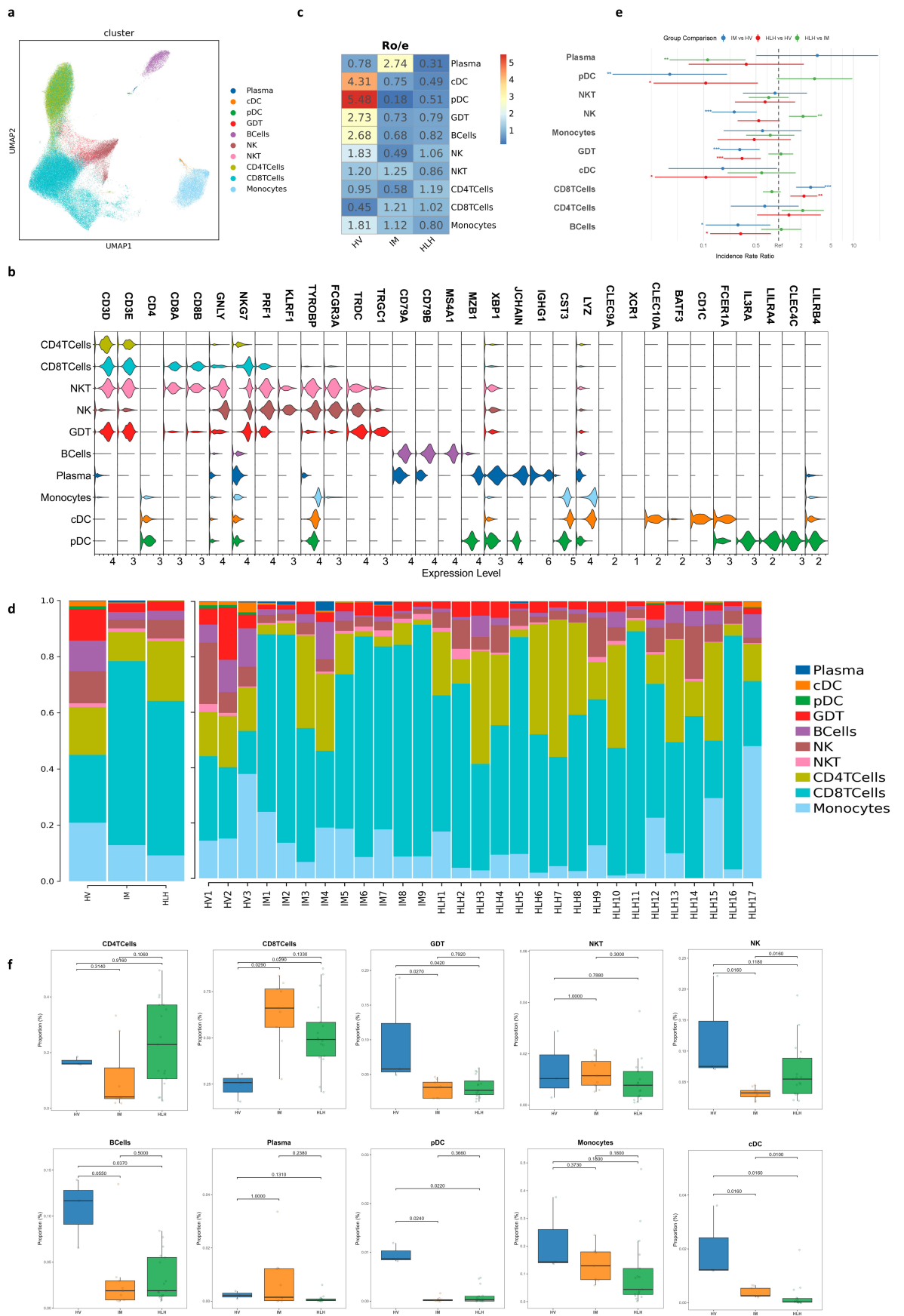
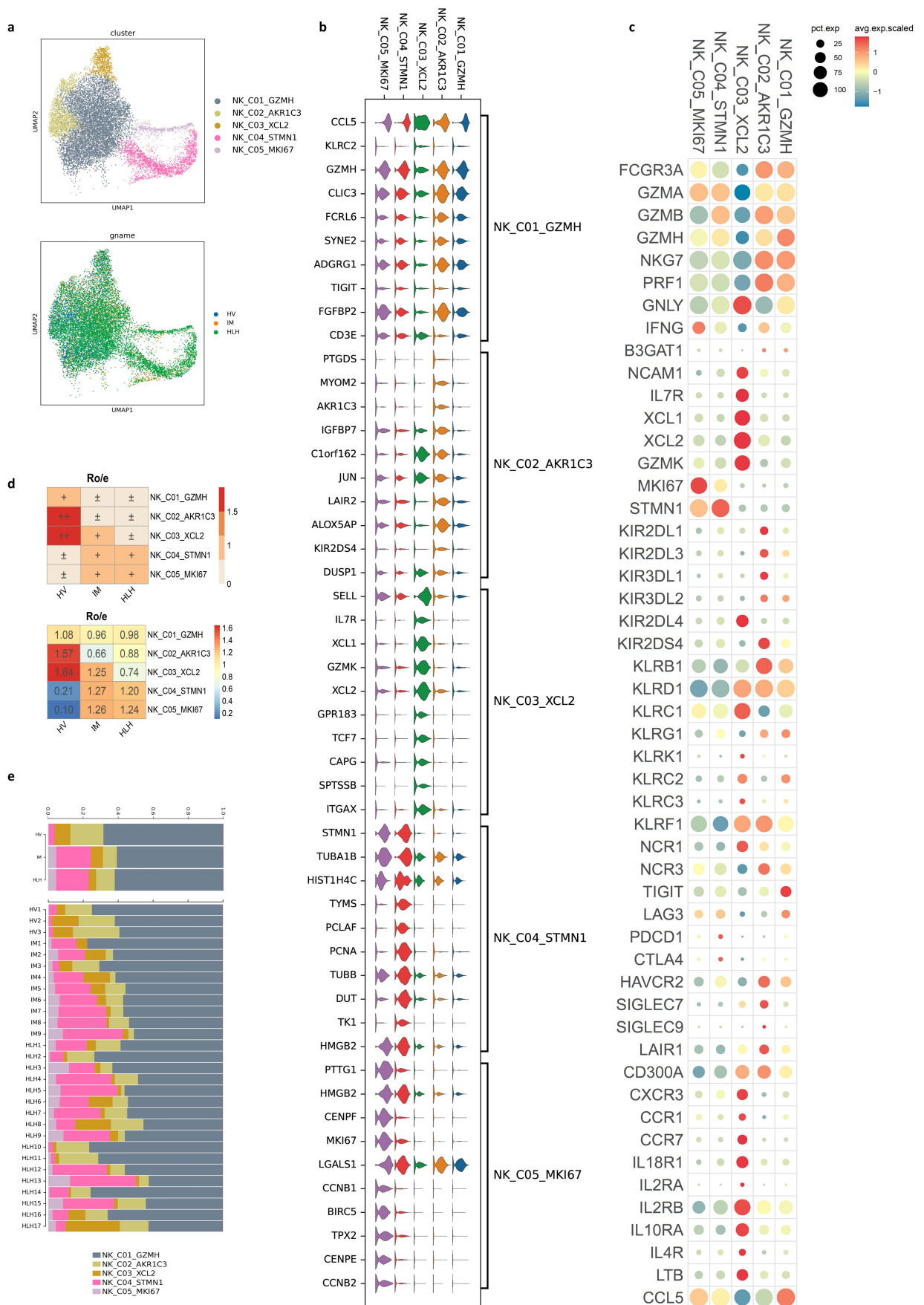


Biomarkers of Pediatric Epstein-Barr Virus-Associated Hemophagocytic Lymphohistiocytosis through Single-Cell Transcriptomics

