Supplemental Appendix

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Supplemental Figure 1. Reproducibility across replicates. tSNEs of data for each time point post ICH are shown and colored by metadata (compartment or sequencing...
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**Supplemental Figure 7.** Waterfall plots of top 10 enriched pathways by IPA for remaining new myeloid clusters. Results, including genes in each pathway, are also shown in Table S5.
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Supplemental Figure 11. Waterfall plots of top 10 enriched pathways by IPA for remaining T cell sub-clusters. Results, including genes in each pathway, are also shown in Table S9. T cell sub-cluster 0 was defined by two marker genes only, TXNIP and LTB, which precluded pathway analysis on this cluster.
Supplemental Figure 12. Dot plots of canonical ligands and receptors for A. myeloid sub-clusters, and B. T cell sub-clusters.
Supplemental Figure 13. A. Gene expression module scores were calculated for selected gene modules from the literature for each cell in our myeloid data and clustered hierarchically. The heatmap is annotated by compartment (blood or hematoma), time, source (control or patient), and T cell sub-cluster. B. Principal component analysis was performed on all module scores. Data are shown across the first two principal components and all module variable loadings are projected onto the top left plot and each subsequent plot shows only the top three module loading (black arrows). Data
from each myeloid sub-cluster is visualized separately (sub-clusters 0-11), or as a function of time in either blood or hematoma, and as patient derived or control blood derived. Plots are grouped by metadata characteristics, predominantly blood, predominantly hematoma, or both. Gene signatures used for module scoring are described in Table S10.
## Supplemental Tables

### Table S1. Patient time course.

| Hrs after onset | Hematoma Volume from Catheter (mL) | Hematoma Volume on CT scan (mL) | Cell Count (x10^6) | Cells (x10^6) / mL | Sample Collection and Study Event | Surgical Event and/or Scan |
|-----------------|------------------------------------|---------------------------------|-------------------|-------------------|-----------------------------------|-----------------------------|
| 0               |                                    |                                 |                   |                   | time of onset                      |                             |
| 35.5            | 85.7                               |                                 |                   |                   | scan                              |                             |
| 50.9            | 45                                 | 2.3                             | 0.12              | SeqWell (9 mL), sort | placement of catheter and removal of liquid hematoma |
| 52.3            | 36.6                               |                                 |                   |                   | scan                              |                             |
| 56.4            |                                    |                                 |                   |                   | catheter pulled back 1.5cm         |                             |
| 63.6            | 33                                 |                                 |                   |                   | scan                              |                             |
| 66              | 11                                 | 0.4                             | 0.09              | SeqWell (4.5 mL)   | sample collection followed by      |                             |
|                 |                                    |                                 |                   |                   | administration of tPA (dose 1)     |                             |
| 73.2            | 38                                 | 4.7                             | 0.36              | SeqWell (13 mL), CyTOF | sample collection followed by      |                             |
|                 |                                    |                                 |                   |                   | administration of tPA (dose 2)     |                             |
| 78.2            | 26.5                               |                                 |                   |                   | scan                              |                             |
| 80.9            | 53                                 |                                 |                   |                   | Sort                              | administration of tPA (dose 3) |
| 89              | 30                                 | 14                              | 0.39              | SeqWell (30 mL)    | Sample collection followed by administration of tPA (dose 4) |
| 93.4            | 25.9                               |                                 |                   |                   | scan                              |                             |
| 97.6            | 33                                 | 1                               |                   |                   | CyTOF                             |                             |
| 105.4           | 30.2                               |                                 |                   |                   | scan                              |                             |
| 112             | 11                                 | 7.8                             | 2.6               | SeqWell (9 mL), CyTOF |                                  |                             |
| 115             | 31.4                               |                                 |                   |                   | scan                              |                             |
| 121             | 13                                 | 2.7                             |                   |                   | Scan                              |                             |
| 130.8           | 12.8                               |                                 |                   |                   | Sort                              |                             |
| 137 | 4 | 2.2 | 0.63 | SeqWell (3.5 mL) |
|-----|---|-----|------|-----------------|
| 140.1 |   |     |      | Catheter removal |
| 165.1 |   | 11.8 |      | scan            |
Table S2. CyTOF antibodies.

| Isotope | Epitope   | Fluidigm Catalog # |
|---------|-----------|--------------------|
| 89Y     | CD45      | 3089003B           |
| 142Nd   | CD19      | 3142001B           |
| 145Nd   | CD4       | 3145001B           |
| 146Nd   | CD8 alpha | 3146001B           |
| 147Sm   | CD11c     | 3147008B           |
| 149Sm   | CD66a     | 3149008B           |
| 151Eu   | CD14      | 3151009B           |
| 167Er   | CD11b     | 3167011B           |
| 170Er   | CD3       | 3170001B           |
| 174Yb   | HLA-DR    | 3174001B           |
| 176Yb   | CD56      | 3176008B           |
| 191Ir   | DNA (Singlets) | 201192A   |
| 193Ir   | DNA (Singlets) | 201192A   |
| 194Pt   | Live/Dead | 201194            |
Table S3. scRNA-seq cell counts shown in Figure 1.

| Condition (Compartment, Time) | B cells | CD1C+ DCs | CD8 T cells | granulocytes | macrophages | monocyte/macrophage | neurons | NK cells | T cells | TOTAL |
|-------------------------------|---------|-----------|-------------|--------------|-------------|---------------------|---------|----------|---------|-------|
| Blood, 51 hrs                | 33      | 72        | 251         | 27           | 20          | 834                 | 0       | 62       | 483     | 1782  |
| Blood, 66 hrs                | 18      | 10        | 0           | 15           | 13          | 181                 | 0       | 11       | 57      | 305   |
| Blood, 73 hrs                | 38      | 4         | 100         | 7            | 36          | 323                 | 0       | 278      | 664     | 1450  |
| Blood, 89 hrs                | 57      | 22        | 110         | 20           | 198         | 872                 | 0       | 209      | 1543    | 3031  |
| Blood, 112 hrs               | 49      | 26        | 147         | 13           | 40          | 158                 | 0       | 358      | 1590    | 2381  |
| Blood, 137 hrs               | 9       | 13        | 10          | 13           | 61          | 165                 | 0       | 59       | 484     | 814   |
| Blood, patient followup      | 133     | 88        | 70          | 20           | 1           | 327                 | 0       | 197      | 794     | 1630  |
| Blood, control 00            | 67      | 13        | 77          | 2            | 0           | 47                  | 0       | 425      | 1184    | 1815  |
| Blood, control 01            | 35      | 74        | 29          | 27           | 9           | 771                 | 0       | 150      | 518     | 1613  |
| Blood, control 02            | 10      | 60        | 4           | 15           | 5           | 1531                | 0       | 21       | 151     | 1797  |
| Blood, control 03            | 56      | 56        | 192         | 9            | 0           | 313                 | 0       | 238      | 756     | 1620  |
| Hematoma, 51 hrs             | 13      | 2         | 9           | 1            | 425         | 0                   | 17      | 18       | 1126    | 1611  |
| Hematoma, 66 hrs             | 2       | 0         | 0           | 0            | 12          | 0                   | 351     | 6        | 248     | 619   |
| Hematoma, 73 hrs             | 91      | 55        | 200         | 20           | 816         | 39                  | 1       | 278      | 2145    | 3645  |
| Hematoma, 89 hrs             | 102     | 9         | 20          | 9            | 121         | 3                   | 0       | 171      | 1422    | 1857  |
| Hematoma, 112 hrs            | 83      | 17        | 12          | 6            | 235         | 13                  | 8       | 601      | 2336    | 3311  |
| Hematoma, 137 hrs            | 32      | 4         | 1           | 2            | 196         | 2                   | 7       | 307      | 1890    | 2441  |
Table S4. Myeloid cell re-clustering analysis cluster membership cell counts.

