SUPPLEMENTARY MATERIALS

MATERIALS AND METHODS

Mass cytometry reagents

PBMC surface and intracellular antibodies were either purchased pre-conjugated to metals from Fluidigm/Standard BioTools or purchased from Biolegend or R&D Systems and conjugated using Fluidigm Maxpar® X8 labeling kits or IONpath MIBItag conjugation kit (for 157Gd only). Antibody-metal conjugations were performed according to manufacturers' instructions with the following deviations for the Maxpar® X8 labeling kits: 30kDa filters were used instead of 50kDa filters; after the final washes, metal-conjugated antibody was recovered in W buffer, the concentration was determined using Qubit 4 Fluorometer (ThermoFisher) per manufacturer instructions, and conjugated antibodies were stored at 4°C for up to 1 month without antibody stabilization buffer. Conjugated antibodies were then titrated, pre-combined into either surface or intracellular staining cocktails (Table S5-6) to ensure staining consistency, filtered through Millex®-VV 0.1µm filter (Millipore #SLVV033RS), aliquoted for single use, and frozen at -80°C for long-term storage.

Live cell barcoding was adapted from Hartmann et al. *(188)*. Briefly, anti-b2-microglobulin mouse monoclonal antibody (clone: 2M2; Biolegend) was conjugated to 113In and 115In via IONpath MIBItag conjugation kits per manufacturer instructions, as well as to Cell-ID cisplatin 194Pt, 195Pt, 196Pt, and 198Pt (Fluidigm/Standard BioTools) according to the Fluidigm Maxpar® X8 labeling kit protocol. Rather than using a polymer with lanthanide metal per manufacturer protocol, a working dilution of each Cell-ID cisplatin (194Pt, 195Pt, 196Pt, and 198Pt) was made by diluting 20µL of the 1mM Cell-ID cisplatin stock solution to 1mL of C-buffer. These cisplatin working solutions were each conjugated to anti-b2-microglobulin antibody adding 400µL of

cisplatin working solution to the 30kDa filter with the purified partially reduced antibody, resuspending the antibody, combining this resuspended antibody with the remaining 600µL of cisplatin working solution, incubating the 1mL antibody-cisplatin solution in a 37°C water bath for 90 minutes, adding half of the solution to 30kDa filter, centrifuging this solution at 12,000 xg for 15 minutes at room temperature, discarding the flow-through, adding the remaining half of the solution into the same 30 kDa filter, repeating centrifugation, and discarding the flow through. Metal conjugated antibody was washed with W-buffer as in Fluidigm Maxpar® X8 labeling kit protocol. The metal conjugated antibodies were recovered, the concentrations were quantified, and the optimal staining concentrations were determined, as described above. For staining consistency, barcodes were pre-combined in a six-choose-three scheme, aliquoted for single use, and frozen at -80°C for long-term storage.

PdCl viability staining was made as previously described *(188)* by re-suspending (Ethylenediamine)palladium(II) chloride (PdCl) (Sigma-Aldrich #574902, CAS #15020-99-2) in DMSO to a final concentration of 100mM, which was then pre-conditioned in a 37°C water bath for 48 hours, subsequently aliquoted into 10µL aliquots, and frozen at -20°C for long-term storage. Cell ID Intercalator (191Ir, 193Ir) at 500µM was purchased from Fluidigm/Standard BioTools, aliquoted upon arrival, and stored at -20°C. Intercalator was titrated for optimal signal intensity between 300 and 1000 dual counts in the 191Ir channel per manufacturer recommendations.

SUPPLEMENTARY FIGURES

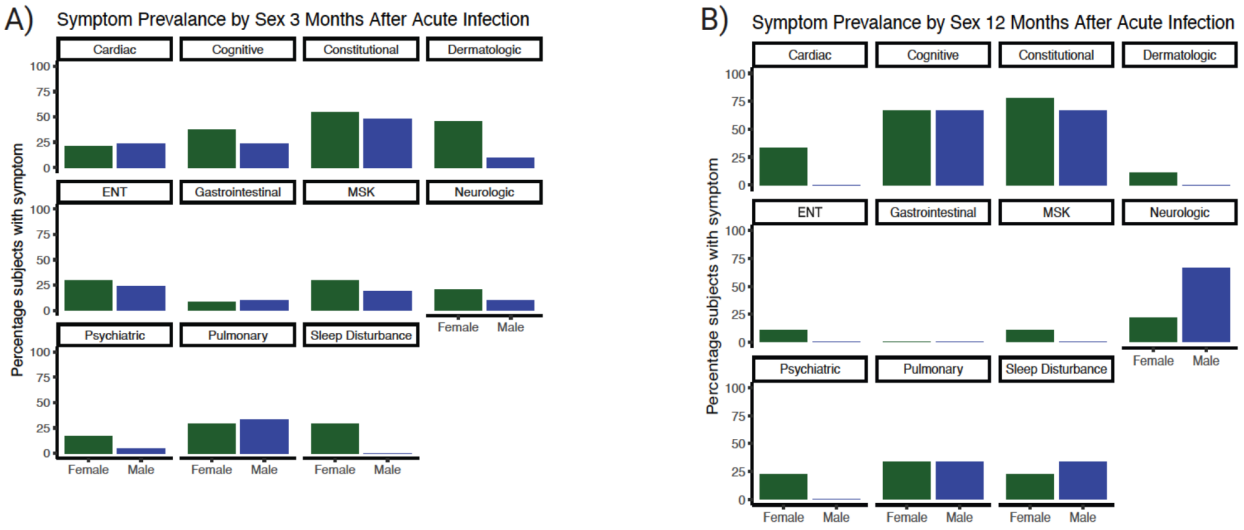

Fig. S1. Symptom prevalence of subjects with LC at (A) 3 months after acute infection (n=36), and **(B)** 12 months after acute infection (n=12). ENT = ear, nose, throat; MSK = musculoskeletal.

