

Supplementary Information

Uncovering the immune mechanisms underlying the emergence of immunotherapy-induced pneumonitis in lung cancer patients

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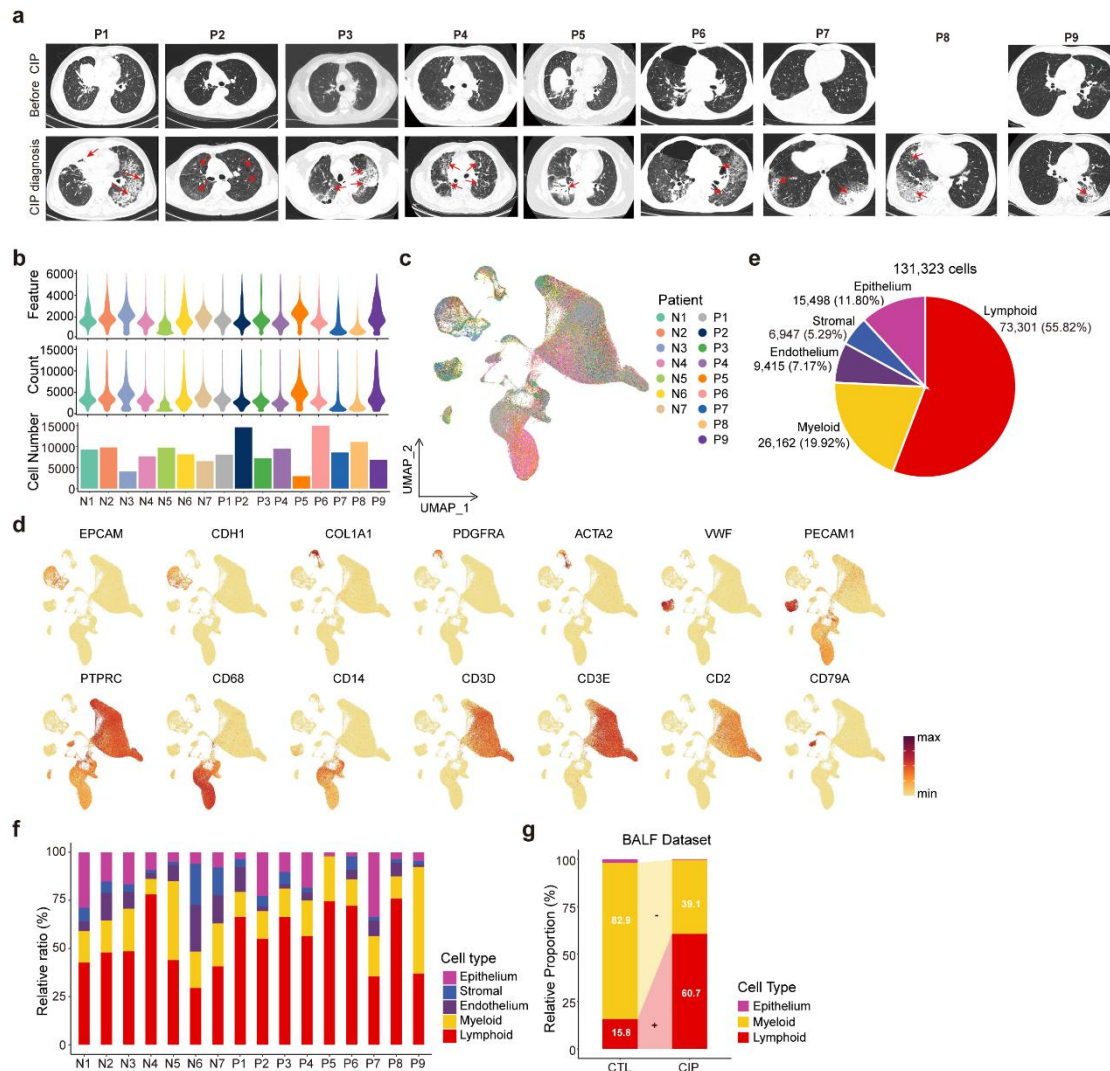
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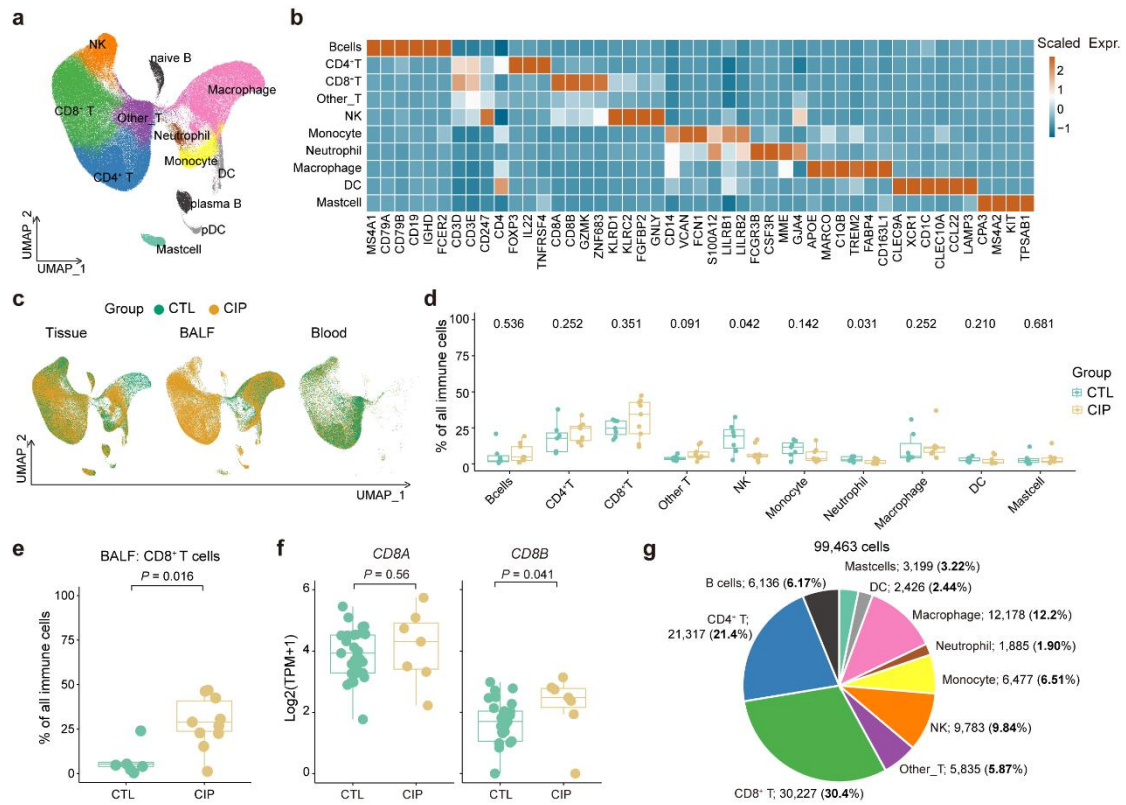
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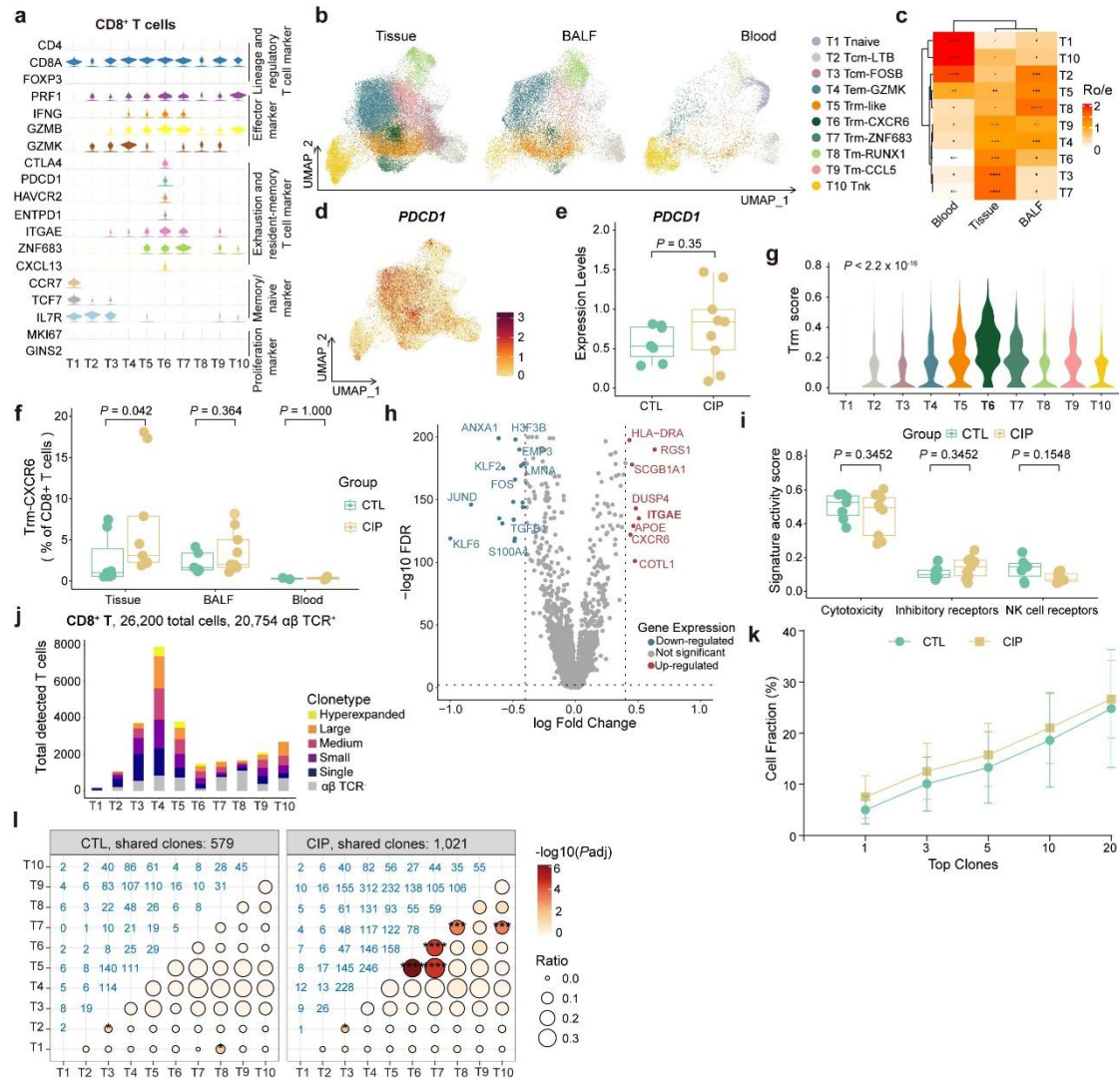
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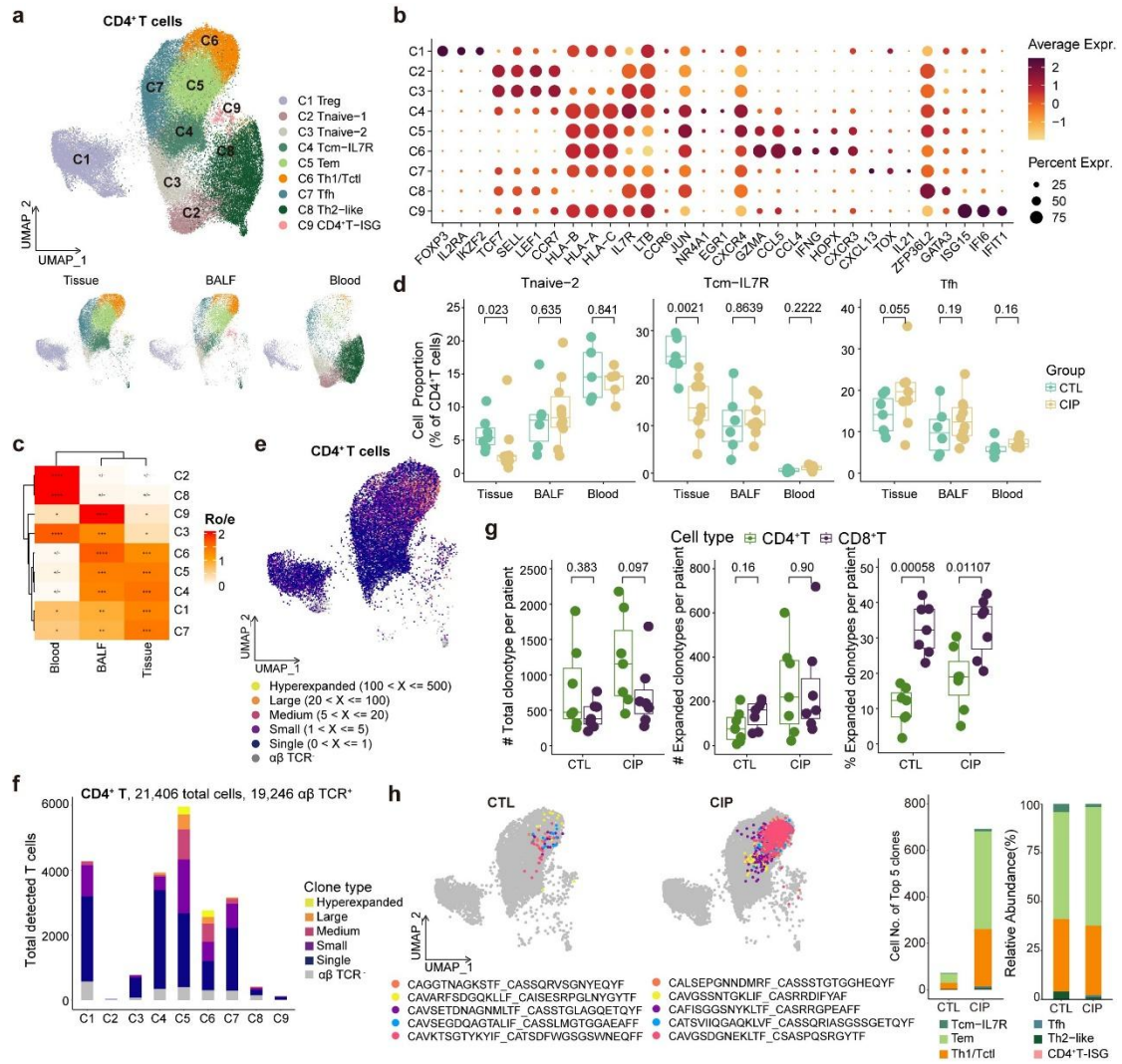
Supplementary Fig. 1: Overview of scRNA-seq transcriptomic profiles from CTL and CIP patients. (a) Representative computed tomography (CT) images of CIP after immunotherapy. The CT image of patient P8 prior to CIP was not available. **(b)** Violin plot showing the number of detected genes, unique molecular identifiers and total cells per individuals. **(c)** UMAP visualization of all cells captured, colored by patient. **(d)** Expression of genes defining the main clusters across all metacells, projected on the 2D map. The color scale represents log-normalized expression, scaled to the minimum and maximum expression levels for each gene. **(e)** Pie charts showing the percentage of cell types. **(f)** Bar plots showing the percentage of cell types in each sample. **(g)** Stacked bar plot showing the fraction of major cell type between CTL and CIP groups in the BALF dataset.



