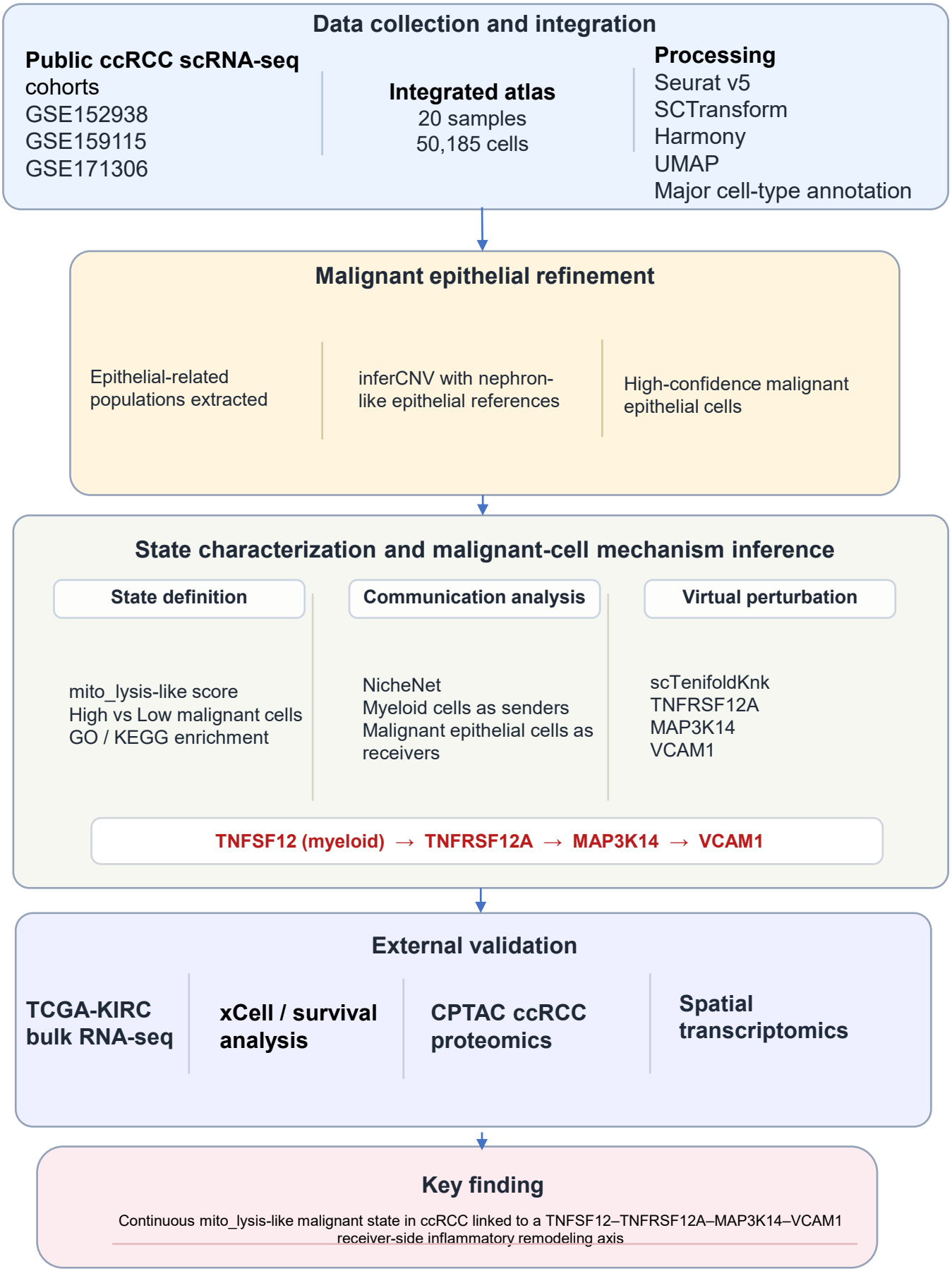
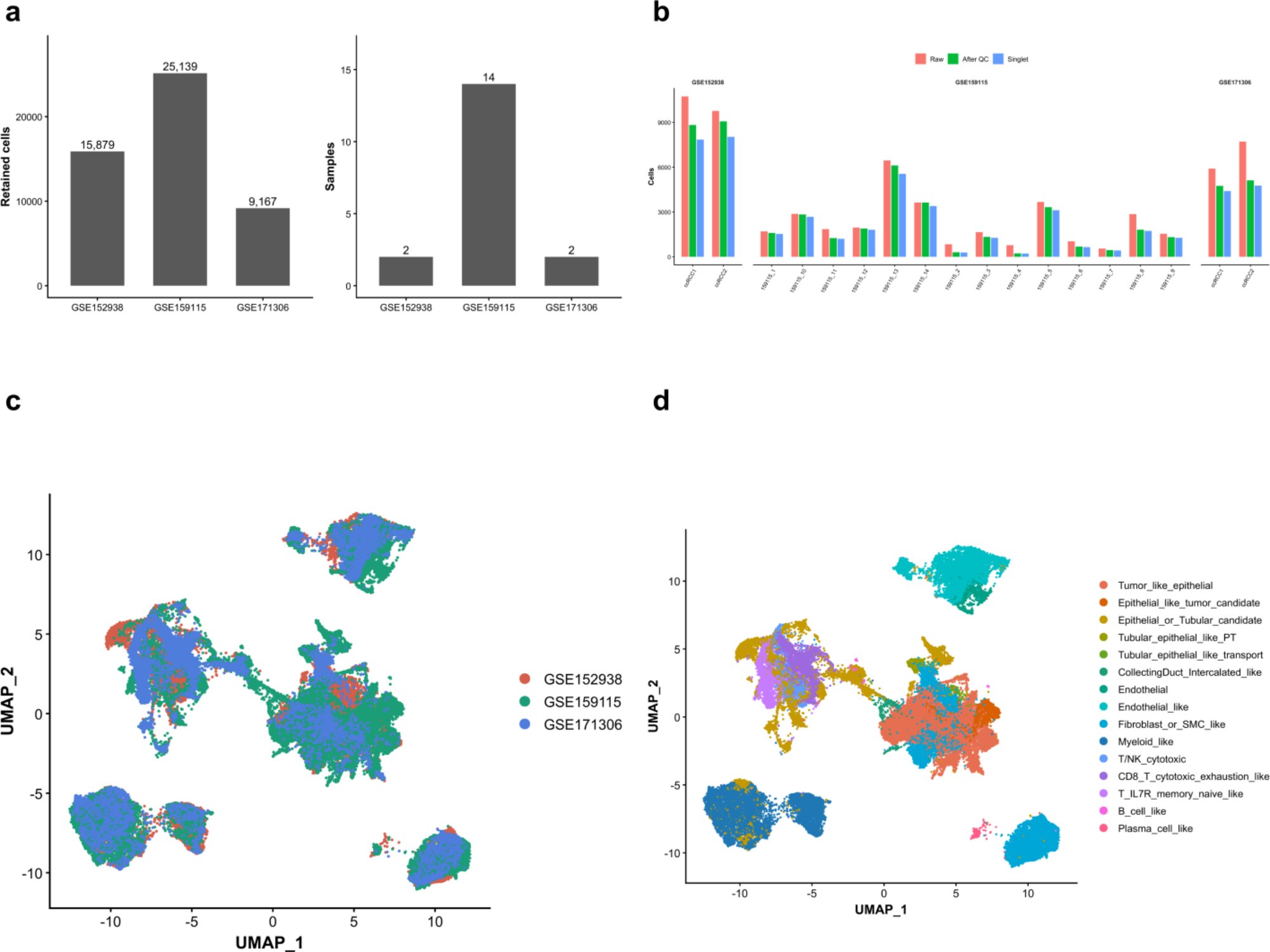
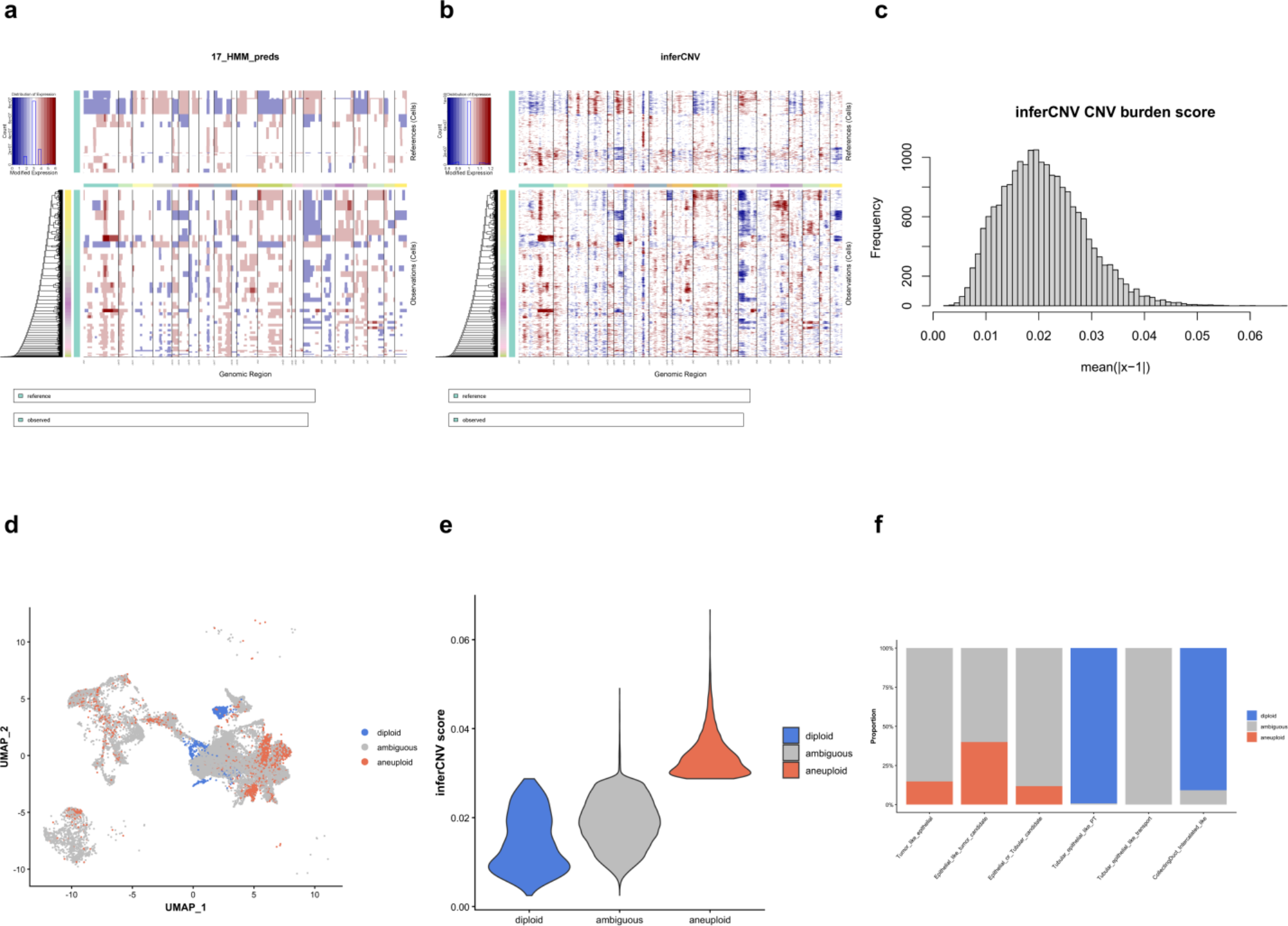
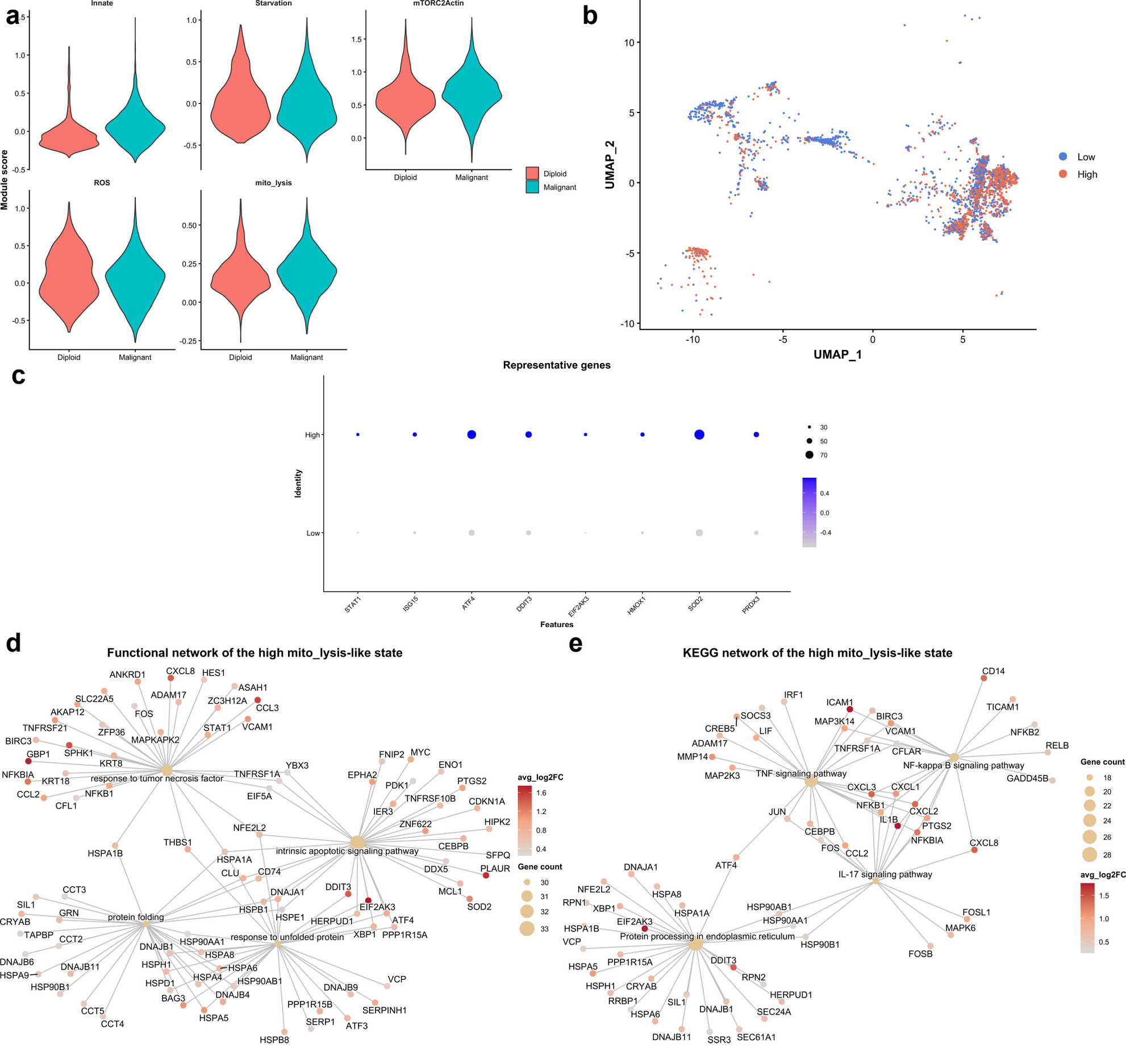
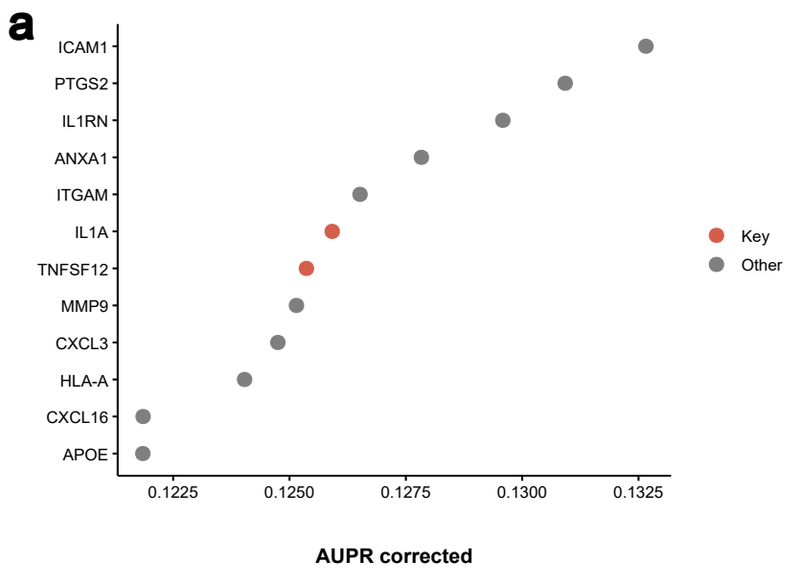
Overall study design and analytical workflow