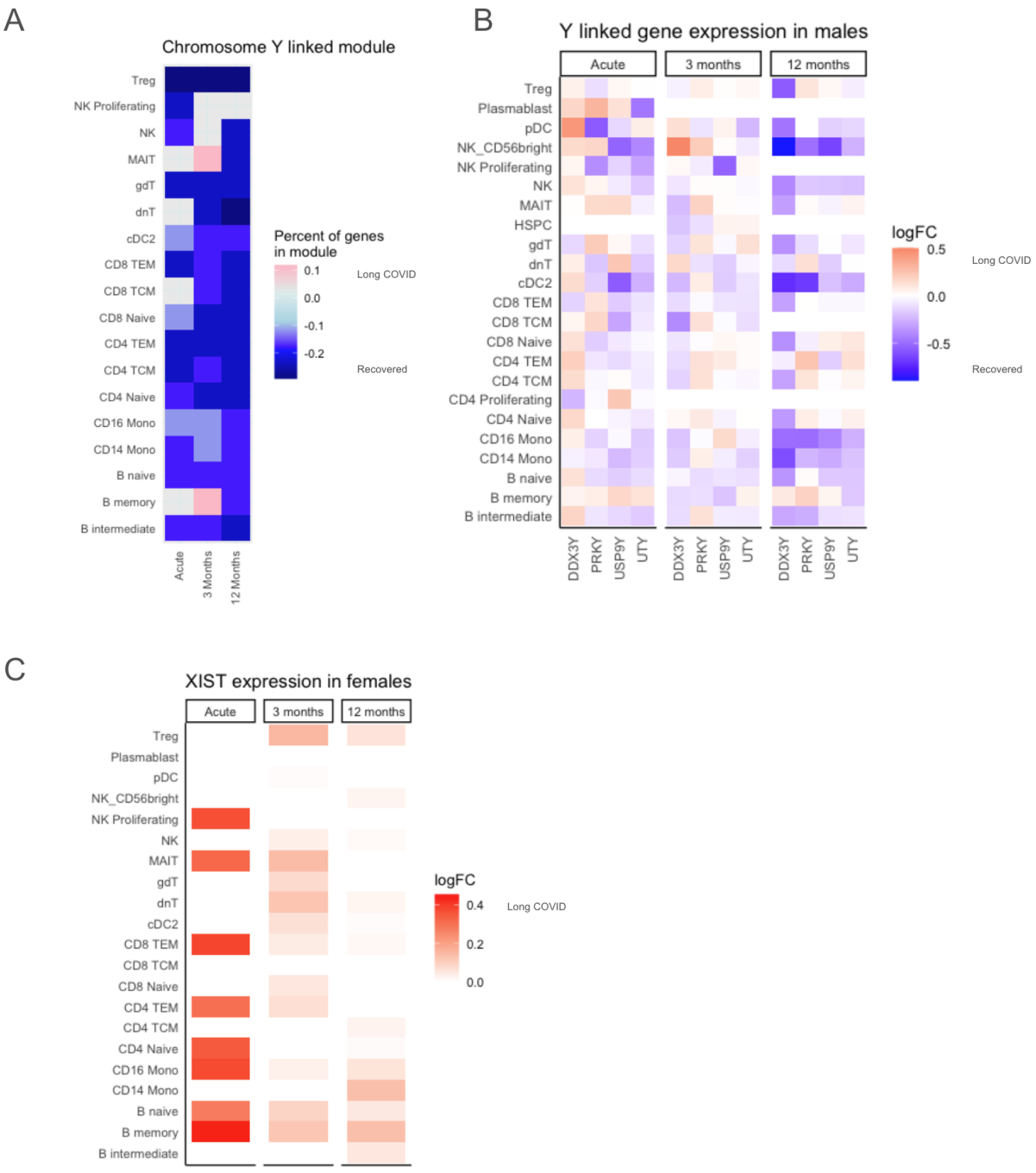

Fig. S2. "Chromosome Y linked" module during acute infection and convalescence. (A) In both sexes combined, the "chromosome Y linked" BTM was downregulated in almost all cell types in those with LC. Percentage of genes in the module with absolute log2FC >0.25 is indicated by tile color in the heatmap, with red indicating higher expression in LC and blue indicating lower expression. **(B)** Pseudobulk expression of the four most variable Y linked genes in males at acute

infection as well as 3 and 12 months post infection. Red indicates higher expression and blue indicates lower expression in LC. **(C)** Pseudobulk expression of the *XIST* gene in females at acute infection as well as 3 and 12 months post infection. Log2FC is indicated by the color bar on the right, with red indicating higher expression in LC.

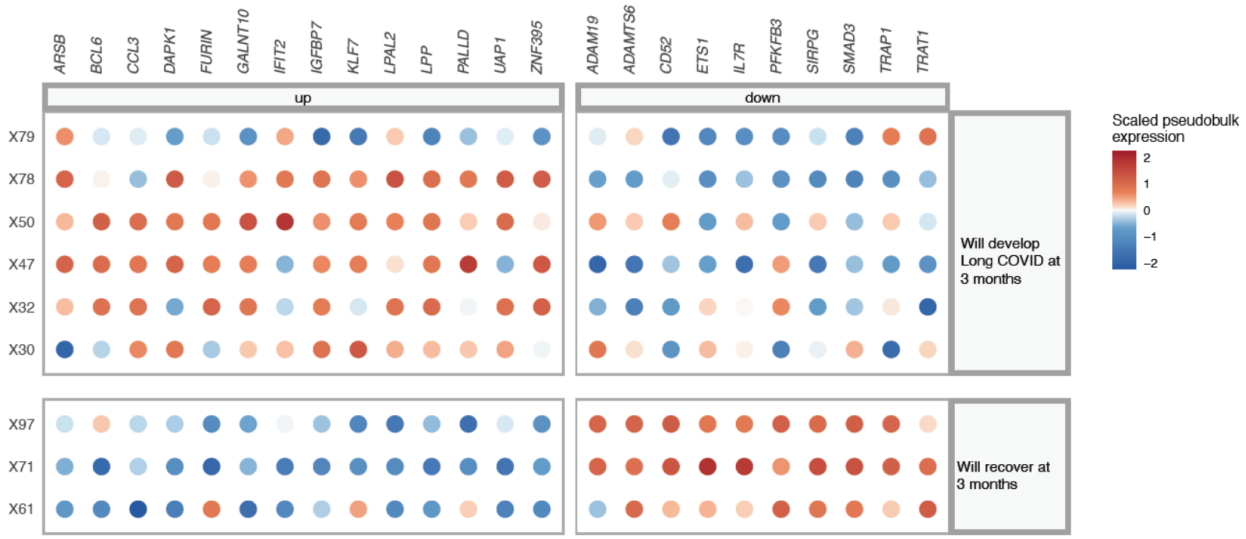

Fig. S3. Patient-level pseudobulk expression of target genes for proliferating NK cells in males during acute infection, divided by those who will develop LC vs. recover at 3 months post infection. Individual subjects are shown on the y-axis, and dot color indicates scaled pseudobulk expression of the target gene.

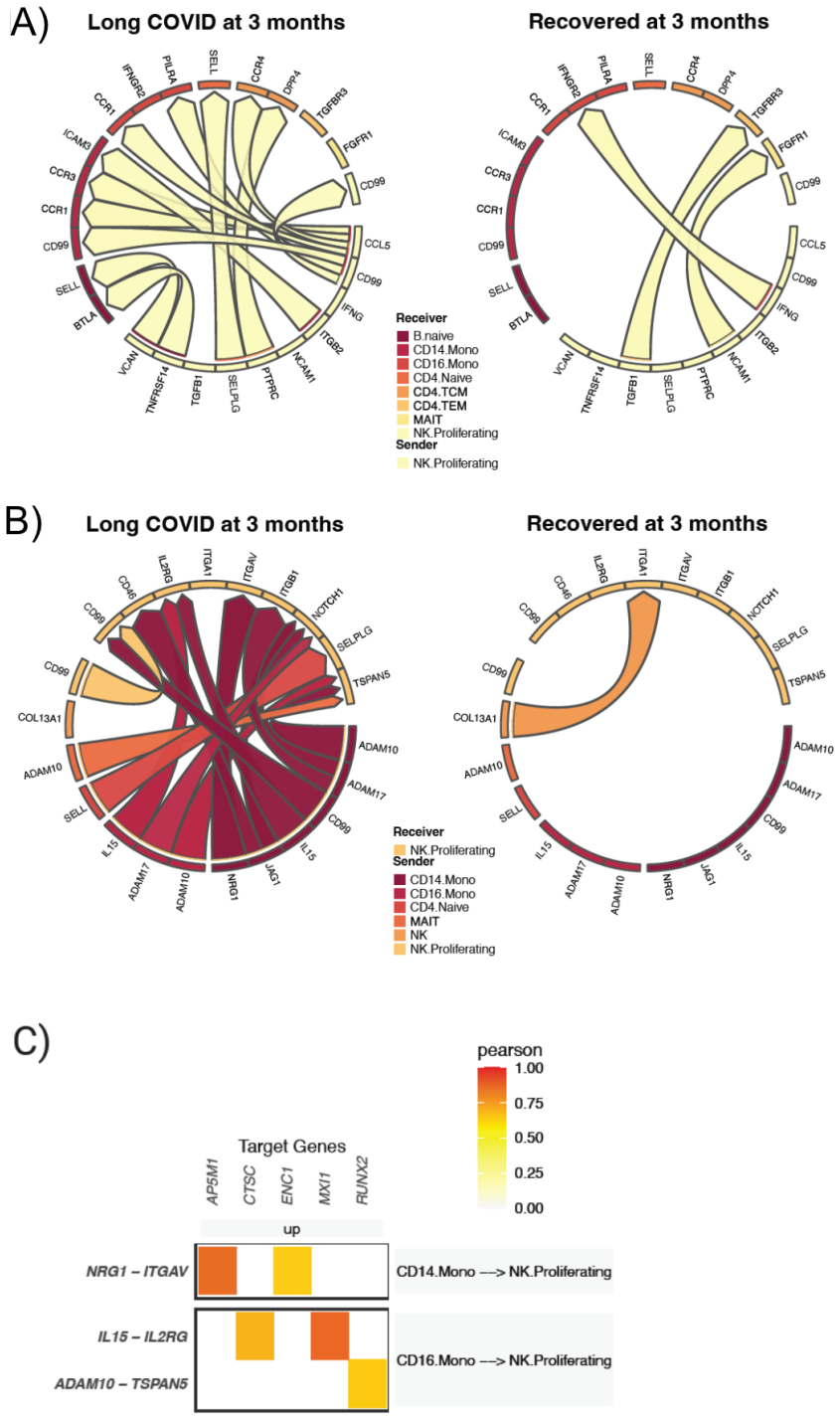

Fig. S4. Proliferating NK cells in females during acute infection. (A-B) Predicted ligand-receptor interactions **(A)** originating from proliferating NK cells, and **(B)** going toward proliferating NK cells, separated by presence of LC symptoms 3 months after acute infection versus resolution of symptoms by 3 months. **(C)** Target genes with increased expression in

proliferating NK cells of acutely infected female subjects who will develop LC at 3 months post infection, with associated ligand-receptor interactions. Tile color in the heatmap indicates the pearson correlation coefficient of expression of the ligand-receptor pair and the target gene.