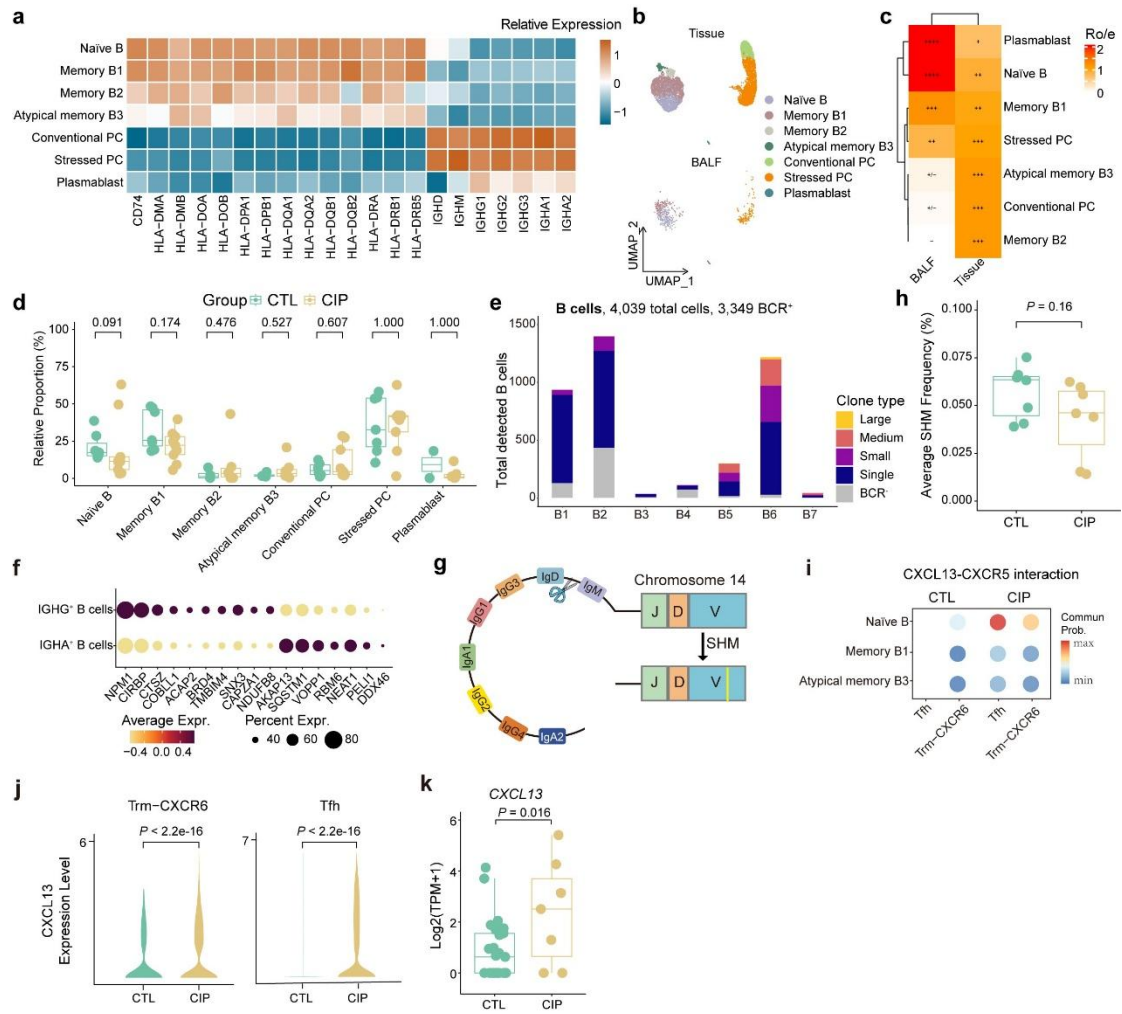
Supplementary Fig. 2: Global analysis of immune cell transcriptomic profiles. (a) UMAP embedding of immune cells that passed quality control, with cells color-coded by inferred cell types based on transcriptional profiles. (b) Expression of genes that identify the clusters. (c) UMAP visualization of all immune cells. (d) Box plot showing the fraction of major immune cell types in CTL ($n = 7$) and CIP ($n = 9$) patients. P values were determined by a two-tailed Mann–Whitney U test. (e) Box plot showing the proportion of CD8⁺ T cells among all immune cells in BALF samples from CTL ($n = 6$) and CIP ($n = 10$) patients. P value was determined by a two-tailed Mann–Whitney U test. (f) Box plots showing differences in *CD8A* and *CD8B* expression in CTL ($n = 29$) and CIP ($n = 7$) patients based on bulk RNA-seq data. P values were determined by a two-tailed Mann–Whitney U test. (g) Pie chart showing the distribution of immune cell types in lung tissues. In the box plots (d–f), the centre line represents the median, the bounds of the box correspond to the 25th and 75th percentiles, the whiskers extend to the largest and smallest values within $1.5\times$ the interquartile range from the quartiles, and individual points beyond the whiskers indicate outliers.



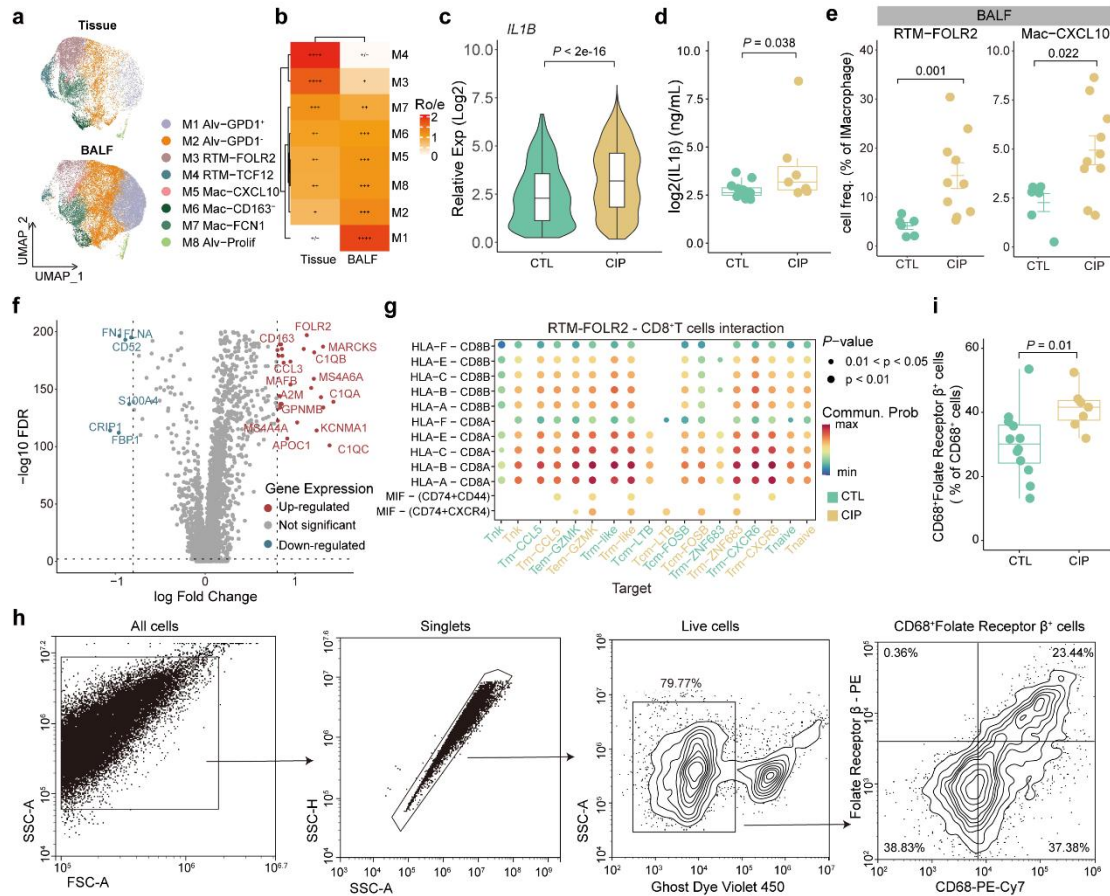
Supplementary Fig. 3: Identification of CIP-related CD8⁺ T cell populations. (a) Violin plot showing expression levels of selected markers. (b) UMAP plots showing the distribution of T-cell subsets. (c) Heatmap showing subcluster enrichment estimated by $R_{o/e}$: +++++, $R_{o/e} > 2$; +++, $1 < R_{o/e} \leq 2$; ++, $0.8 < R_{o/e} \leq 1$; +, $0.2 \leq R_{o/e} \leq 0.8$; +/-, $0 < R_{o/e} < 0.2$. (d) Feature plot showing *PDCD1* expression. (e) Box plot showing *PDCD1* expression in CTL ($n = 7$) and CIP ($n = 9$) groups. (f) Box plot showing the ratio of Trm-CXCR6 cells in lung tissue (CTL, $n = 7$; CIP, $n = 9$), BALF (CTL, $n = 6$; CIP, $n = 10$) and blood (CTL, $n = 5$; CIP, $n = 5$). (g) Violin plot showing Trm signature scores of each CD8⁺ T-cell subcluster. T1, $n = 1,630$; T2, $n = 2,980$; T3, $n = 4,528$; T4, $n = 12,719$; T5, $n = 8,060$; T6, $n = 2,028$; T7, $n = 1,926$; T8, $n = 4,033$; T9, $n = 3,903$; and T10, $n = 5,173$. P value was determined by ANOVA test. (h) Volcano plot showing fold changes in CD8⁺ T cell gene expression (a two-tailed Gaussian approximation of the U statistic with the Benjamini–Hochberg adjustment). (i) Box plot showing cytotoxicity, inhibitory receptors and NK cell receptors signature scores in CTL ($n = 7$) and CIP ($n = 9$) patients. (j) Bar plot showing clonal expansion composition. (k) Line plot showing the cell fraction (%) of the top clones in CTL ($n = 7$) and CIP ($n = 9$) groups. Error bars indicate the standard error of the mean. (l) Sharing of expanded TCR clonotypes across all possible combinations of CD8⁺ T-cell clusters. P values were calculated by hypergeometric test followed with Benjamini-Hochberg correction. * $P < 0.05$; *** $P < 0.001$; **** $P < 0.0001$. In the box plots (e, f, and i), P values were determined by a two-tailed Mann–Whitney U test. The center line denotes the median; boxes indicate the interquartile range; whiskers span $1.5 \times$ IQR, and outliers are shown as individual points.



