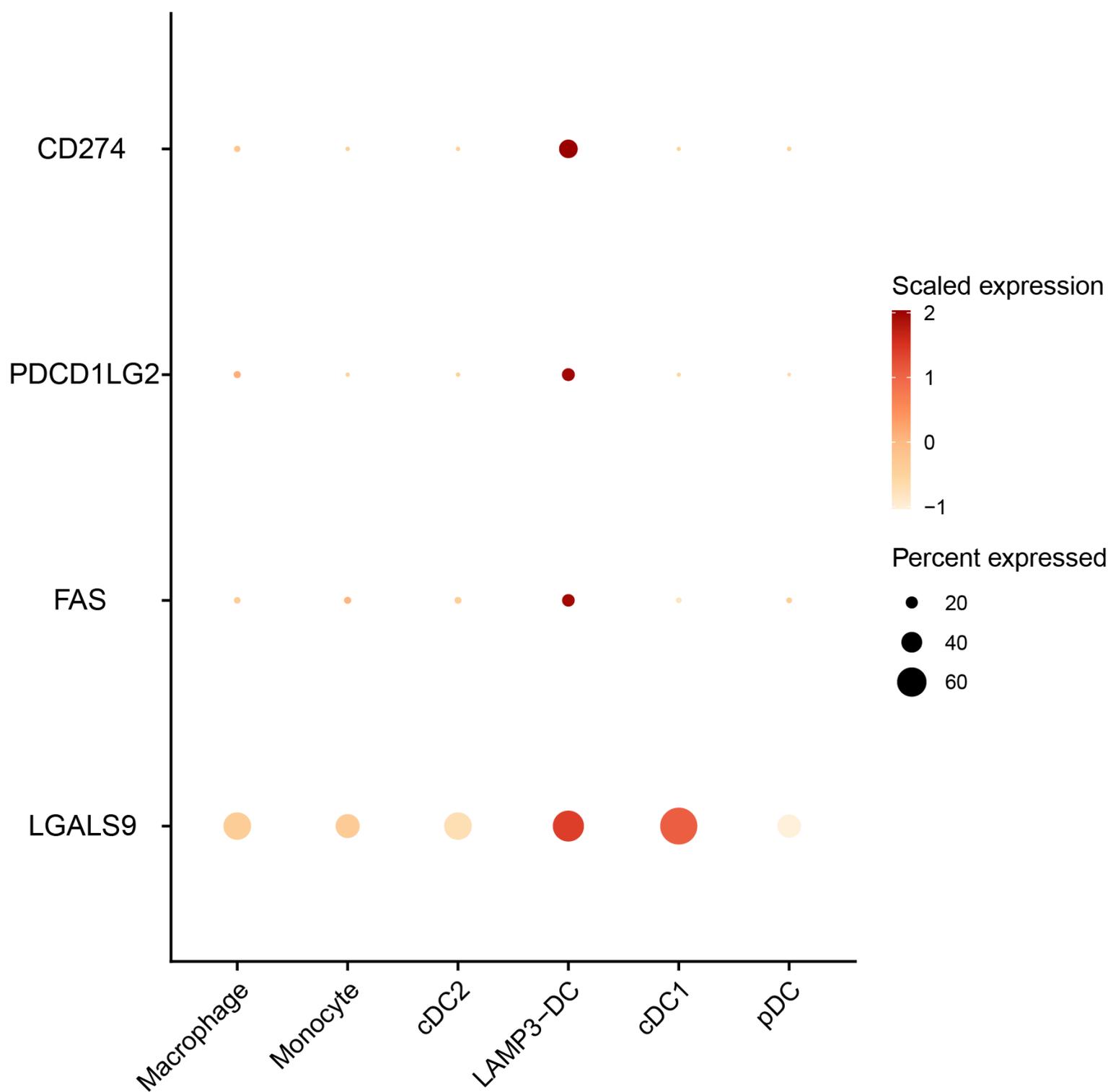
Supplemental Figure 8. Refined classification of myeloid cells.