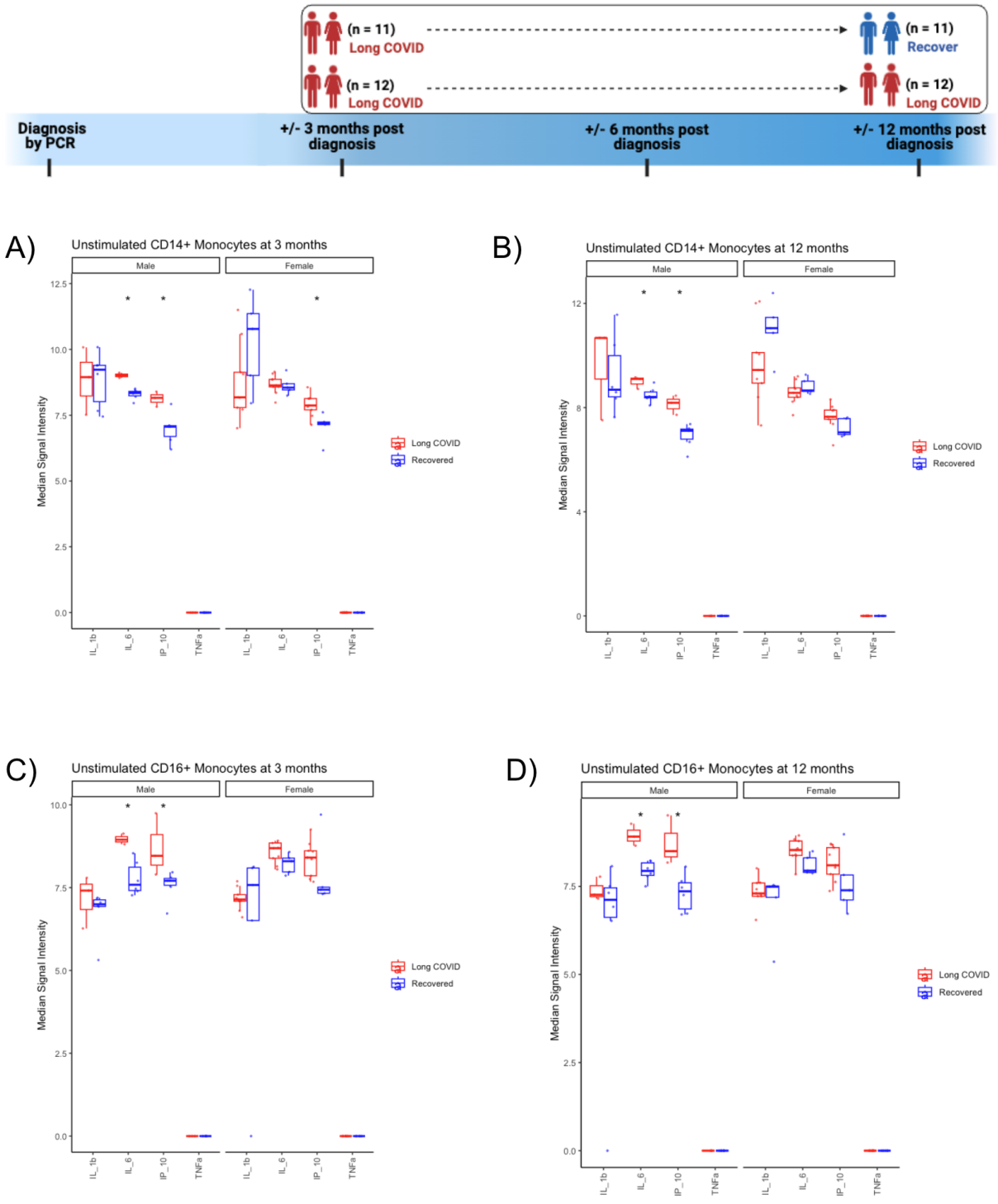

Fig. S5. Increased inflammatory markers in monocytes in those with persistent LC. (A-B) Median signal intensity by CyTOF of intracellular IL-1β, IL-6, IP-10 (aka CXCL10), and TNF**α** in unstimulated samples of $CD14^{+}$ monocytes at **(A)** 3 and **(B)** 12 months after acute infection,

separated by sex. **(C-D)** Median signal intensity by CyTOF of IL-1β, IL-6, IP-10 (aka CXCL10), and TNF**α** in unsimulated samples of $CD16^{+}$ monocytes at **(C)** 3 and **(D)** 12 months after acute infection, separated by sex. * indicates unadjusted $p<0.05$ between those with persistent LC and recovery at 12 months.

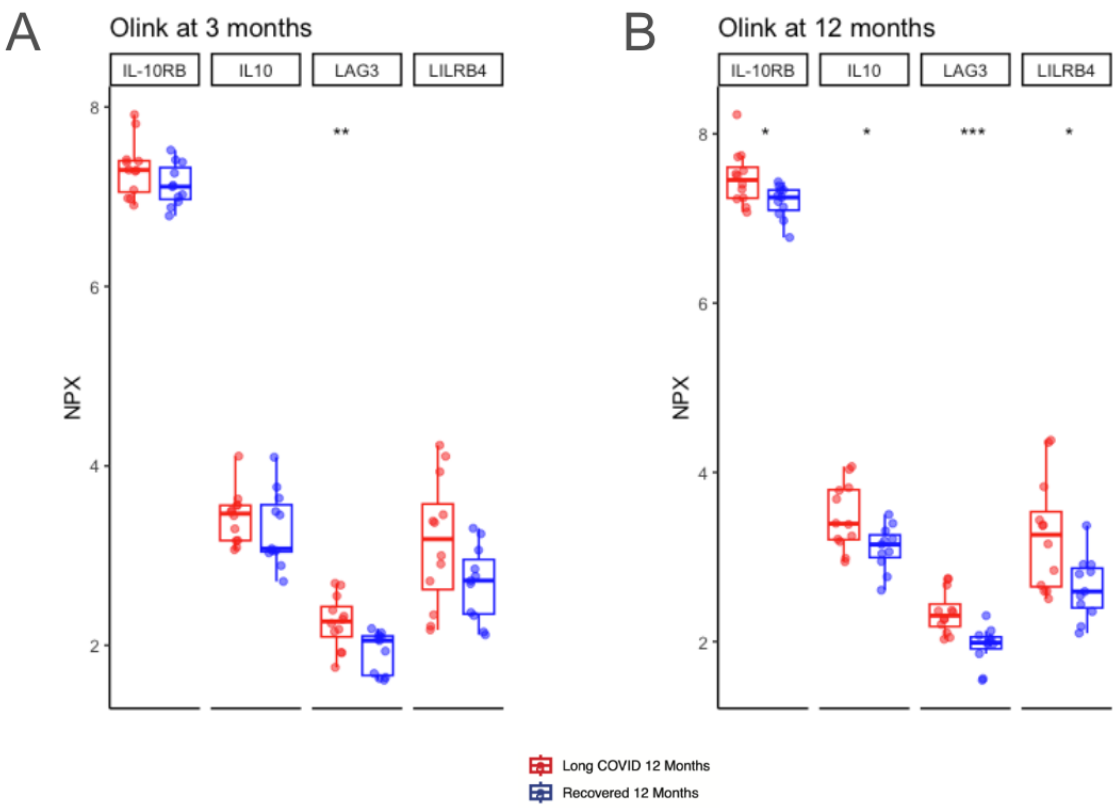

Fig. S6. Plasma proteomic correlates of T cell exhaustion in sexes combined at (A) 3 months and (B) 12 months in those with persistent LC to 12 months compared to those with LC at 3 months but recovery by 12 months post infection. * indicates unadjusted p<0.05, ** indicates unadjusted p<0.01, and *** indicates unadjusted p<0.001.