| Condition (Compartment, Time) | Sub-cluster 0 | Sub-cluster 1 | Sub-cluster 10 | Sub-cluster 11 | Sub-cluster 12 | Sub-cluster 13 | Sub-cluster 14 | Sub-cluster 1 | Sub-cluster 2 | Sub-cluster 3 | Sub-cluster 4 | Sub-cluster 5 | Sub-cluster 6 | Sub-cluster 7 | Sub-cluster 8 | Sub-cluster 9 | TOT AL |
|-------------------------------|--------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|--------------|---------------|--------------|---------------|---------------|---------------|---------------|---------------|---------|-------|
| Blood, 51 hrs                | 11           | 58           | 3             | 119           | 1             | 0             | 1             | 1             | 612          | 0             | 0             | 70            | 6             | 5             | 39            | 926           |         |       |
| Blood, 66 hrs                | 1            | 11           | 0             | 0             | 174           | 0             | 0             | 4             | 0            | 0             | 0             | 8             | 0             | 5             | 1             | 204           |         |       |
| Blood, 73 hrs                | 6            | 290          | 3             | 9             | 3             | 0             | 2             | 0             | 7            | 0             | 0             | 4             | 1             | 32            | 6             | 363           |         |       |
| Blood, 89 hrs                | 8            | 767          | 13            | 14            | 0             | 0             | 3             | 0             | 12           | 0             | 1             | 18            | 4             | 221           | 31            | 2             | 109           |         |       |
| Blood, 112 hrs               | 6            | 51           | 94            | 0             | 1             | 0             | 8             | 0             | 1            | 0             | 0             | 25            | 0             | 25            | 13            | 224           |         |       |
| Blood, 137 hrs               | 10           | 20           | 120           | 1             | 1             | 0             | 2             | 0             | 0            | 0             | 0             | 14            | 0             | 64            | 7             | 239           |         |       |
| Blood, patient followup      | 139          | 2            | 11            | 46            | 0             | 1             | 0             | 0             | 0            | 0             | 0             | 70            | 60            | 2             | 85            | 416           |         |       |
| Blood, control 00            | 29           | 2            | 2             | 3             | 1             | 0             | 0             | 0             | 0            | 0             | 0             | 9             | 1             | 1             | 12            | 60            |         |       |
| Blood, control 01            | 517          | 0            | 38            | 74            | 0             | 11            | 0             | 0             | 0            | 0             | 0             | 65            | 119           | 2             | 28            | 854           |         |       |
| Blood, control 02            | 1169         | 0            | 32            | 31            | 2             | 84            | 0             | 0             | 0            | 0             | 0             | 50            | 167           | 5             | 56            | 159           |         |       |
| Blood, control 03            | 230          | 0            | 8             | 10            | 2             | 11            | 0             | 0             | 0            | 0             | 0             | 53            | 27            | 0             | 28            | 369           |         |       |
| Hematoma, 51 hrs             | 0            | 0            | 0             | 0             | 0             | 0             | 0             | 0             | 0            | 0             | 0             | 418           | 7             | 2             | 0             | 0             | 427           |         |       |
| Hematoma, 66 hrs             | 0            | 0            | 0             | 0             | 0             | 0             | 0             | 0             | 0            | 11            | 0             | 0             | 0             | 0             | 0             | 0             | 12            |         |       |
| Hematoma, 73 hrs             | 1            | 3            | 0             | 8             | 0             | 0             | 3             | 734           | 9            | 57            | 24            | 56            | 0             | 4             | 11            | 910           |         |       |
| Hematoma, 89 hrs             | 0            | 2            | 0             | 0             | 0             | 0             | 1             | 47            | 2             | 6             | 60            | 8             | 0             | 5             | 2             | 133           |         |       |
| Hematoma, 112 hrs            | 0            | 0            | 0             | 2             | 0             | 0             | 5             | 14            | 1             | 6             | 207           | 17            | 0             | 0             | 13            | 265           |         |       |
| Hematoma, 137 hrs            | 0            | 0            | 0             | 0             | 0             | 0             | 2             | 0             | 0             | 2             | 193           | 4             | 0             | 0             | 1             | 202           |         |       |
### Table S5. Monocyte sub-cluster IPA results. Top 10 pathways and associated genes are shown.

| myeloid sub-cluster | Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---------------------|-----------------------------|---------------|-------|-----------|
| myeloid subcluster 0 | Retinoate Biosynthesis II   | 2.68          | 0.25  | RBP7      |
|                     | Pentose Phosphate Pathway (Non-oxidative Branch) | 2.5           | 0.167 | TKT       |
|                     | Clathrin-mediated Endocytosis Signaling | 2.35          | 0.0104 | AP1S2,LYZ |
|                     | Pentose Phosphate Pathway      | 2.28          | 0.1    | TKT       |
|                     | Role of IL-17A in Psoriasis    | 2.16          | 0.0769 | S100A9    |
|                     | The Visual Cycle               | 1.98          | 0.05   | RBP7      |
|                     | Retinoate Biosynthesis I       | 1.75          | 0.0294 | RBP7      |
|                     | Retinol Biosynthesis           | 1.66          | 0.0238 | RBP7      |
|                     | PFKFB4 Signaling Pathway       | 1.62          | 0.0217 | TKT       |
|                     | Autophagy                      | 1.5           | 0.0164 | CTSS      |
|                     | LXR/RXR Activation             | 5.2           | 0.0331 | CD14,CLU,IL1B,PTGS2 |
|                     | IL-10 Signaling                | 4.34          | 0.0435 | CCR1,CD14,IL1B |
|                     | MIF-mediated Glucocorticoid Regulation | 3.27        | 0.0588 | CD14,PTGS2 |
|                     | MIF Regulation of Innate Immunity | 3.08        | 0.0476 | CD14,PTGS2 |
|                     | Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza | 3.06 | 0.0465 | CCR1,IL1B |
|                     | Eicosanoid Signaling           | 2.69          | 0.0303 | LTA4H,PTGS2 |
|                     | Toll-like Receptor Signaling   | 2.57          | 0.0263 | CD14,IL1B |
|                     | Sirtuin Signaling Pathway      | 2.52          | 0.0103 | DUSP6,SOD2,TUBA1A |
|                     | Neuroinflammation Signaling Pathway | 2.48        | 0.01   | IL1B,PTGS2,SOD2 |
|                     | Glucocorticoid Receptor Signaling | 2.34        | 0.00893 | IL1B,PTGS2,SGK1 |
| myeloid subcluster 1 | Granulocyte Adhesion and Diapedesis | 11.5         | 0.0833 | C5AR1,CCL2,CCL7,CXCL16,CXCL2,CXCL3,EZR,FPR1,IL1R1,IL1R2,IL1RAP,IL1RN,ITGA5,ITGB1,TNFRSF1A |