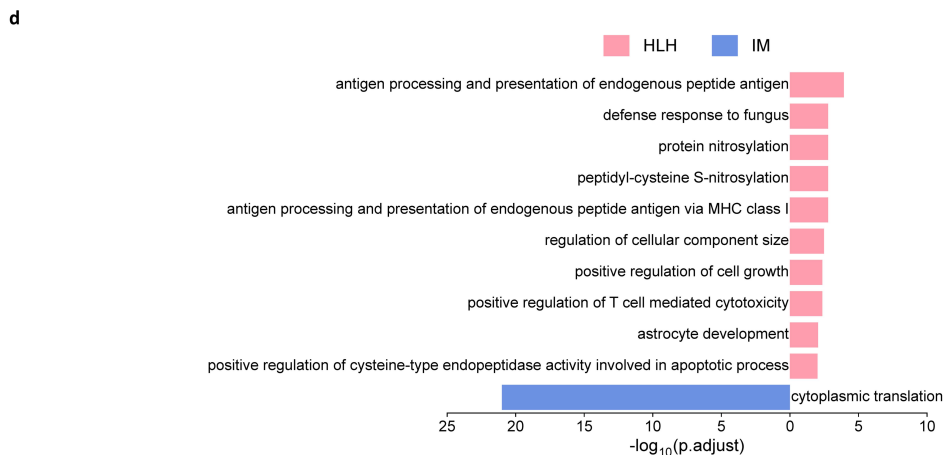
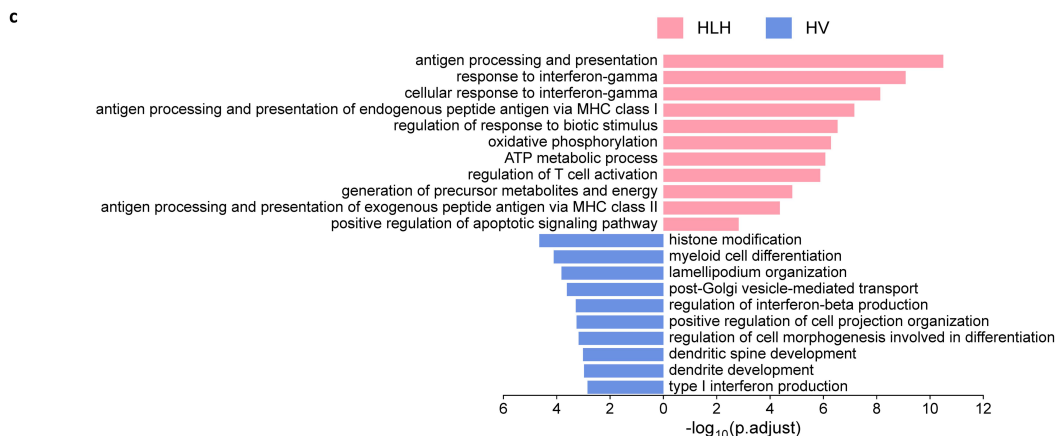
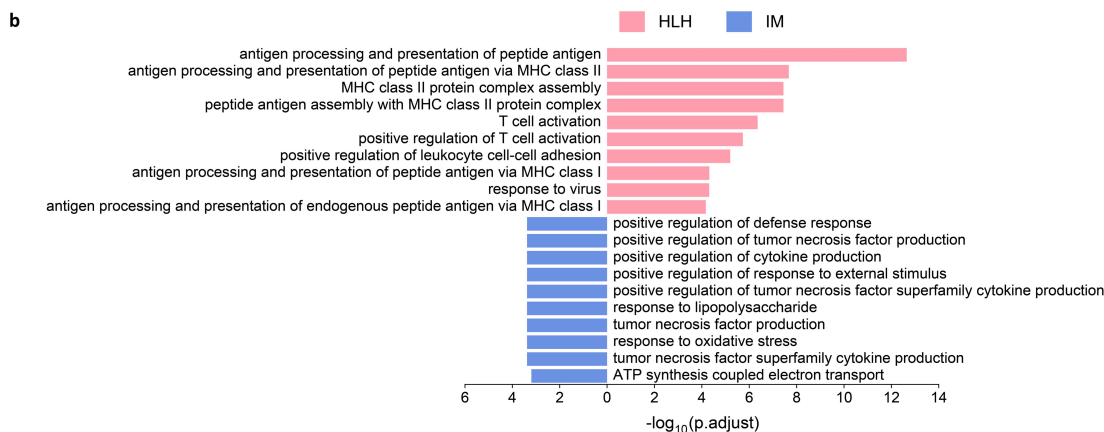
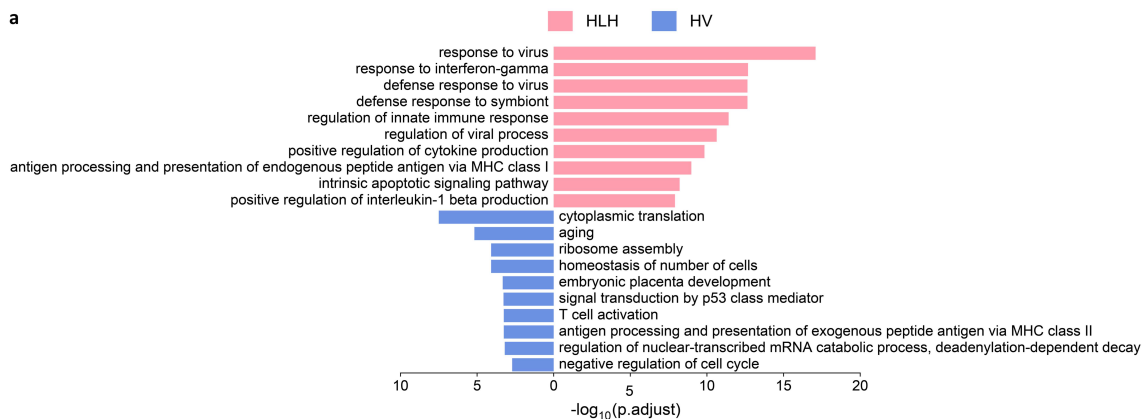
Jie Shen, Yunyan He, Hong Zheng, Jianwen Xiao, Fu Li, Keke Chen, Biyun Guo, Yulei He, Lin Liu, Zhi Lin, Dan Wang, Leping Liu, Shengfeng Wang, Wen Zhou, Yingchi Zhang, Jian Wei, Yunchu Wang, Rong Hu, Daolin Tang, Dao Wang, Minghua Yang