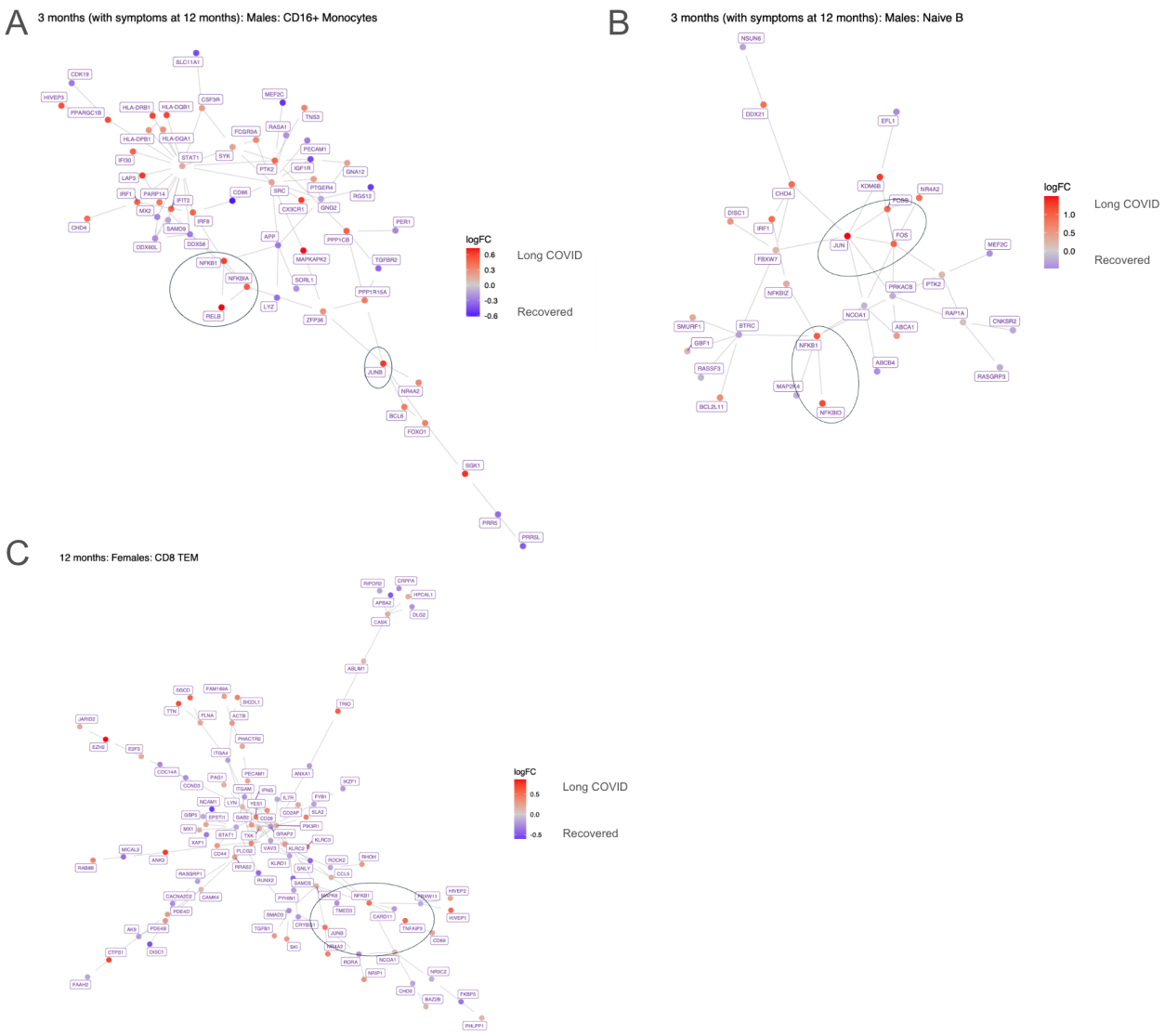

Fig. S7. Increased NF-κB signaling in LC development and persistence. (A) Gene network of CD16^{+} monocytes in males at 3 months post infection, comparing those with persistent LC to 12 months versus those who recover between 3 and 12 months. Red nodes indicate higher expression (log2FC) in those with persistent LC at 12 months, and blue nodes indicate lower expression. Increased expression of *NFkB1, RELB,* and *NFkBIA* are circled. **(B)** Gene network of naive B cells in males at 3 months post infection, comparing those with persistent LC to 12 months versus those who recover between 3 and 12 months. Red nodes indicate higher expression (log2FC) in those with persistent LC at 12 months, and blue nodes indicate lower expression. Increased expression

of *NFkB1,* and *NFkBID* are circled. **(C)** Gene network of $CD8^+$ T effector memory (TEM) cells in females at 12 months post infection, comparing those with persistent LC at 12 months versus those who recovered by 12 months. Red nodes indicate higher expression (log2FC) in those with persistent LC at 12 months, and blue nodes indicate lower expression. Increased expression of *NFkB1* is circled.

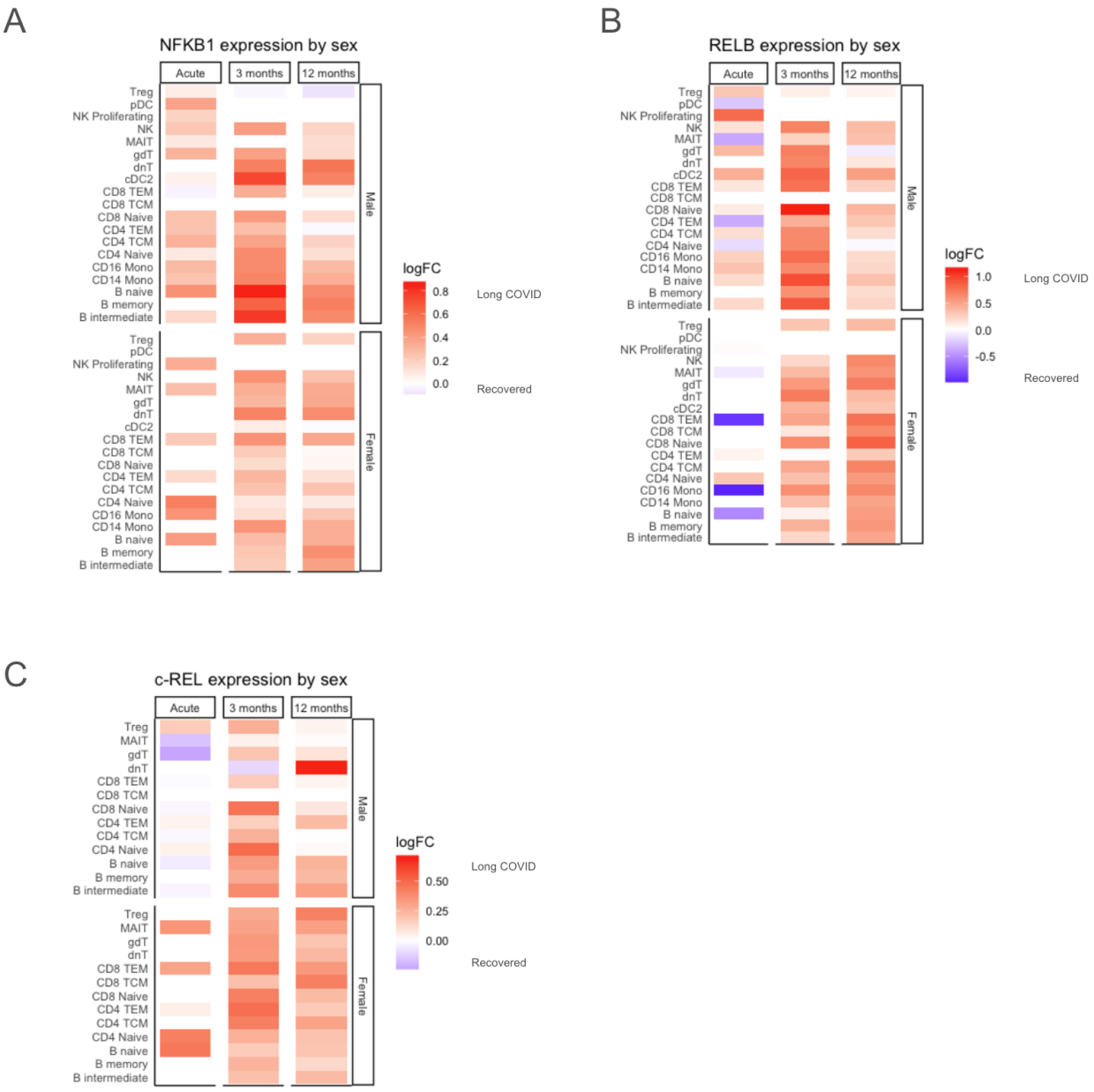

Fig. S8. Increased NF-κB signaling in LC development and persistence is similar between sexes. (A-B) Higher pseudobulk expression of **(A)** *NFkB1* and **(B)** *RELB* across many cell types is associated with LC development after acute infection and persistence for 12 months, separated by sex. **(C)** Increased pseudobulk *c-REL* expression across T and B lymphocytes is associated with LC development after acute infection and persistence for 12 months, separated by sex. Red tiles indicate higher expression (log2FC) in LC and blue tiles indicate lower expression.

