

SUPPLEMENTAL DATA LIST

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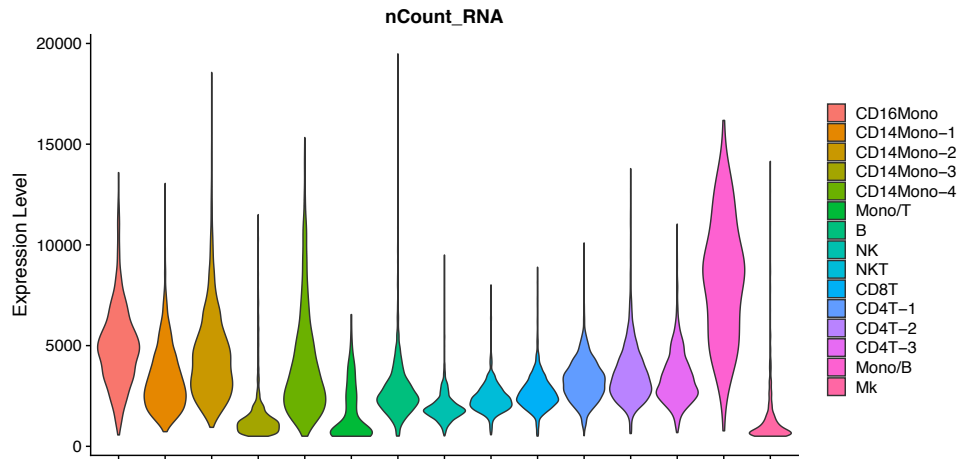
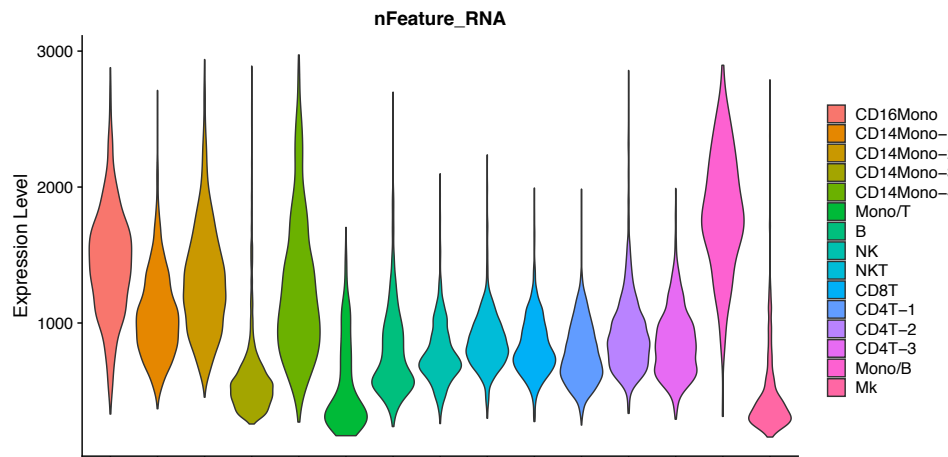
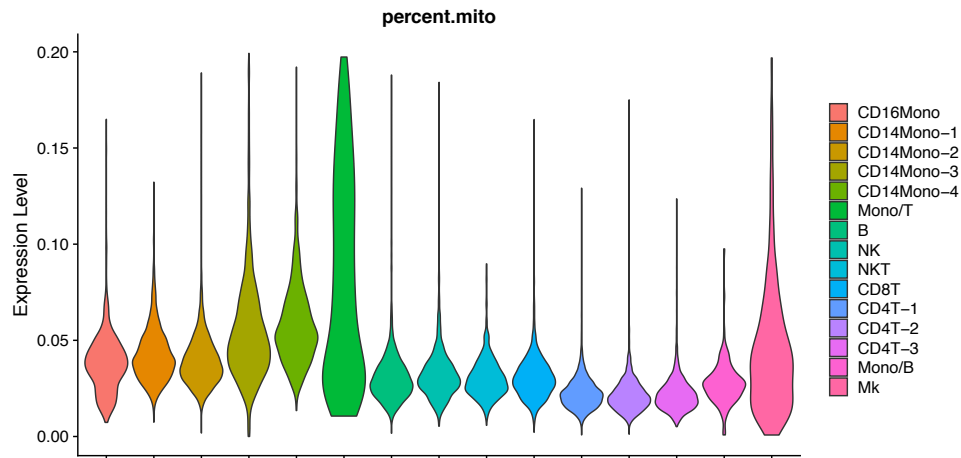
Supplemental Table 4. ClueGO pathway enrichment associated with down-regulated genes in NK cells.