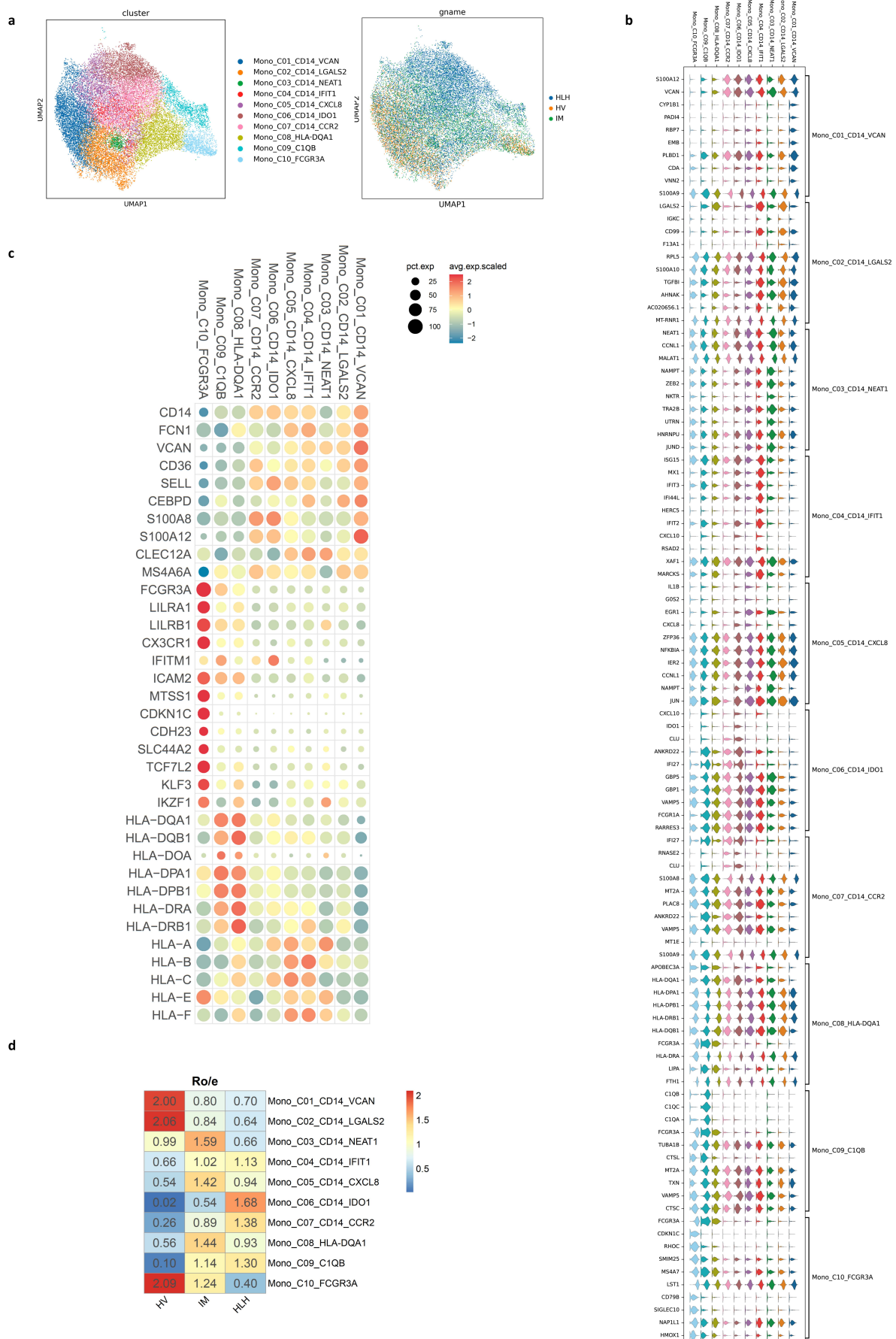
Supplementary Fig. 1: Overview of single-cell atlas. (a) UMAP visualization of 216,817 single cells from 29 samples. (b) Violin plot showing the expression patterns of canonical markers. Each column corresponded to specific marker genes, while rows denoted clusters, colored identically to those in a. (c) Quantification of cell subpopulation enrichment based on Ro/e for cellular populations. (d) Cell compositions at single group and single sample level. (e) The forest plot demonstrating intergroup comparisons of cell subtype counts. Specifically, a negative binomial regression model was employed, with the count of each cellular subset as the dependent variable and group classification as the independent variable. An offset term of log (total captured cell number per sample) was incorporated to control for potential confounding effects caused by variations in total cell capture efficiency across samples. *P* value was subjected to FDR corrected. (f) Box plot depicting the percentage of each cell cluster, with the median indicated by a horizontal line. Two-sided Wilcoxon tests were performed between groups and *P* values were adjusted using the BH correction.



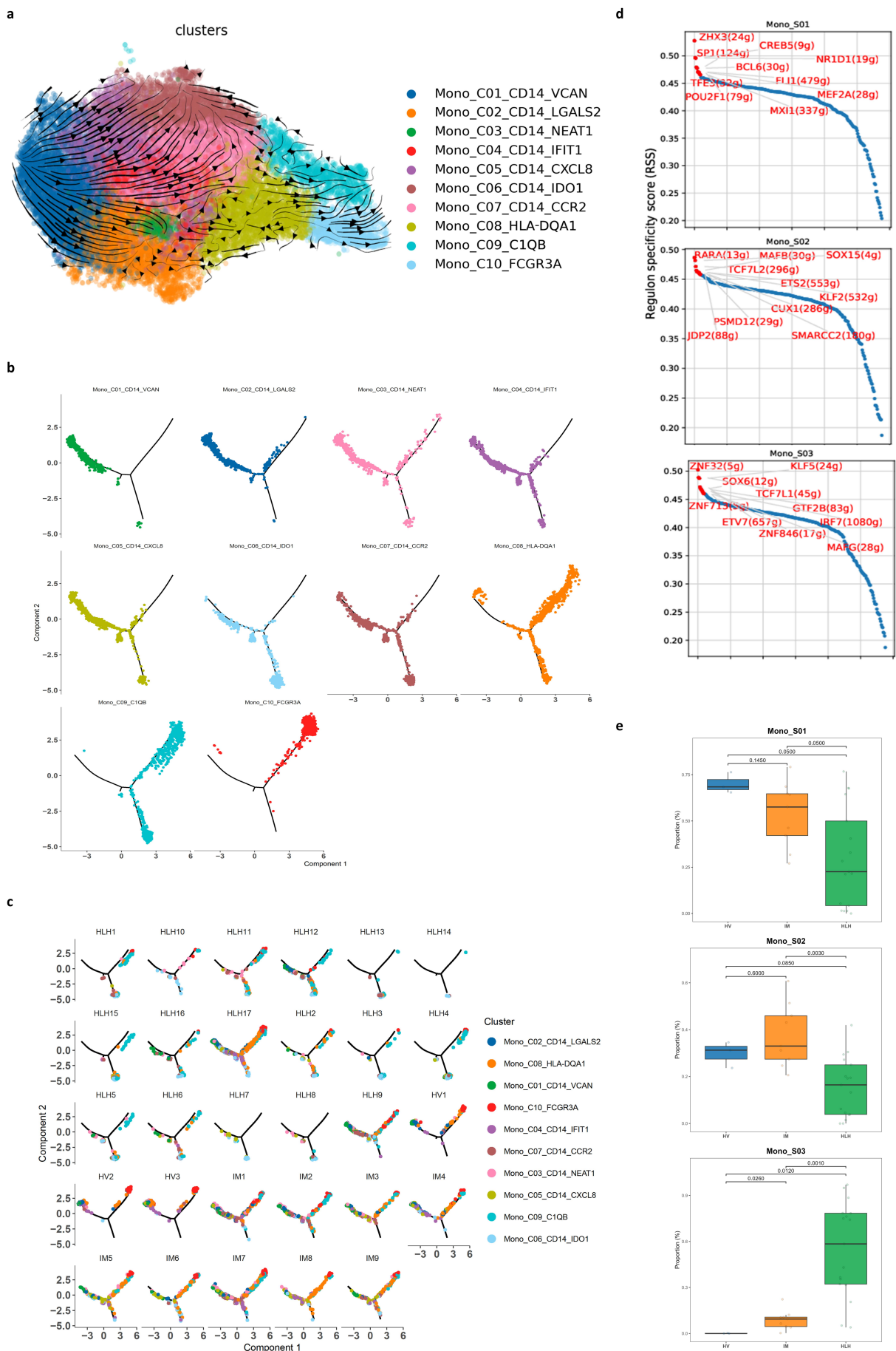
Supplementary Fig. 3: Identification of NK cell clusters. (a) Visualization through UMAP of 13,511 single NK cells derived from 29 samples. Cells were colored according to clusters and groups. (b) Violin plot showing the expression patterns of functional markers. Each column corresponded to specific marker genes, while rows denoted clusters, colored identically to those in a. (c) Expression distribution of canonical markers identifying individual cell clusters in the dot plot. The diameter of each dot reflected the proportion of subtype cells expressing a specific gene, while the color denotes the normalized mean expression. (d) Quantification of cell subpopulation enrichment based on Ro/e for cellular populations. (e) Cell compositions at single group and single sample level.