A. UMAP plot of six myeloid cell subclusters.

B. Bar plots demonstrated the percentage of myeloid cell subclusters in different tissues.

C. Feature plots showed maker genes for myeloid cell subclusters



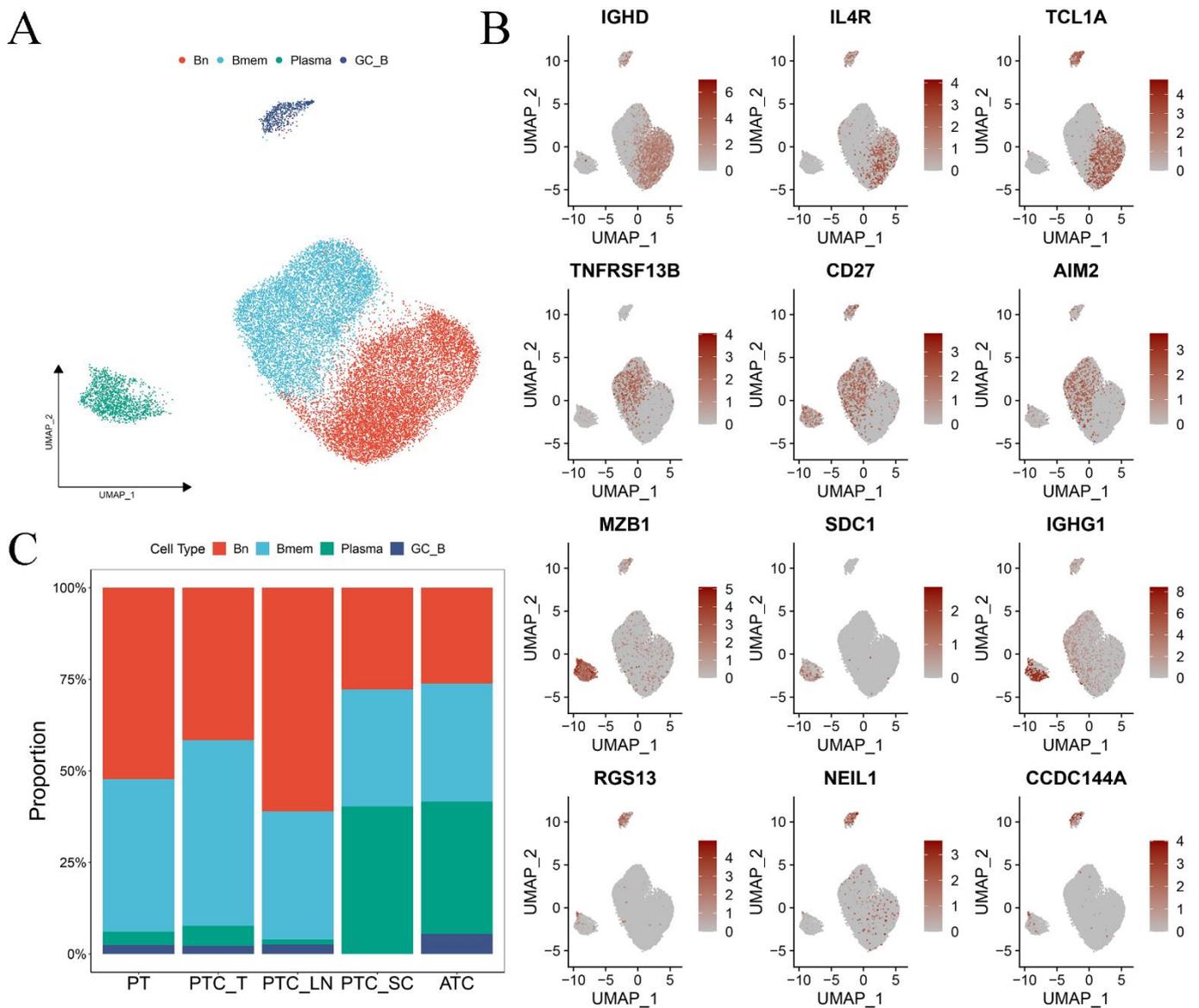
Supplemental Figure 9. Immune inhibitory molecules were upregulated in LAMP3-DC.