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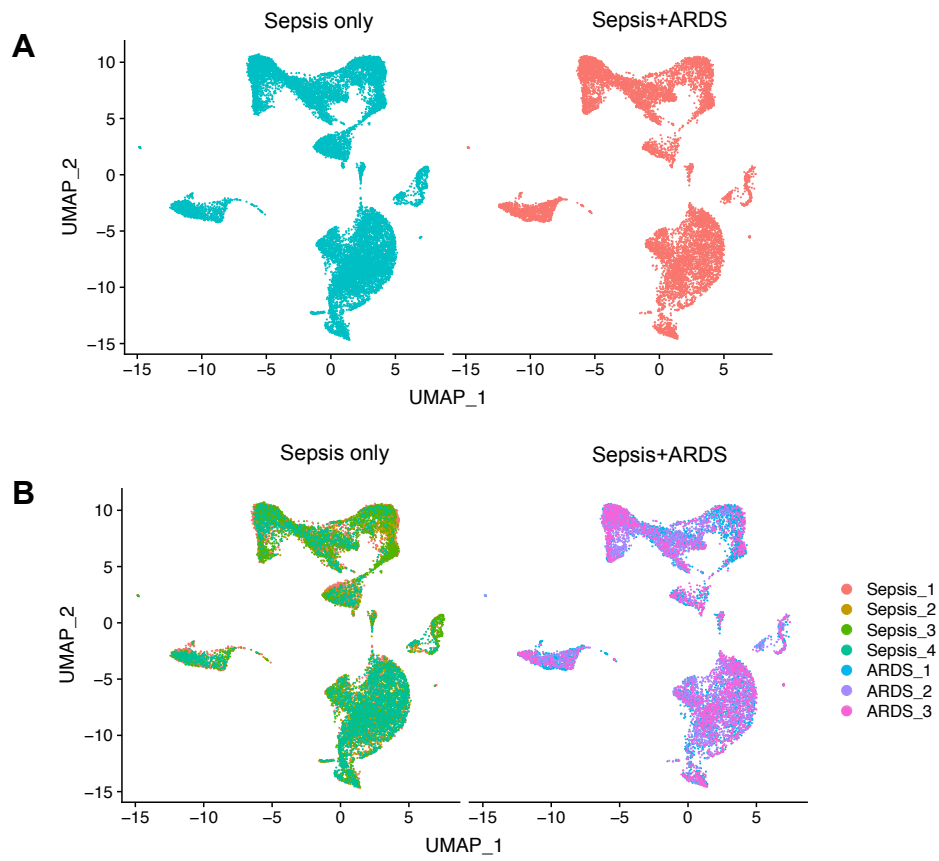
Supplemental Table 6. Differential expression of the 29 genes used for bulk data validation in monocytes from scRNA-seq analysis.

Supplemental Table 7. Description of datasets used for score generation.

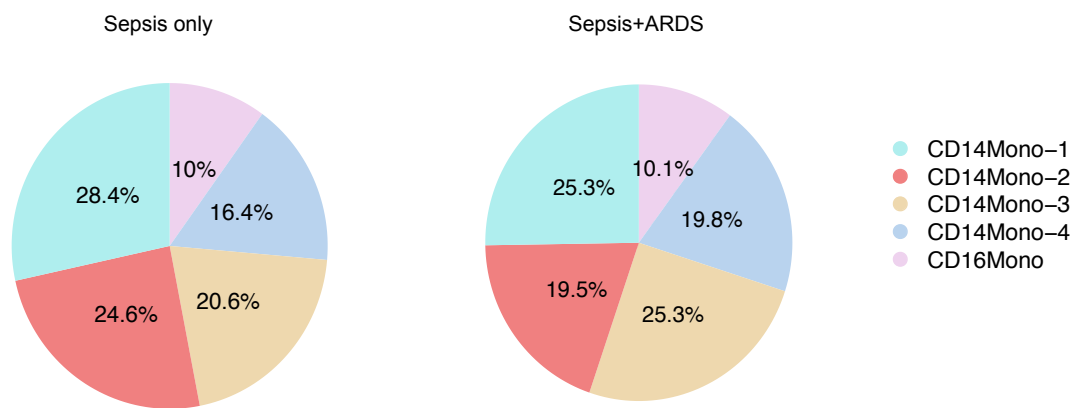
Supplemental Table 8. Reagents and materials.

A**B****C**

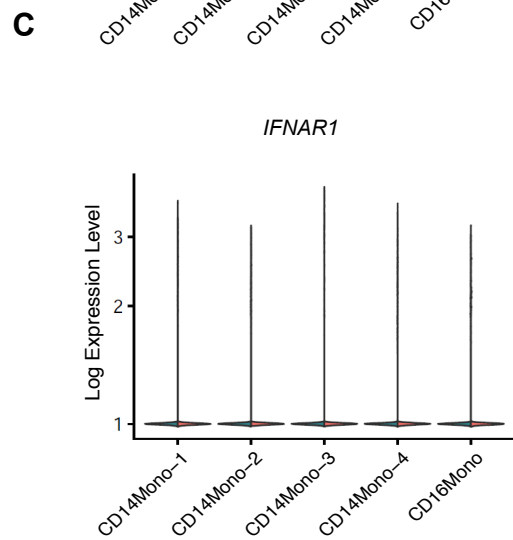
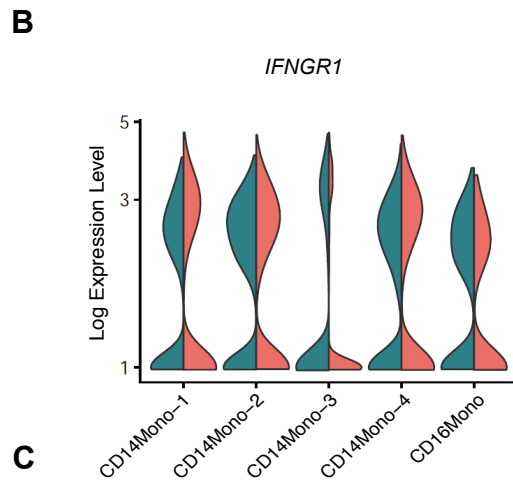
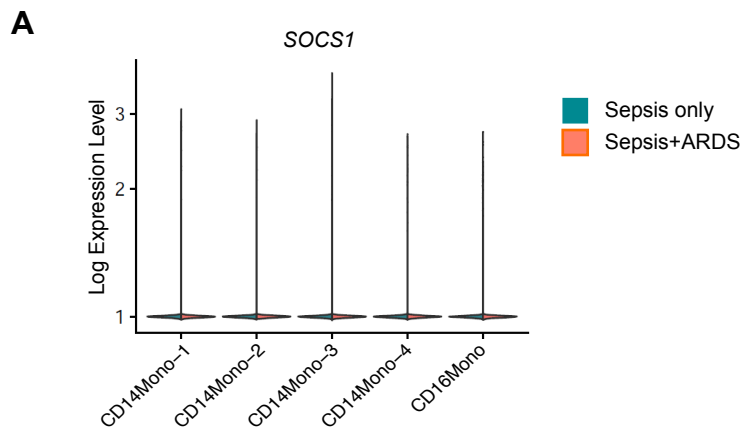
Supplemental Figure 1. scRNA-seq quality control. Violin plots of (A) total UMI count, (B) numbers of unique genes identified, and (C) proportion of mitochondrial genes in each cell cluster.