|                     | Agranulocyte Adhesion and Diapedesis | 9.93         | 0.0725 | ACTB,ACTG1,C5AR1,CCL2,CCL7,CXCL16,CXCL2,CXCL3,EZR,IL1R1,IL1R1,ITGA5,ITGB1,TNFRSF1A |
|                     | Osteoarthritis Pathway         | 7.4           | 0.0569 | CEBPB,CTNNB1,HEMT,HIF1A,IL1R1,IL1R2,IL1RAP,ITGA5,ITGB1,NA-MPT,S100A8,TNFRSF1A |
|                     | Hepatic Fibrosis Signaling Pathway | 6.37         | 0.038  | CCL2,CEBPB,CTNNB1,FTH1,HIF1A,IL1R1,IL1R2,IL1RAP,IL1RN,ITGA5,ITGB1,TFRC,TIMP1,TNFRSF1A |
| Pathway                                                                 | Score | q-value | Genes                                                                                   |
|------------------------------------------------------------------------|-------|---------|----------------------------------------------------------------------------------------|
| Caveolar-mediated Endocytosis Signaling                                | 6.04  | 0.0959  | ACTB,ACTG1,CD55,ITGA5,ITGAX,ITGB1,PTPN1                                                |
| TREM1 Signaling                                                        | 5.96  | 0.0933  | CCL2,CCL7,CXCL2,ITGA5,ITGAX,ITGB1,TREM1                                                |
| LXR/RXR Activation                                                     | 5.59  | 0.0661  | CCL2,CCL7,IL1R1,IL1R2,IL1RAP,IL1RN,S100A8,TNFRSF1A                                     |
| Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes        | 4.23  | 0.0638  | ACTB,ACTG1,CD55,ITGA5,ITGAX,ITGB1,TREM1,CD55,ITGA5,ITGAX,ITGB1                         |
| Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis | 4.07  | 0.0321  | C5AR1,CCL2,CEBPB,CTNNB1,FCGR1A,HMOX1,LCP2,CD55,ITGA5,ITGAX,ITGB1,TREM1                |
| Leukocyte Extravasation Signaling                                     | 4.06  | 0.0406  | ACTB,ACTG1,CD44,CTNNB1,ITGA5,ITGAX,ITGB1,TIMP1,CD55,ITGA5,ITGAX,ITGB1                |
| myeloid subcluster 3                                                   |       |         |                                                                                         |
| Granzyme A Signaling                                                  | 6.06  | 0.158   | H1-2,H1-3,H1-4                                                                         |
| Glucocorticoid Receptor Signaling                                      | 3.48  | 0.0119  | ANXA1,CCNH,HSPA5,TSC22D3                                                                |
| Toll-like Receptor Signaling                                           | 2.57  | 0.0263  | TNFAIP3,UBC                                                                            |
| Sirtuin Signaling Pathway                                              | 2.52  | 0.0103  | H1-2,H1-3,H1-4                                                                         |
| NER Pathway                                                           | 2.32  | 0.0194  | CCNH,H4C3                                                                               |
| Trans, trans-farnesyl Diphosphate Biosynthesis                        | 2.3   | 0.2     | IDI1                                                                                   |
| Protein Kinase A Signaling                                            | 2.14  | 0.00754 | H1-2,H1-3,H1-4                                                                         |
| Necroptosis Signaling Pathway                                         | 1.96  | 0.0127  | PEL1,UBC                                                                               |
| NF-κB Signaling                                                       | 1.85  | 0.0112  | PEL1,TNFAIP3                                                                           |
| Mevalonate Pathway I                                                 | 1.85  | 0.0714  | IDI1                                                                                   |
| myeloid subcluster 4                                                   |       |         |                                                                                         |
| Glycolysis I                                                          | 13    | 0.346   | ALDOA1,ENO1,ENO2,GAPDH,GPI,PFKP,PGK1,PKM,TP1                                            |
| Aldosterone Signaling in Epithelial Cells                              | 11.1  | 0.0886  | DNAJA1,DNAJB1,HSP90AA1,HSP90AB1,HSP90B1,HSPA1,HSPA1B,HSPA2,HSPA3,HSPA4,HSPA5,HSPA6,     |
| Protein Ubiquitination Pathway                                        | 7.97  | 0.0513  | DNAJA1,DNAJB1,HSP90AA1,HSP90AB1,HSP90B1,HSPA1,HSPA1B,HSPA2,HSPA3,HSPA4,HSPA5,HSPA6,     |
| Role of IL-17A in Psoriasis                                           | 7.67  | 0.385   | CCL20,CXCL1,CXCL5,CXCL6,CXCL8                                                          |
| HIF1α Signaling                                                       | 7.61  | 0.231   | ALDOA1,ENO1,ENO2,GAPDH,GPI,PFKP,PGK1,PKM,TP1                                            |
| Role of IL-17A in Arthritis                                           | 6.92  | 0.0796  | EGLN3,HSP90AA1,JUN,LDHA,MMP19,PIK3CB,RALA,SLC2A1,VEGFA                                 |
| Unfolded protein response                                             | 6.84  | 0.125   | CDB2,HSP90B1,HSPA1A,HSPA1B,HSPA6,HSPA8,HSPH1,PIK3CB,RALA,SLC2A1,VEGFA                   |
| Role of PKR in Interferon Induction and Antiviral Response            | 6.79  | 0.0769  | HSP90AA1,HSP90AB1,HSP90B1,HSPA1A,HSPA1B,HSPA6,HSPA8,HSPH1,PIK3CB,RALA,SLC2A1,VEGFA,     |
| Granulocyte Adhesion and Diapedesis                                   | 6.16  | 0.0556  | CCL20,CCL3,CCL4,CXCL1,CXCL5,CXCL6,CXCL8,MMP19,PPBP,SDC2                                  |
| myeloid subcluster 5                                                   |       |         |                                                                                         |
| Senescence Pathway                                                    | 3.96  | 0.0291  | FOXO3,IPK2,MAP2K3,MAPKAPK2,PIK3R5,SEPTINE1,SMAD7,TBK1                                   |
| Phagosome Maturation                                                  | 3.82  | 0.0397  | ATP6V0B,CALR,CTSB,CTSV,RAB5C,TUBA1                                                   |
| Pathway                                                                 | Score | P-value | Genes                                                                 |
|------------------------------------------------------------------------|-------|---------|----------------------------------------------------------------------|
| FGF Signaling                                                          | 2.99  | 0.0476  | ATF4, MAP2K3, MAPKAPK2, PIK3R5                                        |
| Death Receptor Signaling                                               | 2.86  | 0.044   | LMNA, TBK1, TIPARP, TNFRSF21                                          |
| PFKFB4 Signaling Pathway                                               | 2.73  | 0.0652  | ATF4, FBP1, MAP2K3                                                   |
| Type I Diabetes Mellitus Signaling                                     | 2.54  | 0.036   | CD86, IFNGR2, IRAK1, MAP2K3                                          |
| Role of IL-17A in Arthritis                                            | 2.51  | 0.0545  | MAP2K3, MAPKAPK2, PIK3R5                                            |
| p38 MAPK Signaling                                                    | 2.45  | 0.0339  | ATF4, IRAK1, MAP2K3, MAPKAPK2                                        |
| Clathrin-mediated Endocytosis Signaling                               | 2.44  | 0.0259  | APOC1, APOE, DAB2, PIK3R5, RAB5C                                     |
| Autophagy                                                             | 2.38  | 0.0492  | CTSB, CTSV, RB1CC1                                                  |
| myeloid subcluster 6                                                  |       |         |                                                                       |
| EIF2 Signaling                                                        | 29.8  | 0.103   | RPL10A, RPL13A, RPL17, RPL22, RPL23A, RPL27A, RPL3, RPL35, RPL5, RPLP0, RPS11, RPS2, RPS21, RPS23, RPS24, RPS29, RPS3A, RPS4X, RPS5, RPS6, RPS7, RPS8, RPSA |