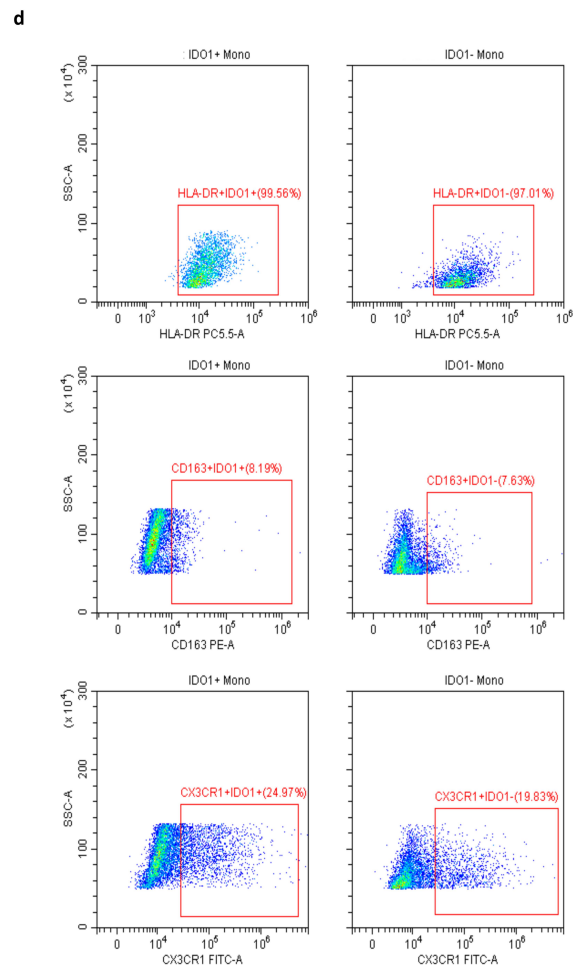
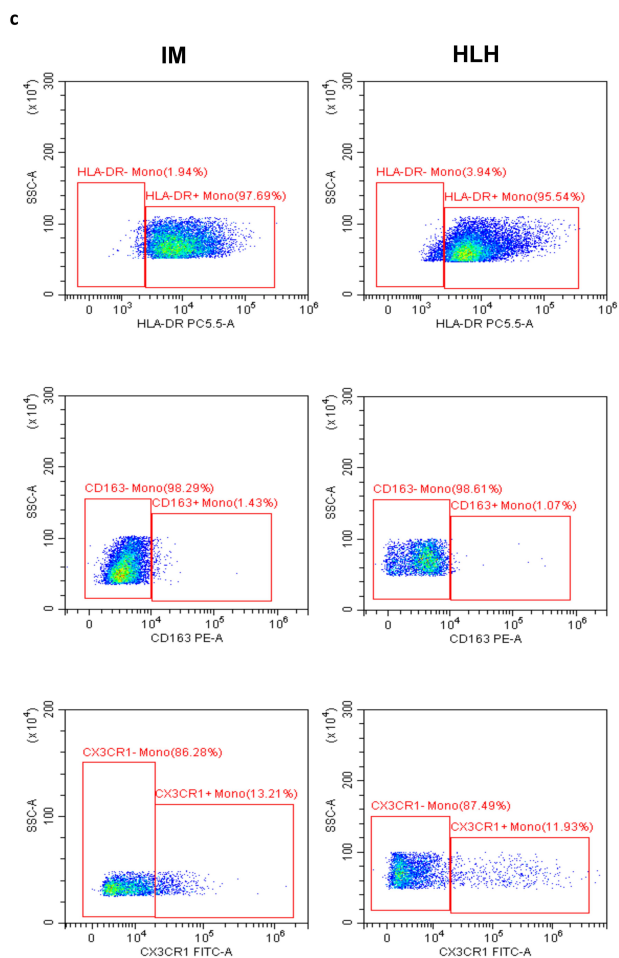
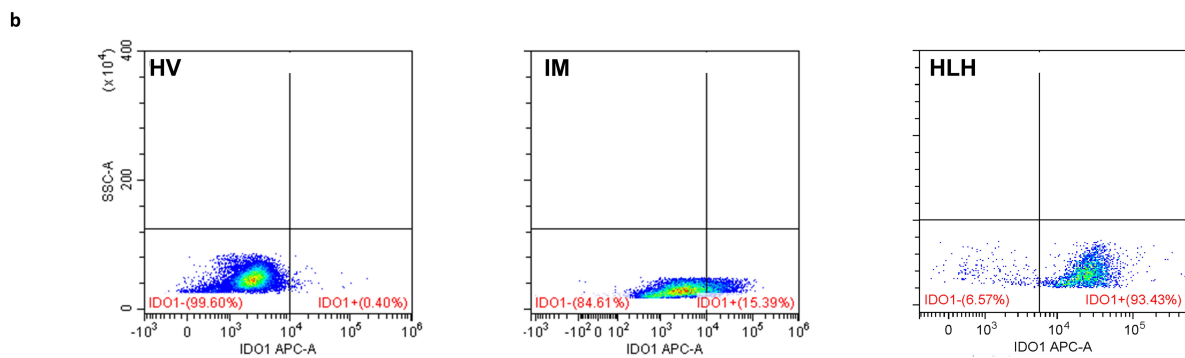
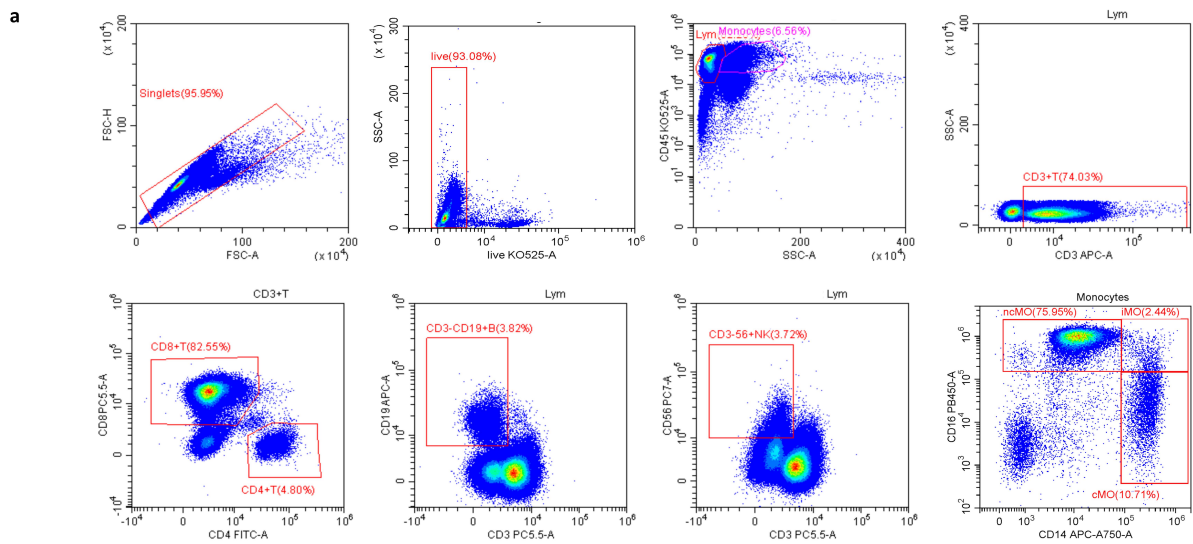
Supplementary Fig. 5: Identification of DCs clusters. (a) Enriched GO terms of differentially expressed genes in cDC between HLH and HV groups. (b) Enriched GO terms of differentially expressed genes in cDC between HLH and IM groups. (c) Enriched GO terms of differentially expressed genes in pDC between HLH and HV groups. (d) Enriched GO terms of differentially expressed genes in pDC between HLH and IM groups. The enrichment results in a – d were produced by clusterProfiler and BH-corrected.