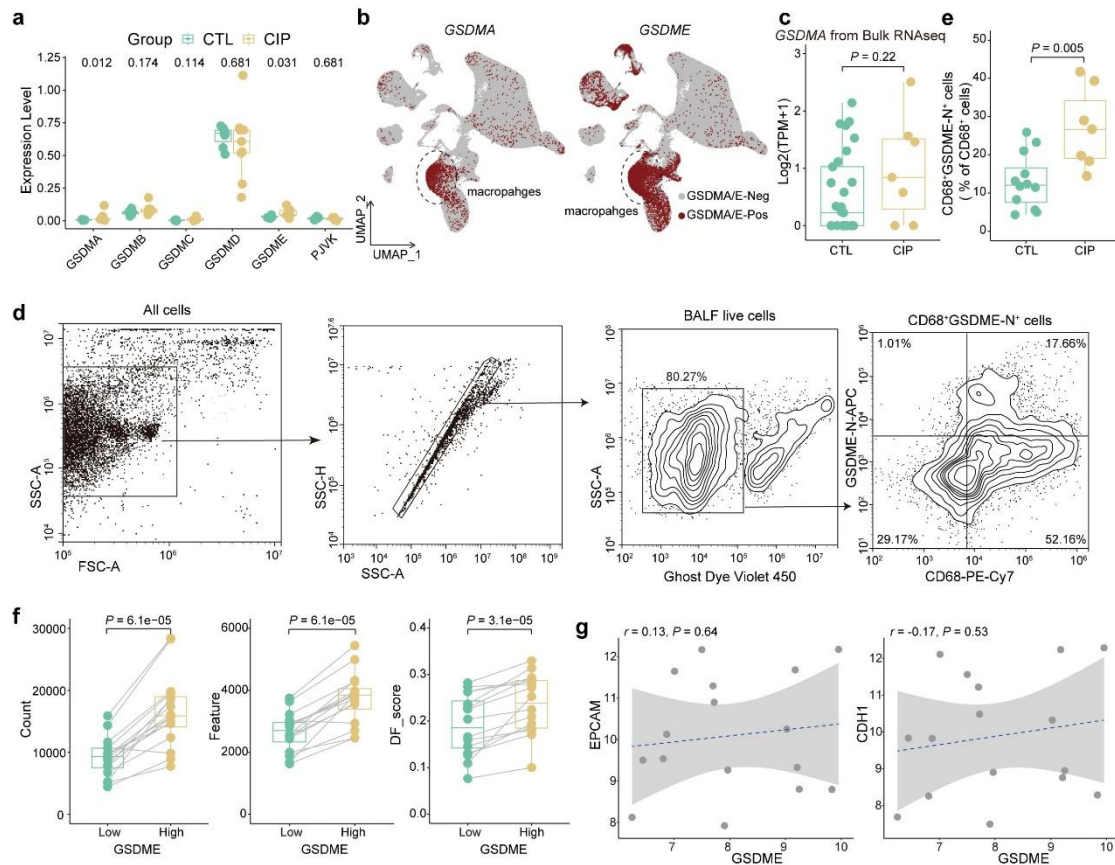
Supplementary Fig. 4: Identification of CIP-related CD4⁺ T populations. (a) UMAP visualization of CD4⁺ T-cell subsets identified across tissue, BALF, and blood samples. Each cluster is color-coded according to inferred cell types. (b) Bubble plot showing the proportions and average expression levels of marker genes for CD4⁺ T cells. (c) Heatmap showing the preference of CD4⁺ T-cell subclusters estimated by $R_{o/e}$, which denotes the ratio of observed to expected cell number. +++, $R_{o/e} > 2$, ++, $1 < R_{o/e} \leq 2$; +, $0.8 < R_{o/e} \leq 1$; +/−, $0 < R_{o/e} < 0.2$. (d) Box plots comparing the proportions of Tnaive-2 and Tcm-IL7R cell subsets across tissue (CTL, $n = 7$; CIP, $n = 9$), BALF (CTL, $n = 6$; CIP, $n = 10$) and blood (CTL, $n = 5$; CIP, $n = 5$) samples. P values were determined by a two-tailed Mann-Whitney U test. (e) UMAP showing the distribution of clonotypes in CD4⁺ T cells. (f) Bar plot showing the cellular composition of clonal expansion of CD4⁺ T cells across CTL and CIP patients. (g) Comparison of the number of total clonotypes per patient, number of expanded clonotypes per patient, and the percentage of expanded clonotypes per patient between CD4⁺ and CD8⁺ T cells (CTL, $n = 7$; CIP, $n = 7$). P values were determined by a two-tailed Mann-Whitney U test. (h) UMAP as in (a) highlighting CD4⁺ T-cells with the five most expanded TCR clonotypes. The accompanying bar graph shows the cellular composition of cell types within the top five CD4⁺ T-cells clones from CTL and CIP patients. In the box plots (d and g), the centre line represents the median, the bounds of the box correspond to the 25th and 75th percentiles, the whiskers extend to the largest and smallest values within $1.5 \times$ the interquartile range from the quartiles, and individual points beyond the whiskers indicate outliers.



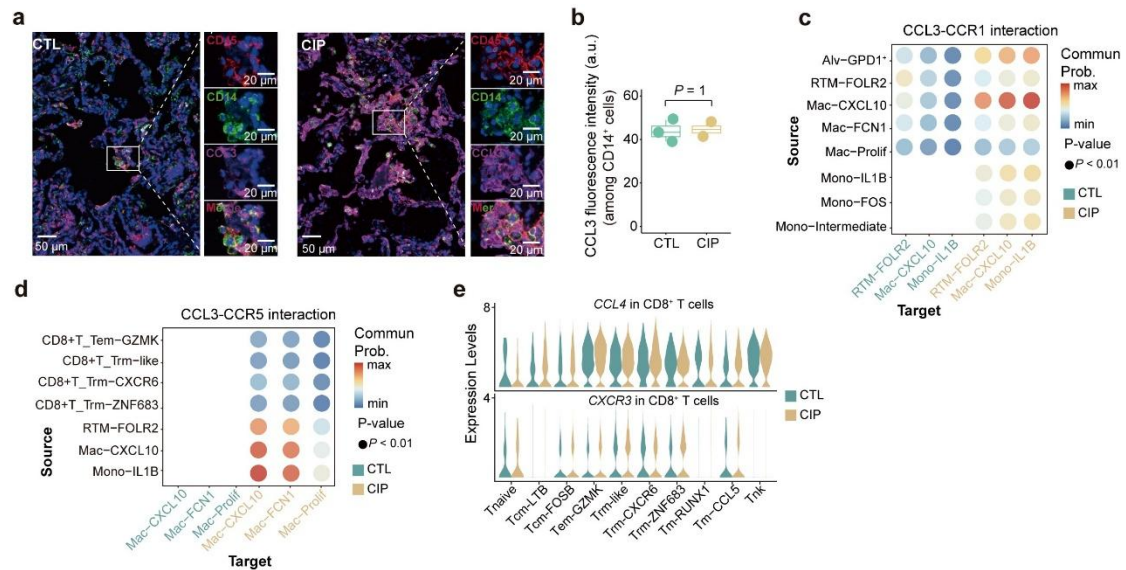
Supplementary Fig. 5: Identification of CIP-related B-cell populations. (a) Heatmap showing the average expression levels of selected genes across B-cell clusters. (b) UMAP visualization of B-cell subsets identified in lung tissue and BALF. (c) Heatmap showing the preference of B cell subcluster estimated by $R_{o/e}$, which denotes the ratio of observed to expected cell number. +++, $R_{o/e} > 2$; ++, $1 < R_{o/e} \leq 2$; +, $0.8 < R_{o/e} \leq 1$; +/-, $0.2 \leq R_{o/e} \leq 0.8$; -, $0 < R_{o/e} < 0.2$. (d) Box plots comparing the relative proportions of B-cell subsets between the CTL ($n = 7$) and CIP ($n = 9$) groups. P values were determined by a two-way Mann–Whitney U tests. (e) Bar plot showing the cellular composition of clonal expansion in B cells across CTL and CIP patients. (f) Dot plot displaying expression levels and percentages of DEGs in *IGHG*⁺ and *IGHA*⁺ B cells. (g) Schematic illustration of BCR class switch recombination and somatic hypermutation (SHM). (h) Box plot showing average SHM frequencies in CTL ($n = 7$) and CIP ($n = 7$) patients. P values were determined by a two-tailed Mann–Whitney U tests. (i) Dot plot illustrating the CXCL13-CXCR5 interaction between B-cell subsets and T-cell subsets in the CTL and CIP groups. P values were calculated by permutation test with Benjamini–Hochberg adjustment. (j) Violin plots showing *CXCL13* expression in Ttrm-CXCR6 and Tfh subsets between CTL and CIP groups. P values were determined by a two-tailed student's *t*-test. (k) Box plot showing *CXCL13* expression in CTL ($n = 29$) and CIP ($n = 7$) patients from bulk RNA-seq dataset. P values were determined by a two-tailed Mann–Whitney U test. In the box plots (d, h and k), the centre line represents the median, the bounds of the box correspond to the 25th and 75th percentiles, the whiskers extend to the largest and smallest values within $1.5 \times$ the interquartile range from the quartiles, and individual points beyond the whiskers indicate outliers.