| Antigen Presentation Pathway                                          | 26.3  | 0.359   | CD74, CIITA, HLA-DMA, HLA-DMB, HLA-DQA, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DBQ1, HLA-DBQ2, HLA-DRA, HLA-DRB1, HLA-DRB5 |
| Allograft Rejection Signaling                                         | 17    | 0.14    | HLA-DMA, HLA-DMB, HLA-DQA, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DBQ1, HLA-DBQ2, HLA-DRA, HLA-DRB1, HLA-DRB5 |
| OX40 Signaling Pathway                                                | 16.8  | 0.133   | HLA-DMA, HLA-DMB, HLA-DQA, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DBQ1, HLA-DBQ2, HLA-DRA, HLA-DRB1, HLA-DRB5 |
| PD-1, PD-L1 cancer immunotherapy pathway                              | 15.9  | 0.113   | HLA-DMA, HLA-DMB, HLA-DQA, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DBQ1, HLA-DBQ2, HLA-DRA, HLA-DRB1, HLA-DRB5 |
| Regulation of eIF4 and p70S6K Signaling                               | 15.4  | 0.0828  | RPS11, RPS2, RPS21, RPS23, RPS24, RPS29, RPS3A, RPS4X, RPS5, RPS6, RPS7, RPS8, RPSA |
| Th1 Pathway                                                           | 15.2  | 0.0992  | HLA-DMA, HLA-DMB, HLA-DQA, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DBQ1, HLA-DBQ2, HLA-DRA, HLA-DRB1, HLA-DRB5 |
| Th2 Pathway                                                           | 14.6  | 0.0882  | RPS11, RPS2, RPS21, RPS23, RPS24, RPS29, RPS3A, RPS4X, RPS5, RPS6, RPS7, RPS8, RPSA |
| mTOR Signaling                                                        | 13.8  | 0.0619  | RPS11, RPS2, RPS21, RPS23, RPS24, RPS29, RPS3A, RPS4X, RPS5, RPS6, RPS7, RPS8, RPSA |
| Cdc42 Signaling                                                       | 13.5  | 0.0719  | HLA-DMA, HLA-DMB, HLA-DQA, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DBQ1, HLA-DBQ2, HLA-DRA, HLA-DRB1, HLA-DRB5 |
| myeloid subcluster 7                                                  |       |         |                                                                       |
| EIF2 Signaling                                                        | 32.6  | 0.0893  | RPL13, RPL14, RPL27, RPL30, RPL31, RPL34, RPL35A, RPL38, RPL39, RPL4, RPL41, RPS10, RPS12, RPS15A, RPS20, RPS25, RPS27A, RPS3, RPS4Y1 |
| Regulation of eIF4 and p70S6K Signaling                               | 12.3  | 0.0573  | RPS10, RPS12, RPS15A, RPS20, RPS25, RPS27, RPS27A, RPS3, RPS4Y1 |
| mTOR Signaling                                                        | 11.2  | 0.0429  | RPS10, RPS12, RPS15A, RPS20, RPS25, RPS27, RPS27A, RPS3, RPS4Y1 |
| CTLA4 Signaling in Cytotoxic T Lymphocytes                            | 3.62  | 0.0337  | CD3D, CD3G, TRAT1                                                    |
| Pathway                                                                 | p-value | q-value | Genes                                                                 |
|------------------------------------------------------------------------|---------|---------|----------------------------------------------------------------------|
| iCOS-iCOSL Signaling in T Helper Cells                                  | 3.34    | 0.027   | CD3D,CD3G,TRAT1                                                       |
| Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells               | 3.01    | 0.0588  | CD3D,CD3G                                                            |
| Antiproliferative Role of TOB in T Cell Signaling                       | 2.89    | 0.0513  | CD3D,CD3G                                                            |
| Hematopoiesis from Pluripotent Stem Cells                              | 2.69    | 0.0408  | CD3D,CD3G                                                            |
| Primary Immunodeficiency Signaling                                      | 2.67    | 0.04    | CD3D,IL7R                                                            |
| Nur77 Signaling in T Lymphocytes                                        | 2.53    | 0.0339  | CD3D,CD3G                                                            |
| Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells               | 3.48    | 0.00893 | RPL2,RPS28                                                           |
| Pathogenesis of Multiple Sclerosis                                      | 2.45    | 0.111   | CCL5                                                                 |
| Differential Regulation of Cytokine Production in Macrophages and T Helper Cells by IL-17A and IL-17F | 2.15    | 0.0556  | CCL5                                                                 |
| Differential Regulation of Cytokine Production in Intestinal Epithelial Cells by IL-17A and IL-17F | 2.04    | 0.0435  | CCL5                                                                 |
| IL-17A Signaling in Gastric Cells                                       | 2.01    | 0.04    | CCL5                                                                 |
| Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza | 1.77    | 0.0233  | CCL5                                                                 |
| Role of IL-17A in Arthritis                                            | 1.67    | 0.0182  | CCL5                                                                 |
| Role of PI3K/AKT Signaling in the Pathogenesis of Influenza             | 1.6     | 0.0156  | CCL5                                                                 |
| VDR/RXR Activation                                                     | 1.52    | 0.0128  | CCL5                                                                 |
| Role of MAPK Signaling in the Pathogenesis of Influenza                 | 1.5     | 0.0125  | CCL5                                                                 |
| Tec Kinase Signaling                                                   | 3.91    | 0.0305  | GNG2,HCK,ITGA4,LYN,RHOC                                              |
| B Cell Receptor Signaling                                              | 3.66    | 0.027   | LYN,PAG1,PIK3AP1,POU2F2,PTPN6                                         |
| Reelin Signaling in Neurons                                             | 3.24    | 0.031   | HCK,ITGA4,ITGAL,LYN                                                  |
| Systemic Lupus Erythematosus In B Cell Signaling Pathway                | 2.88    | 0.0182  | HCK,LYN,PAG1,PIK3AP1,PTPN6                                           |
| Agrin Interactions at Neuromuscular Junction                            | 2.78    | 0.038   | ITGA4,ITGAL,UTRN                                                     |
| Polyamine Regulation in Colon Cancer                                    | 2.72    | 0.0909  | PSME2,SAT1                                                           |
| Tumoricidal Function of Hepatic Natural Killer Cells                    | 2.64    | 0.0833  | BID,ITGAL                                                            |
| Production of Nitric Oxide and Reactive Oxygen Species in Macrophages   | 2.63    | 0.0213  | PTPN6,RHOC,SERPINA1,TNFRSF1B                                          |
| Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes         | 2.57    | 0.0319  | FCGR3A/FCGR3B,HCK,LYN                                                |
| Natural Killer Cell Signaling                                          | 2.56    | 0.0203  | FCGR3A/FCGR3B,ITGAL,LILRB1,PTPN6                                     |
| myeloid subcluster | Interferon Signaling | 12.8 | 0.194 | IFI6,IFIT1,IFIT3,ISG15,MX1,OAS1,STAT1 |
|-------------------|---------------------|-------|-------|-------------------------------------|
|                   | Systemic Lupus Erythematosus In B Cell Signaling Pathway | 6.49  | 0.0255 | FOS,IFIT2,IFIT3,ISG15,STAT1,TNFSF10,TNFSF13B |
|                   | Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses | 5.25  | 0.0325 | EIF2AK2,OAS1,OAS2,TNFSF10,TNFSF13B |
|                   | UVA-Induced MAPK Signaling | 4.67  | 0.0408 | FOS,PARP14,PARP9,STAT1 |
|                   | Role of PKR in Interferon Induction and Antiviral Response | 4.37  | 0.0342 | EIF2AK2,FOS,HSPA4,STAT1 |