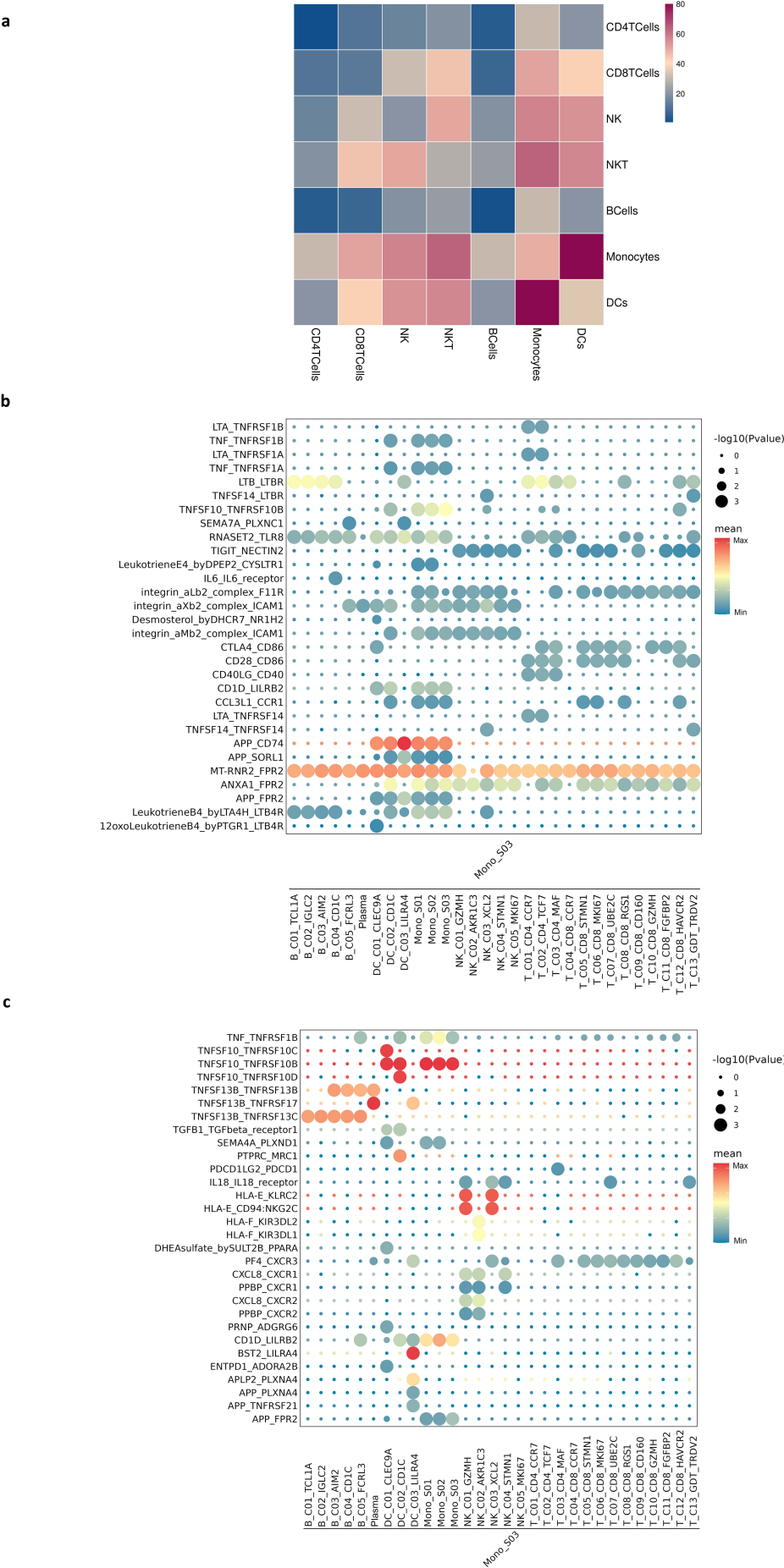
Supplementary Fig. 6: Identification of monocytes clusters. (a) UMAP visualization of 24,913 single monocytes from 29 samples. Cells were colored according to clusters and groups. (b) Violin plot showing the expression patterns of functional markers. Each column corresponded to specific marker genes, while rows denoted clusters, colored identically to those in a. (c) Expression distribution of canonical markers identifying individual cell clusters in the dot plot. The diameter of each dot reflected the proportion of subtype cells expressing a specific gene, while the color denotes the normalized mean expression. (d) Quantification of cell subpopulation enrichment based on Ro/e for cellular populations.



Supplementary Fig. 7: Trajectory comparisons among all monocytic clusters. (a) RNA velocity to transient cell states. Arrows indicated the direction of differentiation. Pseudotime trajectory analysis of monocytes among each cell cluster (b) and sample (c), where each dot signified an individual cell and was colored according to its cluster label. (d) The top 10 transcriptional regulons in each cell type. (e) Box plot depicting the percentage of each cell cluster in HV (n=3), IM (n=9) and HLH (n=17) group, with the median indicated by a horizontal line. Two-sided Wilcoxon tests were performed between groups and *P* values were adjusted using the BH correction.



Supplementary Fig. 8: Flow gating strategy and FACS plots for staining. (a) Flow gating strategy for peripheral blood samples containing T, B, NK and monocytes. (b) FACS plots of IDO1 staining of monocyte populations in the HV, IM and HLH groups. (c) FACS plots of HLA-DR, CD163 and CX3CR1 staining of monocyte populations in the IM and HLH groups. (d) In monocyte subsets of HLH patients, FACS plots of HLA-DR⁺/CD163⁺/CX3CR1⁺ proportions between IDO1⁺ and IDO1⁻ subpopulations.



Supplementary Fig. 9: Analysis of cellular communication within the HLH group. (a) Heatmap depicting the quantity of interaction pairs between two cell types, where intensification of the color gradient signified an increased count of interaction events. Bubble chart depicting the top 30 predicted interaction pairs involving Mono-S03 as the receptor (b) and ligand (c) cells with various other cell types. The circle size in this illustration reflected the significance P value of the ligand-receptor axis, and the color indicated the specificity of the interactions. The interaction results were produced by CellPhoneDB.

Supplementary Table 1: Baseline characteristics of scRNA-seq group

	HV	IM	HLH
Age category — no.			
< 2	0	1	1
[2-6)	2	3	13
[6-12)	1	5	3
[12-18]	0	0	0
Median age (range) — yr	5.3 (4.9 - 6.3)	6.0 (1.5-11.0)	4.1 (1.7-10)
EBV-DNA copy (whole blood) — no.			
< 1000	1	0	0
1000-10000	2	4	2
> 10000	-	5	15
Median EBV-DNA copy(range) — copies/mL	1,310 (634 - 2,410)	15,000 (1,050 - 102,100)	384,000 (1,730 – 9,500,000)
Serum ferritin — no.			
< 500	-	2	1
500-5000	-	1	8
5001-10000	-	-	1
> 10000	-	-	7
unknown	3	6	0
Median Serum ferritin (range) —µg/L	-	156 (114 - 3,707)	4,045 (309 - 40,000)
sCD25— no.			
< 2400	-	-	0
2400-5000	-	-	1
> 5000	-	-	16
Median sCD25(range) —U/mL	-	-	38,360 (4,107 - 227,675)
Efficacy — no.	-		
complete response, CR	-	-	15
partial response, PR	-	-	0
no response, NR	-	-	2
Outcome — no.			
alive	-	9	15
deceased	-	0	2