Supplemental Figure 10. The landscape of B lymphocytes in ATC and PTC

A. UMAP plot of four subclusters of B lymphocytes.

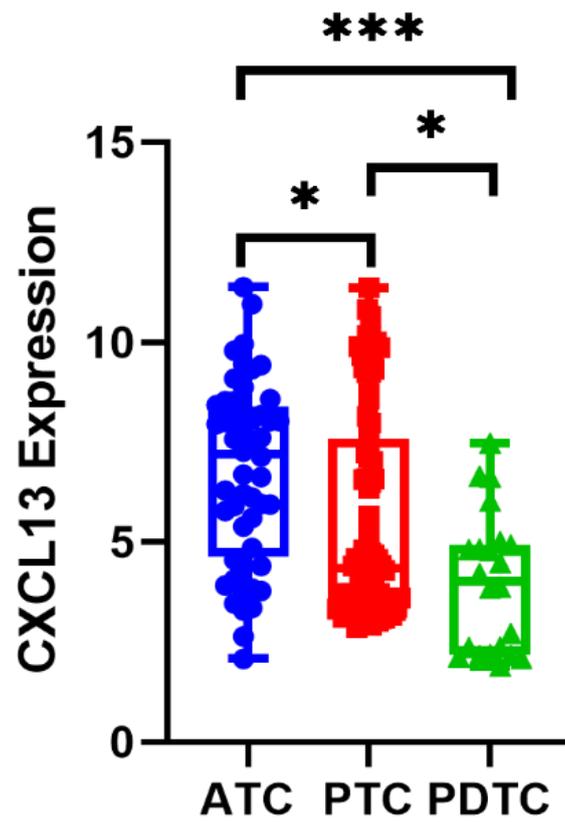
B. Feature plots showed maker genes for B cell subclusters. Bn: Naïve B Cells; Bmem: Memory B Cells; Plasma: Plasma: Plasma Cells; GC_B: Germinal Centre B Cells

C. Bar plots showed the percentage of B cells subclusters in different tissues



Supplemental Figure 11. CXCL13 expression of ATC, PDTC and PTC in the microarray

datasets. Student's t-test: *: $p < 0.05$; **: $p < 0.01$, ***: $p < 0.001$; ns: $p > 0.05$



Supplemental Figure 12. Cell-cell interaction analysis revealed potential key axis for TLS formation in HT.

A. Cell–cell interactions between GC B cells and other cell lineages in HT. A key CXCL12-CXCR4 pair was highlighted with the red box.

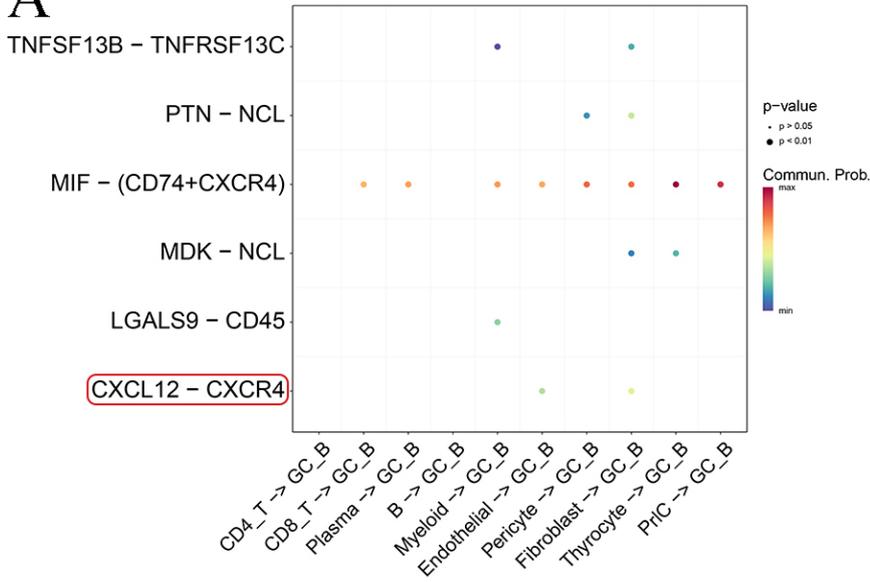
B. Cell–cell interactions between immune cells and stromal cells in HT. A key CXCL12-CXCR4 pair was highlighted with the red box.

C. Dotplot of CXCL12 expression in stromal cells from HT samples and HT-free samples from our own scRNA-seq dataset. HT-No: Samples without Hashimoto’s thyroiditis; HT-Yes: Samples diagnosed with Hashimoto’s thyroiditis

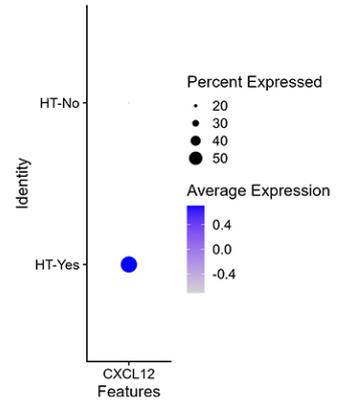
D. Bar plots showed the percentage of B cells subclusters in the integrated scRNA-seq dataset. B cells took a larger percentage in the HT-positive samples than in HT-free samples.