|                   | Inhibition of ARE-Mediated mRNA Degradation Pathway | 4.29  | 0.0328 | TNFSF10,TNFSF13B,ZFP36,ZFP36L2 |
|                   | Retinoic acid Mediated Apoptosis Signaling | 3.86  | 0.05  | PARP14,PARP9,TNFSF10 |
|                   | Activation of IRF by Cytosolic Pattern Recognition Receptors | 3.8   | 0.0476 | IFIT2,ISG15,STAT1 |
|                   | PDGF Signaling | 3.4   | 0.0349 | EIF2AK2,FOS,STAT1 |
|                   | Death Receptor Signaling | 3.32  | 0.033  | PARP14,PARP9,TNFSF10 |

| myeloid subcluster | Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells | 5.27  | 0.0882 | CD247,GZMB,PRF1 |
|-------------------|----------------------------------------------------------|-------|-------|----------------|
|                   | Th1 and Th2 Activation Pathway | 4.61  | 0.0234 | CD247,IL2RB,JUN,KLRD1 |
|                   | Natural Killer Cell Signaling | 4.37  | 0.0203 | CD247,IL2RB,KLRB1,KLRD1 |
|                   | Crosstalk between Dendritic Cells and Natural Killer Cells | 4.01  | 0.0337 | IL2RB,KLRD1,PRF1 |
|                   | Granzyme B Signaling | 3.93  | 0.125  | GZMB,PRF1 |
|                   | Granzyme A Signaling | 3.78  | 0.105  | GZMA,PRF1 |
|                   | Type I Diabetes Mellitus Signaling | 3.73  | 0.027  | CD247,GZMB,PRF1 |
|                   | Tumoricidal Function of Hepatic Natural Killer Cells | 3.57  | 0.0833 | GZMB,PRF1 |
|                   | Th2 Pathway | 3.47  | 0.0221 | CD247,IL2RB,JUN |
|                   | Graft-versus-Host Disease Signaling | 2.97  | 0.0417 | GZMB,PRF1 |

| myeloid subcluster | Primary Immunodeficiency Signaling | 4.65  | 0.06 | IGHA1,LCK,ZAP70 |
|-------------------|-----------------------------------|-------|------|----------------|
|                   | Iron homeostasis signaling pathway | 3.35  | 0.0219 | CIAO2B,HBA1/HBA2,HBB |
|                   | Calcium-induced T Lymphocyte Apoptosis | 2.62  | 0.0303 | LCK,ZAP70 |
|                   | Systemic Lupus Erythematosus In B Cell Signaling Pathway | 2.48  | 0.0109 | IGHA1,ISG20,LCK |
|                   | CTLA4 Signaling in Cytotoxic T Lymphocytes | 2.37  | 0.0225 | LCK,ZAP70 |
|                   | T Cell Receptor Signaling | 2.23  | 0.019  | LCK,ZAP70 |
|                   | PD-1, PD-L1 cancer immunotherapy pathway | 2.22  | 0.0189 | LCK,ZAP70 |
|                   | iCOS-iCOSL Signaling in T Helper Cells | 2.18  | 0.018  | LCK,ZAP70 |
| Pathway                                                                 | Score | P Value | Gene(s)                          |
|------------------------------------------------------------------------|-------|---------|----------------------------------|
| CD28 Signaling in T Helper Cells                                       | 2.12  | 0.0167  | LCK,ZAP70                        |
| IL-15 Production                                                       | 2.11  | 0.0165  | LCK,ZAP70                        |
| Remodeling of Epithelial Adherens Junctions                            | 3.24  | 0.0294  | TUBB1,VCL                        |
| Epithelial Adherens Junction Signaling                                 | 2.55  | 0.0132  | TUBB1,VCL                        |
| Gq Signaling                                                           | 2.52  | 0.0127  | GNG11,RGS18                      |
| Germ Cell-Sertoli Cell Junction Signaling                              | 2.45  | 0.0117  | TUBB1,VCL                        |
| Sertoli Cell-Sertoli Cell Junction Signaling                           | 2.38  | 0.0108  | TUBB1,VCL                        |
| Opioid Signaling Pathway                                               | 2.14  | 0.0081  | GNG11,RGS18                      |
| Extrinsic Prothrombin Activation Pathway                               | 2.07  | 0.0625  | F13A1                            |
| G Protein Signaling Mediated by Tubby                                  | 1.79  | 0.0323  | GNG11                            |
| Coagulation System                                                     | 1.74  | 0.0286  | F13A1                            |
| Intrinsic Prothrombin Activation Pathway                               | 1.66  | 0.0238  | F13A1                            |
| Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells              | 6.89  | 0.118   | B2M,HLA-B,HLA-C,HLA-E            |
| Antigen Presentation Pathway                                           | 6.65  | 0.103   | B2M,HLA-B,HLA-C,HLA-E            |
| Natural Killer Cell Signaling                                          | 6.61  | 0.0305  | B2M,FCGR3A/FCGR3B,HLA-B,HLA-C,HLA-E,LIMK2 |
| Caveolar-mediated Endocytosis Signaling                                | 5.54  | 0.0548  | B2M,HLA-B,HLA-C,HLA-E            |
| Cdc42 Signaling                                                        | 5.53  | 0.0299  | B2M,HLA-B,HLA-C,HLA-E,LIMK2      |
| Granulocyte Adhesion and Diapedesis                                    | 5.37  | 0.0278  | CSF3R,CXCR2,FPR2,MMP25,SELL      |
| Dendritic Cell Maturation                                              | 5.34  | 0.0273  | B2M,FCGR3A/FCGR3B,HLA-B,HLA-C,HLA-E |
| Allograft Rejection Signaling                                          | 5.25  | 0.0465  | B2M,HLA-B,HLA-C,HLA-E            |
| CTLA4 Signaling in Cytotoxic T Lymphocytes                             | 5.19  | 0.0449  | B2M,HLA-B,HLA-C,HLA-E            |
| OX40 Signaling Pathway                                                 | 5.17  | 0.0444  | B2M,HLA-B,HLA-C,HLA-E            |
Table S6. Human monocyte gene sets used for module scoring.

| Gene Set Name                  | Description                                                                 | Reference                  |
|-------------------------------|-----------------------------------------------------------------------------|----------------------------|
| CD141_CLEC9A_Villani          | Generated from unstimulated human PBMCs, identified by scRNA-seq.           | Villani et al.(1)          |
| CD1C_A_Villani                | Generated from unstimulated human PBMCs, identified by scRNA-seq.           | Villani et al.(1)          |
| CD1C_B_Villani                | Generated from unstimulated human PBMCs, identified by scRNA-seq.           | Villani et al.(1)          |
| CD1Cminus_CD141minus_Villani  | Generated from unstimulated human PBMCs, identified by scRNA-seq.           | Villani et al.(1)          |
| New_pop_Villani               | Generated from unstimulated human PBMCs, identified by scRNA-seq.           | Villani et al.(1)          |
| pDC_Villani                   | Generated from unstimulated human PBMCs, identified by scRNA-seq.           | Villani et al.(1)          |
| XUE_Module1 to XUE_Module49   | Generated by comparative/ integrative analysis on several microarray datasets. | Xue et al.(1)              |
| Monocyte_humann               | ImmGenn database                                                            | Shay et al.(2)             |
| MyeloidDC_humann              | ImmGenn database                                                            | Shay et al.(2)             |
| PlasmacytoidDC_humann         | ImmGenn database                                                            | Shay et al.(2)             |
| CD14_Monocytes_blood | Generated from unstimulated human PBMCs, identified by scRNA-seq. | Villani et al. (1) |
|----------------------|-----------------------------------------------------------------|------------------|
| Microglia            | Transcriptional profiling of human microglia and resident macrophages; gene expression in tissue macrophages in mice. | Poel et al., Gautier et al., and Gosselin et al. (3-5) |
| BAMs                 | Single cell atlas of mouse brain macrophages and fate mapping in mice. | Van Hove et al., and Goldmann et al. (6, 7) |
Table S7. Wilcoxon rank sum pairwise test results for CD1CB (CD14⁺ monocyte) signature module scores, data presented in Figure 2. Table displays adjusted p values (p_{adj}) for pairwise comparisons for each indicated myeloid subcluster. P values are colored as follows: blue (0.01 ≤ p_{adj} < 0.05, *), purple (0.001 ≤ p_{adj} < 0.01, **), white (0 ≤ p_{adj} < 0.001, ***), gray (not significant, p_{adj} < 0.05).