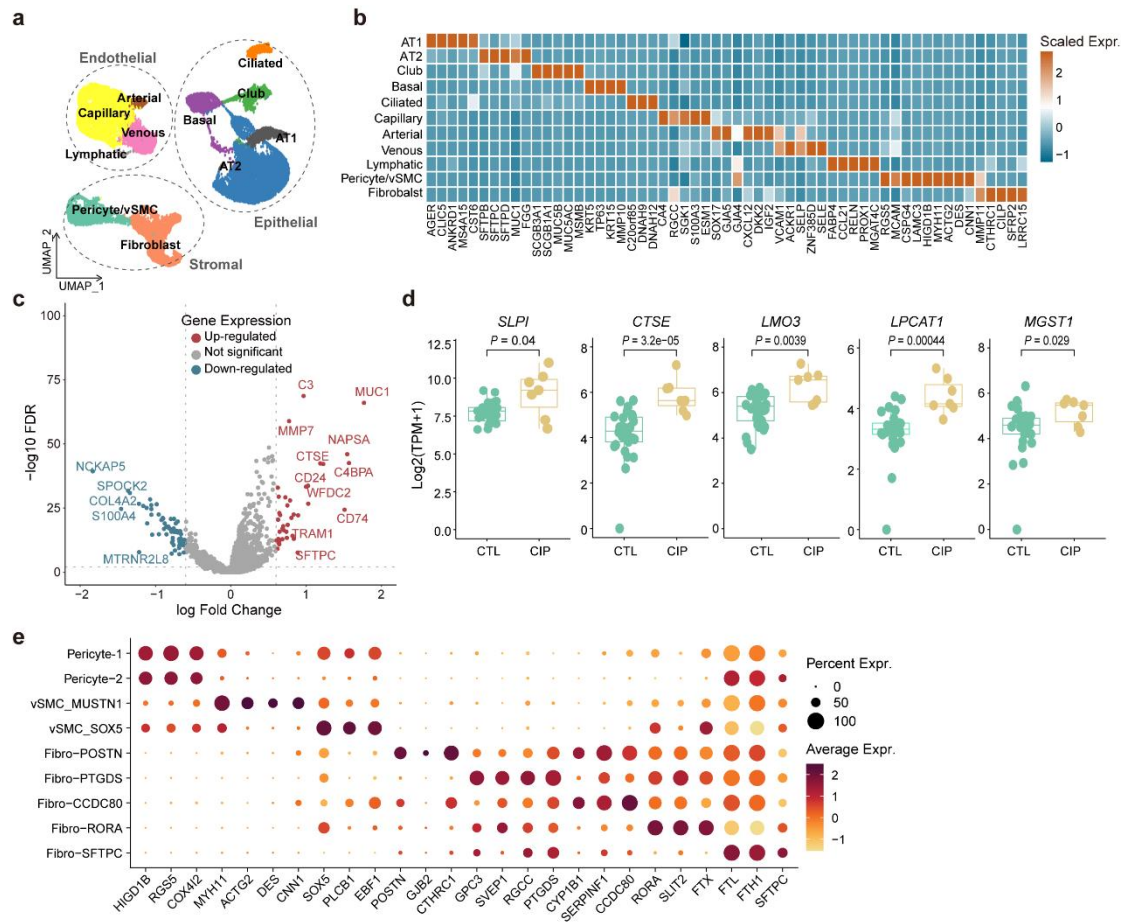
Supplementary Fig. 6: Global analysis of myeloid cells of transcriptomic profiles. (a) UMAP visualization of macrophage subsets identified across tissue and BALF. Each cluster is color-coded by inferred cell types. (b) Heatmap showing the enrichment preference of macrophage subclusters estimated by $R_{o/e}$. +, +, +, $R_{o/e} > 2$; +, +, $1 < R_{o/e} \leq 2$; +, $0.8 < R_{o/e} \leq 1$; +, $0.2 \leq R_{o/e} \leq 0.8$; +/−, $0 < R_{o/e} < 0.2$. (c) Violin plots showing differential expression of *IL1B* between the CIP ($n = 9,372$) and CTL ($n = 5,541$) groups. P value was calculated using a two-tailed student's t -test. (d) Box plots showing $IL1\beta$ concentration (ng/mL) in BALF samples from CIP ($n = 7$) and CTL ($n = 12$) patients. P value was calculated using a two-tailed Mann–Whitney U test. (e) Proportions of RTM-FOLR2 and Mac-CXCL10 subsets among macrophages from lung tissues of CTL ($n = 5$) and CTL ($n = 10$) patients. A two-tailed Mann–Whitney U test was performed. (f) Volcano plot showing $\log_2$ fold changes in gene expression of RTM-FOLR2 compared with other macrophage clusters. P values were calculated using a two-tailed Gaussian approximation of the U statistic and adjusted with the Benjamini–Hochberg procedure. (g) Interaction of RTM-FOLR2 with CD8⁺ T cells. P values were calculated by permutation test with Benjamini–Hochberg adjustment. (h) Gating strategy for CD68⁺ Folate Receptor β^+ macrophages in human BALF. (i) Box plots comparing the proportion of CD68⁺ Folate Receptor β^+ macrophages among CD68⁺ macrophages between the CIP ($n = 7$) and CTL ($n = 12$) groups. P value was calculated using a two-tailed Mann–Whitney U test. In the box plots (d, e and i), the centre line represents the median, the bounds of the box correspond to the 25th and 75th percentiles, the whiskers extend to the largest and smallest values within $1.5 \times$ the interquartile range from the quartiles, and individual points beyond the whiskers indicate outliers.



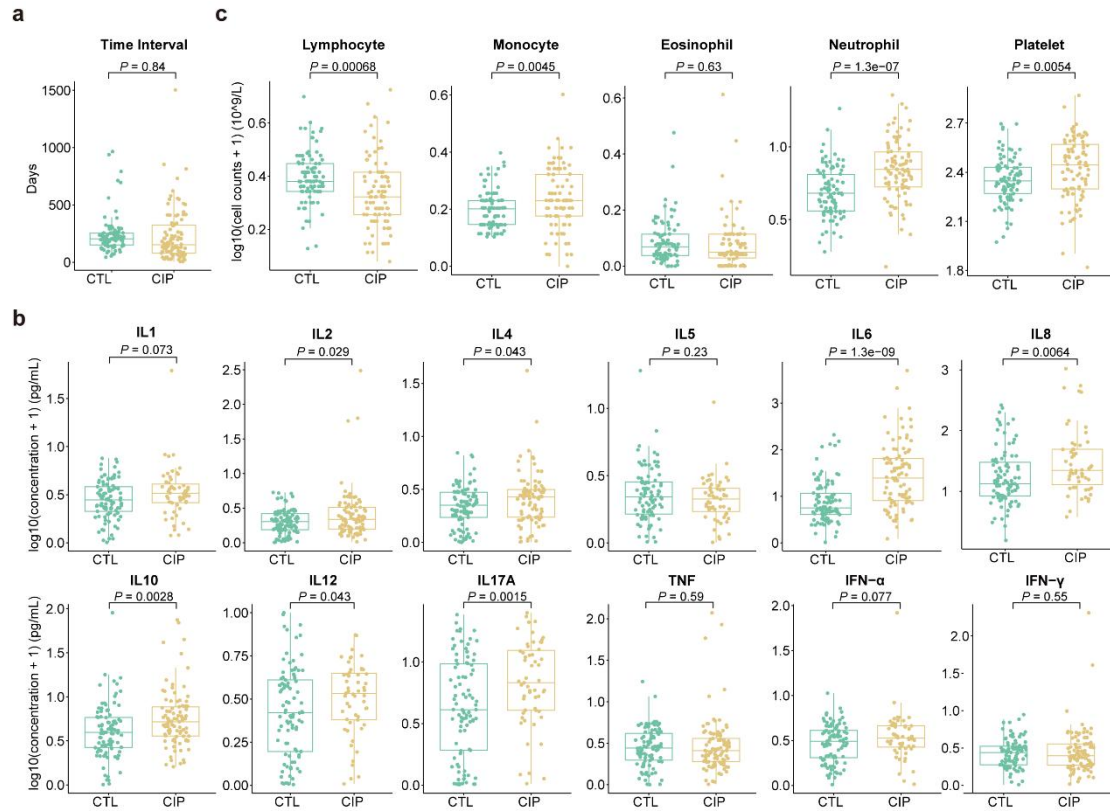
Supplementary Fig. 7: Macrophages in CIP show heightened pyroptosis-associated signatures. (a) Box plots showing the expression of all gasdermin family genes in cells from CTL ($n = 7$) and CIP ($n = 9$) patients based on scRNA-seq. P values were determined by a two-tailed Mann–Whitney U test. (b) UMAP visualization of *GSDMA*- and *GSDME*- positive and negative cells. (c) Box plot showing differences in *GSDMA* expression in bulk RNA-seq data between CIP ($n = 7$) and CTL ($n = 29$) patients. P values were determined by a two-tailed Mann–Whitney U test. (d) Gating strategy for CD68⁺ GSDME-N⁺ macrophages in human BALF. (e) Box plots comparing the proportion of CD68⁺ GSDME-N⁺ macrophages among CD68⁺ macrophages between the CIP ($n = 7$) and CTL ($n = 12$) groups. P values were calculated using a two-tailed Mann–Whitney U test. (f) Box plots showing the read counts, features and doublet scores of macrophages stratified by *GSDME*^{low} and *GSDME*^{high} expression cells ($n = 16$). P values were calculated by a two-tailed paired Mann–Whitney U test. (g) Correlation analysis between *GSDME* and epithelial markers, *EPCAM* and *CDH1*. P values were calculated using Pearson correlation with two-tailed significance testing. In the box plots (a, c, e and f), the centre line represents the median, the bounds of the box correspond to the 25th and 75th percentiles, the whiskers extend to the largest and smallest values within $1.5 \times$ the interquartile range from the quartiles, and individual points beyond the whiskers indicate outliers.



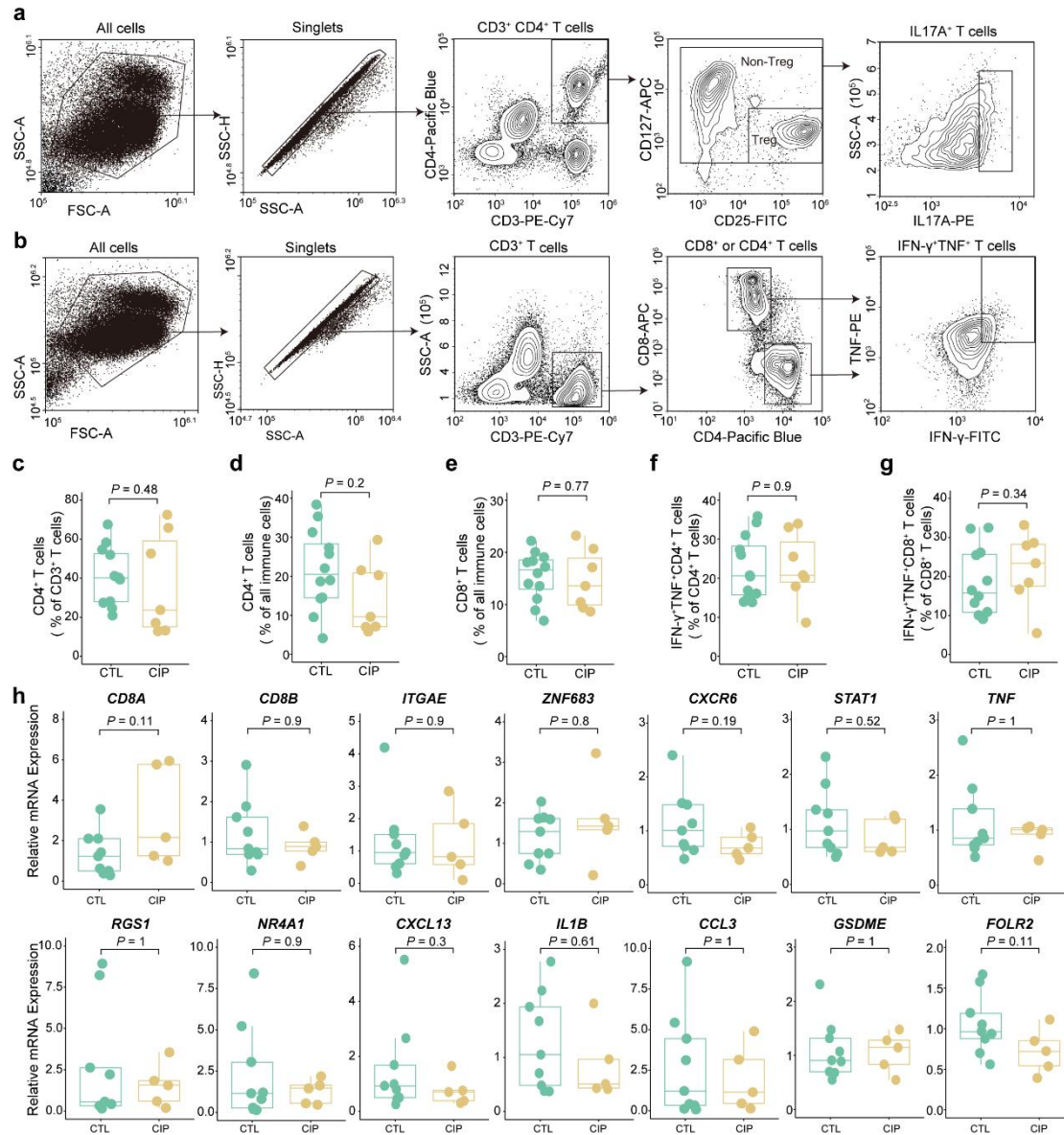
Supplementary Fig. 8: Cell-cell interaction between lymphoid and myeloid cells. (a) Representative multiplex immunofluorescence images showing CCL3⁺CD14⁺ monocytes. (b) Box plot quantifying fluorescence intensity in (a) of CTL ($n = 3$) and CIP ($n = 3$) patients. P values were determined by a one-tailed Mann-Whitney U test. The centre line represents the median, the bounds of the box correspond to the 25th and 75th percentiles, the whiskers extend to the largest and smallest values within $1.5 \times$ the interquartile range from the quartiles, and individual points beyond the whiskers indicate outliers. (c) Dot plot illustrating CCL3-CCR1 interactions in CTL and CIP groups. P values were calculated by permutation test with Benjamini-Hochberg adjustment. (d) Dot plot illustrating the CCL3-CCR5 interactions in CTL and CIP groups. P values were calculated by permutation test with Benjamini-Hochberg adjustment. (e) Violin plot showing the expression of CCL4 and CXCR3 across all clusters of CD8⁺ T-cell clusters.



