SUPPLEMENTARY INFORMATION

In depth transcriptomic profiling defines a landscape of dysfunctional immune responses in patients with VEXAS syndrome

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Supplementary Tables

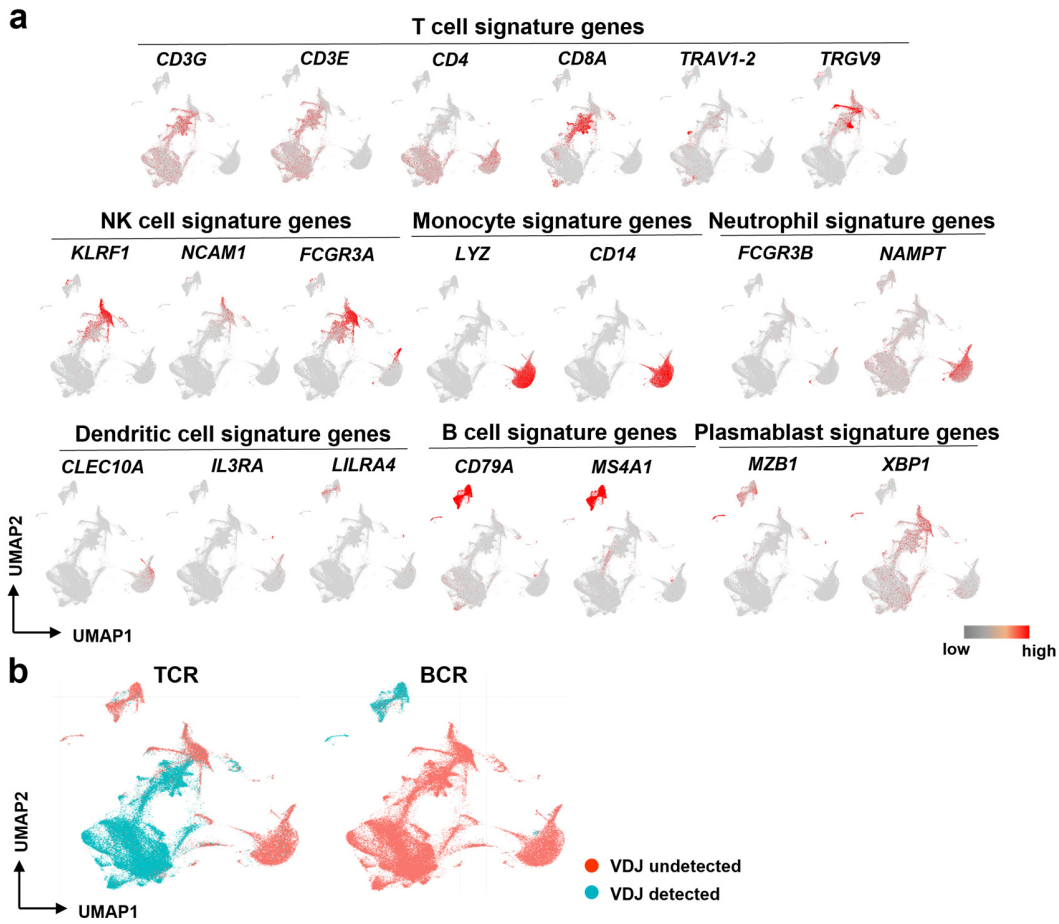
Supplementary Table 1. Clinical and laboratory characteristics of patients with VEXAS syndrome

Supplementary Table 2. *UBA1* genotyping metrics in 10x gene expression data and GoT libraries

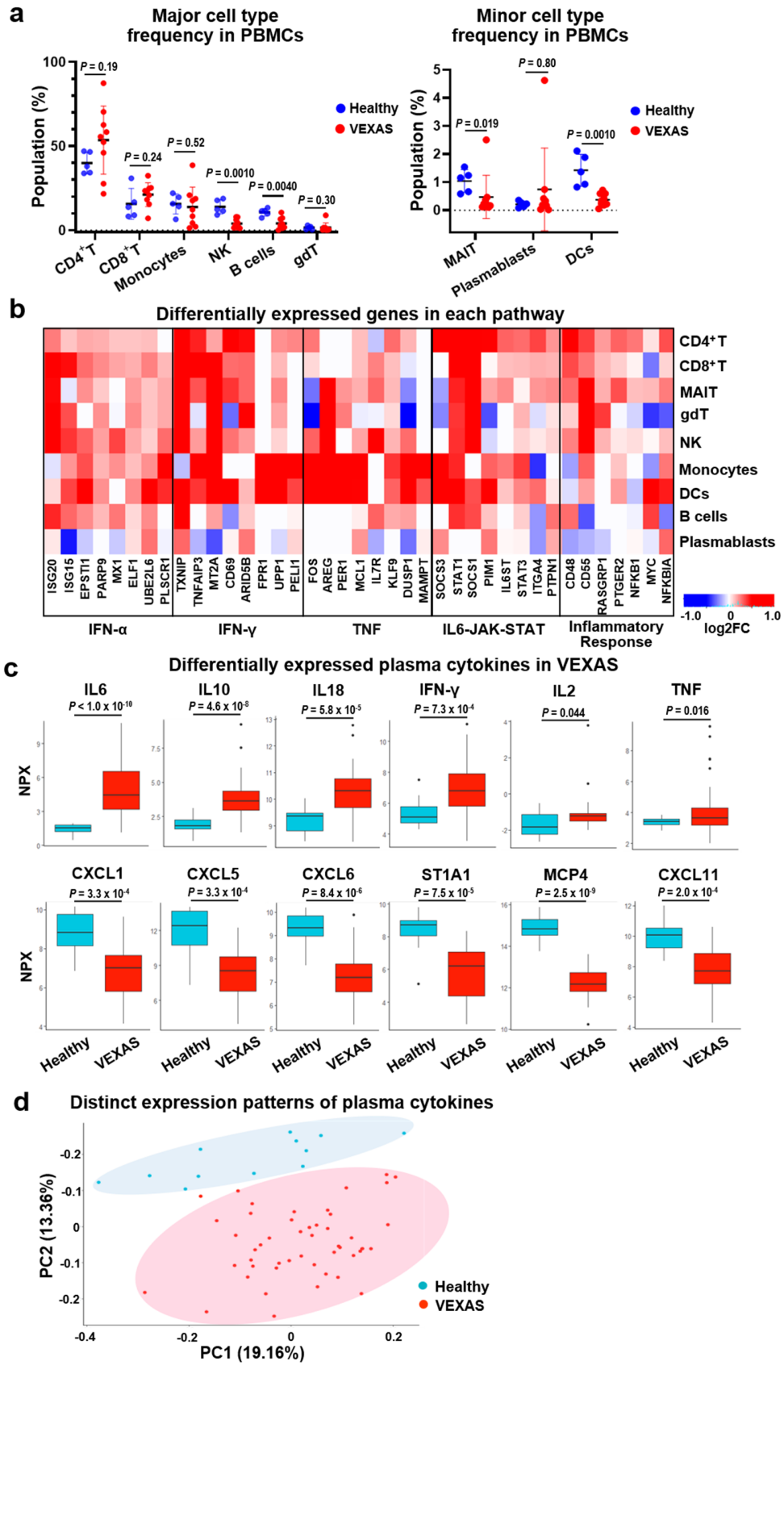
Supplementary Table 3. Differentially expressed genes in monocytes from VEXAS