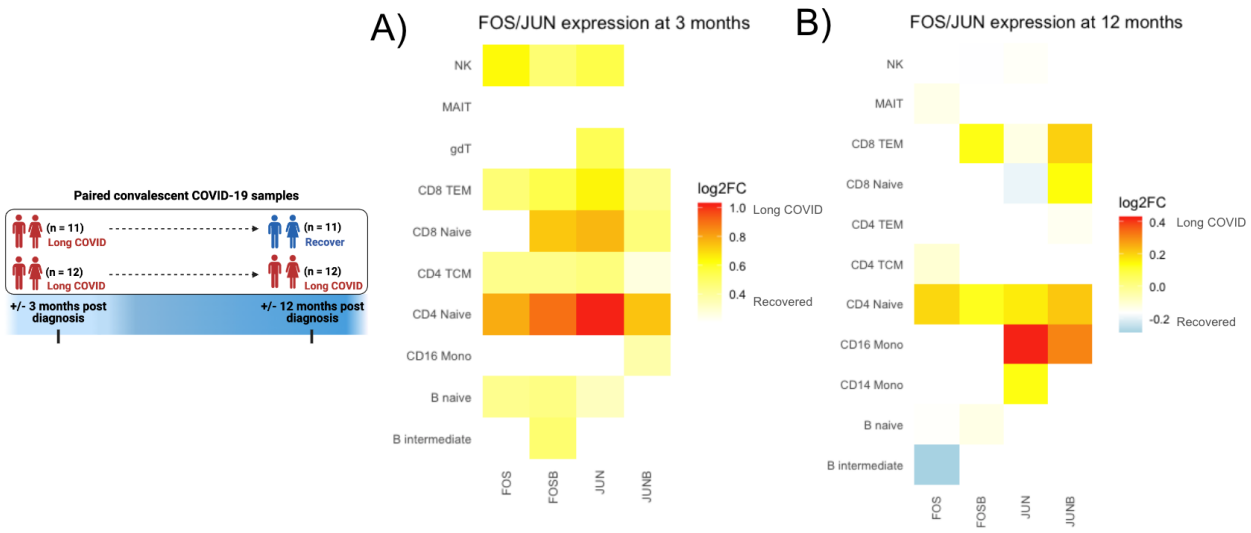

Fig. S9. Higher pseudobulk expression of AP-1 transcription factor genes is associated with LC persistence. (A-B) *FOS, FOSB, JUN,* and *JUNB* expression in lymphocytes at **(A)** 3 months and **(B)** 12 months, comparing those with persistent LC to 12 months and those who recover between 3 and 12 months. Yellow/red tiles indicate higher expression (log2FC) in persistent LC and blue tiles indicate lower expression.

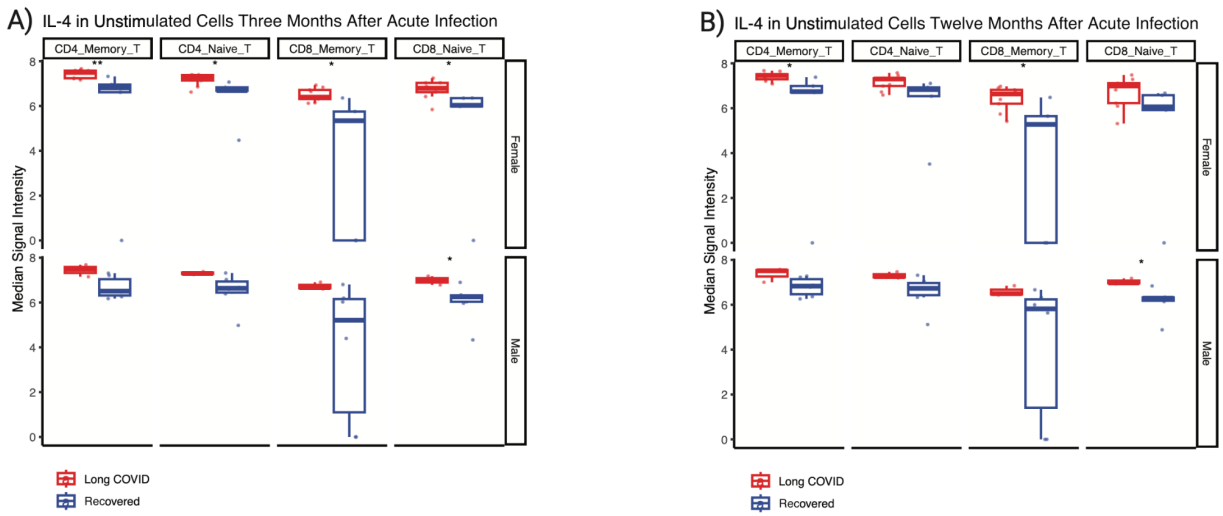

Fig. S10. Intracellular IL-4 as measured by CyTOF is increased across T cell subsets in persistent LC. IL-4 measured at **(A)** 3 months and **(B)** 12 months post infection, comparing those with LC at 3 and 12 months versus those with LC at 3 months but recovery by 12 months, separated by sex. * indicates $p<0.05$, ** indicates $p<0.01$.

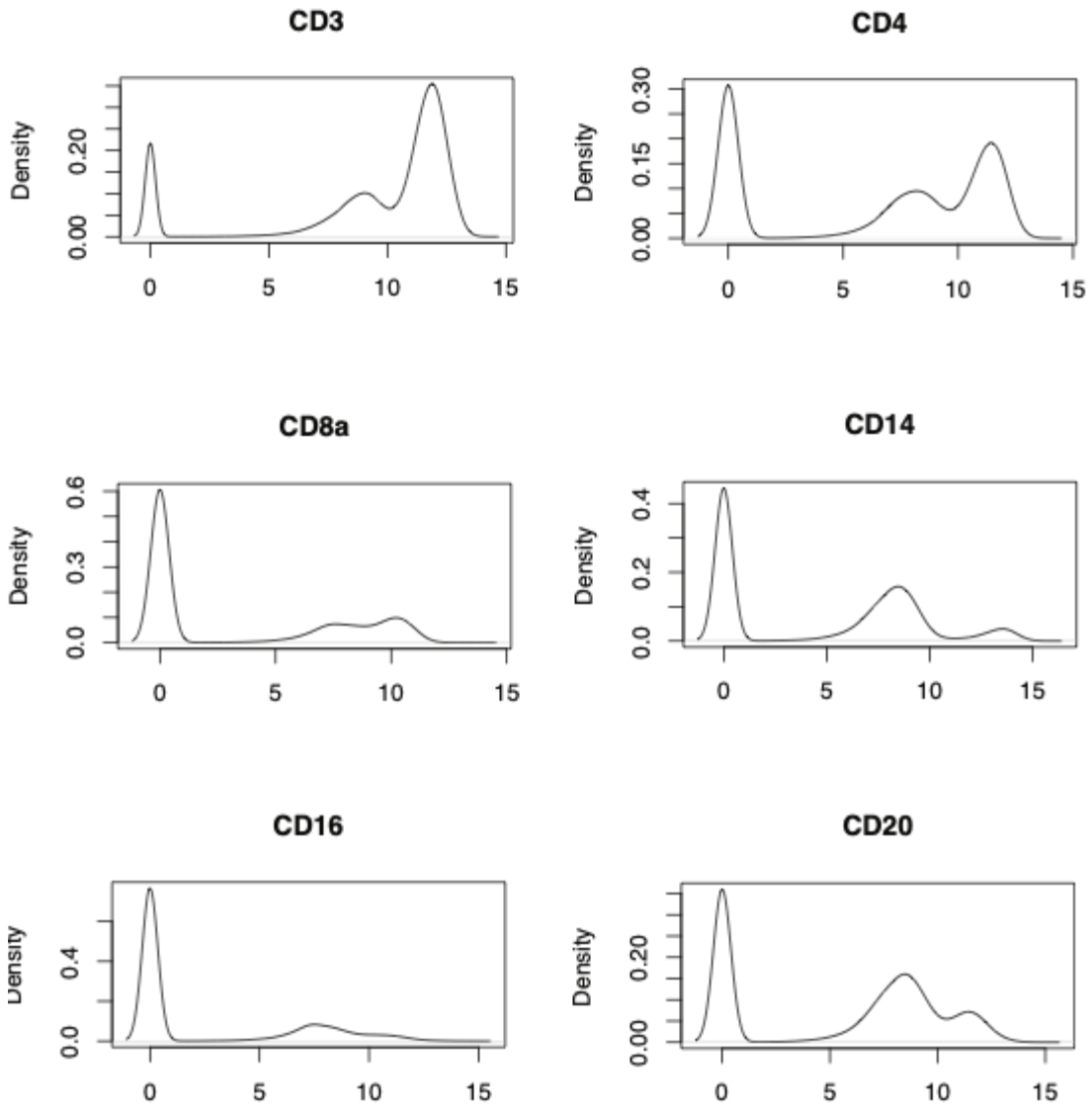

Fig. S11. Density plots of example CyTOF markers, demonstrating multimodality with arsinch transformation cofactor of 0.001.