Supplemental Figure 2. Individual patient UMAP plots. Low dimension UMAP plot of PBMC by (a) group and (b) individual patients.



Supplemental Figure 3. Proportion of monocyte clusters in sepsis only and sepsis+ARDS patients. The proportion of each color-coded monocyte cluster in sepsis only and sepsis+ARDS patients is shown in the pie charts.



Supplemental Figure 4. Expression of *SOCS1* and IFN receptors in the monocyte clusters. Violin plots showing (a) *SOCS1*, (b) *IFNGR1*, and (c) *IFNAR1* expression in each monocyte cluster in sepsis only and sepsis+ARDS patients.

Supplemental Table 1. Cell count for each cell cluster stratified by sample

	Sepsis1	Sepsis2	Sepsis3	Sepsis4	ARDS1	ARDS2	ARDS3
Mk	66	44	211	37	73	56	49
Mono/B	24	35	14	24	23	15	8
CD4T-3	187	69	252	119	245	228	45
CD4T-2	396	231	415	232	360	415	134
CD4T-1	611	208	693	268	339	652	349
CD8T	560	346	538	125	423	156	129
NKT	103	192	290	25	379	12	99
NK	537	242	244	163	198	54	119
B	421	19	252	295	594	359	135
Mono/T	82	21	89	14	36	19	42
CD14Mono-4	236	259	219	338	276	361	148
CD14Mono-3	258	366	156	539	296	422	281
CD14Mono-2	171	629	125	654	282	329	161
CD14Mono-1	178	554	203	888	369	393	237
CD16Mono	113	136	151	239	225	80	95
SUM	3943	3351	3852	3960	4118	3551	2031

Supplemental Table 2. Marker genes used for each cell cluster

# Top 10 marker genes for each cluster										
CD14Mono-1	S100A9	S100A8	S100A12	LYZ	LGALS1	TSPO	CTSD	S100A6	CSTA	RETN
CD14Mono-2	TIMP1	G0S2	CST3	TYROBP	AIF1	CTSS	THBS1	FCN1	SNHG15	MAP3K8
CD14Mono-3	S100A8	S100A12	NAMPT	RETN	CTSD	S100P	LGALS1	BCL2A1	GLUL	CXCL8
CD14Mono-4	PPBP	GNG11	MAP3K8	SLC25A37	THBS1	HIF1A	G0S2	CLEC7A	SOD2	VCAN
CD8T	CMC1	DUSP2	GZMK	CCL5	CD8A	CD3D	JUN	APOBEC3G	CD3E	TRBC2
CD4T-1*	CCR7	PIK3IP1	LEPROTL1	RPS6	SARAF	SOCS3	RPS12	IL7R	RPLP0	RPSA
CD4T-3	RPS6	SARAF	LEPROTL1	CCR7	CD6	IL7R	PIK3IP1	LTB	SPOCK2	ZFP36L2
B	HLA-DQB1	CD79A	CD74	IGKC	HLA-DRA	IGLC2	HLA-DPB1	IGHM	HLA-DRB1	IGHA1
NK	GNLY	NKG7	GZMB	CCL3	FGFBP2	CTSW	KLRB1	SPON2	CD7	CCL4
NKT	GZMH	GNLY	NKG7	CCL5	CCL4	FGFBP2	CST7	CMC1	GZMA	KLRB1
CD16Mono	IFITM2	IFITM3	LILRA1	LST1	COTL1	C10orf54	RHOC	IRF7	PSAP	CD68
Mk	PF4	PPBP	GNG11	GP9	ITGA2B	SDPR	HIST1H2AC	RGS18	TSC22D1	ACRBP
Mono/T	MT-CO2	MT-CO3	MT-ATP6	MT-ND1	TSPYL2	AC016831.7	SPOCK2	RP11-138A9.1	KLF6	TRAC
Mono/B	HLA-DPA1	HLA-DPB1	CD74	HLA-DRA	HLA-DMA	HLA-DRB1	HLA-DQA1	HLA-DQB1	AREG	PTGDS

*the marker genes for CD4T-2 cluster show the same list as CD4T-1 in global differentiation.