| Sub-cluster | 0   | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 |
|-------------|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 1           | 1.68E-47 | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 2           | 6.19E-71 | 3.28E-10 | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 3           | 1.15E-16 | 1.72E-57 | 1.66E-69 | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 4           | 3.08E-249 | 3.56E-225 | 1.74E-193 | 1.74E-152 | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 5           | 2.06E-224 | 2.56E-212 | 3.16E-183 | 5.98E-125 | 2.91E-08 | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 6           | 2.95E-187 | 7.73E-189 | 1.50E-166 | 6.25E-98 | 2.16E-06 | 6.31E-01 | -  | -  | -  | -  | -  | -  | -  | -  |
| 7           | 1.03E-65 | 8.67E-103 | 2.51E-100 | 1.06E-106 | 4.04E-106 | 7.82E-78 | 2.00E-54 | -  | -  | -  | -  | -  | -  | -  |
| 8           | 6.51E-92 | 6.62E-120 | 4.97E-112 | 2.32E-30 | 3.11E-92 | 1.19E-60 | 3.87E-38 | 4.82E-06 | -  | -  | -  | -  | -  | -  |
| 9           | 4.48E-184 | 3.41E-169 | 1.08E-151 | 9.39E-134 | 3.03E-38 | 1.19E-52 | 1.00E-37 | 1.35E-104 | 1.01E-98 | -  | -  | -  | -  | -  |
| 10          | 1.29E-02 | 6.82E-24 | 1.02E-35 | 5.30E-04 | 1.66E-117 | 1.91E-103 | 4.21E-86 | 6.68E-26 | 3.08E-41 | 3.85E-104 | -  | -  | -  | -  |
| 11          | 1.80E-39 | 2.42E-71 | 4.43E-75 | 5.83E-09 | 1.75E-72 | 6.97E-55 | 3.53E-41 | 3.48E-01 | 3.85E-06 | 1.62E-78 | 1.29E-16 | -  | -  | -  |
| 12          | 2.78E-02 | 1.59E-17 | 4.05E-26 | 3.21E-03 | 1.69E-83 | 1.16E-74 | 9.99E-63 | 6.67E-21 | 1.16E-32 | 1.11E-76 | 9.52E-01 | 1.63E-13 | -  | -  |
| 13          | 7.50E-04 | 4.59E-15 | 1.94E-20 | 4.75E-01 | 2.89E-52 | 1.81E-45 | 6.63E-37 | 5.65E-09 | 9.59E-17 | 1.69E-51 | 1.14E-01 | 6.67E-06 | 1.23E-01 | -  | -  |
| 14          | 4.48E-08 | 1.68E-12 | 2.35E-13 | 1.57E-03 | 1.35E-14 | 1.28E-10 | 1.04E-07 | 4.92E-01 | 3.47E-01 | 1.00E-17 | 4.53E-06 | 3.72E-01 | 3.39E-06 | 3.69E-04 | -  | -  |
**Table S8.** T cell sub-clustering analysis cluster membership cell counts. Sub-clusters are indicated by NT0-NT11.

| Condition (Compartment, Time) | NT 0 | NT 1 | NT 2 | NT 3 | NT 4 | NT 5 | NT 6 | NT 7 | NT 8 | NT 9 | NT 10 | NT 11 | Total |
|-------------------------------|------|------|------|------|------|------|------|------|------|------|-------|-------|-------|
| Blood, 51 hrs                 | 34   | 1    | 10   | 323  | 268  | 17   | 0    | 1    | 0    | 52   | 15    | 0     | 721   |
| Blood, 66 hrs                 | 1    | 0    | 17   | 0    | 3    | 0    | 3    | 4    | 0    | 0    | 0     | 0     | 28    |
| Blood, 73 hrs                 | 27   | 0    | 485  | 21   | 118  | 0    | 0    | 14   | 0    | 22   | 8     | 0     | 695   |
| Blood, 89 hrs                 | 3    | 0    | 49   | 1    | 101  | 0    | 1    | 8    | 0    | 10   | 11    | 0     | 184   |
| Blood, 112 hrs                | 326  | 0    | 579  | 8    | 237  | 0    | 3    | 456  | 0    | 55   | 12    | 5     | 1681  |
| Blood, 137 hrs                | 4    | 0    | 365  | 0    | 14   | 0    | 6    | 22   | 1    | 2    | 0     | 53    | 467   |
| Blood, patient follow up      | 645  | 0    | 6    | 6    | 95   | 0    | 0    | 0    | 0    | 58   | 48    | 0     | 858   |
| Blood, control 00             | 1069 | 1    | 1    | 16   | 109  | 0    | 0    | 2    | 0    | 45   | 17    | 0     | 1260  |
| Blood, control 01             | 424  | 0    | 4    | 1    | 61   | 0    | 0    | 0    | 0    | 18   | 15    | 0     | 523   |
| Blood, control 02             | 133  | 0    | 2    | 3    | 5    | 0    | 0    | 0    | 0    | 3    | 3     | 0     | 149   |
| Blood, control 03             | 555  | 1    | 11   | 6    | 325  | 0    | 0    | 4    | 0    | 29   | 8     | 0     | 939   |
| Hematoma, 51 hrs              | 4    | 4    | 2    | 18   | 8    | 1087 | 1    | 11   | 0    | 0    | 0     | 0     | 0     | 1135  |
| Hematoma, 66 hrs              | 3    | 7    | 3    | 1    | 0    | 217  | 4    | 11   | 2    | 0    | 0     | 0     | 0     | 248   |
| Hematoma, 73 hrs              | 194  | 37   | 345  | 1266 | 190  | 19   | 81   | 56   | 0    | 133  | 11    | 0     | 2332  |
| Hematoma, 89 hrs              | 2    | 116  | 54   | 66   | 23   | 4    | 1014 | 122  | 4    | 15   | 4     | 0     | 1424  |
| Hematoma, 112 hrs             | 25   | 1774 | 6    | 45   | 10   | 1    | 43   | 355  | 18   | 54   | 12    | 5     | 2348  |
| Hematoma, 137 hrs             | 2    | 1064 | 2    | 0    | 0    | 5    | 12   | 98   | 692  | 9    | 2     | 5     | 1891  |
Table S9. T cell sub-cluster IPA results. Top 10 pathways and associated genes are shown.