Supplementary Table 4. Differentially expressed genes in *UBA1*-mutated NK cells

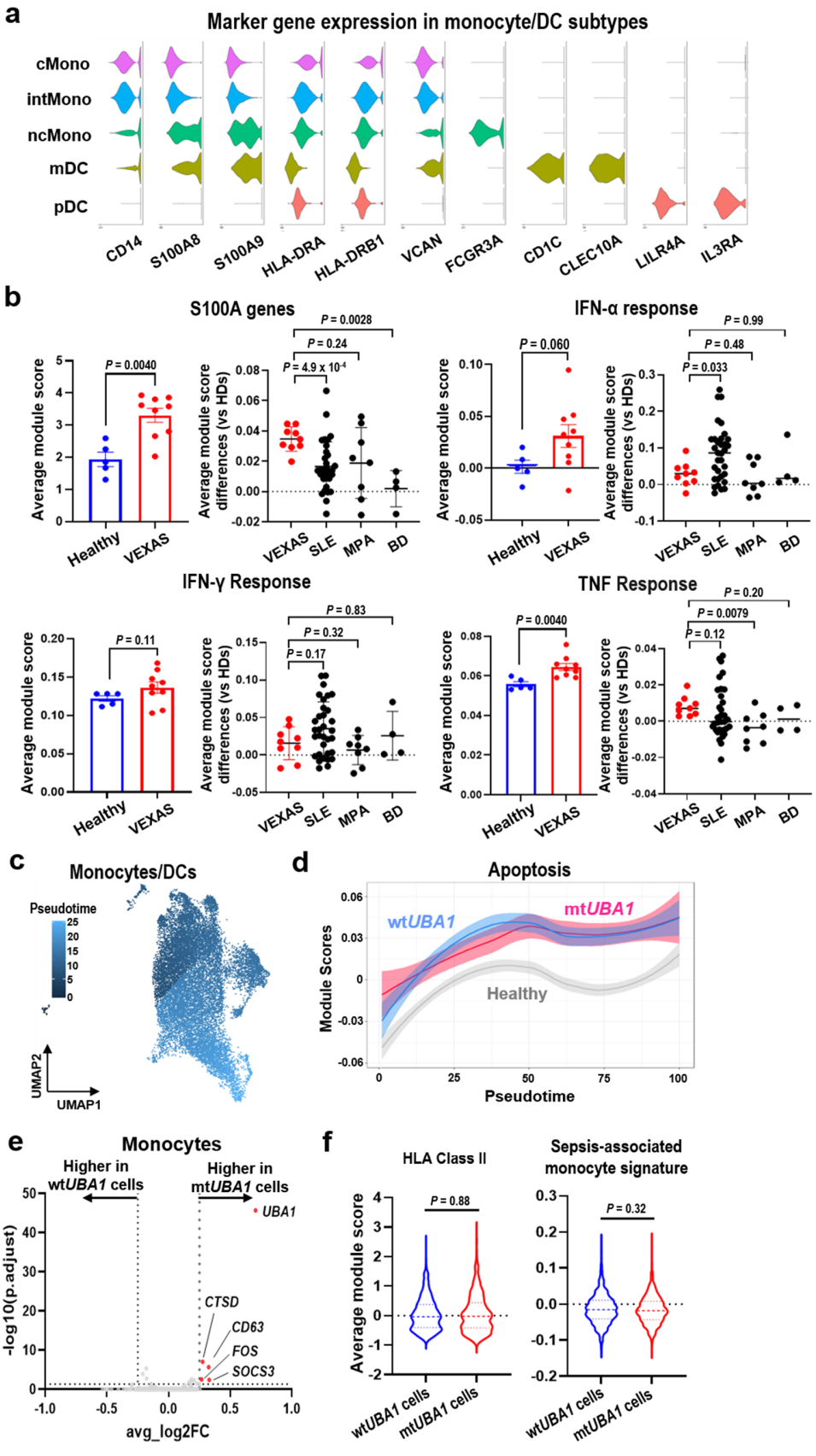
Supplementary Table 5. Sequences of TCR groups with more than five different clones obtained from GLIPH2 analysis


a
T cell signature genes
CD3G
CD3E
CD4
CD8A
TRAV1-2
TRGV9
NK cell signature genes
KLRF1
NCAM1
FCGR3A
Monocyte signature genes
LYZ
CD14
Neutrophil signature genes
FCGR3B
NAMPT
Dendritic cell signature genes
CLEC10A
IL3RA
LILRA4
B cell signature genes
CD79A
MS4A1
Plasmablast signature genes
MZB1
XBP1
UMAP2
UMAP1
low
high
b
TCR
BCR
UMAP2
UMAP1
VDJ undetected
VDJ detected
c
Comparison of UMI numbers covering the UBA1 M41 site
VEXAS 9
VEXAS 10
VEXAS 11
VEXAS 12
VEXAS 13
VEXAS 14
VEXAS 15
VEXAS 17
10x
GoT
Number of UMIs
0
1
2
3
4
5
d
Comparison of genotyping rates
P = 0.0078
Genotyped cells (%)
30
20
10
0
10x
GoT
e
Genotyping rates by GoT
Genotyped cells (%)
50
40
30
20
10
0
Plasmablasts
DCs
MAIT
B cells
NK
CD4+T
CD8+T
gdT
Monocytes