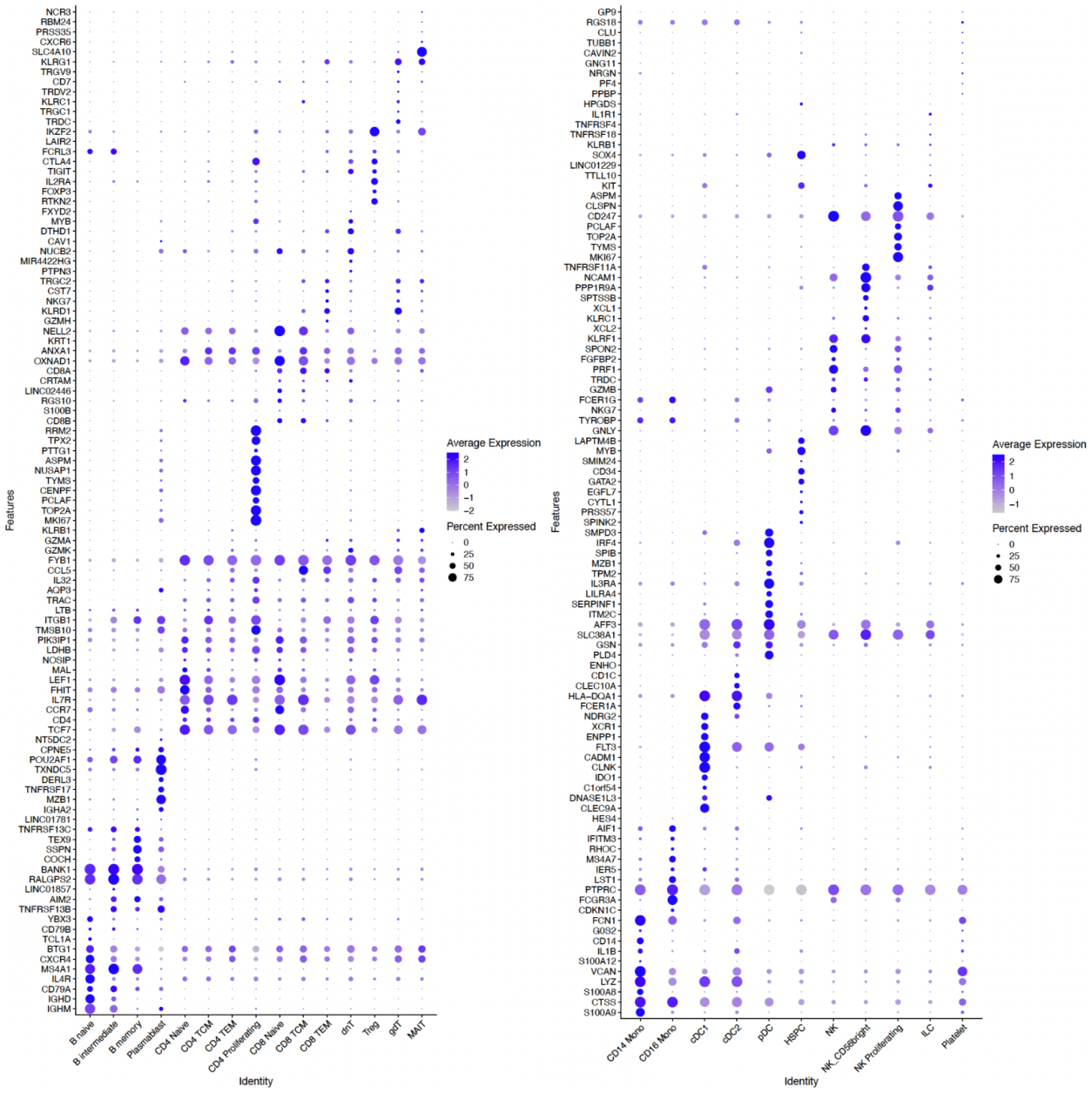

Fig. S12. Canonical gene expression for cell type annotation in scRNAseq data. Dot plot shows average and percent expression of annotation markers by cell type.

SUPPLEMENTARY TABLES

				Female		Male	
	Total (N=45)	Recovered (N=9)	Long COVID (N=36)	Recovered (N=4)	Long COVID (N=20)	Recovered (N=5)	Long COVID (N=16)
Sex							
Female	24 (53.3%)	4 (44.4%)	20 (55.6%)	4 (100%)	20 (100%)	0 (0%)	0 (0%)
Male	21 (46.7%)	5 (55.6%)	16 (44.4%)	0 (0%)	0 (0%)	5 (100%)	16 (100%)
Age (years)							
Mean (SD)	42.8 (12.3)	41.7 (9.45)	43.0 (13.0)	41.8 (10.4)	41.2 (12.2)	41.6 (9.89)	45.3 (14.1)
Median [Min, Max]	43.0 [20.0, 67.0]	42.0 [27.0, 53.0]	43.0 [20.0, 67.0]	45.5 [27.0, 49.0]	40.0 [20.0, 63.0]	41.0 [27.0, 53.0]	43.0 [26.0, 67.0]
Race							
White	36 (80.0%)	5 (55.6%)	31 (86.1%)	1 (25.0%)	19 (95.0%)	4 (80.0%)	12 (75.0%)
Asian	7 (15.6%)	3 (33.3%)	4 (11.1%)	2 (50.0%)	1 (5.0%)	1 (20.0%)	3 (18.8%)
Black or African American	1 (2.2%)	0 (0%)	1 (2.8%)	0 (0%)	0 (0%)	0 (0%)	1 (6.3%)
American Indian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	1 (2.2%)	1 (11.1%)	0 (0%)	1 (25.0%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity							
Not Hispanic or Latino	27 (60.0%)	8 (88.9%)	19 (52.8%)	4 (100%)	8 (40.0%)	4 (80.0%)	11 (68.8%)
Hispanic or Latino	18 (40.0%)	1 (11.1%)	17 (47.2%)	0 (0%)	12 (60.0%)	1 (20.0%)	5 (31.3%)
Body Mass Index							
Mean (SD)	30.2 (5.87)	31.3 (7.86)	30.0 (5.37)	34.0 (10.1)	31.1 (6.12)	29.0 (5.78)	28.7 (4.04)
Median [Min, Max]	29.0 [19.6, 45.1]	27.8 [22.4, 44.6]	29.4 [19.6, 45.1]	34.1 [23.3, 44.6]	30.4 [19.6, 45.1]	27.2 [22.4, 38.0]	28.3 [22.9, 36.9]
Hospitalized							
No	36 (80.0%)	8 (88.9%)	28 (77.8%)	4 (100%)	17 (85.0%)	4 (80.0%)	11 (68.8%)
Yes	9 (20.0%)	1 (11.1%)	8 (22.2%)	0 (0%)	3 (15.0%)	1 (20.0%)	5 (31.3%)
Intensive Care Unit							
No	41 (91.1%)	8 (88.9%)	33 (91.7%)	4 (100%)	19 (95.0%)	4 (80.0%)	14 (87.5%)
Yes	4 (8.9%)	1 (11.1%)	3 (8.3%)	0 (0%)	1 (5.0%)	1 (20.0%)	2 (12.5%)
Intubated							
No	44 (97.8%)	9 (100%)	35 (97.2%)	4 (100%)	19 (95.0%)	5 (100%)	16 (100%)
Yes	1 (2.2%)	0 (0%)	1 (2.8%)	0 (0%)	1 (5.0%)	0 (0%)	0 (0%)
Treatment during acute COVID-19							
Remdesivir	8 (17.8%)	1 (11.1%)	7 (19.4%)	0 (0%)	2 (10.0%)	1 (20.0%)	5 (31.3%)
Peginterferon Lambda-1a	13 (28.9%)	2 (22.2%)	11 (30.6%)	1 (25.0%)	5 (25.0%)	1 (20.0%)	6 (37.5%)
Favipiravir	8 (17.8%)	3 (33.3%)	5 (13.9%)	3 (75.0%)	3 (15.0%)	0 (0%)	2 (12.5%)
None or placebo	16 (35.6%)	3 (33.3%)	13 (36.1%)	0 (0%)	10 (50.0%)	3 (60.0%)	3 (18.8%)

Table S1. Demographics of overall cohort at 3 months post SARS-CoV-2 infection, separated by LC versus recovered symptom status at 3 months after acute infection.