Supplemental Table 3. Differential gene expression in all cells

Gene	avg_logFC	Sepsis only %	Sepsis+ARDS%	p_val mast	p_val adj mast
IGLC2	0.685	0.384	0.278	4.35E-68	8.70E-65
CD79A	0.293	0.598	0.552	1.00E-43	2.00E-40
HLA-DQB1	0.260	0.914	0.665	0.00E+00	0.00E+00
IGHA1	0.250	0.795	0.583	1.52E-270	3.03E-267
CD74	0.224	0.864	0.759	1.31E-98	2.62E-95
HLA-DRA	0.212	0.844	0.726	1.81E-109	3.63E-106
HLA-DPB1	0.199	0.833	0.69	2.59E-148	5.18E-145
IGHM	0.167	0.439	0.476	1.67E-66	3.33E-63
MS4A1	0.161	0.546	0.506	1.09E-39	2.18E-36
EZR	0.159	0.832	0.763	2.24E-43	4.47E-40
HLA-DRB1	0.153	0.805	0.665	8.97E-142	1.79E-138
IGLC3	0.151	0.337	0.21	2.00E-106	4.00E-103
KLF2	0.127	0.754	0.648	3.58E-70	7.17E-67
IFNGR2	0.126	0.73	0.641	4.60E-52	9.20E-49
NAMPT	0.121	0.922	0.791	2.31E-223	4.63E-220
IFI44L	0.120	0.418	0.36	0.00E+00	0.00E+00
LTB	0.118	0.749	0.681	1.23E-39	2.45E-36
CD83	0.114	0.89	0.726	1.41E-229	2.82E-226
TSC22D3	0.112	0.975	0.928	6.13E-64	1.23E-60
TNFRSF13C	0.111	0.728	0.627	8.16E-74	1.63E-70
CXCR4	0.110	0.98	0.942	1.24E-51	2.47E-48
RGS2	0.109	0.766	0.692	1.77E-39	3.54E-36
GLUL	0.108	0.799	0.681	1.60E-121	3.21E-118
HLA-DPA1	0.107	0.76	0.629	1.49E-111	2.98E-108
VNN2	0.104	0.441	0.463	5.55E-13	1.11E-09
ATP6V0B	0.102	0.738	0.641	1.25E-90	2.50E-87
MAFF	-0.101	0.931	0.696	0.00E+00	0.00E+00
TMSB4X	-0.102	0.999	0.998	4.44E-28	8.88E-25
XCL2	-0.110	0.882	0.748	2.16E-169	4.33E-166
CD7	-0.111	0.8	0.716	1.64E-81	3.27E-78
PPBP	-0.118	0.799	0.678	1.19E-107	2.39E-104
RGS18	-0.119	0.725	0.642	8.84E-45	1.77E-41
GP9	-0.121	0.583	0.516	1.19E-26	2.38E-23
GZMH	-0.122	0.81	0.678	3.30E-156	6.60E-153
PF4	-0.127	0.862	0.687	1.44E-247	2.89E-244
CCL5	-0.131	0.894	0.782	8.82E-169	1.76E-165
AREG	-0.132	0.937	0.673	0.00E+00	0.00E+00
KLRD1	-0.135	0.75	0.619	3.34E-130	6.67E-127
GZMA	-0.140	0.731	0.645	3.22E-67	6.44E-64
MT2A	-0.145	0.906	0.86	8.69E-77	1.74E-73
CST7	-0.170	0.822	0.729	2.45E-105	4.91E-102
GZMB	-0.173	0.731	0.661	1.25E-51	2.49E-48
CCL4	-0.189	0.884	0.732	6.85E-230	1.37E-226
KLRB1	-0.200	0.764	0.68	4.36E-64	8.73E-61
SPON2	-0.201	0.874	0.696	7.01E-292	1.40E-288
CTSW	-0.209	0.514	0.466	8.62E-38	1.72E-34
CMC1	-0.238	0.774	0.657	5.17E-126	1.03E-122
DUSP2	-0.238	0.908	0.778	1.75E-223	3.50E-220
FGFBP2	-0.249	0.859	0.695	1.33E-257	2.66E-254
NKG7	-0.274	0.875	0.778	4.55E-155	9.11E-152
PTGDS	-0.283	0.761	0.629	4.74E-127	9.47E-124
CCL3	-0.326	0.908	0.735	8.92E-297	1.78E-293
GNLY	-0.347	0.817	0.767	3.15E-51	6.31E-48

Supplemental Table 4. ClueGO pathway enrichment associated with down-regulated genes in NK cells