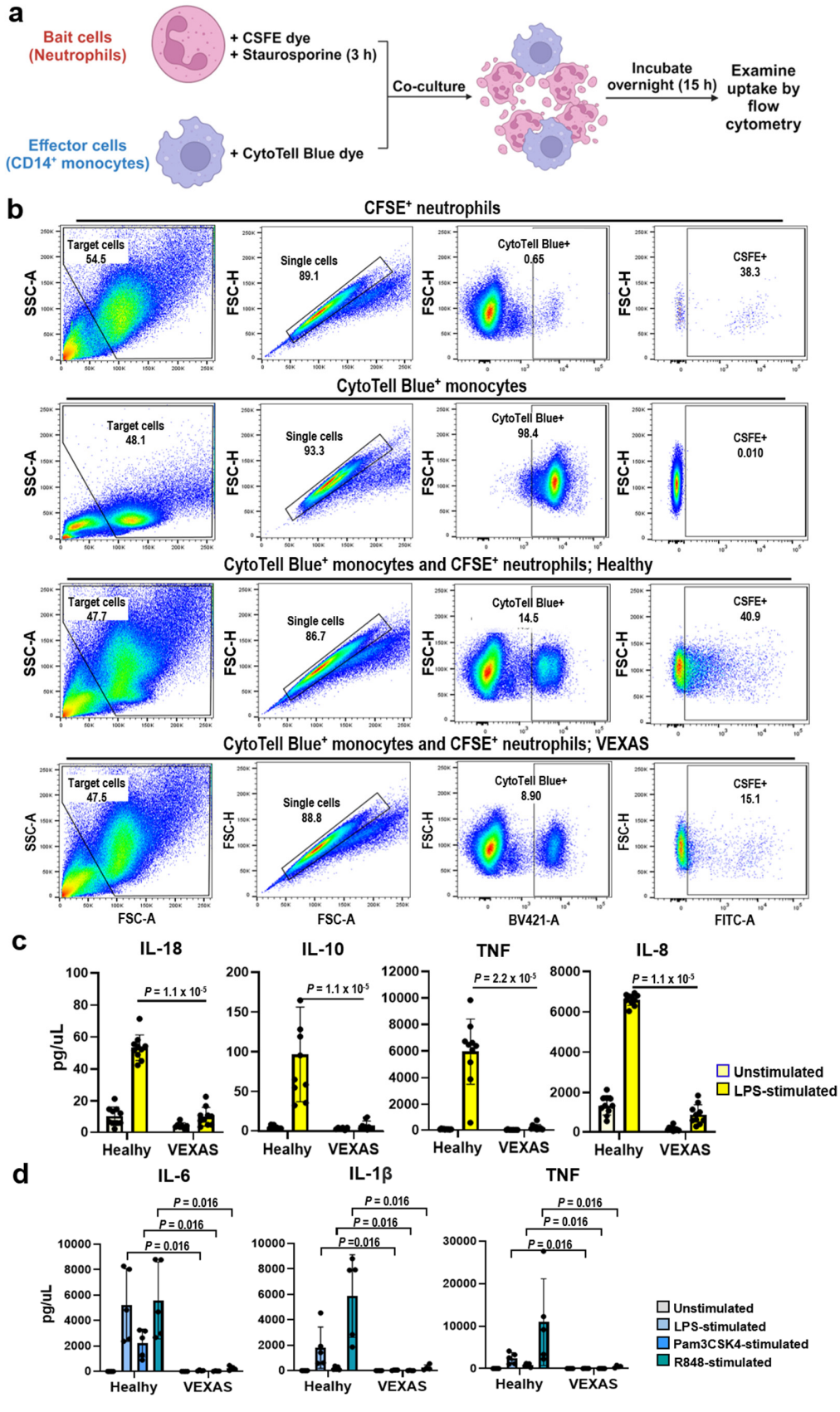
Supplementary Fig. 1: Cell type annotation and genotyping of PBMCs from VEXAS patients. **a**, Expression of cell-type specific genes highlighted in uniform manifold approximation and projection (UMAP) plots of peripheral blood mononuclear cells (PBMC) from all VEXAS patients and healthy donors. **b**, Expression of TCR (left) and BCR (right) highlighted in UMAP plots of PBMCs of all VEXAS patients and healthy donors. **c**, Fractions of cells by the numbers of unique molecular identifier (UMI) with the *UBA1 M41* locus coverages in standard 10x gene expression data processed with cb_sniffer (left) and UMIs with *UBA1 M41* locus coverages in genotyping of transcriptomes (GoT) amplicon libraries (right) (see Supplementary Table 2 for cell numbers in each sample). **d**, Comparison of genotyping rates obtained from standard 10x gene expression data (n = 8) and GoT data (n = 8). Data are presented as a mean value with SD. *P* values were calculated using the two-sided Wilcoxon matched-pairs signed rank test. **e** Genotyping rates through GoT in major cell types. Cell types with more than 100 cells were analyzed. DCs, dendritic cells; MAIT, mucosa-associated invariant T cell; gdT, gamma delta T cells.


a
Major cell type frequency in PBMCs
Minor cell type frequency in PBMCs
Population (%)
Healthy
VEXAS
P = 0.19
P = 0.24
P = 0.52
P = 0.0010
P = 0.0040
P = 0.30
P = 0.80
P = 0.019
P = 0.0010
CD4+T
CD8+T
Monocytes
NK
B cells
gdT
MAIT
Plasmablasts
DCs
b
Differentially expressed genes in each pathway
CD4+T
CD8+T
MAIT
gdT
NK
Monocytes
DCs
B cells
Plasmablasts
ISG20 ISG15 EPSTI1 PARP9 MX1 ELF1 UBE2L6 PLSCR1
TXNIP TNFAIP3 MT2A CD69 ARID5B FPR1 UPP1 PELI1
FOS AREG PER1 MCL1 IL7R KLF9 DUSP1 MAMPT
SOCS3 STAT1 SOCS1 PIM1 IL6ST STAT3 ITGA4 PTPN1
CD48 CD55 RASGRP1 PTGER2 NFKB1 MYC NFKBIA
IFN-α
IFN-γ
TNF
IL6-JAK-STAT
Inflammatory Response
-1.0 0 1.0
log2FC
c
Differentially expressed plasma cytokines in VEXAS
IL6 P < 1.0 x 10-19
IL10 P = 4.6 x 10-8
IL18 P = 5.8 x 10-5
IFN-γ P = 7.3 x 10-4
IL2 P = 0.044
TNF P = 0.016
CXCL1 P = 3.3 x 10-4
CXCL5 P = 3.3 x 10-4
CXCL6 P = 8.4 x 10-6
ST1A1 P = 7.5 x 10-5
MCP4 P = 2.5 x 10-9
CXCL11 P = 2.0 x 10-4
NPX
Healthy
VEXAS
d
Distinct expression patterns of plasma cytokines
PC2 (13.36%)
PC1 (19.16%)
Healthy
VEXAS