Supplementary Fig. 9: Global analysis of non-immune cells. (a) UMAP embedding of the non-immune cells that passed quality control. Cells are color-coded by their inferred cell types. (b) Expression of marker genes identifying the clusters defined in (a). (c) Volcano plot showing gene expression fold change (log2) of AT1 cells compared with other epithelial clusters. P values were calculated using a two-tailed Gaussian approximation of the U statistic and adjusted with the Benjamini–Hochberg procedure. (d) Box plots showing differences in the expression levels of *SLPI*, *CTSE*, *LMO3*, *LPCAT1* and *MGST1* in CTL ($n = 29$) and CIP ($n = 7$) patients based on bulk RNA-seq data. P values were determined by a two-tailed Mann–Whitney U test. The centre line represents the median, the bounds of the box correspond to the 25th and 75th percentiles, the whiskers extend to the largest and smallest values within $1.5 \times$ the interquartile range from the quartiles, and individual points beyond the whiskers indicate outliers. (e) Bubble plot showing the proportions and average expression levels of selected marker genes for stromal cells. Bubble size indicates the percentage of cells expressing a specific gene in a given cluster, and the color depicts the average expression level of the gene relative to other clusters.



Supplementary Fig. 10: Cytokines and cells in the blood of CIP. (a) Box plot comparing the time intervals (from the initiation of immunotherapy to the blood collection point) between CTL ($n = 94$) and CIP ($n = 94$) groups. (b) Box plots comparing the concentration of cytokines (IL1, IL2, IL4, IL5, IL6, IL8, IL10, IL12, IL17A, TNF, IFN- α , and IFN- γ) between CTL ($n = 94$) and CIP ($n = 94$) groups. (c) Box plots comparing the frequencies of lymphocytes, monocytes, eosinophils, neutrophils and platelets between CTL ($n = 94$) and CIP ($n = 94$) groups. In the box plots (a-c), a two-tailed student's t test was performed. The centre line represents the median, the bounds of the box correspond to the 25th and 75th percentiles, the whiskers extend to the largest and smallest values within $1.5 \times$ the interquartile range from the quartiles, and individual points beyond the whiskers indicate outliers.



Supplementary Fig. 11: Flow cytometric analysis and qRT-PCR of PMBCs from CIP patients. (a-b) Gating strategy to sort Treg/Th17 cells (a) and IFN- γ ⁺/TNF⁺ CD4⁺/CD8⁺ T cells (b) from human PBMCs. (c-g) Box plots comparing the ratios of CD4⁺ T cells among CD3⁺ T cells (c), CD4⁺ T cells among all immune cells (d), CD8⁺ T cells among all immune cells (e), IFN- γ ⁺ TNF⁺ CD4⁺ T cells (f), and IFN- γ ⁺ TNF⁺ CD8⁺ T cells (g) between CTL ($n = 12$) and CIP ($n = 7$) patients based on flow cytometric analysis. (h) Relative mRNA levels of the indicated genes in PBMCs between the CTL ($n = 9$) and CIP ($n = 5$) groups. In the box plots (c-h), P values were determined by a two-tailed Mann-Whitney U test. The centre line represents the median, the bounds of the box correspond to the 25th and 75th percentiles, the whiskers extend to the largest and smallest values within 1.5 $\times$ the interquartile range from the quartiles, and individual points beyond the whiskers indicate outliers.

Supplementary Table 1. Demographic and clinical characteristics of patients subjected scRNA sequencing.

Characteristic	CIP (<i>n</i> = 9)	CTL (<i>n</i> = 7)
Median age (range)	62.8 years (55-73)	58.7years (50-67)
Sex		
Male	8(88.9%)	6(85.7%)
Female	1(11.1%)	1(14.3%)
BMI (range)	21.87 (15.0-24.7)	23.16 (20.3-29.3)
Smoking status		
Current/former	6	3
Never	3	4
Lung cancer pathology		
LUAD	5	1
LUSC	2	5
SCLC	1	0
Others†	1	1
Neoplasm staging		
I	0	2
II	0	3
III	3	2
IV	6	0
ICI(s) ‡		
PD-1	8	7
PD-L1	1	0
ICI strategy		
Immunochemotherapy	8	7
Monotherapy	1	0
Grade of CIP		
1-2	2	NA
≥3	7	NA
Pattern of CIP*		
OP	7	NA
GGO	4	NA
NSIP	1	NA
Median time from first ICI infusion to sampling (range)	34.1 weeks (11.8-67.8)	16.5 weeks (9.3-21.6)

† Other cancers include large cell neuroendocrine carcinoma in CIP group (*n* = 1) and lung carcinoid tumor in CTL group (*n* = 1). ‡ PD-1 inhibitors include: Tislelizumab (*n* = 6), Camrelizumab (*n* = 3), Serplulimab (*n* = 1), Ivonescimab (*n* = 1), Sintilimab (*n* = 3), and Toripalimab (*n* = 1). PD-L1 inhibitors include: Durvalumab (*n* = 1).

* Some patients present with two or more types of CIP patterns. Abbreviations: CIP, checkpoint inhibitor-related pneumonitis; CTL, control; BMI, body mass index; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; OP, organizing pneumonitis; GGO, ground glass opacification/opacity; NSIP, nonspecific interstitial pneumonitis; NA, not applicable.

Supplementary Table 2. Comprehensive clinical information for all patients included in the study.

No.	Group	scRNA-seq	scTCR/BCR	IHC/IF	ELISA	Flow cytometry	qRT-PCR
P1	CIP	✓	✓	✓			
P2	CIP	✓	✓	✓			
P3	CIP	✓	✓	✓			
P4	CIP	✓	✓	✓			
P5	CIP	✓	✓	✓			
P6	CIP	✓	✓	✓			
P7	CIP	✓	✓				
P8	CIP	✓					
P9	CIP	✓					
P10	CIP				✓	✓	
P11	CIP					✓	
P12	CIP					✓	✓
P13	CIP					✓	✓
P14	CIP			✓	✓	✓	✓
P15	CIP				✓	✓	✓
P16	CIP					✓	✓
P17	CIP				✓		
P18	CIP				✓		
P19	CIP				✓		
P20	CIP				✓		
P21	CIP				✓		
P22	CIP				✓		
P23	CIP				✓		
P24	CIP				✓		
P25	CIP				✓		
P26	CIP			✓			
P27	CIP			✓			
P28	CIP			✓			
P29	CIP			✓			
P30	CIP			✓			
P31	CIP			✓			
P32	CIP				✓	✓	
P33	CIP				✓	✓	
P34	CIP				✓	✓	
P35	CIP				✓	✓	
P36	CIP				✓	✓	
P37	CIP				✓	✓	
P38	CIP				✓	✓	
N1	CTL	✓	✓	✓			
N2	CTL	✓	✓	✓			
N3	CTL	✓	✓	✓			
N4	CTL	✓	✓	✓			
N5	CTL	✓	✓	✓			
N6	CTL	✓	✓				
N7	CTL	✓	✓				

N8	CTL		✓	✓	
N9	CTL		✓	✓	
N10	CTL			✓	
N11	CTL		✓	✓	✓
N12	CTL		✓	✓	✓
N13	CTL		✓	✓	✓
N14	CTL		✓	✓	✓
N15	CTL		✓	✓	✓
N16	CTL		✓	✓	✓
N17	CTL		✓	✓	✓
N18	CTL		✓	✓	✓
N19	CTL		✓	✓	✓
N20	CTL		✓		
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N33	CTL		✓	✓	
N34	CTL		✓	✓	
N35	CTL		✓	✓	
N36	CTL		✓	✓	
N37	CTL		✓	✓	
N38	CTL		✓	✓	
N39	CTL		✓	✓	
N40	CTL		✓	✓	
N41	CTL		✓	✓	
N42	CTL		✓	✓	

Abbreviations: CIP, checkpoint inhibitor-related pneumonitis; CTL, control.

Supplementary Table 3. Clinical characteristics of the retrospective cohort.

Characteristic	CIP (<i>n</i> = 94)	CTL (<i>n</i> = 94)
Median age(range)	64.0 years (37-84)	61.5years (40-84)
Sex		
Male	80(85.1%)	64(68.1%)
Female	14(14.9%)	30(31.9%)
Smoking status		
Current/former	59(62.8%)	28(29.8%)
Never	35(37.2%)	66(70.2%)
Lung cancer pathology		
LUAD	41(43.6%)	41(43.6%)
LUSC	40(42.5%)	33(35.1%)
SCLC	9(9.6%)	14(14.9%)
Others†	4(4.3%)	6(6.4%)
Neoplasm staging		
≤ III	35(37.2%)	24(25.5%)
IV	59(62.8%)	70(74.5%)
ICI(s)		
PD-1	90(95.7%)	84(89.4%)
PD-L1	4(4.3%)	10(10.6%)
ICI strategy		
Combination therapy‡	84(89.4%)	92(97.9%)
Monotherapy	10(10.6%)	2(2.1%)
Grade of CIP		
1-2	60(63.8%)	NA
≥3	34(36.2%)	NA
Median time from first ICI infusion to development of CIP(range)	24.1 weeks (0.7-214.9)	29.9 weeks (4.3-138)

† Other cancers include large cell neuroendocrine carcinoma (CIP, *n* = 1; CTL, *n* = 1) and poorly differentiated non-small cell lung cancer (CIP, *n* = 3; CTL, *n* = 5).

‡ Combination therapies include immunochemotherapy, immunotherapy combined with targeted therapy, immunotherapy combined with anti-vascular therapy, immunochemotherapy combined with anti-vascular therapy.

Supplementary Table 4. Clinical characteristics of the BALF cohort.

Characteristic	CIP (<i>n</i> = 7)	CTL (<i>n</i> = 12)
Median age (range)	70.3 years (52-82)	65.5years (50-79)
Sex		
Male	6(85.7%)	9(75.0%)
Female	1(14.3%)	3(25.0%)
BMI (range)	21.4 (17.2-24.6)	21.3 (17.8-25.7)
Smoking status		
Current/former	5	9
Never	2	3
Lung cancer pathology		
LUAD	3	6
LUSC	4	4
SCLC	0	2
Neoplasm staging		
≤ III	4	6
IV	3	6
Grade of CIP		
1-2	2	NA
≥3	5	NA
Pattern of CIP		
OP	4	NA
GGO	2	NA
NSIP	1	NA
Median time from first ICI infusion to development of CIP(range)	26.7 weeks (12.7-46.1)	NA

Abbreviations: CIP, checkpoint inhibitor-related pneumonitis; CTL, control; BMI, body mass index; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer; ICI, immune checkpoint inhibitor; OP, organizing pneumonitis; GGO, ground glass opacification/opacity; NSIP, nonspecific interstitial pneumonitis; NA, not applicable.

Supplementary Table 5. Differentially expressed genes in all cells between CTL and CIP patients based on scRNA-seq, related to Fig. 1g.

Gene	Group	avgExpr	logFC	Pval	Padj	pct_in	pct_out	Status
RGS1	CIP	1.14206	0.62509438	0	1E-183	47.299	26.1567	Up
SCGB1A1	CIP	0.61643	0.491719017	0	1E-181	26.327	7.02871	Up
APOE	CIP	0.82928	0.407531114	0	1E-120	34.9018	17.4765	Up
SCGB3A1	CIP	0.55864	0.371900381	0	1E-164	24.4025	10.6802	Up
CTSB	CIP	1.0173	0.331887496	0	1E-187	48.6654	39.1265	Up
CCL5	CIP	1.49505	0.330890216	2.14E-285	1E-120	46.7726	37.6236	Up
CD2	CIP	0.77618	0.317906318	0	1E-149	37.1448	24.5186	Up
HSP90AA1	CIP	2.49207	0.314937546	0	1E-131	88.0772	86.3902	Up
DHFR	CIP	0.3521	0.313190127	0	1E-105	19.2416	3.81341	Up
FKBP5	CIP	0.6474	0.302527012	0	1E-127	38.2637	24.4709	Up
SPTBN1	CIP	0.43702	-0.30575636	0	1E-158	27.0019	38.9798	Down
CAV1	CIP	0.21762	-0.3059747	0	1E-155	12.434	22.7109	Down
DUSP1	CIP	1.91134	-0.30670446	0	1E-141	73.2873	83.0949	Down
RASGEF1B	CIP	0.60475	-0.31156361	0	1E-183	37.3173	52.8201	Down
CRIP1	CIP	1.26325	-0.32017175	0	1E-191	57.6132	64.986	Down
PPP1R15A	CIP	0.99805	-0.32812073	0	1E-107	54.0495	67.3137	Down
KLF6	CIP	1.47844	-0.33224871	0	1E-178	68.2153	78.1329	Down
MYADM	CIP	0.54001	-0.3402831	0	1E-132	34.8041	49.2009	Down
CSRNP1	CIP	0.34567	-0.35142033	0	1E-149	24.9099	44.6866	Down
EPAS1	CIP	0.38677	-0.35557906	0	1E-114	24.0866	35.2197	Down
H3F3A	CIP	1.39493	-0.37964432	0	1E-192	64.3066	81.8377	Down
FOSB	CIP	0.99587	-0.38012112	0	1E-184	49.098	60.725	Down
SOCS3	CIP	0.53233	-0.38847418	0	1E-147	34.4096	48.2333	Down
TAGLN2	CIP	1.28247	-0.40817682	0	1E-165	65.253	78.1443	Down
ANXA1	CIP	1.15748	-0.40855768	0	1E-149	57.3975	70.0223	Down
RHOB	CIP	0.42216	-0.41162202	0	1E-107	27.8481	44.2999	Down
S100A6	CIP	1.9368	-0.41953131	0	1E-192	76.3346	85.9864	Down
FLNA	CIP	0.81188	-0.43262097	0	1E-188	46.2803	63.6241	Down
AHNAK	CIP	1.4702	-0.43946685	0	1E-190	69.3456	81.2035	Down
FOS	CIP	2.0332	-0.45246166	0	1E-155	72.9156	82.2035	Down
JUNB	CIP	1.979	-0.47540777	0	1E-130	76.3283	84.8397	Down
NR4A1	CIP	0.6227	-0.48244252	0	1E-137	34.1876	50.7	Down
LMNA	CIP	0.51512	-0.55390142	0	1E-188	30.7888	51.3095	Down
MTRNR2L8	CIP	0.07666	-0.57783166	0	1E-156	6.82406	22.2728	Down
KLF2	CIP	0.60349	-0.61937216	0	1E-192	32.8834	56.8277	Down
H3F3B	CIP	1.85094	-0.65562562	0	1E-140	71.4579	91.8684	Down
ZFP36	CIP	1.62897	-0.67704171	0	1E-138	69.2429	84.4549	Down
JUND	CIP	1.09888	-0.88615015	0	1E-187	56.9928	79.2148	Down