GOID	GO Term	Term PValue	Term PValue Corrected with Bonferroni step down	Group PValue	Group PValue Corrected with Bonferroni step down	GO Groups	Associated Genes Found
GO:0002576	platelet degranulation	3.56E-05	3.31E-03	3.56E-05	2.14E-04	Group00	[APLP2, CD63, GSTP1, IER3, PSAP, TIMP1, TUBA4A]
GO:0043124	negative regulation of I-kappaB kinase/NF-kappaB signaling	5.07E-05	4.61E-03	5.07E-05	2.03E-04	Group01	[BIRC3, GSTP1, RHOA, RIOK3, TNFAIP3]
GO:0046632	alpha-beta T cell differentiation	4.28E-05	3.94E-03	4.28E-05	2.14E-04	Group02	[NFKBIZ, PRDM1, PTGER4, RHOA, TCF7, ZNF683]
GO:0008347	glial cell migration	1.99E-06	2.01E-04	1.99E-06	1.60E-05	Group03	[BIRC3, CCL3, CCL4, GPX4, IDH2, TSPO]
GO:0010951	negative regulation of endopeptidase activity	8.93E-06	8.93E-04	8.93E-06	6.25E-05	Group04	[APLP2, BIN1, BIRC3, CST7, GSTP1, HERPUD1, SERPINB1, SPOCK2, TIMP1, TNFRSF1B]
GO:0031663	lipopolysaccharide-mediated signaling pathway	7.34E-05	6.31E-03	7.34E-05	2.20E-04	Group05	[CCL3, CCL4, NFKBIA, PRDM1, TNFAIP3]
GO:0043407	negative regulation of MAP kinase activity	2.61E-05	2.48E-03	9.63E-05	9.63E-05	Group06	[BIRC3, DUSP1, DUSP2, GSTP1, KLF6, RGS2]
GO:0071901	negative regulation of protein serine/threonine kinase activity	9.63E-05	7.99E-03	9.63E-05	9.63E-05	Group06	[BIRC3, DUSP1, DUSP2, GSTP1, KLF6, RGS2, TNFAIP3]
GO:0071216	cellular response to biotic stimulus	1.50E-10	1.59E-08	8.36E-12	8.36E-11	Group07	[BIRC3, CCL3, CCL4, CEBPB, GSTP1, HSPA5, IRF8, NFKBIA, PRDM1, RHOA, TNFAIP3, TNFRSF1B, TSPO, ZFP36]
GO:0002237	response to molecule of bacterial origin	3.58E-11	3.83E-09	8.36E-12	8.36E-11	Group07	[BIRC3, CCL3, CCL4, CEBPB, FOS, GSTP1, IRF8, JUN, JUNB, NFKBIA, PRDM1, PTGER4, RHOA, TIMP1, TNFAIP3, TNFRSF1B, TSPO, ZFP36]
GO:0032496	response to lipopolysaccharide	1.60E-11	1.73E-09	8.36E-12	8.36E-11	Group07	[BIRC3, CCL3, CCL4, CEBPB, FOS, GSTP1, IRF8, JUN, JUNB, NFKBIA, PRDM1, PTGER4, RHOA, TIMP1, TNFAIP3, TNFRSF1B, TSPO, ZFP36]
GO:0071219	cellular response to molecule of bacterial origin	6.18E-10	6.43E-08	8.36E-12	8.36E-11	Group07	[BIRC3, CCL3, CCL4, CEBPB, GSTP1, IRF8, NFKBIA, PRDM1, RHOA, TNFAIP3, TNFRSF1B, TSPO, ZFP36]
GO:0071222	cellular response to lipopolysaccharide	3.16E-10	3.32E-08	8.36E-12	8.36E-11	Group07	[BIRC3, CCL3, CCL4, CEBPB, GSTP1, IRF8, NFKBIA, PRDM1, RHOA, TNFAIP3, TNFRSF1B, TSPO, ZFP36]
GO:0046683	response to organophosphorus	6.30E-05	5.61E-03	9.24E-05	1.85E-04	Group08	[DUSP1, FOS, HSP90B1, HSPA5, JUN, JUNB, ZFP36L1]
GO:0071241	cellular response to inorganic substance	8.14E-05	6.92E-03	9.24E-05	1.85E-04	Group08	[ALOX5AP, FOS, HSPA5, JUN, JUNB, MT2A, RHOA, TSPO]
GO:0014074	response to purine-containing compound	1.16E-04	9.39E-03	9.24E-05	1.85E-04	Group08	[DUSP1, FOS, HSP90B1, HSPA5, JUN, JUNB, ZFP36L1]
GO:0051591	response to cAMP	7.01E-05	6.17E-03	9.24E-05	1.85E-04	Group08	[DUSP1, FOS, HSPA5, JUN, JUNB, ZFP36L1]
GO:0051592	response to calcium ion	5.88E-05	5.30E-03	9.24E-05	1.85E-04	Group08	[ALOX5AP, DUSP1, FOS, HSPA5, JUN, JUNB, RHOA]
GO:0071248	cellular response to metal ion	2.96E-05	2.78E-03	9.24E-05	1.85E-04	Group08	[ALOX5AP, FOS, HSPA5, JUN, JUNB, MT2A, RHOA, TSPO]
GO:0071277	cellular response to calcium ion	1.50E-05	1.47E-03	9.24E-05	1.85E-04	Group08	[ALOX5AP, FOS, HSPA5, JUN, JUNB, RHOA]
GO:0043900	regulation of multi-organism process	3.24E-08	3.30E-06	6.35E-08	5.71E-07	Group09	[BIRC3, CCL3, CCL4, IFITM1, IRF8, JUN, PFN1, PRDM1, PRF1, PTGDS, RIOK3, SNX3, TIMP1, TNFAIP3, ZFP36]
GO:0043901	negative regulation of multi-organism process	1.21E-09	1.24E-07	6.35E-08	5.71E-07	Group09	[CCL3, CCL4, IFITM1, IRF8, JUN, PRDM1, PTGDS, RIOK3, SNX3, TIMP1, TNFAIP3, ZFP36]
GO:0043903	regulation of symbiosis, encompassing mutualism through parasitism	7.11E-05	6.19E-03	6.35E-08	5.71E-07	Group09	[CCL3, CCL4, IFITM1, IRF8, JUN, PFN1, SNX3, ZFP36]
GO:0048525	negative regulation of viral process	2.61E-05	2.48E-03	6.35E-08	5.71E-07	Group09	[CCL3, CCL4, IFITM1, JUN, SNX3, ZFP36]
GO:0019080	viral gene expression	8.73E-05	7.34E-03	6.35E-08	5.71E-07	Group09	[CCL3, CCL4, JUN, PFN1, ZFP36]
GO:0019083	viral transcription	1.85E-05	1.80E-03	6.35E-08	5.71E-07	Group09	[CCL3, CCL4, JUN, PFN1, ZFP36]
GO:0032897	negative regulation of viral transcription	2.17E-05	2.08E-03	6.35E-08	5.71E-07	Group09	[CCL3, CCL4, JUN, ZFP36]
GO:0046782	regulation of viral transcription	1.33E-05	1.31E-03	6.35E-08	5.71E-07	Group09	[CCL3, CCL4, JUN, PFN1, ZFP36]
GO:0043922	negative regulation by host of viral transcription	1.14E-04	9.37E-03	6.35E-08	5.71E-07	Group09	[CCL3, CCL4, JUN]