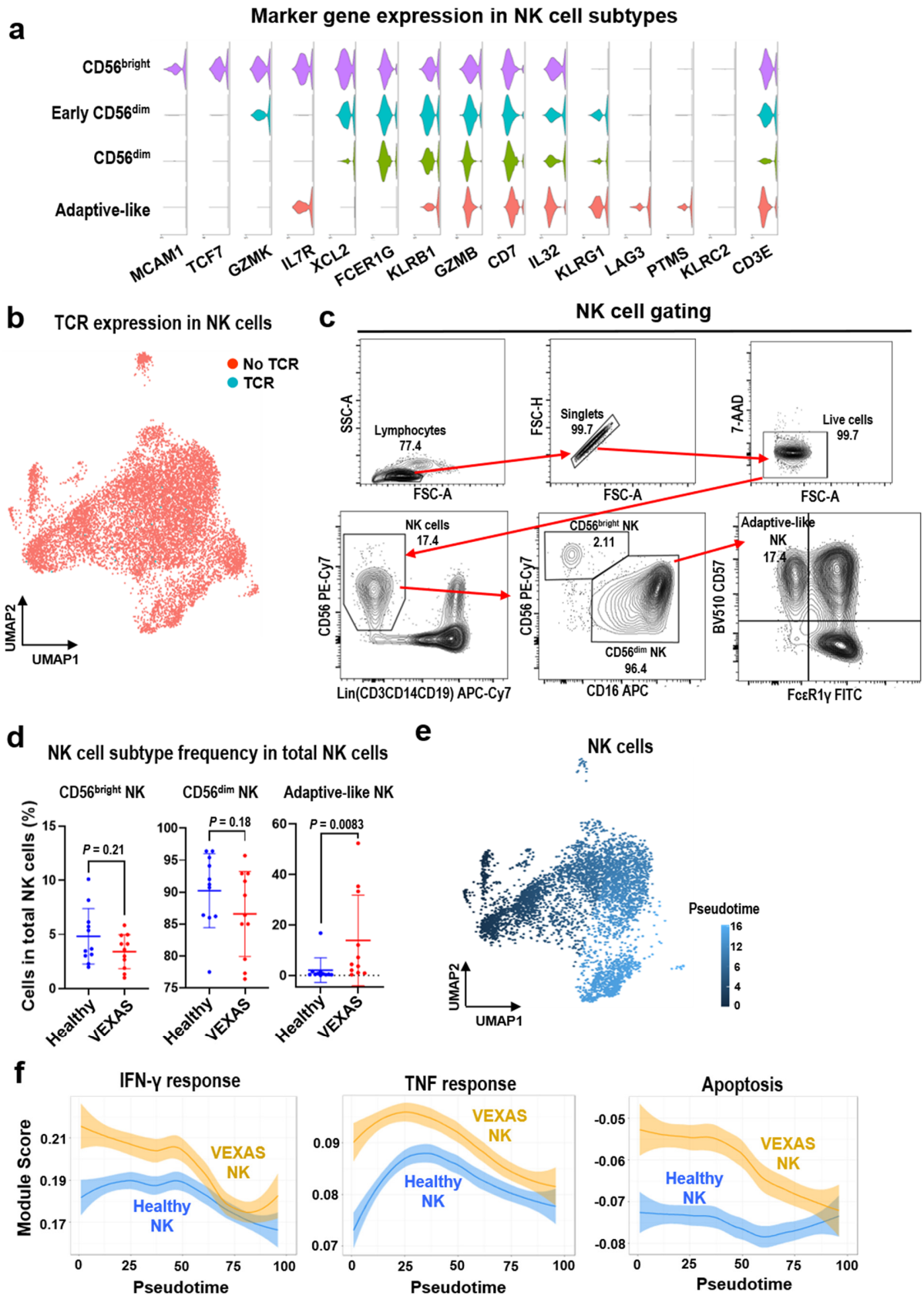
Supplementary Fig. 2: Differences in cellular composition, gene expression, and cytokine production between VEXAS patients and healthy donors. a, Percentages of each major cell type relative to the total number of PBMCs derived from VEXAS patients (n = 9, red dots) and healthy donors (n = 5, blue dots): major cell types with an average ratio of 2% or greater (left), and less than 2% (right). Data are presented as a mean value with SD. *P* values were calculated using the two-sided unpaired Mann-Whitney *U* test. **b**, Heatmap showing expression of differentially expressed representative genes grouped by their functional pathways in IFN-α signaling, IFN-γ signaling, TNF signaling, IL6-JAK-STAT signaling, and inflammatory response pathways among the major cell types of VEXAS patients (n = 9) as compared to those of healthy donors (n = 5). Values are presented as log2-fold change (FC). **c**, Box and whisker plots showing normalized plasma protein expression (NPX) levels of IL-6, IL-10, IL-18, IFN-γ, IL-2, TNF, CXCL1, CXCL5, CXCL6, ST1A1, MCP4, and CXCL11. A box plot shows median and interquartile ranges (IQR); Lower and upper hinges correspond to the first and third quartiles. A upper whisker extends from the hinge to the largest value no further than 1.5*IQR from a hinge. A lower whisker extends from the hinge to the smallest value at most 1.5*IQR from the hinge. *P* values were calculated using the two-sided unpaired Mann-Whitney *U* test. **d**, Principal component (PC) analysis plot of individual plasma samples based on cytokine expression levels measured by the Olink inflammatory panel multiplex immunoassay. Each dot represents one individual sample from VEXAS patients (red dots) and from healthy donors (blue dots). DCs, dendritic cells; MAIT, mucosa-associated invariant T cells; gdT, gamma delta T cells.