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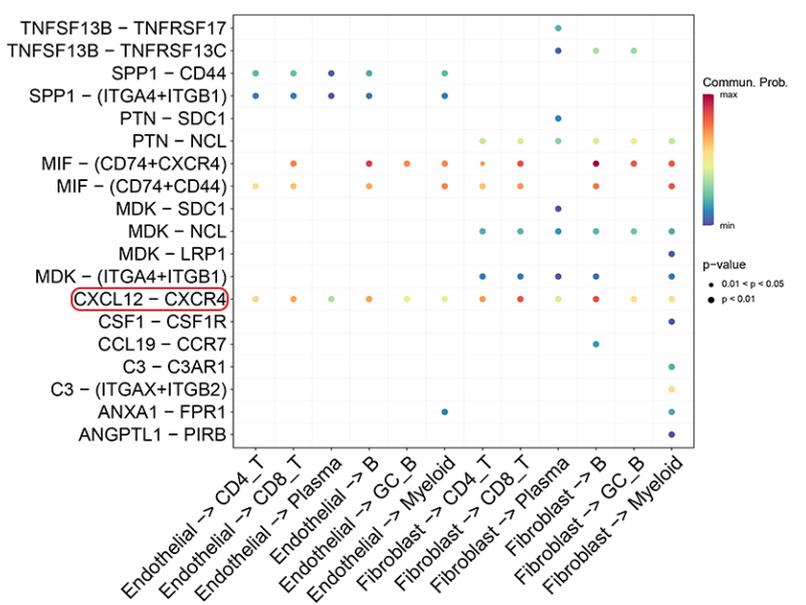
A



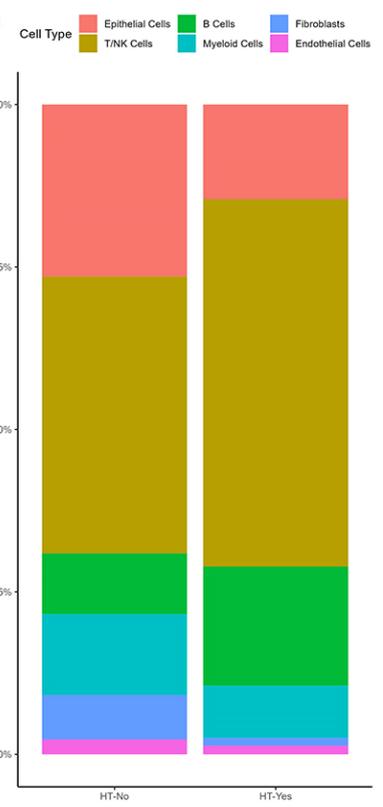
C



B



D



Supplemental Figure 13. Construction of BPC, a murine thyroid cancer cell line

A. Schematic diagram of the development of BPC cell line.

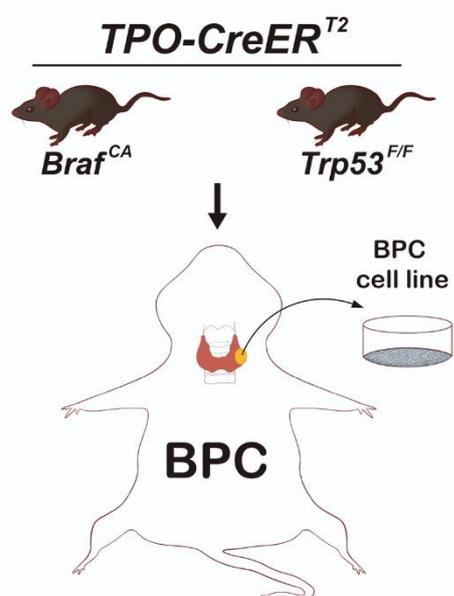
B. Ultrasound image of a BPC mouse's thyroid. The thyroid tumor was circled by the green line.

C. Left: HE image of the primary thyroid tumor from a BPC transgenic mouse (15X); Right: Spotty TTF-1 (A marker of thyroid-specific differentiation) expression in the primary thyroid tumor from a BPC transgenic mouse (15X).