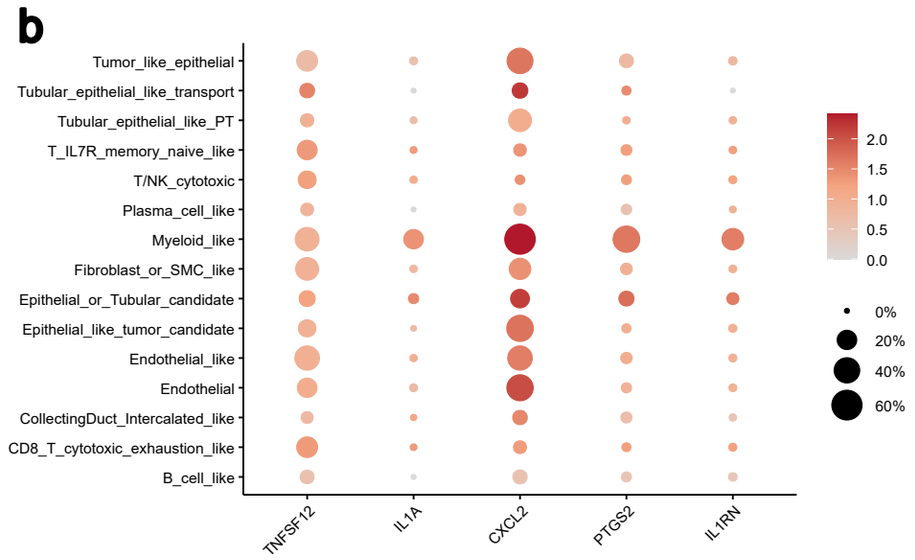


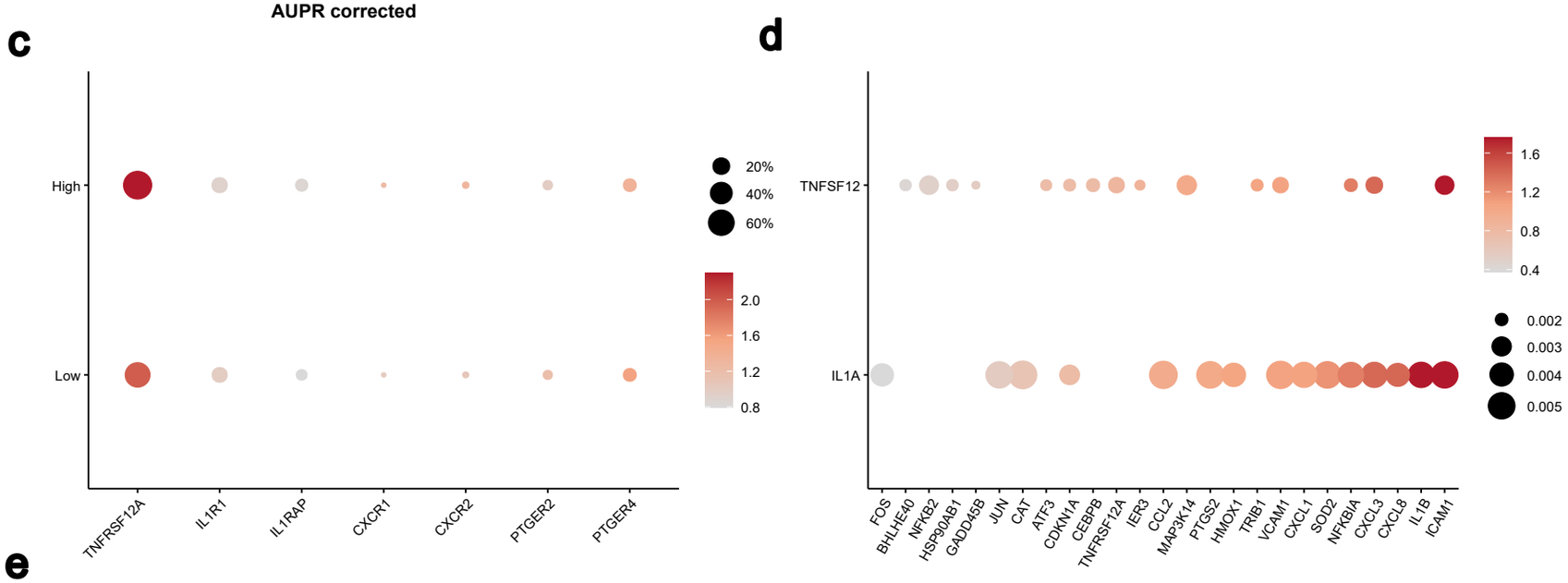

a
Retained cells
20000
10000
0
15,879
25,139
9,167
GSE152938
GSE159115
GSE171306
Samples
15
10
5
0
2
14
2
GSE152938
GSE159115
GSE171306
b
Raw
After QC
Singlet
GSE152938
GSE159115
GSE171306
Cells
9000