a
Marker gene expression in monocyte/DC subtypes
cMono
intMono
ncMono
mDC
pDC
CD14
S100A8
S100A9
HLA-DRA
HLA-DRB1
VCAN
FCGR3A
CD1C
CLEC10A
LILR4A
IL3RA
b
S100A genes
IFN-α response
IFN-γ Response
TNF Response
Average module score
Average module score differences (vs HDs)
Healthy
VEXAS
SLE
MPA
BD
P = 0.0040
P = 0.0028
P = 0.24
P = 4.9 x 10-4
P = 0.060
P = 0.99
P = 0.48
P = 0.033
P = 0.11
P = 0.83
P = 0.32
P = 0.17
P = 0.0040
P = 0.20
P = 0.0079
P = 0.12
c
Monocytes/DCs
Pseudotime
UMAP2
UMAP1
d
Apoptosis
wtUBA1
mtUBA1
Healthy
Module Scores
Pseudotime
e
Monocytes
Higher in wtUBA1 cells
Higher in mtUBA1 cells
UBA1
CTSD
CD63
FOS
SOCS3
-log10(p.adjust)
avg_log2FC
f
HLA Class II
Sepsis-associated monocyte signature
P = 0.88
P = 0.32
Average module score
wtUBA1 cells
mtUBA1 cells

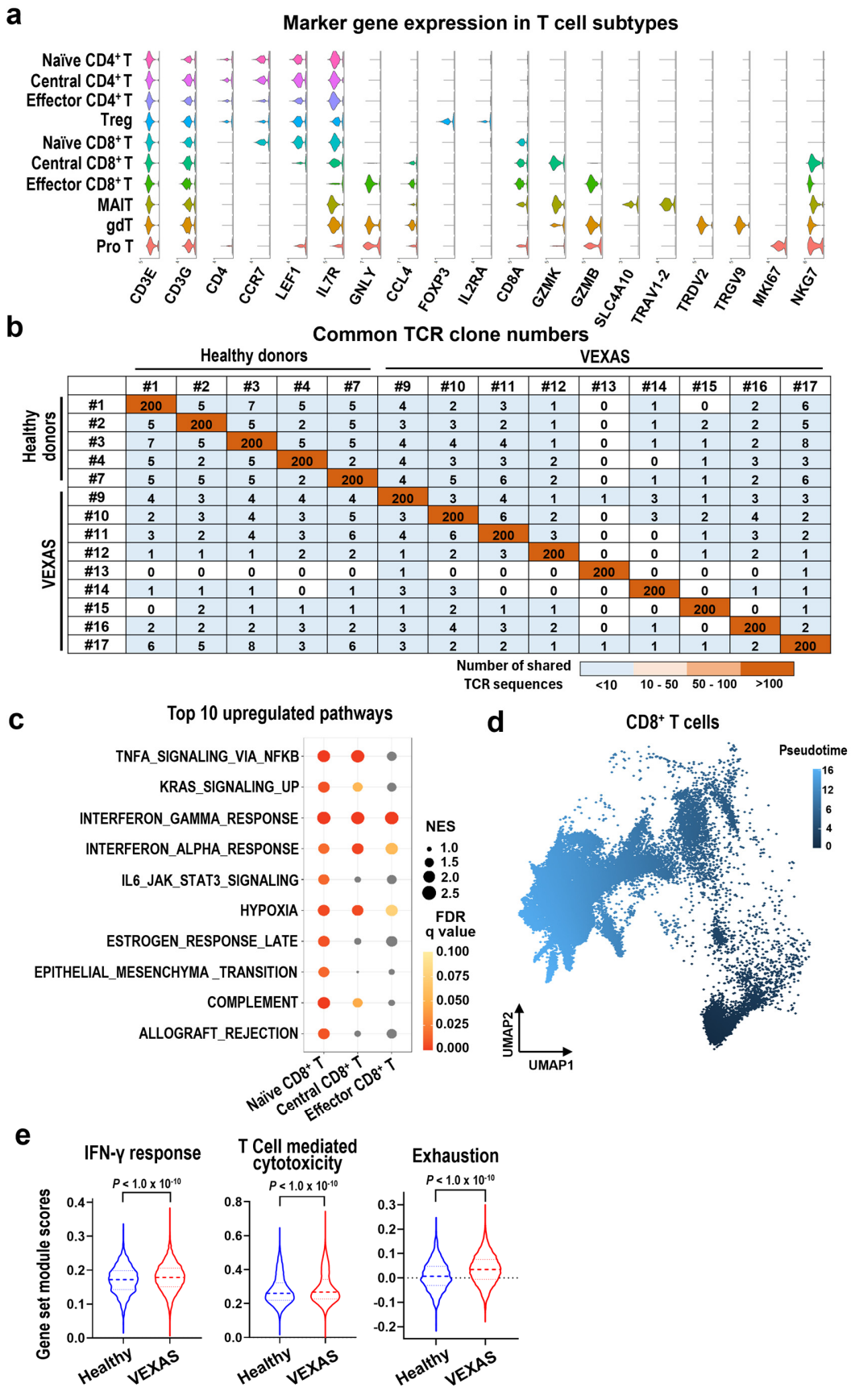
Supplementary Fig. 3: Immunological features of monocytes in VEXAS. a, Violin plot showing expression distributions of selected canonical markers in five subtypes of monocytes and dendritic cells (DC). Rows and columns represent selected marker genes and cell types, respectively. **b**, Gene module scores of alarmin-related S100A genes, IFN-α response, IFN-γ response, and TNF response pathways in monocytes across VEXAS (n = 9), healthy donors (n = 5), and other multisystem autoimmune diseases (Systemic lupus erythematosus (SLE), n = 33; microscopic polyangiitis (MPA), n = 8; Behcet's disease (BD), n = 4). For comparison among diseases, differences of gene module scores between VEXAS and healthy donors are displayed. Data are presented as mean with SD. *P* values were calculated using two-sided unpaired Mann-Whitney *U* test. **c**, UMAP plot visualizing pseudotime trajectories of all monocytes/DCs in VEXAS. A color code indicates cellular moments in the calculated pseudotime. **d,** Dynamic changes of gene module scores of the apoptosis pathway in wild-type *UBA1* (wt*UBA1*) and *UBA1*-mutated (mt*UBA1*) monocytes from VEXAS and monocytes from healthy donors along differentiation. Data are presented as a mean value with 1.96*SE. x axis, pseudotime ordering from classical monocytes to nonclassical monocytes estimated by slingshot; y axis, gene module scores of apoptosis pathway. **e**, Volcano plots of differentially expressed genes between wt*UBA1* and mt*UBA1* monocytes. A horizontal dotted line and vertical dotted lines represent an adjusted *p* value (*p*adj) = 0.05 and absolute log2FC = 0.25, respectively. Genes upregulated in mt*UBA1* monocytes (red) are highlighted. *P* values were calculated with a two-sided Wilcoxon rank-sum test and Bonferroni correction for multiple comparisons. **f,** Gene module scores in wt*UBA1*and mt*UBA1* monocytes for HLA class II genes and sepsis-associated monocyte signature scores. *P* values were calculated using the two-sided unpaired Mann-Whitney *U* test.