Supplementary Table 2: Clinical characteristics of scRNA-seq group

Sample	Gender	Race	Age at onset (years)	Interval between onset and admission (days)	Treatment	Therapeutic success (weeks)	Response (n)	Clinical Outcomes	EBV-DNA (<400 copies/mL)	EBV-infected cell type	EBV-VCA-IgM	EBV-VCA-IgG	EBV-EA-IgG	Hepato-megaly	Splenomegaly	Lymphadenopathy by biopsy	Marrow biopsy agerocyte	Serum ferritin (pg/L)	Natural killer cell function assay	CD25+ blood cell count	White blood cell count	Absolute lymphocyte count	Absolute monocyte count	Absolute neutrophil count	Red blood cell count	Hemoglobin (g/L)	Platelet count	Triglyceride (nmol/L)	Aspartate aminotransferase (U/L)	Alanine aminotransferase (U/L)	Lactate dehydrogenase (U/L)	Total Protein (g/L)	Albumin (g/L)	Total Bilirubin (μmol/L)	Direct Bilirubin (μmol/L)	APTT (s)	PT (s)	TT (s)	FIB		
reference ranges																		20 - 110	>14%	3.5-9.5	1.1-3.2	0.1-0.6 (10 ⁹ /L)	1.8-6.3 (10 ⁹ /L)	3.8-6.1 (10 ¹² /L)	115-150 (10 ¹² /L)	125-380 (10 ⁹ /L)	<1.7 (10 ³ /L)	13-15 (U/L)	7-40 (U/L)	120-250 (U/L)	65-85 (g/L)	40-55 (g/L)	3.42-20.5 (μmol/L)	0.6-0.4 (μmol/L)	20-40 (s)	9-14 (s)	14-21 (s)	2-4 (g/L)			
HLJ11	Female	East Asian (China)	0 (46)	1	HLJE-1994	8	CR	alive	9.29E+05	B, NK, T	(+)	(+)	(+)	(+)	Yes	Yes	No	Yes	20000	1.35%	44020	0.89	0.02	0.48	1.76	45	25	4.46	343	104	1752	41.9	24.4	6.1	3.4	45.2	12.9	25.4	0.77		
HLJ12	Male	East Asian (China)	0 (46)	2	HLJE-1994	8	CR	alive	1.73E+03	B	(+)	(+)	(+)	(+)	Yes	No	No	Yes	8866	3.85%	4107	972	2.1574	0.16524	0.48916	1.81	106.7	179.5	3.75	1478	1011	1856	73.1	39.0	52.1	46.8	50.9	12.0	11.6	2.26	
HLJ13	Male	East Asian (China)	0 (46)	1	HLJE-1994	8	CR	alive	3.84E+05	B, NK, T	(+)	(+)	(+)	(+)	Yes	No	Yes	4045	227675	1.06	0.88	0.06	0.15	2.97	91	57	2.76	143	8.8	3.5	46.2	12.4	22.5	1.18							
HLJ14	Male	East Asian (China)	0 (46)	2	HLJE-1994	8	CR	alive	1.14E+06	B, NK, T	(+)	(+)	(+)	(+)	Yes	No	Yes	Yes	2740	19.07%	44000	0.41	0.17	0.06	0.36	3.43	107	61	2.65	51	31	478	50.1	27.4	6.5	0.0	25.2	11.7	21.6	0.91	
HLJ15	Male	East Asian (China)	0 (46)	1	HLJE-1994	8	CR	alive	3.08E+04	B, NK	(+)	(+)	(+)	(+)	Yes	Yes	No	Yes	1650	33.67%	39977	1.25	7.76	0.23	3.03	3.67	90	120	3.62	565.2	81.4	3116.3	42.7	23.4	55.6	37.7	34.1	13.1	21.7	0.89	
HLJ16	Female	East Asian (China)	0 (46)	0	HLJE-1994	2	CR	alive	9.46E+03	B, NK	(+)	(+)	(+)	(+)	Yes	Yes	No	Yes	1232	10.60%	13680	1.87	1.28	0.15	0.44	3.33	83.9	44	2.64	310	126	726	61.7	30.9	10.5	5.3	42.6	12.3	24.4	1.15	
HLJ17	Female	East Asian (China)	0 (46)	0	HLJE-1994	0 (1 day)	NR	deceased	5.04E+06	B, NK, T	(+)	(+)	(+)	(+)	Yes	Yes	Yes	Yes	1983	8.11%	19760	1.95	1.47	0.08	0.39	4.18	108.2	21	9.46	876	384	4389	40.3	21.0	147.3	132.0	49.8	16.7	28.6	0.73	
HLJ18	Female	East Asian (China)	0 (46)	2	HLJE-1994	8	CR	alive	2.24E+04	B, NK, T	(+)	(+)	(+)	(+)	Yes	Yes	No	Yes	38851	19.51%	44000	1.52	0.96	0.0592	0.5	3.56	107	71	4.59	555	1177	616	45.0	25.2	47.7	45.1	24.5	11.3	22.1	0.92	
HLJ19	Female	East Asian (China)	0 (46)	2	HLJE-1994	2	CR	alive	3.40E+04	B, NK, T	(+)	(+)	(+)	(+)	Yes	Yes	No	Yes	2297	13.36%	9499	0.66	0.56	0.02	0.07	3.41	92.2	38	3.8	333	118	2840	54.2	31.6	64.0	59.7	22.1	11.5	21.9	1.03	
HLJ20	Male	East Asian (China)	0 (46)	2	HLJE-1994	8	CR	alive	9.50E+06	B, NK, T	(+)	(+)	(+)	(+)	Yes	Yes	No	Yes	309	19.00%	33742	2.58	1.49	0.03226	1.05	2.81	86	84	4.02	310	162	680	84.0	34.9	11.5	8.7	30.3	11.2	21.1	1.00	
HLJ21	Female	East Asian (China)	0 (46)	3	HLJE-1994	8	CR	alive	2.87E+06	B	(+)	(+)	(+)	(+)	Yes	Yes	Yes	Yes	947	35.38%	85750	15.12	13.71	0.28	1.09	3.68	103	40	3.77	96	82	668	68.6	33.6	10.2	5.3	50.1	12.3	12.3	1.22	
HLJ22	Female	East Asian (China)	0 (46)	3	HLJE-1994	2	CR	alive	1.50E+05	B, NK, T	(+)	(+)	(+)	(+)	Yes	Yes	No	No	13644	29.97%	33743	3.37	2.28	0.12	0.96	4.07	111.0	46	3.50	381	108	799	61.7	28.7	14.20	12.80	32.30	10.70	21.2	2.30	
HLJ23	Male	East Asian (China)	0 (46)	2	HLJE-1994	8	CR	alive	1.48E+06	B, NK, T	(+)	(+)	(+)	(+)	No	No	No	Yes	40000	17.13%	8680	1.48	0.47	0.12	0.88	2.57	68	74.7	3.39	350	262	2269	46.9	30.0	74.1	56.5	37	11.8	14.8	1.26	
HLJ24	Female	East Asian (China)	0 (46)	1	HLJE-1994	8	CR	alive	2.59E+04	B, NK	(+)	(+)	(+)	(+)	Yes	No	No	Yes	1650	19.37%	19943	2.04	1.63	0.26	0.14	2.88	67	34	2.23	119	93	1144	55.1	33.5	3.2	2.3	55.6	12.8	23.2	1.04	
HLJ25	Male	East Asian (China)	0 (46)	2	HLJE-1994	8	CR	alive	1.07E+06	B, NK, T	(+)	(+)	(+)	(+)	Yes	Yes	No	Yes	19852	14.08%	38360	0.64	0.41	0.0368	0.19	3.05	89	62	3.37	641	467	2880	42.3	22.1	15.4	0.0	44.3	14.5	23.2	0.97	
HLJ26	Female	East Asian (China)	0 (46)	1	HLJE-1994	2	NR	deceased	2.03E+06	B, NK	(+)	(+)	(+)	(+)	Yes	Yes	No	No	31470	0.25%	40467	6.94	4.26	0.11	2.49	3.22	85	17	3.86	399	135.4	2403.3	57.3	36.2	10.8	2.4	39.4	11.8	34.4	0.87	
HLJ27	Female	East Asian (China)	0 (46)	2	HLJE-1994	8	CR	alive	2.75E+05	B, NK, T	(+)	(+)	(+)	(+)	Yes	Yes	No	Yes	26503	16.23%	40514	3.18	1.95	0.2	0.95	2.87	73.7	46.4	5.60	358	285	1605	44.4	23.1	109.1	91.2	42.7	14.4	16.9	0.95	
IM1	Male	East Asian (China)	0 (46)	1	Symptomatic treatment (without hormones or chemotherapy)	1	CR	alive	1.50E+04	NA	(+)	(+)	(+)	(+)	Yes	Yes	Yes	NA	NA	NA	NA	10.88	4.46	1.05	5.33	4.89	130	500	0.98	77	35	390	60.3	40.2	5.1	2.7	NA	NA	NA	NA	
IM2	Male	East Asian (China)	0 (46)	1	Symptomatic treatment (without hormones or chemotherapy)	1	CR	alive	1.02E+05	NA	(+)	(+)	(+)	(+)	Yes	No	Yes	NA	114	NA	NA	NA	14.08	7.20	1.11	5.41	4.67	131	225	1.76	34	17	462	71.3	42.3	5.7	2.2	27.9	13.1	16.8	2.87
IM3	Male	East Asian (China)	0 (46)	2	Symptomatic treatment (without hormones or chemotherapy)	1	CR	alive	2.99E+04	NA	(+)	(+)	(+)	(+)	No	No	Yes	NA	NA	NA	NA	14.92	7.06	1.82	6.01	4.48	122	188	1.24	64	71	552	67.6	38.2	4.4	1.4	NA	NA	NA	NA	
IM4	Male	East Asian (China)	0 (46)	0	Symptomatic treatment (without hormones or chemotherapy)	1	CR	alive	4.03E+03	NA	(+)	(+)	(+)	(+)	No	No	Yes	NA	NA	NA	NA	10.71	4.82	0.92	4.9	4.81	122	347	0.69	135	218	352	70.4	41.4	6	2.9	25.8	12.8	16.9	2.15	
IM5	Female	East Asian (China)	0 (46)	1	Symptomatic treatment (without hormones or chemotherapy)	1	CR	alive	5.00E+03	NA	(+)	(+)	(+)	(+)	Yes	Yes	Yes	NA	NA	NA	NA	9.11	5.17	0.64	2.87	4.02	111	349	1.08	70	117	532	69.2	41.7	4.4	1.6	NA	NA	NA	NA	
IM6	Female	East Asian (China)	0 (46)	1	Symptomatic treatment (without hormones or chemotherapy)	1	CR	alive	7.88E+03	NA	(+)	(+)	(+)	(+)	Yes	No	Yes	NA	NA	NA	NA	14.84	13.03	0.33	1.22	4.05	107	217	1.03	83	205	526	68.4	38.2	4.5	1.8	25.8	11.6	17.5	2.82	
IM7	Male	East Asian (China)	0 (46)	0	Symptomatic treatment (without hormones or chemotherapy)	1	CR	alive	2.21E+04	NA	(+)	(+)	(+)	(+)	Yes	Yes	Yes	NA	156	NA	NA	NA	11.19	5.99	1.22	3.95	4.18	125	230	1.10	93	196	442	63.3	37.9	6.7	2.1	28.7	12.8	18.2	3.03
IM8	Female	East Asian (China)	0 (46)	1	Symptomatic treatment (without hormones or chemotherapy)	1	CR	alive	3.35E+04	NA	(+)	(+)	(+)	(+)	Yes	Yes	Yes	NA	NA	NA	NA	13.6	8.17	1.60	3.81	4.47	126	122	1.61	116	115	604	80.4	35.4	5.4	2.4	NA	NA	NA	NA	
IM9	Male	East Asian (China)	0 (46)	1	Symptomatic treatment (without hormones or chemotherapy)	1	CR	alive	1.05E+03	NA	(+)	(+)	(+)	(+)	Yes	Yes	Yes	NA	397	NA	NA	NA	14.16	7.45	0.65	6.05	4.57	122	286	1.43	233	268	506	61.1	34.2	5.2	2.3	NA	NA	NA	NA
HPV1	Female	East Asian (China)	0 (46)	0	NA	NA	NA	alive	1.31E+03	NA	NA	NA	NA	NA	No	No	NA	NA	NA	NA	NA	6.82	2.24	0.42	3.55	3.96	131	311	NA	NA	27	15	70.2	45.4	10.9	1.9	NA	NA	NA	NA	
HPV2	Male	East Asian (China)	0 (46)	0	NA	NA	NA	alive	6.34E+02	NA	NA	NA	NA	NA	No	No	NA	NA	NA	NA	NA	4.94	2.39	0.41	1.87	4.13	115	244	NA	NA	24	11	NA	67.7	44.9	9.5	2.9	NA	NA	NA	NA
HPV3	Male	East Asian (China)	0 (46)	0	NA	NA	NA	alive	2.41E+03	NA	NA	NA	NA	NA	No	No	NA	NA	NA	NA	NA	5.98	1.99	0.74	3.14	4.97	125	332	NA	NA	27	16	NA	74.1	48.7	9.2	1.8	NA	NA	NA	NA