	Total (N=21)	Recovered (N=6)	Long COVID (N=15)	Female		Male	
				Recovered (N=3)	Long COVID (N=9)	Recovered (N=3)	Long COVID (N=6)
Sex							
Female	12 (57.1%)	3 (50.0%)	9 (60.0%)	3 (100%)	9 (100%)	0 (0%)	0 (0%)
Male	9 (42.9%)	3 (50.0%)	6 (40.0%)	0 (0%)	0 (0%)	3 (100%)	6 (100%)
Age (years)							
Mean (SD)	44.7 (12.5)	41.8 (9.00)	45.8 (13.7)	39.3 (11.2)	42.1 (13.4)	44.3 (7.57)	51.3 (13.3)
Median [Min, Max]	42.0 [26.0, 65.0]	41.5 [27.0, 53.0]	47.0 [26.0, 65.0]	42.0 [27.0, 49.0]	36.0 [26.0, 63.0]	41.0 [39.0, 53.0]	54.0 [34.0, 65.0]
Race							
White	19 (90.5%)	4 (66.7%)	15 (100%)	1 (33.3%)	9 (100%)	3 (100%)	6 (100%)
Asian	2 (9.5%)	2 (33.3%)	0 (0%)	2 (66.7%)	0 (0%)	0 (0%)	0 (0%)
Black or African American	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
American Indian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity							
Not Hispanic or Latino	16 (76.2%)	6 (100%)	10 (66.7%)	3 (100%)	4 (44.4%)	3 (100%)	6 (100%)
Hispanic or Latino	5 (23.8%)	0 (0%)	5 (33.3%)	0 (0%)	5 (55.6%)	0 (0%)	0 (0%)
Body Mass Index							
Mean (SD)	30.8 (6.22)	31.2 (6.64)	30.6 (6.28)	30.5 (8.86)	31.5 (7.55)	31.9 (5.48)	29.4 (4.04)
Median [Min, Max]	29.8 [19.6, 45.1]	29.2 [23.3, 40.4]	29.8 [19.6, 45.1]	27.8 [23.3, 40.4]	29.8 [19.6, 45.1]	30.6 [27.2, 38.0]	29.4 [23.8, 35.8]
Hospitalized							
No	20 (95.2%)	6 (100%)	14 (93.3%)	3 (100%)	8 (88.9%)	3 (100%)	6 (100%)
Yes	1 (4.8%)	0 (0%)	1 (6.7%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)
Intensive Care Unit							
No	20 (95.2%)	6 (100%)	14 (93.3%)	3 (100%)	8 (88.9%)	3 (100%)	6 (100%)
Yes	1 (4.8%)	0 (0%)	1 (6.7%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)
Intubated							
No	20 (95.2%)	6 (100%)	14 (93.3%)	3 (100%)	8 (88.9%)	3 (100%)	6 (100%)
Yes	1 (4.8%)	0 (0%)	1 (6.7%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)
Treatment during acute COVID-19							
Remdesivir	1 (4.8%)	0 (0%)	1 (6.7%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)
Peginterferon Lambda-1a	11 (52.4%)	2 (33.3%)	9 (60.0%)	1 (33.3%)	4 (44.4%)	1 (33.3%)	5 (83.3%)
Favipiravir	5 (23.8%)	2 (33.3%)	3 (20.0%)	2 (66.7%)	2 (22.2%)	0 (0%)	1 (16.7%)
None or placebo	4 (19.0%)	2 (33.3%)	2 (13.3%)	0 (0%)	2 (22.2%)	2 (66.7%)	0 (0%)

Table S2. Demographics of study participants with acute COVID-19 samples based on LC vs. recovery status at 3 months post infection.

Differentially expressed gene (DEG)	Long COVID (3 mo)	Cell Type of DEG	Function of Encoded Protein
XIST	↑	B intermediate, B naïve, CD4 naïve, CD4 TCM, CD4 TEM, CD8 naïve, CD8 TEM, gdT, MAIT, Treg, NK, cDC2, pDC, CD14 mono, CD16 mono	Involved in X chromosome inactivation; regulated by TGF-β/BMP signaling
DDX3Y	↓	B intermediate, B naïve, CD4 naïve, CD4 TCM, CD4 TEM, CD8 naïve, CD8 TEM, gdT, MAIT, Treg, NK, cDC2, pDC, CD14 mono, CD16 mono	RNA helicase; may enhance IFNB1 expression via IRF3/IRF7 pathway
UTY/KDM6C	↓	B intermediate, B naïve, CD4 naïve, CD4 TCM, CD4 TEM, CD8 naïve, CD8 TEM, gdT, MAIT, Treg, NK, pDC, CD14 mono, CD16 mono	minor histocompatibility antigen important for B and T cell development/maturation
KDM5D	↓	Treg, pDC	minor histocompatibility antigen; suppresses stimulator of interferon genes (STING)
USP9Y	↓	B intermediate, B naïve, CD4 naïve, CD4 TCM, CD4 TEM, CD8 naïve, CD8 TEM, gdT, MAIT, Treg, NK, pDC, CD14 mono	ubiquitin-specific peptidase; essential component of TGF-β/BMP signaling
PRKY	↓	CD4 naïve, CD4 TCM, CD4 TEM, CD8 naïve, CD8 TEM, gdT, MAIT, Treg, NK, CD16 mono	pseudogene

Table S3. Characteristics of the differentially expressed genes driving the "chromosome Y linked" BTM.

				Female		Male	
	Total (N=23)	Recovered (N=11)	Long COVID (N=12)	Recovered (N=5)	Long COVID (N=9)	Recovered (N=6)	Long COVID (N=3)
Sex							
Female	14 (60.9%)	5 (45.5%)	9 (75.0%)	5 (100%)	9 (100%)	0 (0%)	0 (0%)
Male	9 (39.1%)	6 (54.5%)	3 (25.0%)	0 (0%)	0 (0%)	6 (100%)	3 (100%)
Age (years)							
Mean (SD)	41.2 (12.7)	37.3 (9.90)	44.8 (14.3)	38.8 (12.5)	42.1 (13.4)	36.0 (8.20)	53.0 (16.6)
Median [Min, Max]	43.0 [20.0, 65.0]	43.0 [20.0, 49.0]	41.5 [26.0, 65.0]	46.0 [20.0, 49.0]	36.0 [26.0, 63.0]	37.0 [26.0, 44.0]	60.0 [34.0, 65.0]
Race							
White	20 (87.0%)	8 (72.7%)	12 (100%)	4 (80.0%)	9 (100%)	4 (66.7%)	3 (100%)
Asian	3 (13.0%)	3 (27.3%)	0 (0%)	1 (20.0%)	0 (0%)	2 (33.3%)	0 (0%)
Black or African American	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
American Indian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity							
Not Hispanic or Latino	12 (52.2%)	5 (45.5%)	7 (58.3%)	2 (40.0%)	4 (44.4%)	3 (50.0%)	3 (100%)
Hispanic or Latino	11 (47.8%)	6 (54.5%)	5 (41.7%)	3 (60.0%)	5 (55.6%)	3 (50.0%)	0 (0%)
Body Mass Index							
Mean (SD)	29.6 (5.97)	28.4 (4.94)	30.7 (6.80)	29.9 (6.27)	31.5 (7.55)	27.2 (3.65)	28.4 (4.01)
Median [Min, Max]	29.8 [19.6, 45.1]	28.2 [21.9, 38.9]	30.1 [19.6, 45.1]	29.8 [21.9, 38.9]	29.8 [19.6, 45.1]	27.6 [22.9, 32.0]	30.4 [23.8, 31.0]
Hospitalized							
No	19 (82.6%)	8 (72.7%)	11 (91.7%)	5 (100%)	8 (88.9%)	3 (50.0%)	3 (100%)
Yes	4 (17.4%)	3 (27.3%)	1 (8.3%)	0 (0%)	1 (11.1%)	3 (50.0%)	0 (0%)
Intensive Care Unit							
No	21 (91.3%)	10 (90.9%)	11 (91.7%)	5 (100%)	8 (88.9%)	5 (83.3%)	3 (100%)
Yes	2 (8.7%)	1 (9.1%)	1 (8.3%)	0 (0%)	1 (11.1%)	1 (16.7%)	0 (0%)
Intubated							
No	22 (95.7%)	11 (100%)	11 (91.7%)	5 (100%)	8 (88.9%)	6 (100%)	3 (100%)
Yes	1 (4.3%)	0 (0%)	1 (8.3%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)
Treatment during acute COVID-19							
Remdesivir	4 (17.4%)	3 (27.3%)	1 (8.3%)	0 (0%)	1 (11.1%)	3 (50.0%)	0 (0%)
Peginterferon Lambda-1a	8 (34.8%)	1 (9.1%)	7 (58.3%)	0 (0%)	4 (44.4%)	1 (16.7%)	3 (100%)
Favipiravir	4 (17.4%)	2 (18.2%)	2 (16.7%)	1 (20.0%)	2 (22.2%)	1 (16.7%)	0 (0%)
None or placebo	7 (30.4%)	5 (45.5%)	2 (16.7%)	4 (80.0%)	2 (22.2%)	1 (16.7%)	0 (0%)

Table S4. Demographics of study participants with paired 3 and 12 month samples based on persistent Long COVID vs. recovery status at 12 months post infection.