| T cell sub-cluster | Ingenuity Canonical Pathways                                      | -log(p-value) | Ratio   | Molecules                      |
|--------------------|------------------------------------------------------------------|---------------|---------|-------------------------------|
| T cell subcluster 1| EIF2 Signaling                                                   | 3.16          | 0.0134  | PABPC1,RPL9,RPS3A             |
|                    | Regulation of elf4 and p70S6K Signaling                         | 2.17          | 0.0127  | PABPC1,RPS3A                  |
|                    | Antiproliferative Role of TOB in T Cell Signaling                | 1.52          | 0.0256  | PABPC1                        |
|                    | Hepatic Fibrosis Signaling Pathway                              | 1.47          | 0.00543 | FTH1,PDCD4                    |
|                    | Transcriptional Regulatory Network in Embryonic Stem Cells       | 1.38          | 0.0185  | SKIL                          |
|                    | SAPK/JNK Signaling                                              | 1.11          | 0.0098  | DUSP4                         |
|                    | PD-1, PD-L1 cancer immunotherapy pathway                        | 1.09          | 0.00943 | PDCD4                         |
|                    | Inhibition of ARE-Mediated mRNA Degradation Pathway              | 1.03          | 0.0082  | CNOT1                         |
|                    | Iron homeostasis signaling pathway                              | 0.987         | 0.0073  | FTH1                          |
|                    | Granulocyte Adhesion and Diapedesis                             | 0.873         | 0.00556 | PPBP                          |
| T cell subcluster 2| Role of IL-17A in Psoriasis                                     | 5.2           | 0.154   | S100A8,S100A9                 |
|                    | LXR/RXR Activation                                              | 3.24          | 0.0165  | LYZ,S100A8                    |
|                    | Atherosclerosis Signaling                                       | 3.2           | 0.0159  | LYZ,S100A8                    |
|                    | IL-12 Signaling and Production in Macrophages                   | 3.16          | 0.0152  | LYZ,S100A8                    |
|                    | Production of Nitric Oxide and Reactive Oxygen Species in Macrophages | 2.86          | 0.0106  | LYZ,S100A8                    |
|                    | Clathrin-mediated Endocytosis Signaling                         | 2.83          | 0.0104  | LYZ,S100A8                    |
|                    | Osteoarthritis Pathway                                          | 2.76          | 0.00948 | S100A8,S100A9                 |
|                    | Autophagy                                                       | 1.73          | 0.0164  | CTSS                          |
|                    | Adipogenesis pathway                                            | 1.39          | 0.00746 | TXNIP                         |
|                    | Phagosome Maturation                                            | 1.34          | 0.00662 | CTSS                          |
| T cell subcluster 3| GADD45S Signaling                                               | 3.86          | 0.105   | CDKN1A,GADD45A                 |
|                    | HGF Signaling                                                   | 3.85          | 0.027   | CDKN1A,FOS,ITGB1              |
|                    | Systemic Lupus Erythematosus In T Cell Signaling Pathway         | 3.65          | 0.012   | CREM,FOS,GADD45A,ICOS         |
|                    | TNFR2 Signaling                                                 | 3.46          | 0.0667  | FOS,TNFAIP3                   |
|                    | Cell Cycle: G2/M DNA Damage Checkpoint Regulation                | 3.03          | 0.0408  | CDKN1A,GADD45A                 |
| T cell subcluster 4                                      |                          | FOS,TNFAIP3                  |
|--------------------------------------------------------|--------------------------|------------------------------|
| TNFR1 Signaling                                        | 3.01                     | 0.04                         |
| CD40 Signaling                                         | 2.79                     | 0.0308                       |
| Toll-like Receptor Signaling                           | 2.65                     | 0.0263                       |
| VDR/RXR Activation                                     | 2.63                     | 0.0256                       |
| Role of BRCA1 in DNA Damage Response                   | 2.61                     | 0.025                        |
| IL-17A Signaling in Gastric Cells                      | 5.28                     | 0.12                         |
| Chemokine Signaling                                    | 3.75                     | 0.0375                       |
| Granzyme B Signaling                                   | 3.67                     | 0.125                        |
| CCR5 Signaling in Macrophages                          | 3.55                     | 0.0319                       |
| Granzyme A Signaling                                   | 3.52                     | 0.105                        |
| Tumoricidal Function of Hepatic Natural Killer Cells   | 3.31                     | 0.0833                       |
| Neuroprotective Role of THOP1 in Alzheimer's Disease   | 3.27                     | 0.0256                       |
| Renin-Angiotensin Signaling                            | 3.26                     | 0.0254                       |
| TNFR2 Signaling                                        | 3.12                     | 0.0667                       |
| Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells | 3.01                     | 0.0588                       |
| Aldosterone Signaling in Epithelial Cells              | 14.2                     | 0.0759                       |
| Protein Ubiquitination Pathway                         | 14.2                     | 0.0513                       |
| Unfolded protein response                              | 8.2                      | 0.107                        |
| Glucocorticoid Receptor Signaling                      | 7.91                     | 0.0298                       |
| Role of PKR in Interferon Induction and Antiviral Response | 7.71                     | 0.0598                       |
| BAG2 Signaling Pathway                                 | 7.09                     | 0.116                        |
| Huntington's Disease Signaling                         | 6.82                     | 0.0338                       |
| eNOS Signaling                                         | 5.49                     | 0.0377                       |
| NRF2-mediated Oxidative Stress Response                | 5.06                     | 0.0317                       |
| Natural Killer Cell Signaling                          | 3.83                     | 0.0254                       |
| Role of IL-17A in Psoriasis                            | 7.76                     | 0.308                        |
| TREM1 Signaling                                        | 7.72                     | 0.08                         |
| Hepatic Fibrosis Signaling Pathway                     | 6.86                     | 0.0245                       |
| Pathway                                                                 | Score | P-value | Genes                                                                 |
|------------------------------------------------------------------------|-------|---------|----------------------------------------------------------------------|
| Agranulocyte Adhesion and Diapedesis                                   | 6.56  | 0.0363  | CCL2, CCL7, CXCL3, CXCL8, IL1B, MYL6, PPBP                           |
| Role of IL-17F in Allergic Inflammatory Airway Diseases               | 5.59  | 0.0952  | CCL2, CCL7, CXCL8, IL1B                                             |
| Granulocyte Adhesion and Diapedesis                                    | 5.46  | 0.0333  | CCL2, CCL7, CXCL3, CXCL8, IL1B, PPBP                              |
| Neuroinflammation Signalining Pathway                                  | 5.28  | 0.0233  | CCL2, CXCL8, FOS, HLA-DRA, IL1B, SOD2, TYROBP                       |
| Role of IL-17A in Arthritis                                           | 5.12  | 0.0727  | CCL2, CCL7, CXCL3, CXCL8                                           |
| LXR/RXR Activation                                                    | 5.08  | 0.0413  | CCL2, CCL7, IL1B, LYZ, S100A8                                      |
| Osteoarthritis Pathway                                                | 5.07  | 0.0284  | CXCL8, HIF1A, IL1B, NAMPT, S100A8, S100A9                           |