a
Bait cells (Neutrophils)
+ CSFE dye
+ Staurosporine (3 h)
Effector cells (CD14+ monocytes)
+ CytoTell Blue dye
Co-culture
Incubate overnight (15 h)
Examine uptake by flow cytometry
b
CFSE+ neutrophils
Target cells 54.5
Single cells 89.1
CytoTell Blue+ 0.65
CSFE+ 38.3
CytoTell Blue+ monocytes
Target cells 48.1
Single cells 93.3
CytoTell Blue+ 98.4
CSFE+ 0.010
CytoTell Blue+ monocytes and CFSE+ neutrophils; Healthy
Target cells 47.7
Single cells 86.7
CytoTell Blue+ 14.5
CSFE+ 40.9
CytoTell Blue+ monocytes and CFSE+ neutrophils; VEXAS
Target cells 47.5
Single cells 88.8
CytoTell Blue+ 8.90
CSFE+ 15.1
SSC-A
FSC-H
FSC-A
BV421-A
FITC-A
c
IL-18
IL-10
TNF
IL-8
P = 1.1 x 10-5
P = 2.2 x 10-5
pg/uL
Healhy
VEXAS
Unstimulated
LPS-stimulated
d
IL-6
IL-1β
TNF
P = 0.016
Unstimulated
LPS-stimulated
Pam3CSK4-stimulated
R848-stimulated

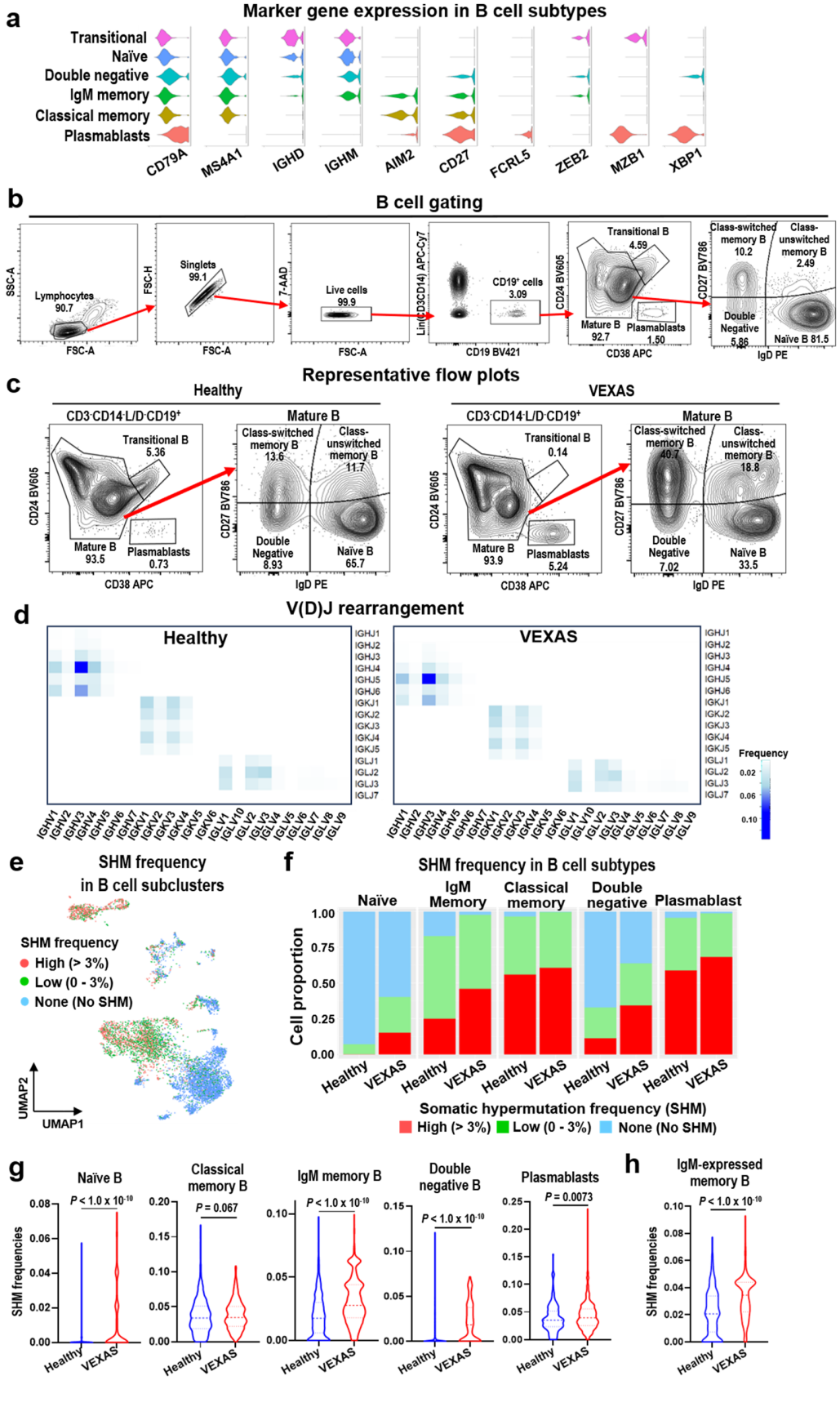
Supplementary Fig. 4: Functional in vitro assay using CD14$^+$ monocytes from VEXAS patients. a, Schematic representation of the efferocytosis assay. Neutrophils isolated from fresh blood of an unrelated healthy donor were stained with CSFE and induced apoptosis with Staurosporine. CD14$^+$ monocytes isolated from frozen peripheral blood mononuclear cells (PBMC) of VEXAS patients and healthy donors were stained with CytoTell Blue. CSFE-labeled apoptotic "bait" neutrophils were then cocultured with "effector" CD14$^+$ monocytes overnight. Frequency of CSFE$^+$ apoptotic cell uptake in CytoTell Blue$^+$ efferocytes (CD14$^+$ monocytes) were measured with a flow cytometer. Figure was created in BioRender. Mizumaki, H. (2025) [https://BioRender.com/w79k163]. **b**, Representative flow plots showing a gating strategy for identifying efferocytes that engulfed apoptotic neutrophils. Cells were gated on monocytes/neutrophils, singlets, CytoTell Blue$^+$ and CFSE$^+$. Frequency of efferocytes was expressed as frequency of CFSE$^+$ cells in CytoTell Blue$^+$ monocytes. CFSE$^+$ neutrophils (upper panel) and CytoTell Blue$^+$ monocytes (second panel) not cocultured were used as controls for setting the gates. Representative third and bottom panels show cocultured CFSE$^+$ neutrophils and CytoTell Blue$^+$ monocytes from a healthy donor and a VEXAS patient, respectively. **c**, Cytokine detection of IL-18, IL-10, TNF, and IL-8 in culture supernatants of purified CD14$^+$ monocytes (VEXAS patients, n = 10; healthy donors, n = 10) after 8 h in-vitro incubation with or without 100 ng/mL of lipopolysaccharide (LPS). Data are presented as a mean value with SD. *P* values were calculated using the two-sided unpaired Mann-Whitney *U* test. **d**, Cytokine detection of IL-6, IL-1β, and TNF in culture supernatants of purified CD14$^+$ monocytes (VEXAS patients, n = 4; healthy donors, n = 5) after 8 h in-vitro incubation with or without 100 ng/mL of lipopolysaccharide (LPS), 100 ng/mL of Pam3CSK4, and 2.5 μM of R848. Data are presented as mean with SD. *P* values were calculated using the two-sided unpaired Mann-Whitney *U* test.