NA: Not Applicable; CR: Complete Response; NR: No Response

Supplementary Table 3: Panel of excluded gene mutations associated with HLH and primary immunodeficiency diseases based on whole-exome sequencing results

Gene lists
ADA, AK2, AP3B1, ARHGAP21, ATM, BLM, BLOC1S6, BTK, CADPS2, CARD11, CASP10, CASP8, CCDC141, CD127, CD27, CD3E, CD40LG, CD70, CDC42, COG1, COG6, CORO1A, CTPS1, CYBB, DCLRE1C, DKC1, DNMT3B, DOCK8, EXPH5, FADD, FAM160A2, FAS, FASLG, FKBPL, GATA2, GDI1, IFNGR1, IFNGR2, IKBKG, IL10, IL21R, IL27RA, IL2RA, IL2RG, IRF5, IRF8, ITK, JAK3, KIR2DS5, KIR3DS1, LRBA, LRGUK, LYST, MAGT1, MCM4, MEFV, MICAL2, MVK, NCF2, NCF4, NLRC4, NLRP12, NLRP3, OSTM1, PIK3CD, PIK3R1, PLCG2, PNP, PRF1, PRKCD, RAB27A, RAG1, RAG2, RASGRP1, RECQL4, SH2D1A, SH3BP2, SLC29A3, SLC7A7, STAT1, STX11, STXBP2, TCIRG1, TGFB, TNFRSF11A, TNFRSF13B, TNFRSF1A, UNC13D, UNG, WAS, XIAP, XIRP2, ZAP70