Supplemental Table 5. Enriched pathways and up-regulated genes in each monocyte subpopulation

GOID	GOTerm	Term PValue	Term PValue Corrected with Bonferroni step down	Group PValue	Group PValue Corrected with Bonferroni step down	GOGroups	Associated Genes Found
CD14Mono-1							
GO:0051607	defense response to virus	4.85E-06	3.15E-04	4.85E-06	9.69E-06	Group0	[GBP1, IFI44L, IFIT2, IFIT3, IFITM1, IRF7, RNASE2, SAMHD1, SEC14L1, UNC93B1]
GO:0034340	response to type I interferon	4.33E-05	2.73E-03	4.33E-05	4.33E-05	Group1	[GBP2, IFIT2, IFIT3, IFITM1, IRF7, SAMHD1]
GO:0071357	cellular response to type I interferon	3.12E-05	2.00E-03	4.33E-05	4.33E-05	Group1	[GBP2, IFIT2, IFIT3, IFITM1, IRF7, SAMHD1]
GO:0060337	type I interferon signaling pathway	3.12E-05	2.00E-03	4.33E-05	4.33E-05	Group1	[GBP2, IFIT2, IFIT3, IFITM1, IRF7, SAMHD1]
CD14Mono-2							
GO:0002576	platelet degranulation	2.66E-06	4.52E-05	2.66E-06	2.13E-05	Group0	[ITGA2B, PECAM1, PLEK, PPBP, SERPING1, SPARC, VCL]
GO:0003229	ventricular cardiac muscle tissue development	2.74E-03	5.49E-03	2.74E-03	5.49E-03	Group1	[HERPUD1, ID2, PPBP]
GO:0090502	RNA phosphodiester bond hydrolysis, endonucleolytic	5.25E-03	5.25E-03	5.25E-03	5.25E-03	Group2	[RNASE1, RNASE2, RNASET2]
GO:0071295	cellular response to vitamin	8.35E-04	6.68E-03	8.35E-04	3.34E-03	Group3	[ATP2B1, BACH1, PPBP]
GO:2000257	regulation of protein activation cascade	1.34E-03	5.36E-03	1.34E-03	4.02E-03	Group4	[C1QB, C3AR1, IGKC, SERPING1]
GO:0030449	regulation of complement activation	1.23E-03	6.15E-03	1.34E-03	4.02E-03	Group4	[C1QB, C3AR1, IGKC, SERPING1]
GO:0034109	homotypic cell-cell adhesion	6.79E-04	6.79E-03	6.79E-04	3.40E-03	Group5	[HSPB1, ITGA2B, PLEK, VCL]
GO:0070527	platelet aggregation	1.66E-04	2.48E-03	6.79E-04	3.40E-03	Group5	[HSPB1, ITGA2B, PLEK, VCL]
GO:0034340	response to type I interferon	5.91E-04	7.09E-03	5.91E-04	3.55E-03	Group6	[GBP2, IFIT2, IFIT3, ISG20]
GO:0071357	cellular response to type I interferon	4.74E-04	6.16E-03	5.91E-04	3.55E-03	Group6	[GBP2, IFIT2, IFIT3, ISG20]
GO:0060337	type I interferon signaling pathway	4.74E-04	6.16E-03	5.91E-04	3.55E-03	Group6	[GBP2, IFIT2, IFIT3, ISG20]
GO:1902622	regulation of neutrophil migration	1.04E-03	7.29E-03	2.46E-04	1.72E-03	Group7	[C3AR1, PPBP, RNASE1]
GO:1990266	neutrophil migration	1.48E-04	2.36E-03	2.46E-04	1.72E-03	Group7	[C3AR1, LGALS3, PECAM1, PPBP, RNASE1]
GO:0030593	neutrophil chemotaxis	1.06E-03	6.38E-03	2.46E-04	1.72E-03	Group7	[C3AR1, LGALS3, PPBP, RNASE1]
GO:0071622	regulation of granulocyte chemotaxis	1.69E-03	5.07E-03	2.46E-04	1.72E-03	Group7	[C3AR1, PPBP, RNASE1]
GO:1902624	positive regulation of neutrophil migration	6.99E-04	6.29E-03	2.46E-04	1.72E-03	Group7	[C3AR1, PPBP, RNASE1]
GO:0071624	positive regulation of granulocyte chemotaxis	6.17E-04	6.78E-03	2.46E-04	1.72E-03	Group7	[C3AR1, PPBP, RNASE1]
GO:0090022	regulation of neutrophil chemotaxis	6.99E-04	6.29E-03	2.46E-04	1.72E-03	Group7	[C3AR1, PPBP, RNASE1]
GO:0090023	positive regulation of neutrophil chemotaxis	4.71E-04	6.60E-03	2.46E-04	1.72E-03	Group7	[C3AR1, PPBP, RNASE1]
CD14Mono-3							
GO:0061082	myeloid leukocyte cytokine production	7.55E-05	6.27E-03	7.55E-05	1.51E-04	Group0	[BCL6, CD36, FCER1G, IRAK3]
GO:2000107	negative regulation of leukocyte apoptotic process	9.98E-05	8.18E-03	9.98E-05	9.98E-05	Group1	[BCL6, CCR7, FCER1G, IRF7, TSC22D3]
GO:0002526	acute inflammatory response	1.10E-05	9.56E-04	1.10E-05	5.50E-05	Group2	[ALOX5AP, C5AR2, CAPG, CCR7, CD6, CFP, CSRP1, FCER1G, IGKC, TIMP1, TREM1]
GO:0002576	platelet degranulation	3.80E-10	3.61E-08	3.80E-10	3.04E-09	Group3	[APLP2, APP, CD36, CD63, CFD, CFP, F13A1, FCER1G, PLEK, SPARC, TAGLN2, TIMP1, TUBA4A]
GO:007229	integrin-mediated signaling pathway	5.74E-05	4.82E-03	5.74E-05	1.72E-04	Group4	[BST1, CD63, FCER1G, ITGB1, ITGB7, PLEK, TIMP1]
GO:0009615	response to virus	2.26E-05	1.94E-03	2.26E-05	9.03E-05	Group5	[CXCR4, GBP1, IFI44L, IFIT3, IFITM1, IFNGR2, IRAK3, IRF7, OASL, RNASE2, SEC14L1, UNC93B1]