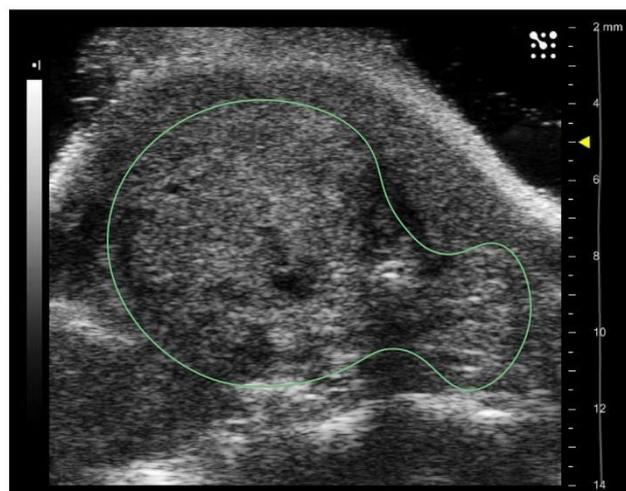
D. Left: HE image of a BPC xenograft (15X); Right: Spotty TTF-1 expression in the BPC xenograft (15X).

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A

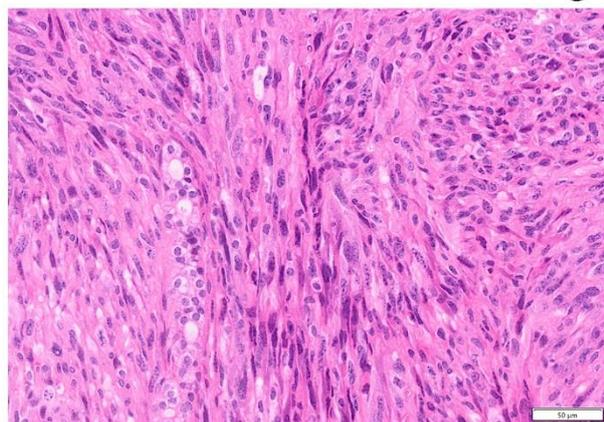


B



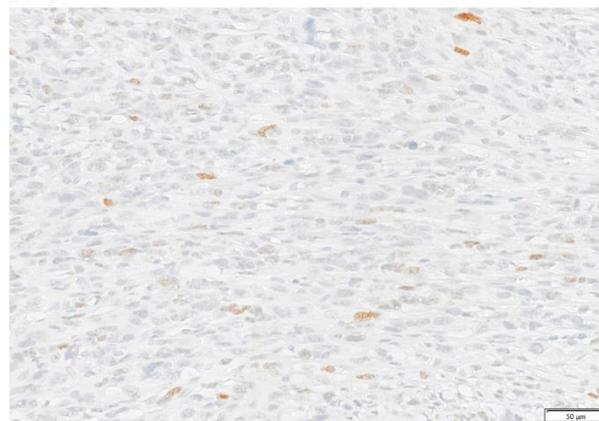
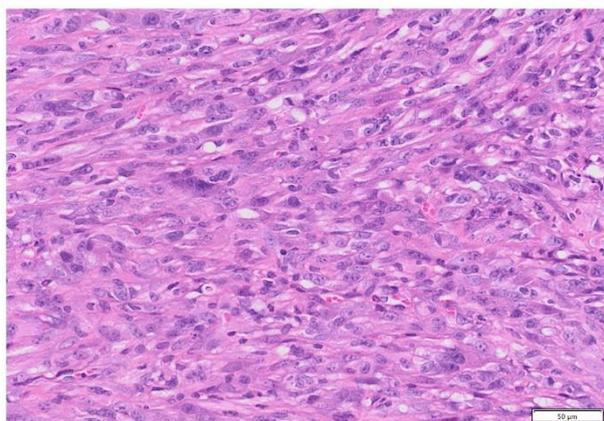
C

Transgenic mouse



D

Allograft



Supplemental Figure 14. Famitinib plus aPD-1 might potentiate anti-tumor action and TLS development in MC38 mouse xenografts.

A. Tumor images of the control group, anti-PD-1 (aPD-1) group and Famitinib plus aPD-1 (aPD-1+ Fami) group of MC38 xenografts.