| Oxidative Phosphorylation                                             | 6.1   | 0.0642  | MT-ATP6, MT-CO2, MT-CO3, MT-CYB, MT-ND2, MT-ND3, MT-ND5            |
| Mitochondrial Dysfunction                                             | 5.85  | 0.0468  | CASP8, MT-ATP6, MT-CO2, MT-CO3, MT-CYB, MT-ND2, MT-ND3, MT-ND5     |
| DNA Double-Strand Break Repair by Homologous Recombination            | 2.72  | 0.143   | ATM, ATRX                                                           |
| DNA Methylation and Transcriptional Repression Signaling              | 1.94  | 0.0571  | ARID4B, CHD4                                                        |
| Sirtuin Signaling Pathway                                             | 1.93  | 0.0172  | MT-ATP6, MT-CYB, MT-ND2, MT-ND3, MT-ND5                           |
| Cell Cycle: G2/M DNA Damage Checkpoint Regulation                     | 1.66  | 0.0408  | ATM, MDM4                                                           |
| Transcriptional Regulatory Network in Embryonic Stem Cells             | 1.58  | 0.037   | KAT6A, RIF1                                                        |
| PCP pathway                                                           | 1.49  | 0.0333  | JUND, ROCK1                                                        |
| HOTAIR Regulatory Pathway                                             | 1.41  | 0.0187  | KMT2A, KMT2C, ROCK1                                                |
| Ephrin B Signaling                                                    | 1.35  | 0.0278  | ITSN2, ROCK1                                                       |
| Role of IL-17A in Arthritis                                           | 3.36  | 0.0545  | CCL5, CXCL8, MAPKAPK2                                              |
| Autophagy                                                              | 3.23  | 0.0492  | CTSL, RB1CC1, SQSTM1                                                |
| IL-17A Signaling in Gastric Cells                                     | 2.69  | 0.08    | CCL5, CXCL8                                                        |
| p53 Signaling                                                         | 2.63  | 0.0306  | HIF1A, JMY, PMAIP1                                                  |
| Hepatic Fibrosis Signaling Pathway                                    | 2.51  | 0.0136  | CCL5, CXCL8, HIF1A, PDCD4, SPP1                                   |
| Adipogenesis pathway                                                  | 2.25  | 0.0224  | DDIT3, HIF1A, NR1D2                                                |
| Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza | 2.22  | 0.0465  | CCL5, CXCL8                                                        |
| BAG2 Signaling Pathway                                                | 2.22  | 0.0465  | HSPA4, MAPKAPK2                                                    |
| Unfolded protein response                                             | 2     | 0.0357  | DDIT3, HSPA4                                                       |
| Granulocyte Adhesion and Diapedesis                                   | 1.9   | 0.0167  | CCL5, CXCL8, PPBP                                                 |
| Cdc42 Signaling                                                       | 20.3  | 0.0958  | ARPC1B, ARPC2, ARPC3, ARPC5, CD3D, CD3G, CFL1, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQA2, HLA-DRA, HLA-
| Pathway                                      | Score | P-value | Genes                                                                 | Subcluster |
|----------------------------------------------|-------|---------|----------------------------------------------------------------------|------------|
| Actin Cytoskeleton Signaling                 | 13.7  | 0.0596  | ACTB, ACTG1, ARPC1B, ARPC2, ARPC3, ARPC5, CFL1, FLNA, ITGB1, MYL6, PFN1, TMSB10/TMSB4X, TTN | 10         |
| Antigen Presentation Pathway                 | 13    | 0.205   | CD74, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DRA, HLA-DRB1, HLA-DRB5 | 10         |
| CD28 Signaling in T Helper Cells             | 12.1  | 0.0833  | ARPC1B, ARPC2, ARPC3, ARPC5, CD3D, CD3G, HLA-DQA1, HLA-DRA, HLA-DRB1, HLA-DRB5 | 10         |
| RhoA Signaling                               | 12    | 0.0813  | ACTB, ACTG1, ARPC1B, ARPC2, ARPC3, ARPC5, CFL1, MYL6, PFN1, TTN       | 10         |
| OX40 Signaling Pathway                       | 11.6  | 0.0957  | CD30, CD3G, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DRA, HLA-DRB1, HLA-DRB5, MAF | 10         |
| Th2 Pathway                                  | 11.5  | 0.0735  | CD30, CD3G, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DRA, HLA-DRB1, HLA-DRB5, MAF | 10         |
| Regulation of Actin-based Motility by Rho    | 11.5  | 0.0957  | ACTB, ARPC1B, ARPC2, ARPC3, ARPC5, CFL1, ITGB1, MYL6, PFN1             | 10         |
| OX40 Signaling Pathway                       | 11.5  | 0.0735  | CD30, CD3G, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DRA, HLA-DRB1, HLA-DRB5, MAF | 10         |
| Th2 Pathway                                  | 11.5  | 0.0735  | CD30, CD3G, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DQA2, HLA-DRA, HLA-DRB1, HLA-DRB5, MAF | 10         |
| Oxidative Phosphorylation                    | 31.8  | 0.303   | ATP5F1A, ATP5F1B, ATP5F1C, ATP5F1E, ATP5MC1, ATP5MC3, ATP5F1G, ATP5F1H, ATP5F1I | 10         |
| Mitochondrial Dysfunction                    | 31    | 0.222   | ATP5F1A, ATP5F1B, ATP5F1C, ATP5F1E, ATP5MC1, ATP5MC3, ATP5F1G, ATP5F1H, ATP5F1I | 10         |
| Sirtuin Signaling Pathway                    | 21.2  | 0.127   | ATP5F1A, ATP5F1B, ATP5F1C, ATP5F1E, ATP5MC1, ATP5MC3, ATP5F1G, ATP5F1H, ATP5F1I | 10         |
| Granzyme A Signaling                         | 12.9  | 0.526   | ANP32A, GZMA, H1-2, H1-3, H1-4, H1-5, HMG12B, MME1, PRF1, SET         | 10         |
| Actin Cytoskeleton Signaling                 | 10.7  | 0.101   | ACTB, ACTG1, ACTR2, ACTR3, ARPC1B, ARPC2, ARPC3, ARPC4, ARPC5, CDC42, CFL1, FLNA, IQGAP1, MSN, MYH9, MYL6, PFN1, RAC2, RHOA, TTN, TMSB10/TMSB4X, WAS | 10         |
| Regulation of Actin-based Motility by Rho    | 10.3  | 0.16    | ACTB, ACTR2, ACTR3, ARPC1B, ARPC2, ARPC3, ARPC4, ARPC5, CD42, CFL1, FLNA, MYL6, PFN1, RAC2, RHOA, WAS | 10         |
| Remodeling of Epithelial Adherens Junctions  | 10.1  | 0.191   | ACTB, ACTG1, ACTR2, ACTR3, ARPC1B, ARPC2, ARPC3, ARPC4, ARPC5, CD42, CFL1, FLNA, MYL6, PFN1, RAC2, RHOA, WAS | 10         |
| Antigen Presentation Pathway                 | 9.21  | 0.256   | CALR, CD74, HLA-DPA1, HLA-DBP1, HLA-DQA1, HLA-DRB1, HLA-DRB5, IFNG, PSMB8, PSMB9 | 10         |
| Epithelial Adherens Junction Signaling       | 9.13  | 0.112   | ACTB, ACTG1, ACTR2, ACTR3, ARPC1B, ARPC2, ARPC3, ARPC4, ARPC5, CD42, CFL1, FLNA, IQGAP1, MSN, MYH9, MYL6, RHOA, TUBA1B, TUBB, WAS | 10         |
| T cell subcluster 11 | Signaling by Rho Family GTPases | 9 | 0.0861 | ACTB,ACTG1,ACTR2,ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,CDC42,CFI1,GNAI2,IQGAP1,MSN,MYL6,RAC2,RHOA,SEPTIN6,STMN1,VIM,WAS |
|---------------------|---------------------------------|----|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Role of IL-17A in Psoriasis | 4.96 | 0.231 | CXCL8,S100A8,S100A9 |
| Polyamine Regulation in Colon Cancer | 2.59 | 0.0909 | MXD1,SAT1 |
| Lipid Antigen Presentation by CD1 | 2.44 | 0.0769 | FCER1G,PSAP |
| Dendritic Cell Maturation | 2.44 | 0.0219 | FCER1G,HLA-DRA,PLCE1,TYROBP |
| Communication between Innate and Adaptive Immune Cells | 2.35 | 0.0312 | CXCL8,FCER1G,HLA-DRA |
| Osteoarthritis Pathway | 2.22 | 0.019 | CXCL8,FGFR1,S100A8,S100A9 |
| Cardiac Hypertrophy Signaling (Enhanced) | 2.18 | 0.0123 | CACNA1A,CXCL8,CYBB,FGFR1,GNAQ,PLCE1 |
| GPCR-Mediated Nutrient Sensing in Enteroendocrine Cells | 2.17 | 0.0268 | CACNA1A,GNAQ,PLCE1 |
| LXR/RXR Activation | 2.08 | 0.0248 | HMGCR,LYZ,S100A8 |
| Phagosome Formation | 2.04 | 0.024 | CLEC7A,FCER1G,PLCE1 |
Table S10. Human monocyte gene sets used for module scoring.

| Gene Set Name          | Description                                                                 | Reference          |
|------------------------|------------------------------------------------------------------------------|--------------------|
| Szabo gene sets        | Generated from resting and stimulated human T cells isolated from blood and   | Szabo et al.(8)    |
|                        | tissues (lungs, lymph nodes, bone marrow).                                    |                    |
| Miao gene sets         | Generated from summary of marker genes across the literature (Table S1).     | Miao et al.(9)     |
| Cano-Gamez gene sets   | Generated from unstimulated and stimulated human T cells, identified by scRNA-seq. | Cano-Gamez et al.(10) |
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