GO:0051607	defense response to virus	2.86E-05	2.43E-03	2.26E-05	9.03E-05	Group5	[GBP1, IFI44L, IFIT3, IFITM1, IFNGR2, IRF7, OASL, RNASE2, SEC14L1, UNC93B1]
GO:0002237	response to molecule of bacterial origin	7.56E-06	6.66E-04	7.56E-06	4.54E-05	Group6	[AKIRIN2, CCR7, CD36, CD6, CSF2RB, IRAK3, JUNB, MGST1, NFKBIA, PTGER2, SPARC, TIMP1, TNFRSF1B, ZFP36]
GO:0032496	response to lipopolysaccharide	4.32E-06	3.85E-04	7.56E-06	4.54E-05	Group6	[AKIRIN2, CCR7, CD36, CD6, CSF2RB, IRAK3, JUNB, MGST1, NFKBIA, PTGER2, SPARC, TIMP1, TNFRSF1B, ZFP36]
GO:0036230	granulocyte activation	2.31E-08	2.10E-06	3.28E-08	2.30E-07	Group7	[BST1, CD36, CD63, CD68, CD93, CFD, CFP, CKAP4, FCER1G, FGL2, FPR2, GLIPR1, GNS, LAMTOR2, LTA4H, MGST1, QPCT, RNASE2, SELL, TIMP1, TNFRSF1B]
GO:0002446	neutrophil mediated immunity	2.37E-08	2.13E-06	3.28E-08	2.30E-07	Group7	[BST1, CD36, CD63, CD68, CD93, CFD, CFP, CKAP4, FCER1G, FGL2, FPR2, GLIPR1, GNS, LAMTOR2, LTA4H, MGST1, QPCT, RNASE2, SELL, TIMP1, TNFRSF1B]
GO:0042119	neutrophil activation	1.93E-08	1.78E-06	3.28E-08	2.30E-07	Group7	[BST1, CD36, CD63, CD68, CD93, CFD, CFP, CKAP4, FCER1G, FGL2, FPR2, GLIPR1, GNS, LAMTOR2, LTA4H, MGST1, QPCT, RNASE2, SELL, TIMP1, TNFRSF1B]
GO:0002283	neutrophil activation involved in immune response	1.38E-08	1.28E-06	3.28E-08	2.30E-07	Group7	[BST1, CD36, CD63, CD68, CD93, CFD, CFP, CKAP4, FCER1G, FGL2, FPR2, GLIPR1, GNS, LAMTOR2, LTA4H, MGST1, QPCT, RNASE2, SELL, TIMP1, TNFRSF1B]
GO:0043312	neutrophil degranulation	1.27E-08	1.19E-06	3.28E-08	2.30E-07	Group7	[BST1, CD36, CD63, CD68, CD93, CFD, CFP, CKAP4, FCER1G, FGL2, FPR2, GLIPR1, GNS, LAMTOR2, LTA4H, MGST1, QPCT, RNASE2, SELL, TIMP1, TNFRSF1B]
CD14Mono-4							
GO:0001836	release of cytochrome c from mitochondria	2.16E-04	5.62E-03	2.16E-04	1.08E-03	Group0	[ARRB2, JUN, LMNA, TNFSF10]
GO:0003151	outflow tract morphogenesis	6.05E-03	6.05E-03	6.05E-03	6.05E-03	Group1	[CXCR4, JUN, NR3C1]
GO:0070373	negative regulation of ERK1 and ERK2 cascade	3.57E-04	8.20E-03	3.57E-04	7.13E-04	Group2	[DUSP3, DUSP6, GBP1, GSTP1]
GO:0071277	cellular response to calcium ion	6.05E-03	6.05E-03	6.05E-03	6.05E-03	Group3	[ALOX5AP, JUN, JUNB]
GO:0050858	negative regulation of antigen receptor-mediated signaling pathway	3.53E-04	8.48E-03	3.53E-04	1.06E-03	Group4	[DUSP3, GBP1, LILRB4]
GO:0050860	negative regulation of T cell receptor signaling pathway	2.29E-04	5.71E-03	3.53E-04	1.06E-03	Group4	[DUSP3, GBP1, LILRB4]
GO:0032692	negative regulation of interleukin-1 production	4.13E-04	9.09E-03	3.13E-04	1.25E-03	Group5	[ARRB2, GSTP1, TNFAIP3]
GO:1903556	negative regulation of tumor necrosis factor superfamily cytokine production	1.01E-04	2.84E-03	3.13E-04	1.25E-03	Group5	[ARRB2, GSTP1, RPSA, TNFAIP3]
GO:0032691	negative regulation of interleukin-1 beta production	1.70E-04	4.58E-03	3.13E-04	1.25E-03	Group5	[ARRB2, GSTP1, TNFAIP3]
GO:0032720	negative regulation of tumor necrosis factor production	8.97E-05	2.60E-03	3.13E-04	1.25E-03	Group5	[ARRB2, GSTP1, RPSA, TNFAIP3]
CD16Mono							
GO:0070373	negative regulation of ERK1 and ERK2 cascade	5.97E-04	5.97E-04	5.97E-04	5.97E-04	Group0	[DUSP6, GBP1, KLF4]
GO:0034340	response to type I interferon	1.36E-06	5.45E-06	1.36E-06	4.09E-06	Group1	[IFI6, IFIT2, IFIT3, IRF1, RSAD2]
GO:0071357	cellular response to type I interferon	1.02E-06	5.10E-06	1.36E-06	4.09E-06	Group1	[IFI6, IFIT2, IFIT3, IRF1, RSAD2]
GO:0060337	type I interferon signaling pathway	1.02E-06	5.10E-06	1.36E-06	4.09E-06	Group1	[IFI6, IFIT2, IFIT3, IRF1, RSAD2]
GO:0002920	regulation of humoral immune response	3.19E-07	2.24E-06	1.63E-06	3.25E-06	Group2	[C1QA, C2, C3AR1, FCGR2A, IGKC, SERPING1]
GO:2000257	regulation of protein activation cascade	4.02E-06	8.04E-06	1.63E-06	3.25E-06	Group2	[C1QA, C2, C3AR1, IGKC, SERPING1]
GO:0002673	regulation of acute inflammatory response	8.85E-07	5.31E-06	1.63E-06	3.25E-06	Group2	[C1QA, C2, C3AR1, FCGR2A, IGKC, SERPING1]
GO:0030449	regulation of complement activation	3.59E-06	1.08E-05	1.63E-06	3.25E-06	Group2	[C1QA, C2, C3AR1, IGKC, SERPING1]