P values were calculated using a two-tailed Gaussian approximation of the U statistic and adjusted with the Benjamini–Hochberg procedure. avgExpr, mean value of feature in group; logFC, log fold change between observations in group vs out; *P*val, nominal *P* value, from two-tailed Gaussian approximation of U statistic; *P*adj, Benjamini-Hochberg adjusted *P* value; pct_in, percent of observations in the group with non-zero feature value; pct_out, percent of observations out of the group with non-zero feature value.

Supplementary Table 6. Differentially expressed genes in CD8⁺ T-cells between CTL and CIP patients based on scRNA-seq, related to Supplementary Fig. 3h.

Gene	Group	avgExpr	logFC	Pval	Padj	pct_in	pct_out	Status
RGS1	CIP	1.49777	0.63301	0	1E-190	61.882	41.3094	Up
ITGAE	CIP	0.85467	0.50693	0	1E-135	42.8041	20.5233	Up
DUSP4	CIP	0.86831	0.48265	3.83E-301	1E-143	41.6528	20.6179	Up
COTL1	CIP	1.47884	0.4753	3.619E-244	1E-101	67.106	49.422	Up
APOE	CIP	0.56139	0.4633	0	1E-129	30.5429	5.96889	Up
SCGB1A1	CIP	0.54308	0.45279	0	1E-178	24.4526	5.43296	Up
CXCR6	CIP	0.71686	0.44021	0	1E-122	37.7899	16.2884	Up
HLA-DRA	CIP	1.28401	0.43135	4.651E-201	3E-198	59.4286	42.3813	Up
IFITM1	CIP	1.69806	-0.4155	5.793E-182	3E-179	72.6906	85.2354	Down
TGFB1	CIP	1.20557	-0.4204	3.894E-221	1E-144	59.7084	75.7251	Down
ZFP36	CIP	1.83288	-0.4215	5.51E-151	2E-148	73.3039	83.2282	Down
EMP3	CIP	0.98333	-0.435	8.753E-229	1E-177	50.417	70.082	Down
TAGLN2	CIP	1.18196	-0.4476	5.796E-228	1E-190	58.7077	74.5902	Down
H3F3B	CIP	2.32986	-0.4787	6.081E-241	1E-198	83.9135	95.0715	Down
LMNA	CIP	0.23296	-0.4822	0	1E-166	13.2082	34.8781	Down
LGALS1	CIP	0.72697	-0.4835	4.376E-259	1E-119	35.6809	55.7482	Down
S100A4	CIP	1.89132	-0.4869	8.787E-220	1E-117	73.7935	85.7818	Down
FLNA	CIP	0.98105	-0.4931	2.008E-279	1E-134	49.7014	69.4935	Down
FOS	CIP	1.86901	-0.4966	1.552E-151	6E-149	68.3757	77.2383	Down
MTRNR2L8	CIP	0.07084	-0.5759	0	1E-175	4.41707	21.3115	Down
KLF6	CIP	1.71059	-0.5835	0	1E-131	72.2602	85.5191	Down
AHNAK	CIP	1.61875	-0.6076	0	1E-135	71.5231	87.1375	Down
ANXA1	CIP	1.27344	-0.6133	0	1E-199	58.8691	76.5763	Down
KLF2	CIP	0.48237	-0.8338	0	1E-146	21.9616	52.48	Down
JUND	CIP	1.29611	-0.9994	0	1E-119	59.0413	81.2736	Down

P values were calculated using a two-tailed Gaussian approximation of the U statistic and adjusted with the Benjamini–Hochberg procedure.

avgExpr, mean value of feature in group; logFC, log fold change between observations in group vs out; *P*val, nominal *P* value, from two-tailed Gaussian approximation of U statistic; *P*adj, Benjamini-Hochberg adjusted *P* value; pct_in, percent of observations in the group with non-zero feature value; pct_out, percent of observations out of the group with non-zero feature value.

Supplementary Table 7. Differentially expressed genes in B-cells between CTL and CIP patients based on scRNA-seq, related to Fig. 4c.

Gene	Group	avgExpr	logFC	pval	padj	pct_in	pct_out	Status
IER2	CIP	2.30772	1.29928	8.573E-136	3.285E-131	83.1701	54.7531	Up
NR4A1	CIP	2.36571	1.2132	2.65E-115	5.076E-111	83.2591	55.5637	Up
NFKBIA	CIP	2.16461	1.16235	3.581E-110	4.573E-106	81.4782	50.7001	Up
DUSP2	CIP	1.77389	1.08767	5.6739E-83	1.8117E-79	65.8059	36.0354	Up
EGR1	CIP	1.51591	1.07635	1.7195E-92	1.6471E-88	58.8602	22.5497	Up
CD69	CIP	3.09823	0.99055	1.6428E-84	5.7225E-81	91.4515	81.1349	Up
BTG2	CIP	2.16078	0.94302	2.471E-92	1.8936E-88	82.992	64.4068	Up
NR4A3	CIP	1.40491	0.92984	2.6089E-89	1.4281E-85	62.1549	27.6345	Up
NFKB1	CIP	1.54875	0.87346	2.3E-74	5.8752E-71	66.5183	40.4569	Up
BIRC3	CIP	1.58653	0.86705	3.9102E-88	1.8728E-84	73.8201	42.3729	Up
HSP90AA1	CIP	2.71998	0.84854	4.3188E-86	1.6548E-82	92.8762	82.8298	Up
KDM6B	CIP	1.49407	0.8183	7.512E-81	2.2141E-77	69.813	40.678	Up
HERPUD1	CIP	1.9645	0.74953	3.9311E-63	7.9275E-60	79.252	63.2277	Up
JUN	CIP	2.52746	0.73307	2.8206E-46	3.4862E-43	87.0882	74.7237	Up
JUNB	CIP	2.99647	0.72779	3.8411E-54	5.8871E-51	92.431	83.7878	Up
NFKBID	CIP	1.10101	0.6974	1.0915E-71	2.4602E-68	57.0793	24.6131	Up
TNFAIP3	CIP	0.95094	0.6533	1.8276E-64	3.8903E-61	48.8869	19.6758	Up
DNAJA1	CIP	1.4426	0.63838	1.8241E-55	3.0389E-52	72.7516	47.4576	Up
DNAJB1	CIP	1.54998	0.63254	5.8909E-41	5.7876E-38	68.0321	43.8467	Up
NR4A2	CIP	2.21678	0.6289	6.7242E-41	6.4411E-38	85.0401	71.7023	Up
HSPH1	CIP	1.22274	0.60662	1.4096E-49	1.8624E-46	62.5111	35.3721	Up
VPS37B	CIP	1.37689	0.60483	3.5427E-45	3.9924E-42	66.4292	44.2889	Up
ZFP36	CIP	2.15776	0.57181	6.8156E-38	5.2879E-35	82.7248	74.5763	Up
ZNF331	CIP	1.68149	0.56355	1.453E-30	6.9591E-28	69.3678	54.0162	Up
ELL2	CIP	1.09847	0.55325	2.323E-46	2.9669E-43	58.415	34.6352	Up
FOS	CIP	2.69706	0.53607	1.8792E-23	5.9018E-21	87.5334	79.5136	Up
HSPA1B	CIP	1.2269	0.53184	4.3119E-22	1.1972E-19	47.3731	30.2874	Up
DUSP1	CIP	2.72844	0.53081	1.8881E-35	1.2347E-32	90.472	84.7458	Up
FOSB	CIP	1.50936	0.519	1.5507E-27	6.5294E-25	68.3882	50.1842	Up
ACTG1	CIP	1.92983	-0.5011	4.919E-39	4.2835E-36	83.081	90.7885	Down
KLF6	CIP	1.56623	-0.5201	4.6299E-32	2.4301E-29	73.553	85.7038	Down
GAPDH	CIP	1.36927	-0.5251	2.9779E-39	2.7167E-36	70.5254	84.0088	Down
TMSB4X	CIP	3.38923	-0.541	8.6037E-87	3.6629E-83	97.1505	97.8629	Down
ARHGAP24	CIP	0.60051	-0.6017	1.5822E-50	2.2453E-47	33.8379	65.5122	Down
JUND	CIP	1.90186	-0.6339	1.6843E-31	8.6048E-29	73.9982	90.8622	Down
HLA-DRB5	CIP	2.10408	-0.7484	1.1007E-91	7.0293E-88	89.1362	96.6839	Down

P values were calculated using a two-tailed Gaussian approximation of the U statistic and adjusted with the Benjamini–Hochberg procedure.

avgExpr, mean value of feature in group; logFC, log fold change between observations in group vs out; *P*val, nominal *P* value, from two-tailed Gaussian approximation of U statistic; *P*adj, Benjamini-Hochberg adjusted *P* value; pct_in, percent of observations in the group with non-zero feature value; pct_out, percent of observations out of the group with non-zero feature value.

Supplementary Table 8. Differentially expressed genes between RTM-FOLR2 and other macrophage cells based on scRNA-seq, related to Supplementary Fig. 6f.