Isotope	Antibody	Clone	Company
89Y	CD45	HI30	Fluidigm/Standard BioTools (pre-conjugated)
141Pr	CD57	HNK-1	BioLegend
142Nd	CD19	HIB19	Fluidigm/Standard BioTools (pre-conjugated)
143Nd	CD45RA	HI100	Fluidigm/Standard BioTools (pre-conjugated)
144Nd	CD38	HIT2	Fluidigm/Standard BioTools (pre-conjugated)
145Nd	CD4	RPA-T4	Fluidigm/Standard BioTools (pre-conjugated)
146Nd	NKB1 (KIR3DL1)	DX9	R&D Systems
147Sm	CD8a	RPA-T8	BioLegend
148Nd	CD14	RMO52	Fluidigm/Standard BioTools (pre-conjugated)
150Nd	CD28	CD28.2	BioLegend
151Eu	CD123	6H6	Fluidigm/Standard BioTools (pre-conjugated)
152Sm	TCRγδ	11F2	Fluidigm/Standard BioTools (pre-conjugated)
153Eu	CD20	2H7	BioLegend
154Sm	CD3	UCHT1	Fluidigm/Standard BioTools (pre-conjugated)
155Gd	CD158b (KIR2DL2/L3)	DX27	BioLegend
157Gd	CD294/CRTH2	BM16	BioLegend
159Tb	CD11c	Bu15	Fluidigm/Standard BioTools (pre-conjugated)
162Dy	CD25	M-A251	BioLegend
163Dy	CD183/CXCR3	G025H7	Fluidigm/Standard BioTools (pre-conjugated)
164Dy	CD161	HP-3G10	Fluidigm/Standard BioTools (pre-conjugated)
166Er	CD197/CCR7	G043H7	BioLegend
167Er	CD27	O323	Fluidigm/Standard BioTools (pre-conjugated)

168Er	CD196/CCR6	G034E3	BioLegend
171Yb	CD185/CXCR5	RF8B2	Fluidigm/Standard BioTools (pre-conjugated)
172Yb	CD194/CCR4	L291H4	BioLegend
173Yb	HLA-DR	L243	Fluidigm/Standard BioTools (pre-conjugated)
174Yb	CD127	A019D5	BioLegend
176Yb	CD56	NCAM16.2	Fluidigm/Standard BioTools (pre-conjugated)
209Bi	CD16	3G8	Fluidigm/Standard BioTools (pre-conjugated)

Table S5. CyTOF surface staining panel.

Isotope	Antibody	Clone	Company
149Sm	APC**	APC003	BioLegend
156Gd	IL-6	MQ2-12A5	Fluidigm/Standard BioTools (pre-conjugated)
158Gd	IFNg	B27	Fluidigm/Standard BioTools (pre-conjugated)
160Gd	IL-4	MP4-25D2	BioLegend
161Dy	IL-1b	JK1B-1	BioLegend
165Ho	CXCL10	J034D6	BioLegend
169Tm	IL-17A	BL168	Fluidigm/Standard BioTools (pre-conjugated)
170Er	TNFa	MAb11	BioLegend
175Lu	Perforin	B-D48	Fluidigm/Standard BioTools (pre-conjugated)

***NOTE: Anti-APC-149Sm is to target anti-human APC - CD107a (Biolegend, clone H4A3)*

Table S6. CyTOF intracellular staining panel.

Time Point	Sex	Cell type	Sender or Receiver	Ligand	Receptor
Acute infection	Male	Proliferating NK	receiver	CRTAM	ILDR2
Acute infection	Male	Proliferating NK	receiver	COL4A4	ITGB1
Acute infection	Male	Proliferating NK	sender	TGFB1	APP
Acute infection	Male	Proliferating NK	sender	NETO2	IL18R1
Acute infection	Female	Proliferating NK	receiver	TGFB1	ITGA5
Acute infection	Female	Proliferating NK	receiver	SPON2	ITGA5
Acute infection	Female	Proliferating NK	receiver	ENG	ITGAV
Acute infection	Female	Proliferating NK	receiver	FAM3C	ADGRG5
Acute infection	Female	Proliferating NK	receiver	COL4A4	ITGA1
Acute infection	Female	Proliferating NK	receiver	COL4A4	ITGA2
Acute infection	Female	Proliferating NK	receiver	COL4A4	CD47
Acute infection	Female	Proliferating NK	receiver	COL4A4	ITGB1
Acute infection	Female	Proliferating NK	receiver	COL4A4	ITGAV
Acute infection	Female	Proliferating NK	sender	PTPRC	CD247
Acute infection	Female	Proliferating NK	sender	PTPRC	CD4
Acute infection	Female	Proliferating NK	sender	ITGB2	CD82
Acute infection	Female	Proliferating NK	sender	FAM3C	ADGRG5
Acute infection	Female	Proliferating NK	sender	CLEC2B	KLRB1
Acute infection	Female	Proliferating NK	sender	CALR	TAP1
Acute infection	Female	Proliferating NK	sender	CALR	TAP2
Acute infection	Female	Proliferating NK	sender	CALM3	PDE1B
Acute infection	Female	Proliferating NK	sender	ITGAL	CD226
Acute infection	Female	Proliferating NK	sender	CALR	ITGAV
Acute infection	Female	Proliferating NK	sender	PAM	DPP4
Acute infection	Male	CD14 mono	receiver	TGFB1	SDC2
Acute infection	Male	CD14 mono	receiver	CD55	ADGRE2

Acute infection	Male	CD14 mono	receiver	CD55	CR1
Acute infection	Male	CD14 mono	receiver	HBEGF	CD9
Acute infection	Male	CD14 mono	receiver	CD55	ADGRE2
Acute infection	Male	CD14 mono	receiver	SPON2	ITGAM
Acute infection	Male	CD14 mono	receiver	BMP8B	BMPR2
Acute infection	Male	CD14 mono	receiver	BMP8B	PLAUR
Acute infection	Male	CD14 mono	receiver	LILRA6	CD300E
Acute infection	Male	CD16 mono	receiver	CD55	ADGRE2
Acute infection	Male	CD16 mono	receiver	LRP1B	PLAUR
Acute infection	Male	CD16 mono	receiver	CD55	CR1
Acute infection	Male	CD16 mono	receiver	NECTIN2	PVR
Acute infection	Male	CD16 mono	receiver	JAM3	ITGB2
Acute infection	Male	CD16 mono	receiver	JAM3	ITGB2
Acute infection	Male	CD16 mono	receiver	S100A8	ITGB2
Acute infection	Male	CD16 mono	receiver	TGFB2	ENG
Acute infection	Male	CD16 mono	receiver	EMC1	PRLR
Acute infection	Male	CD16 mono	receiver	ANGPT1	ITGA5
Acute infection	Male	CD16 mono	receiver	JAM3	ITGB2
Acute infection	Female	CD14 mono	receiver	ITGB2	CD82
Acute infection	Female	CD14 mono	receiver	HLA.DRA	CD53
Acute infection	Female	CD14 mono	receiver	TSPAN3	ADAM10
Acute infection	Female	CD14 mono	receiver	HLA.DRA	CD82
Acute infection	Female	CD14 mono	receiver	CD300C	PTPRO
Acute infection	Female	CD14 mono	receiver	HLA.DRA	CD82
Acute infection	Female	CD14 mono	receiver	HLA.DRB5	CD4
Acute infection	Female	CD14 mono	receiver	HLA.DRA	CD63
Acute infection	Female	CD14 mono	receiver	HLA.C	LILRB1

Acute infection	Female	CD16 mono	receiver	FCN1	LRP1
Acute infection	Female	CD16 mono	receiver	SEMA4A	PLXNA2
Acute infection	Female	CD16 mono	receiver	ADAM10	TSPAN14
Acute infection	Female	CD16 mono	receiver	HLA.DQA2	CD4
Acute infection	Female	CD16 mono	receiver	COL4A4	ITGAV
Acute infection	Female	CD16 mono	receiver	TSPAN33	ADAM10
Acute infection	Female	CD16 mono	receiver	NCAM1	NPTN
Acute infection	Female	CD16 mono	receiver	HLA.C	LILRB1
Acute infection	Female	CD16 mono	receiver	LAMB3	CD151
Acute infection	Female	CD16 mono	receiver	SIGLEC1	PTPRC
Acute infection	Female	CD16 mono	receiver	COL4A4	CD93
Acute infection	Female	CD16 mono	receiver	ADAM17	NOTCH2

Table S7. MultiNicheNet ligand-receptor pair curation. Pairs that were excluded due to lack of experimental evidence or the interaction is known to occur within the same cell.