Supplementary Table 4: Genes related to functional module scores

Categories	Gene lists
Inflammatory	ABCA1, ABI1, ACVR1B, ACVR2A, ADGRE1, ADM, ADORA2B, ADRM1, AHR, APLNR, AQP9, ATP2A2, ATP2B1, ATP2C1, AXL, BDKRB1, BEST1, BST2, BTG2, C3AR1, C5AR1, CALCRL, CCL17, CCL2, CCL20, CCL22, CCL24, CCL5, CCL7, CCR7, CCRL2, CD14, CD40, CD48, CD55, CD69, CD70, CD82, CDKN1A, CHST2, CLEC5A, CMKLR1, CSF1, CSF3, CSF3R, CX3CL1, CXCL10, CXCL11, CXCL6, CXCL8, CXCL9, CXCR6, CYBB, DCBLD2, EBI3, EDN1, EIF2AK2, EMP3, EREG, F3, FFAR2, FPR1, FZD5, GABBR1, GCH1, GNA15, GNAI3, GP1BA, GPC3, GPR132, GPR183, HAS2, HBEGF, HIF1A, HPN, HRH1, ICAM1, ICAM4, ICOSLG, IFITM1, IFNAR1, IFNGR2, IL10, IL10RA, IL12B, IL15, IL15RA, IL18, IL18R1, IL18RAP, IL1A, IL1B, IL1R1, IL2RB, IL4R, IL6, IL7R, INHBA, IRAK2, IRF1, IRF7, ITGA5, ITGB3, ITGB8, KCNA3, KCNJ2, KCNMB2, KIF1B, KLF6, LAMP3, LCK, LCP2, LDLR, LIF, LPAR1, LTA, LY6E, LYN, MARCO, MEFV, MEP1A, MET, MMP14, MSR1, MXD1, MYC, NAMPT, NDP, NFKB1, NFKBIA, NLRP3, NMI, NMUR1, NOD2, NPFFR2, OLR1, OPRK1, OSM, OSMR, P2RX4, P2RX7, P2RY2, PCDH7, PDE4B, PDPN, PIK3R5, PLAUR, PROK2, PSEN1, PTAFR, PTGER2, PTGER4, PTGIR, PTPRE, PVR, RAF1, RASGRP1, RELA, RGS1, RGS16, RHOG, RIPK2, RNF144B, ROS1, RTP4, SCARF1, SCN1B, SELE, SELENOS, SELL, SEMA4D, SERPINE1, SGMS2, SLAMF1, SLC11A2, SLC1A2, SLC28A2, SLC31A1, SLC31A2, SLC4A4, SLC7A1, SLC7A2, SPHK1, SRI, STAB1, TACR1, TACR3, TAPBP, TIMP1, TLR1, TLR2, TLR3, TNFAIP6, TNFRSF1B, TNFRSF9, TNFSF10, TNFSF15, TNFSF9, TPBG, VIP
Cytokines	IL2, IL7, CSF3, CXCL10, CCL2, CCL3, TNF, TFTN1, IL6, CCL7, IL1RN, CSF1, IFNG, IL2RA, IL10, IL18, HGF, CXCL9, CCL27, TGFB1, IL1B, LTA, CSF2, LTB, TNFSF13, IL4, CCL12, CXCL8, CXCL11, CCL4, CXCL1, CXCL2, CXCL3, CCL3L1, CCL8, CXCL16, CCL5, CCL11, IFNA2, IFNA1, CCL20, CCL4L2, OSM, TNFSF14, SA100A12, FGF19, CXCL5, CCL19, IL18R1, TGFA, IFNB1, IL8, IL17C, TNFSF10, FGF7, XCL1, FGF13, LIF, TGFB3, INHBE, CERS1, TXLNA, IFNW1, IL22, XCL2, CCL25, CCL16, CD40LG, IL20, FASLG, TPO, SCYL3, PF4V1, TNFSF8, GDF15, IL1A, VEGFA, GDF7, BMP6, PDGFA, IL21, ABCD-1, ABCD-2, PDGFB, TNFSF4, FAM19A1, HBEGF, PDGFD, IL12RB2, GH1, VEGFB, MIP3B, IL27, PF4, BMP8B, TNFSF12, IL15, SCYL2, SCYL1, TSLP, GDF11, SDF1B, INHBA, PPBP, FGF11, IFNG-AS1, FGF22, VEGFC, CCL18, TNFSF11, IL12A, EBI3, AMH, IL26, IL32, PDGFC, FGF23, IGF1, IL1F11, CCL28, CLCF1, TNFSF9, BMP3, IL24, GDF10, CXCL6, GDF9, IL23A, IL16, CD70, IL5, FGF9, IFNL1, TSC1, FGF2, IL23R, IL1G, SPP1, IL12RB1, BMP4, IL13, TPAR1, TGFB2, FAM19A2, AGIF3, EDA, MIF, TNFSF13B, BMP7, FGF18, CCL23, IL12B, IL17A, CD163, IL33
Naïve	CCR7, TCF7, LEF1, SELL
Cytotoxicity	PRF1, IFNG, GNLY, NKG7, GZMB, GZMA, GZMH, KLRK1, KLRB1, KLRD1, CTSW, CST7
Exhausted	LAG3, TIGIT, PDCD1, CTLA4, HAVCR2

Supplementary Table 5: qRT-PCR primer sequences

Primer Name	Forward primer sequences (5'- 3')	Reverse primer sequences (5'- 3')
<i>IL1A</i>	TGTATGTGACTGCCCAAGATGAAG	AGAGGAGGTTGGTCTCACTACC
<i>IL1B</i>	CCACAGACCTTCCAGGAGAATG	GTGCAGTTCAGTGATCGTACAGG
<i>IL6</i>	AGACAGCCACTCACCTCTTCAG	TTCTGCCAGTGCCTCTTTGCTG
<i>CXCL8</i>	GAGAGTGATTGAGAGTGGACCAC	CACAACCCTCTGCACCCAGTTT
<i>IL10</i>	TCTCCGAGATGCCTTCAGCAGA	TCAGACAAGGCTTGGCAACCCA
<i>IL12A</i>	TGCCTTCACCACTCCCAAACC	CAATCTCTTCAGAAGTGCAAGGG
<i>IL17A</i>	CGGACTGTGATGGTCAACCTGA	GCACTTTGCCTCCCAGATCACA
<i>IL18</i>	GATAGCCAGCCTAGAGGTATGG	CCTTGATGTTATCAGGAGGATTCA
<i>CSF2</i>	GGAGCATGTGAATGCCATCCAG	CTGGAGGTCAAACATTTCTGAGAT
<i>CCL2</i>	AGAATCACCAGCAGCAAGTGTCC	TCCTGAACCCACTTCTGCTTGG
<i>CCL3</i>	ACTTTGAGACGAGCAGCCAGTG	TTTCTGGACCCACTCCTCACTG
<i>CCL4</i>	GCTTCCTCGCAACTTTGTGGTAG	GGTCATACACGTA CTCTGGAC
<i>CCL5</i>	CCTGCTGCTTTGCCTACATTGC	ACACACTTGGCGGTTCTTTCGG
<i>CCL7</i>	ACAGAAGGACCACCAGTAGCCA	GGTGCTTCATAAAGTCCTGGACC
<i>TNF</i>	CTCTTCTGCCTGCTGCACTTTG	ATGGGCTACAGGCTTG TCACTC
<i>LTA</i>	ACACCTTCAGCTGCCCAGACTG	TCCGTGTTTGCTCTCCAGAGCA
<i>TGFB1</i>	TACCTGAACCCGTGTTGCTCTC	GTTGCTGAGGTATCGCCAGGAA
<i>PTGS2</i>	CGGTGAAACTCTGGCTAGACAG	GCAAACCGTAGATGCTCAGGGA
<i>IFNG</i>	GAGTGTGGAGACCATCAAGGAAG	TGCTTTGCGTTGGACATTCAAGTC
<i>IL2RA</i>	GAGACTTCCTGCCTCGTCACAA	GATCAGCAGGAAAACACAGCCG

Supplementary Table 6: Antibody for flow cytometry

Antidody	Supplier name	Catalog number	Dilutions
BV510 Mouse Anti-Human CD45	BD	563204	1 : 50
APC/Cyanine7 anti-human CD14	BioLegend	325619	1 : 50
BV421 Mouse Anti-Human CD16	BD	562874	1 : 100
PERCP Anti-Human HLA-DR	BioLegend	307628	1 : 100
PE Mouse Anti-Human CD163	BD	560933	1 : 100
BB515 Rat Anti-Human CX3CR1	BD	565902	1: 100
AF647 Mouse Anti-Human IDO1	BD	566648	1 : 100
APC anti-human CD3	Biolegend	317318	1 : 25
FITC Mouse Anti-Human CD4	BD	555346	1 : 8
PerCP/Cyanine5.5 anti-human CD8	Biolegend	344710	1 : 20
PerCP/Cyanine5.5 anti-human CD3	Biolegend	317336	1 : 20
APC anti-human CD19	Biolegend	302212	1 : 20
RB780 Mouse Anti-Human CD56	BD	568763	1 : 20
Alexa Fluor 700 Mouse anti-Human CD14	BD	557923	1 : 25
BV421 Mouse Anti-Human CD16	BD	562874	1 : 25
PE Mouse anti-NF-κB p65 (pS529)	BD	558423	1 : 10