Gene	Group	avgExpr	logFC	pval	padj	pct_in	pct_out	Status
APOE	RTM-FOLR2	3.99954	1.5383		0	1E-168	92.3179	Up
RNASE1	RTM-FOLR2	1.98502	1.42467		0	1E-139	78.5872	Up
C1QC	RTM-FOLR2	3.23853	1.38227		0	1E-101	98.0795	Up
C1QA	RTM-FOLR2	3.39998	1.31277		0	1E-134	98.543	Up
C1QB	RTM-FOLR2	3.49219	1.30948		0	1E-187	98.4106	Up
LGMN	RTM-FOLR2	2.27688	1.28688		0	1E-143	94.4592	Up
SELENOP	RTM-FOLR2	1.52174	1.23787		0	1E-114	74.128	Up
PLTP	RTM-FOLR2	1.66636	1.21149		0	1E-182	83.4879	Up
MS4A6A	RTM-FOLR2	2.36751	1.20717		0	1E-159	97.7704	Up
SLC40A1	RTM-FOLR2	1.42168	1.17841		0	1E-151	76.7991	Up
FOLR2	RTM-FOLR2	1.40189	1.12934		0	1E-197	80.8389	Up
MARCKS	RTM-FOLR2	1.76596	1.09531		0	1E-185	93.5982	Up
TMEM176B	RTM-FOLR2	1.92643	1.02286		0	1E-121	93.3996	Up
GPNMB	RTM-FOLR2	2.24556	0.94742		0	1E-154	89.6468	Up
MAFB	RTM-FOLR2	1.7869	0.94711		0	1E-174	92.34	Up
F13A1	RTM-FOLR2	1.3149	0.9124		0	1E-107	65.7395	Up
A2M	RTM-FOLR2	1.49856	0.87107		0	1E-173	85.298	Up
CCL3	RTM-FOLR2	1.67659	0.85739	5.167E-296	1E-179	70.3753	39.7958	Up
DAB2	RTM-FOLR2	1.72325	0.85162		0	1E-185	92.4945	Up
PLD3	RTM-FOLR2	1.90166	0.84975		0	1E-137	91.5673	Up
FTL	RTM-FOLR2	6.12532	0.84227	9.815E-298	1E-189	99.9779	98.7961	Up
MS4A4A	RTM-FOLR2	1.65578	0.83359		0	1E-137	90.4636	Up
KCNMA1	RTM-FOLR2	1.44371	0.83358		0	1E-134	79.8675	Up
CTSB	RTM-FOLR2	3.6044	0.82812		0	1E-189	99.3819	Up
TMEM176A	RTM-FOLR2	1.43176	0.8231		0	1E-144	86.4018	Up
CD14	RTM-FOLR2	1.74598	0.81437		0	1E-179	89.0066	Up
APOC1	RTM-FOLR2	3.45353	0.80698	2.877E-125	3E-123	90.6843	74.7857	Up
NPC2	RTM-FOLR2	2.68563	0.80579		0	1E-133	98.3885	Up
CD163	RTM-FOLR2	1.83263	0.80315		0	1E-184	91.4349	Up
FLNA	RTM-FOLR2	0.55607	-0.823		0	1E-195	46.6446	Down
S100A4	RTM-FOLR2	1.56459	-0.8449		0	1E-137	81.0817	Down
CD52	RTM-FOLR2	0.36555	-0.8878		0	1E-193	33.4216	Down
FN1	RTM-FOLR2	0.99653	-0.9537	2.039E-199	4E-197	47.9029	63.6425	Down
FBP1	RTM-FOLR2	0.56158	-0.9612		0	1E-112	50.6623	Down
CRIP1	RTM-FOLR2	0.93955	-1.0568		0	1E-114	54.415	Down

P values were calculated using a two-tailed Gaussian approximation of the U statistic and adjusted with the Benjamini–Hochberg procedure. avgExpr, mean value of feature in group; logFC, log fold change between observations in group vs out; *P*val, nominal *P* value, from two-tailed Gaussian approximation of U statistic; *Padj*, Benjamini-Hochberg adjusted *P* value; pct_in, percent of observations in the group with non-zero feature value; pct_out, percent of observations out of the group with non-zero feature value.

Supplementary Table 9. Differentially expressed genes in macrophage cells between CTL and CIP patients based on scRNA-seq, related to Fig. 5i.

Gene	Group	avgExpr	logFC	pval	padj	pct_in	pct_out	Status
APOE	CIP	3.37478	1.20105	0	1E-168	85.51	67.8397	Up
PLTP	CIP	1.23117	1.09889	0	1E-139	66.4426	11.9293	Up
RNASE1	CIP	1.38346	1.05058	0	1E-101	60.8408	17.3254	Up
MS4A6A	CIP	1.91431	1.04234	0	1E-134	87.9001	52.0484	Up
ABCA1	CIP	1.42722	1.03375	0	1E-187	80.2177	24.5263	Up
CTSB	CIP	3.40233	1.00793	0	1E-143	96.9697	87.4391	Up
LGMN	CIP	1.75435	1.00509	0	1E-114	78.201	45.5152	Up
TMEM176B	CIP	1.5731	0.96575	0	1E-182	81.7008	35.878	Up
KCNMA1	CIP	1.2122	0.93891	0	1E-159	68.2032	23.4615	Up
GPNMB	CIP	1.91316	0.88072	0	1E-151	79.8656	54.6833	Up
CCL3	CIP	1.39097	0.83791	0	1E-197	62.4733	26.4393	Up
MARCKS	CIP	1.3132	0.83389	0	1E-185	76.2911	29.6156	Up
NPC2	CIP	2.42941	0.82033	0	1E-121	91.3252	72.6403	Up
APOC1	CIP	3.18931	0.80103	4.108E-163	5E-161	86.2569	68.3812	Up
TMEM176A	CIP	1.14569	0.77244	0	1E-154	73.2074	26.4393	Up
MAFB	CIP	1.4095	0.75901	0	1E-174	80.4204	44.667	Up
NPL	CIP	1.02525	0.74477	0	1E-107	70.5826	27.7748	Up
SOD2	CIP	1.89573	0.73822	0	1E-173	87.2599	62.7685	Up
PLA2G7	CIP	0.88622	0.72152	0	1E-179	60.7661	12.3443	Up
RASSF4	CIP	1.02627	0.71577	0	1E-185	73.0687	29.9224	Up
IGSF6	CIP	1.51923	0.70535	0	1E-137	81.5514	53.6726	Up
CTSZ	CIP	2.71147	0.70485	0	1E-189	93.3099	81.303	Up
FYB1	CIP	1.38304	0.69939	0	1E-137	84.4857	48.7638	Up
CD163	CIP	1.5226	0.67057	0	1E-134	80.4524	55.1164	Up
SAT1	CIP	2.8679	0.66993	0	1E-189	96.0201	84.8944	Up
LILRB4	CIP	0.97143	0.66197	0	1E-144	70.8707	28.1538	Up
FMN1	CIP	0.90716	0.65749	0	1E-179	63.8498	19.5994	Up
CPM	CIP	1.07938	0.64773	0	1E-133	70.0064	38.2061	Up
CD84	CIP	0.85847	0.64337	0	1E-184	68.6406	21.6928	Up
CTSC	CIP	2.15151	0.64148	1.499E-249	1E-135	90.557	71.1243	Up
IER3	CIP	1.24833	0.63898	5.49E-301	1E-170	67.5843	32.9002	Up
GLUL	CIP	2.48104	0.63633	7.902E-268	1E-174	92.0294	79.2456	Up
VAMP5	CIP	0.89871	0.628	0	1E-142	64.0952	23.7683	Up
SRGN	CIP	2.42187	0.6066	3.237E-235	1E-138	94.2382	78.4335	Up
CD14	CIP	1.39818	0.58994	6.692E-260	1E-120	77.9983	48.9262	Up
SLC40A1	CIP	0.81523	0.57597	0	1E-128	48.3995	14.1671	Up
PLEK	CIP	1.38203	0.57047	2.079E-287	1E-120	82.0529	54.5028	Up
BASP1	CIP	0.84789	0.56854	0	1E-144	62.3986	19.5633	Up
CCL4	CIP	1.30547	0.56827	5.167E-146	5E-144	54.8442	32.0881	Up
BMP2K	CIP	0.95056	0.56304	0	1E-187	70.7213	33.8026	Up
CD63	CIP	2.39823	0.56278	2.167E-222	1E-170	90.9624	77.5853	Up
DPYD	CIP	1.54355	0.56228	1.022E-237	1E-140	85.4673	60.2418	Up
MS4A4A	CIP	1.28273	0.55798	2.65E-296	1E-144	76.9526	50.0812	Up
A2M	CIP	1.09705	0.55163	3.354E-277	1E-125	67.4349	36.5457	Up

CREG1	CIP	1.20356	0.54403	0	1E-170	76.1737	50.0812	Up
TNS3	CIP	1.13386	0.54171	0	1E-139	74.4345	45.9664	Up
AIF1	CIP	2.12319	0.541	7.45E-212	1E-151	88.1989	74.0661	Up
FOLR2	CIP	0.81641	0.54046	0	1E-142	53.9693	16.9644	Up
STAT1	CIP	1.21307	0.53838	8.127E-290	1E-106	76.8993	48.4931	Up
PMP22	CIP	0.79124	0.53757	0	1E-124	62.644	23.8585	Up
RBPJ	CIP	1.29412	0.52265	4.8E-215	1E-132	79.1293	55.73	Up
F13A1	CIP	0.87295	0.52024	7.982E-250	1E-114	47.4925	18.1195	Up
NFKBIA	CIP	1.86108	0.51977	1.787E-138	2E-136	85.7021	67.551	Up
S100A10	CIP	2.14836	-0.5124	7.775E-212	1E-167	87.3986	86.9157	Down
ALDH2	CIP	0.93116	-0.5125	9.956E-171	1E-168	68.4486	67.19	Down
AHNAK	CIP	1.534	-0.5329	6.922E-226	1E-173	84.0269	88.179	Down
CD9	CIP	0.73018	-0.5373	2.529E-193	4E-191	54.9723	63.5084	Down
MYADM	CIP	0.56314	-0.5428	1.784E-244	1E-117	51.7926	64.0859	Down
INHBA	CIP	0.10761	-0.5611	0	1E-184	8.16261	38.567	Down
PDLIM1	CIP	0.0859	-0.583	0	1E-105	10.4567	42.5916	Down
SVIL	CIP	0.15631	-0.596	0	1E-141	16.9227	47.3741	Down
LSAMP	CIP	0.04002	-0.598	0	1E-191	3.35041	30.4458	Down
LTA4H	CIP	0.77088	-0.5983	2.541E-224	1E-131	60.286	66.3599	Down
MARCO	CIP	1.03479	-0.6164	3.279E-146	3E-144	55.5378	60.8735	Down
TREM1	CIP	0.37364	-0.6171	5.187E-303	1E-172	36.5237	56.1812	Down
JUND	CIP	0.94866	-0.6189	0	1E-136	69.6756	75.1669	Down
FBP1	CIP	0.98638	-0.6578	2.669E-165	3E-163	59.379	65.656	Down
ALOX5AP	CIP	0.64002	-0.6699	1.3E-234	1E-149	46.2015	60.3682	Down
LY6E	CIP	0.57636	-0.6711	1.287E-267	1E-141	51.9099	61.7037	Down
S100A6	CIP	2.38061	-0.6816	8.649E-268	1E-129	86.6944	89.8755	Down
FLNA	CIP	0.8511	-0.7482	0	1E-185	58.9309	75.4376	Down
CD52	CIP	0.70483	-0.7504	9.994E-271	1E-164	48.0794	62.9128	Down
CES1	CIP	0.12846	-0.7806	0	1E-101	12.516	43.494	Down
TAGLN2	CIP	1.3755	-0.7819	0	1E-153	79.6948	84.9486	Down
LMNA	CIP	0.87601	-0.8177	0	1E-184	58.5254	74.8962	Down
S100A4	CIP	1.83603	-0.8526	0	1E-157	79.6628	86.2299	Down
MCEMP1	CIP	0.26214	-0.8767	0	1E-188	18.2458	51.164	Down
RETN	CIP	0.25385	-0.8867	0	1E-153	18.8754	50.4783	Down
FN1	CIP	1.30391	-0.9598	2.482E-209	1E-186	55.1216	65.1868	Down
RGCC	CIP	0.54372	-0.9778	0	1E-150	39.554	68.327	Down
FABP4	CIP	0.06068	-1.2688	0	1E-180	3.84123	46.941	Down
CRIP1	CIP	1.12586	-1.4789	0	1E-130	59.6244	81.303	Down

P values were calculated using a two-tailed Gaussian approximation of the U statistic and adjusted with the Benjamini–Hochberg procedure. avgExpr, mean value of feature in group; logFC, log fold change between observations in group vs out; *P*val, nominal *P* value, from two-tailed Gaussian approximation of U statistic; *P*adj, Benjamini-Hochberg adjusted *P* value; pct_in, percent of observations in the group with non-zero feature value; pct_out, percent of observations out of the group with non-zero feature value.

Supplementary Table 10. Differentially expressed genes in monocytes between CTL and CIP patients based on scRNA-seq, related to Fig. 6c.

Gene	Group	avgExpr	logFC	pval	padj	pct_in	pct_out	Status
IER3	CIP	1.88654	0.93391	2.969E-126	1.137E-121	78.8308	50.3064	Up
CCL3	CIP	1.21052	0.81622	6.845E-101	1.3113E-96	48.1231	21.1867	Up
CCL4	CIP	1.15479	0.73996	7.9777E-76	3.8209E-72	43.2615	20.3483	Up
S100A8	CIP	3.4164	0.6809	4.97E-36	1.9235E-33	87.3846	80.8771	Up
IL1B	CIP	2.84753	0.67123	4.0856E-50	4.3484E-47	84.6769	80.3289	Up
EGR1	CIP	1.26006	0.61948	7.5173E-67	1.9202E-63	59.1385	38.3425	Up
S100A9	CIP	3.81417	0.60924	6.917E-41	3.681E-38	95.9385	93.3247	Up
CXCL8	CIP	1.45548	0.58157	1.7064E-38	7.9736E-36	55.4462	40.1161	Up
MTRNR2L8	CIP	0.07601	-0.5872	2.6888E-55	4.6828E-52	6.89231	24.089	Down
AREG	CIP	0.6106	-0.5904	7.8475E-49	7.3338E-46	32.3692	51.5318	Down

P values were calculated using a two-tailed Gaussian approximation of the U statistic and adjusted with the Benjamini–Hochberg procedure. avgExpr, mean value of feature in group; logFC, log fold change between observations in group vs out; *P*val, nominal *P* value, from two-tailed Gaussian approximation of U statistic; *P*adj, Benjamini-Hochberg adjusted *P* value; pct_in, percent of observations in the group with non-zero feature value; pct_out, percent of observations out of the group with non-zero feature value.