a
Marker gene expression in NK cell subtypes
CD56bright
Early CD56dim
CD56dim
Adaptive-like
MCAM1
TCF7
GZMK
IL7R
XCL2
FCER1G
KLRB1
GZMB
CD7
IL32
KLRG1
LAG3
PTMS
KLRC2
CD3E
b
TCR expression in NK cells
No TCR
TCR
UMAP2
UMAP1
c
NK cell gating
SSC-A
Lymphocytes
77.4
FSC-A
FSC-H
Singlets
99.7
FSC-A
7-AAD
Live cells
99.7
FSC-A
NK cells
17.4
CD56 PE-Cy7
Lin(CD3CD14CD19) APC-Cy7
CD56bright NK
2.11
CD56dim NK
96.4
CD56 PE-Cy7
CD16 APC
Adaptive-like
NK
17.4
BV510 CD57
FcεR1γ FITC
d
NK cell subtype frequency in total NK cells
CD56bright NK
CD56dim NK
Adaptive-like NK
Cells in total NK cells (%)
P = 0.21
P = 0.18
P = 0.0083
Healthy
VEXAS
e
NK cells
Pseudotime
UMAP2
UMAP1
f
IFN-γ response
TNF response
Apoptosis
Module Score
VEXAS NK
Healthy NK
Pseudotime

Supplementary Fig. 5: Immunological features of NK cells in VEXAS. a, Violin plot of gene expression distributions of selected canonical markers in the four NK cell subtypes. Rows and columns show selected marker genes and represent cell types. **b**, UMAP plot embedding of expression of TCR in subclustered NK cells. **c**, Representative flowcharts for identification of adaptive-like NK cells in peripheral blood. Adaptive-like NK cells were identified as (lowSSC/Singlets/Live/$CD56^{+}CD3^{-}CD14^{-}CD19^{-}$/$CD16^{+}CD56^{dim}$/$CD57^{+}Fc\varepsilon R1\gamma^{-}$). **d**, Proportions of NK cell subtypes relative to the total number of NK cells in healthy donors (n = 11, blue dots) and VEXAS patients (n = 11, red dots) by flow cytometry. Data are presented as a mean value with SD. *P* values were calculated using the two-sided unpaired Mann-Whitney *U* test. **e**, UMAP plot visualizing the pseudotime trajectory of all NK cells in VEXAS. Color code indicates cellular moments in the calculated pseudotime. **f**, Dynamic changes of gene module scores of the IFN-γ response, TNF# response and apoptosis pathways in NK cells from VEXAS patients and healthy donors along differentiation. Data are presented as a mean value with 1.96*SE. x axis, pseudotime ordering from $CD56^{bright}$ NK cells to adaptive-like NK cells estimated by slingshot; y axis, gene module scores for each pathway.


a
Marker gene expression in T cell subtypes
Naïve CD4+ T
Central CD4+ T
Effector CD4+ T
Treg
Naïve CD8+ T
Central CD8+ T
Effector CD8+ T
MAIT
gdT
Pro T
CD3E
CD3G
CD4
CCR7
LEF1
IL7R
GNLY
CCL4
FOXP3
IL2RA
CD8A
GZMK
GZMB
SLC4A10
TRAV1-2
TRDV2
TRGV9
MKI67
NKG7
b
Common TCR clone numbers
Healthy donors
VEXAS
Healthy donors
VEXAS
#1 200 5 7 5 5 4 2 3 1 0 1 0 2 6
#2 5 200 5 2 5 3 3 2 1 0 1 2 2 5
#3 7 5 200 5 5 4 4 4 1 0 1 1 2 8
#4 5 2 5 200 2 4 3 3 2 0 0 1 3 3
#7 5 5 5 2 200 4 5 6 2 0 1 1 2 6
#9 4 3 4 4 4 200 3 4 1 1 3 1 3 3
#10 2 3 4 3 5 3 200 6 2 0 3 2 4 2
#11 3 2 4 3 6 4 6 200 3 0 0 1 3 2
#12 1 1 1 2 2 1 2 3 200 0 0 1 2 1
#13 0 0 0 0 0 1 0 0 0 200 0 0 0 1
#14 1 1 1 0 1 3 3 0 0 0 200 0 1 1
#15 0 2 1 1 1 1 2 1 1 0 0 200 0 1
#16 2 2 2 3 2 3 4 3 2 0 1 0 200 2
#17 6 5 8 3 6 3 2 2 1 1 1 1 2 200
Number of shared TCR sequences
<10
10 - 50
50 - 100
>100
c
Top 10 upregulated pathways
TNFA_SIGNALING_VIA_NFKB
KRAS_SIGNALING_UP
INTERFERON_GAMMA_RESPONSE
INTERFERON_ALPHA_RESPONSE
IL6_JAK_STAT3_SIGNALING
HYPOXIA
ESTROGEN_RESPONSE_LATE
EPITHELIAL_MESENCHYMA _TRANSITION
COMPLEMENT
ALLOGRAFT_REJECTION
Naïve CD8+ T
Central CD8+ T
Effector CD8+ T
NES
1.0
1.5
2.0
2.5
FDR q value
0.100
0.075
0.050
0.025
0.000
d
CD8+ T cells
Pseudotime
16
12
6
4
0
UMAP2
UMAP1
e
IFN-γ response
T Cell mediated cytotoxicity
Exhaustion
P < 1.0 x 10-10
Gene set module scores
Healthy
VEXAS