Supplemental Table 6. 29 genes differentially expressed in the scRNA-seq data used for cross-validation against bulk RNA-seq data

Gene	mean_sepsis	mean_ARDS	t-test P value
ATP2B1	-1.17	-0.58	4.73E-08
C1orf56	-1.08	-0.57	3.86E-06
C3AR1	0.55	0.10	8.05E-03
CDC42SE1	-0.45	-0.33	1.18E-01
CLEC4E	-0.22	-0.56	3.44E-03
CLTC	-0.57	-0.57	9.64E-01
CRISPLD2	-0.24	-0.07	2.03E-01
GBP2	1.12	0.17	4.67E-04
GNG11	-0.74	-0.56	1.59E-02
GNS	2.04	3.72	6.33E-14
HIST1H2AC	0.17	-0.57	8.00E-07
HSPB1	1.02	-0.54	2.48E-07
MAP3K7CL	0.71	-0.48	8.20E-07
MARCKS	2.00	-0.25	9.24E-15
MBOAT7	0.18	-0.31	3.62E-06
MMD	-0.60	-0.44	1.23E-04
MYL9	-1.26	-0.58	4.29E-08
NRGN	-0.95	-0.58	4.80E-05
NT5C3A	0.09	0.01	6.88E-01
NUP214	0.39	0.30	5.47E-01
PK4	-1.08	0.01	1.51E-07
PDLIM7	-0.26	-0.54	5.79E-03
PLEK	1.46	0.13	4.41E-08
RAB11A	0.60	2.34	2.33E-21
RAB11FIP1	-1.33	-0.36	6.28E-10
SPARC	-1.22	-0.59	1.47E-06
TUBA4A	-0.41	-0.25	5.04E-02
VNN2	0.05	0.08	8.01E-01
YWHAH	1.21	1.87	5.01E-10

*Expression profile of the 29 genes in GEO datasets. The values were standardized and normalized.

The third column shows P values in t test between the expression levels of the two groups of patients for each gene.

Genes highlighted show similar trends in scRNA-seq and bulk RNA-seq data.

Supplemental Table 7. Description of datasets used for score generation

GEO dataset	Description	Sample size (used in this analysis)	Platform*
GSE89953	Human Peripheral Blood Monocytes from patients with ARDS at baseline	N=26 ARDS patients	Illumina HumanRef-8 BeadChip
GSE46955	Human Blood Monocytes from gram-negative sepsis patients during sepsis and following their recovery	N=8 patients with sepsis;	Illumina humanRef-8 v2.0 expression beadchip

* The two datasets have comparable preprocessing and normalization in spite of slightly different platforms.

Supplemental Table 8. Reagents and Materials

Reagents	Company	Catalog Number
Phosphate-buffered saline (PBS)	Fisher Scientific	BW17516Q12
Ficoll Paque PLUS	GE Healthcare	17144002
Dimethyl Sulfoxide	Sigma-Aldrich	D2650
Fetal Bovine Serum(FBS)	Benchmark	100106
X-VIVO15 medium	Lonza	04744Q
RPMI medium	ATCC	30-2001
Human AB serum	Fisher Scientific	ICN2938249
2-mercaptoethanol	Gibco	21985-023
Bovine Serum Albumin (BSA)	Gibco	15260037
Chromium Single Cell 3' Library & Gel Bead Kit	10x Genomics	120267
Chromium Single Cell A Chip Kit, 48 runs	10x Genomics	120236
RBC lysis buffer	BioLegend	420301
Acid citrate dextrose blood collection tube	Fisher Scientific	02-684-26
50ml Falcon tube	ThermoFisher	352098
5ml Falcon staining tube	Fisher Scientific	14-959-5
Nalgene Cryo 1 ^o C freezing container	ThermoFisher	5100-0001