Supplementary Table 11. Differentially expressed genes in epithelial cells between CTL and CIP patients based on scRNA-seq, related to Fig. 7f.

Gene	Group	avgExpr	logFC	pval	padj	pct_in	pct_out	Status
SCGB3A1	CIP	1.90735	1.25338	0	1.00E-176	69.7249	31.3012	Up
SCGB1A1	CIP	1.47352	1.21246	0	1.00E-180	57.2762	7.92532	Up
WFDC2	CIP	2.22201	0.96803	0	1.00E-133	89.5182	75.5191	Up
KRT17	CIP	1.05304	0.92524	0	1.00E-162	37.7568	5.48676	Up
B2M	CIP	3.66413	0.87931	0	1.00E-106	98.8049	97.6186	Up
HLA-B	CIP	2.66536	0.79832	0	1.00E-160	95.4438	91.465	Up
HLA-A	CIP	2.24852	0.75666	0	1.00E-146	93.34	85.7497	Up
PABPC1	CIP	2.05084	0.72344	0	1.00E-119	92.6926	81.7489	Up
CLU	CIP	1.07585	0.66814	0	1.00E-176	70.92	35.9688	Up
TXNIP	CIP	1.32433	0.63581	0	1.00E-151	78.8871	52.9625	Up
KRT15	CIP	0.78154	0.62602	1.18E-203	1.00E-104	35.7525	13.3549	Up
SCGB3A2	CIP	1.43991	0.62291	6.42E-70	1.84E-68	48.2261	35.321	Up
AGR2	CIP	1.39182	0.61681	1.14E-252	1.00E-174	75.4637	56.887	Up
IGFBP2	CIP	0.68245	0.60772	0	1.00E-115	35.7774	4.55325	Up
IFI27	CIP	1.11163	0.60592	4.58E-308	1.00E-120	67.4468	33.6826	Up
AGER	CIP	0.27389	-0.602	1.13E-109	6.54E-108	22.6939	36.7118	Down
SUSD2	CIP	0.43169	-0.6107	0	1.00E-122	37.4206	70.5277	Down
SYNE1	CIP	0.9934	-0.6288	1.83E-270	1.00E-192	64.7205	83.2159	Down
SFTPA2	CIP	2.75101	-0.6411	1.80E-20	1.34E-19	72.5009	76.7194	Down
AFF3	CIP	0.36339	-0.6478	0	1.00E-109	29.329	62.4881	Down
SGMS2	CIP	0.65629	-0.6497	0	1.00E-169	55.7202	77.4433	Down
IER2	CIP	1.34232	-0.6589	1.27E-284	1.00E-140	74.6421	88.0549	Down
PHACTR1	CIP	0.51906	-0.6631	0	1.00E-193	40.9436	72.8901	Down
DLG2	CIP	0.66528	-0.6731	1.04E-292	1.00E-137	42.4001	69.9181	Down
ICAM1	CIP	0.89573	-0.6799	4.05E-294	1.00E-193	60.5876	80.1295	Down
SFTA2	CIP	1.3595	-0.6877	1.31E-168	1.70E-166	58.9693	85.3496	Down
JUNB	CIP	1.52987	-0.6947	2.94E-267	1.00E-102	76.2604	90.1315	Down
KLF6	CIP	1.02232	-0.7057	0	1.00E-155	62.7661	86.3784	Down
MTRNR2L8	CIP	0.1323	-0.7257	1.83E-122	1.28E-120	16.4447	29.9486	Down
CXCL2	CIP	1.06324	-0.7264	8.12E-198	1.46E-195	56.6414	70.8897	Down
ZNF385B	CIP	0.73697	-0.7271	0	1.00E-143	46.9065	75.6906	Down
ATP11A	CIP	0.91851	-0.7361	0	1.00E-145	58.2348	87.9025	Down
LDLR	CIP	0.64651	-0.7382	0	1.00E-155	55.0355	82.7586	Down
NFKBIA	CIP	1.382	-0.744	0	1.00E-142	75.6753	89.8076	Down
SFTPB	CIP	3.3478	-0.7468	3.34E-74	1.04E-72	79.8083	85.3686	Down
SFTA3	CIP	0.68752	-0.7644	0	1.00E-193	50.8901	84.9114	Down
WIF1	CIP	0.31873	-0.7722	0	1.00E-189	29.1672	64.4504	Down
LMNA	CIP	1.07003	-0.7773	0	1.00E-185	69.6502	91.2174	Down
NEDD4L	CIP	1.36004	-0.7931	0	1.00E-190	81.327	95.3515	Down
CLDN18	CIP	0.37051	-0.794	0	1.00E-173	29.3788	71.4993	Down
CELF2	CIP	0.90184	-0.798	0	1.00E-178	63.2765	88.7026	Down
EGR1	CIP	1.45008	-0.8053	2.96E-291	1.00E-162	70.8079	87.8453	Down
FOS	CIP	2.04977	-0.8101	6.44E-302	1.00E-134	82.7586	94.6275	Down
NAPSA	CIP	1.81165	-0.8145	9.82E-151	9.96E-149	59.5917	81.1202	Down

P3H2	CIP	0.39674	-0.8256	0	1.00E-148	35.1301	73.976	Down
ACOXL	CIP	0.42967	-0.8377	0	1.00E-172	31.022	69.7276	Down
JUN	CIP	2.21076	-0.8647	0	1.00E-176	85.8459	95.18	Down
RNASE1	CIP	1.69962	-0.8827	0	1.00E-169	69.7996	90.5315	Down
CEBPD	CIP	1.1605	-0.9109	0	1.00E-127	69.5631	84.5494	Down
DLC1	CIP	0.67976	-0.9534	0	1.00E-183	45.9231	87.2928	Down
SFTPA1	CIP	2.6737	-0.9839	1.32E-83	5.05E-82	73.1234	77.7291	Down
FOSB	CIP	1.34569	-0.9951	0	1.00E-170	69.8992	91.5031	Down
SFTPD	CIP	1.12831	-1.018	0	1.00E-123	51.7864	79.558	Down
PGC	CIP	0.46411	-1.0272	0	1.00E-108	28.5821	66.8508	Down
NR4A1	CIP	0.91268	-1.0355	0	1.00E-131	55.3342	84.0732	Down
C11orf96	CIP	0.40138	-1.129	0	1.00E-195	30.3996	65.8983	Down
ZFP36	CIP	1.35962	-1.207	0	1.00E-160	72.364	93.7702	Down
JUND	CIP	0.96451	-1.2898	0	1.00E-197	65.2185	91.8842	Down
SFTPC	CIP	3.30333	-1.9715	0	1.00E-136	82.6092	85.4829	Down

P values were calculated using a two-tailed Gaussian approximation of the U statistic and adjusted with the Benjamini–Hochberg procedure. avgExpr, mean value of feature in group; logFC, log fold change between observations in group vs out; *P*val, nominal *P* value, from two-tailed Gaussian approximation of U statistic; *P*adj, Benjamini-Hochberg adjusted *P* value; pct_in, percent of observations in the group with non-zero feature value; pct_out, percent of observations out of the group with non-zero feature value.

Supplementary Table 12. qRT-PCR primers used in this study.

Primers	Sequence
TNF-F	CTCTTCTGCCTGCTGCACTTTG
TNF-R	ATGGGCTACAGGCTTGTCACCTC
NR4A1-F	GGACAACGCTTCATGCCAGCAT
NR4A1-R	CCTTGTTAGCCAGGCAGATGTAC
CD8A-F	ACTTGTGGGGTCCTTCTCCTGT
CD8A-R	TGTCTCCCGATTTGACCACAGG
CD8B-F	AAGACAGTGGCATCTACTTCTGC
CD8B-R	TTGAGGGTGGACTTCTTGGTGG
ITGAE-F	GACATGGATGGAAGCACGGACT
ITGAE-R	CTCAGTATGCGTGCCAAGGAGA
ZNF683-F	AGCCTTGCCTTACCCGCTGAAA
ZNF683-R	AATGGACGCTCTCCACTGTGCA
GSDME-F	GATCTCTGAGCACATGCAGGTC
GSDME-R	GTTGGAGTCCTTGGTGACATTCC
IL1B-F	CCACAGACCTTCCAGGAGAATG
IL1B-R	GTGCAGTTCAGTGATCGTACAGG
CXCL13-F	TATCCCTAGACGCTTCATTGATCG
CXCL13-R	CCATTCAGCTTGAGGGTCCACA
CXCR6-F	CAGTTCAGCAAGGTCTTTCTGCC
CXCR6-R	AGGTTCACCAGGAACACATCCG
STAT1-F	ATGGCAGTCTGGCGGCTGAATT
STAT1-R	CCAAACCAGGCTGGCACAATTG
GAPDH-F	GTCTCCTCTGACTTCAACAGCG
GAPDH-R	ACCACCCTGTTGCTGTAGCCAA
RGS1-F	TTGTGCATTGAGATGCTGCTAAAC
RGS1-R	GAGGAACCTGGGATAAGAGTCC
CCL3-F	ACTTTGAGACGAGCAGCCAGTG
CCL3-R	TTTCTGGACCCACTCCTCACTG
FOLR2-F	CCACTTCATCCAGGACACCTGT
FOLR2-R	CATCCAGGAAGCGTTCTTTGCG

Supplementary Table 13. Primary antibodies used for IHC, MIF and Flow cytometry.

Antibodies	Source	Identifier	Clone	Dilution	Application
Anti-human IgG antibody	Abcam	ab109489	EPR4421	1:500	IHC
Anti-human CD8 antibody	CST	98941	D4W2Z	1:100	MIF
Anti-human IFN- γ antibody	Abcam	ab231036	EPR21704	1:500	MIF
Anti-human CD103 antibody	Abcam	ab224202	EPR22590-27	1:200	MIF
Anti-human CD45 antibody	Abcam	ab208022	EPR20033	1:2000	MIF
Anti-human CD14 antibody	Abcam	ab133335	EPR3653	1:2000	MIF
Anti-human CCL3 antibody	Abcam	ab259372	EPR23751-54	1:1000	MIF
Anti-human CCL4 antibody	Bioss	bs-2475R	Polyclonal	1:200	MIF
Anti-human CD68 antibody	ABclonal	A23205	Monoclonal	1:2000	MIF
Anti-human GSDME antibody	Abcam	ab230482	Polyclonal	1:100	MIF
Anti-human FR- β (FOLR2) antibody	Abcam	ab302532	EPR25731-70	1:100	MIF
PE/Cyanine7 anti-human CD3 antibody	BioLegend	300420	UCHT1	5 μ L per million cells	FC
Pacific Blue anti-human CD4 antibody	BioLegend	344620	SK3	5 μ L per million cells	FC
FITC anti-human CD25 antibody	BioLegend	356105	M-A251	5 μ L per million cells	FC
APC anti-human CD127 (IL-7R α) antibody	BioLegend	351315	A019D5	5 μ L per million cells	FC
PE anti-human IL-17A Recombinant antibody	BioLegend	385905	QA18A46	5 μ L per million cells	FC
APC anti-human CD8 antibody	BioLegend	344721	SK1	5 μ L per million cells	FC
FITC anti-human IFN- γ antibody	BioLegend	502505	4S.B3	5 μ L per million cells	FC
PE anti-human TNF- α antibody	BioLegend	502908	MAb11	5 μ L per million cells	FC
PE/Cyanine7 anti-human CD68 antibody	BioLegend	333816	Y1/82A	1 μ L per million cells	FC
Anti-cleaved N-terminal DFNA5 / GSDME antibody	Abcam	ab222408	EPR20867-248	1 μ L per million cells	FC
PE anti-human Folate Receptor β (FR- β) antibody	BioLegend	391704	94b/FOLR2	1 μ L per million cells	FC

CST, cell signaling technology; IHC, Immunohistochemistry; MIF, Multiplex Immunofluorescence; FC, flow cytometry.