Supplementary Fig. 6: Immunological features of T cells and TCR analysis. a, Violin plot showing expression distributions of selected canonical cell markers in ten T cell subtypes. Rows and columns represent clusters and selected marker genes, respectively. **b**, Heatmap showing the numbers of common TCR clones in VEXAS patients (n = 9) and healthy donors (n = 5) among top 200 TCR clones. Both x- and y-axes indicate samples of VEXAS patients and healthy donors. Numbers indicate counts of identical TCR clones shared among samples. A color scheme ranging from dark orange to blue represents the numbers of shared CDR sequences from high to low. In general, there was few common TCR usage in VEXAS patients or healthy donors. There was also few common TCR usage among VEXAS patients and healthy donors. **c**, Dot plot showing gene set enrichment scores of top 10 upregulated hallmark pathways across $CD8^+$ T cell subtypes. Dot size indicates mean normalized enrichment score (NES) difference between VEXAS patients and healthy donors, and color scale indicates false discovery rate (FDR) value. Non-significant pathways (FDR $\geq$ 0.10) are in grey. **d**, UMAP plot illustrating the pseudotime trajectory of all $CD8^+$ T cells. A color code indicates cellular moments in the calculated pseudotime. **e**, Gene module scores in expanded $CD8^+$ T cells from healthy donors versus those of VEXAS patients for IFN-γ response, and T-cell mediated cytotoxicity and exhaustion pathways.


a
Marker gene expression in B cell subtypes
Transitional
Naïve
Double negative
IgM memory
Classical memory
Plasmablasts
CD79A
MS4A1
IGHD
IGHM
AIM2
CD27
FCRL5
ZEB2
MZB1
XBP1
b
B cell gating
SSC-A
Lymphocytes 90.7
FSC-A
FSC-H
Singlets 99.1
7-AAD
Live cells 99.9
Lin(CD3CD14) APC-Cy7
CD19+ cells 3.09
CD19 BV421
CD24 BV605
Transitional B 4.59
Mature B 92.7
Plasmablasts 1.50
CD38 APC
CD27 BV786
Class-switched memory B 10.2
Class-unswitched memory B 2.49
Double Negative 5.86
Naïve B 81.5
IgD PE
c
Representative flow plots
Healthy
VEXAS
CD3-CD14-L/D-CD19+
Mature B
Transitional B 5.36
Mature B 93.5
Plasmablasts 0.73
Class-switched memory B 13.6
Class-unswitched memory B 11.7
Double Negative 8.93
Naïve B 65.7
Transitional B 0.14
Mature B 93.9
Plasmablasts 5.24
Class-switched memory B 40.7
Class-unswitched memory B 18.8
Double Negative 7.02
Naïve B 33.5
d
V(D)J rearrangement
Healthy
VEXAS
IGHJ1
IGHJ2
IGHJ3
IGHJ4
IGHJ5
IGHJ6
IGKJ1
IGKJ2
IGKJ3
IGKJ4
IGKJ5
IGLJ1
IGLJ2
IGLJ3
IGLJ7
IGHV1
IGHV2
IGHV3
IGHV4
IGHV5
IGHV6
IGHV7
IGKV1
IGKV2
IGKV3
IGKV4
IGKV5
IGKV6
IGLV1
IGLV10
IGLV2
IGLV3
IGLV4
IGLV5
IGLV6
IGLV7
IGLV8
IGLV9
Frequency
0.02
0.06
0.10
e
SHM frequency in B cell subclusters
SHM frequency
High (> 3%)
Low (0 - 3%)
None (No SHM)
UMAP2
UMAP1
f
SHM frequency in B cell subtypes
Naïve
IgM Memory
Classical memory
Double negative
Plasmablast
Cell proportion
1.00
0.75
0.50
0.25
0.00
Healthy
VEXAS
Somatic hypermutation frequency (SHM)
High (> 3%)
Low (0 - 3%)
None (No SHM)
g
Naïve B
P < 1.0 x 10-10
Classical memory B
P = 0.067
IgM memory B
P < 1.0 x 10-10
Double negative B
P < 1.0 x 10-10
Plasmablasts
P = 0.0073
SHM frequencies
h
IgM-expressed memory B
P < 1.0 x 10-10
SHM frequencies
Healthy
VEXAS

Supplementary Fig. 7: Immunological features of B cells and TCR analysis. a, Violin plot of gene expression distributions of selected canonical cell markers in six B cell subtypes. Rows and columns indicate clusters and selected marker genes. **b**, Identification of B cell subsets in peripheral blood. **c**, Representative flow plots for B cell subsets in peripheral blood from VEXAS patients (right) and healthy donors (left). **d**, V(D)J rearrangement differences between VEXAS patients and healthy donors. Colors indicate usage percentages of specific V-J gene pairs. **e**, UMAP plot embedding subclustered B cells colored by levels of somatic hypermutation (SHM) in their corresponding BCRs. Cells with both scRNA-seq data and scBCR-seq data are shown. **f**, SHM frequency distribution in each B-cell subtype according to VEXAS and healthy donors. **g**, Comparison of SHM frequency between each B cell subtype of VEXAS patients and that of healthy donors. *P* values were calculated using the two-sided unpaired Mann-Whitney *U* test. **h**, Comparison of SHM frequency between IgM-expressed memory B cells of VEXAS patients and those of healthy donors. *p* values were calculated using the two-sided unpaired Mann-Whitney *U* test.