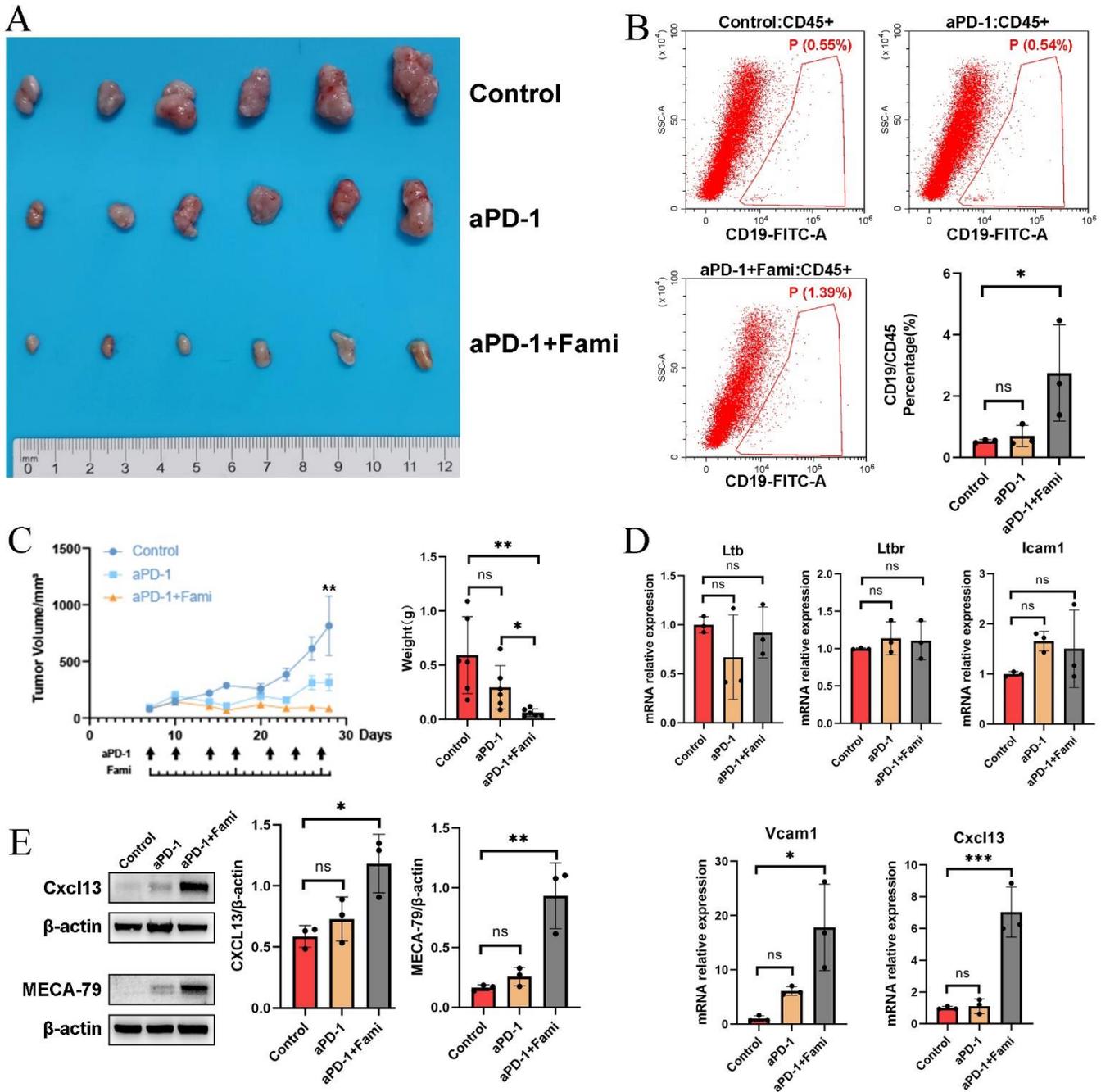
B. Representative flowmetry images of each group of xenografts and the bar plot showed an increase of infiltrated CD19+ B cells in the aPD-1+Fami group

C. Growth curve and weight of control group, anti-PD-1 (aPD-1) group and Famitinib plus aPD-1 (aPD-1+ Fami) group of MC38 xenografts.

D. RT-PCR results indicated that some of the biomarkers related to TLS development were upregulated in the aPD-1+Fami group (*Vcam1* and *Cxcl13*), while *Icam1*, *Ltb*, and *Ltbr* showed no upregulation.

E. WB images and histograms suggested upregulation of *Cxcl13* and MECA-79 in the aPD-1+Fami group. One-way ANOVA or Kruskal-Wallis test: *: $p < 0.05$; **: $p < 0.01$, ***: $p < 0.001$; ns: $p > 0.05$

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Supplemental Figure 15. Feature plots showed that key molecular inducers generally expressed in cells from Famtinib+Camrelizumab-treated A37 patient.