6000
3000
0
ccRCC1
ccRCC2
159115_1
159115_10
159115_11
159115_12
159115_13
159115_14
159115_2
159115_3
159115_4
159115_5
159115_6
159115_7
159115_8
159115_9
ccRCC1
ccRCC2
c
UMAP_2
10
5
0
-5
-10
-10
-5
0
5
10
UMAP_1
GSE152938
GSE159115
GSE171306
d
UMAP_2
10
5
0
-5
-10
-10
-5
0
5
10
UMAP_1
Tumor_like_epithelial
Epithelial_like_tumor_candidate
Epithelial_or_Tubular_candidate
Tubular_epithelial_like_PT
Tubular_epithelial_like_transport
CollectingDuct_Intercalated_like
Endothelial
Endothelial_like
Fibroblast_or_SMC_like
Myeloid_like
T/NK_cytotoxic
CD8_T_cytotoxic_exhaustion_like
T_IL7R_memory_naive_like
B_cell_like
Plasma_cell_like

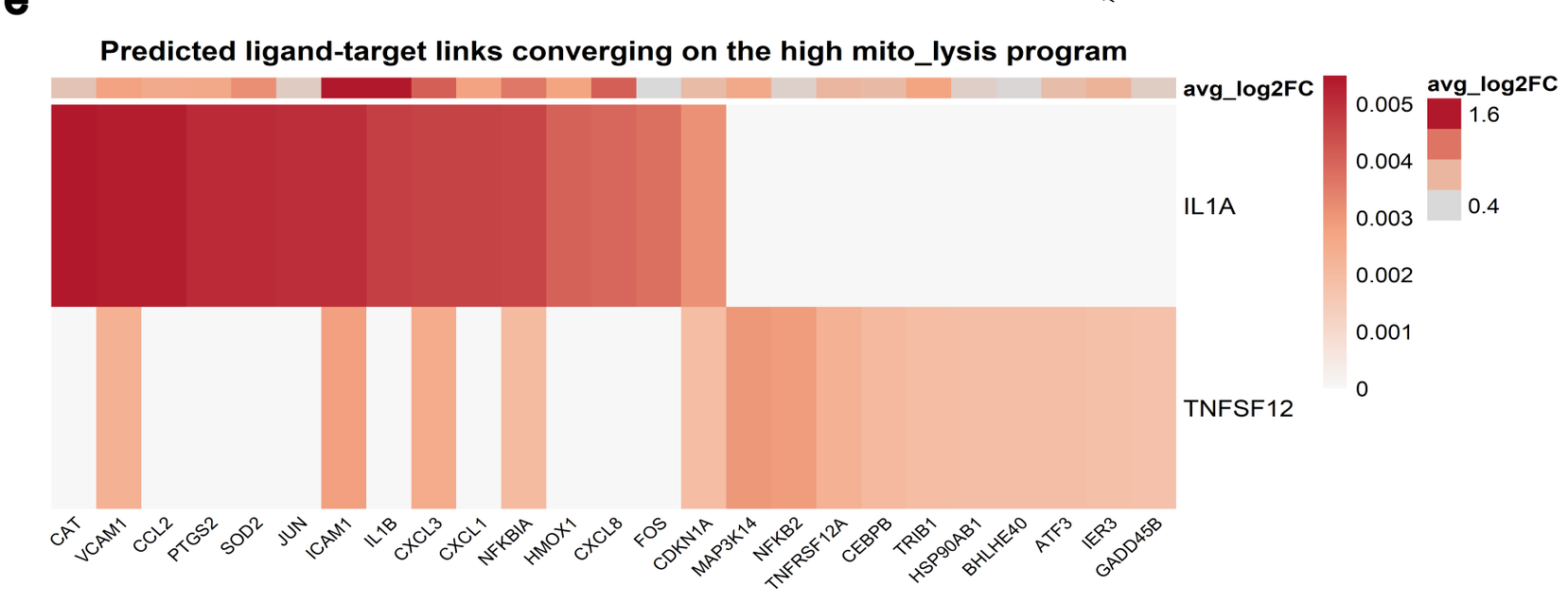

a
17_HMM_preds
Modified Expression
References (Cells)
Observations (Cells)
Genomic Region
reference
observed
b
inferCNV
Modified Expression
References (Cells)
Observations (Cells)
Genomic Region
reference
observed
c
inferCNV CNV burden score
Frequency
0
200
600
1000
0.00
0.01
0.02
0.03
0.04
0.05
0.06
mean(|x−1|)
d
UMAP_2
UMAP_1
diploid
ambiguous
aneuploid
e
inferCNV score
0.00
0.02
0.04
0.06
diploid
ambiguous
aneuploid
f
Proportion
100%
75%
50%
25%
0%
diploid
ambiguous
aneuploid
Tumor_like_epithelial
Epithelial_like_tumor_candidate
Epithelial_or_Tubular_candidate
Tubular_epithelial_like_PT
Tubular_epithelial_like_transport
CollectingDuct_intercalated_like

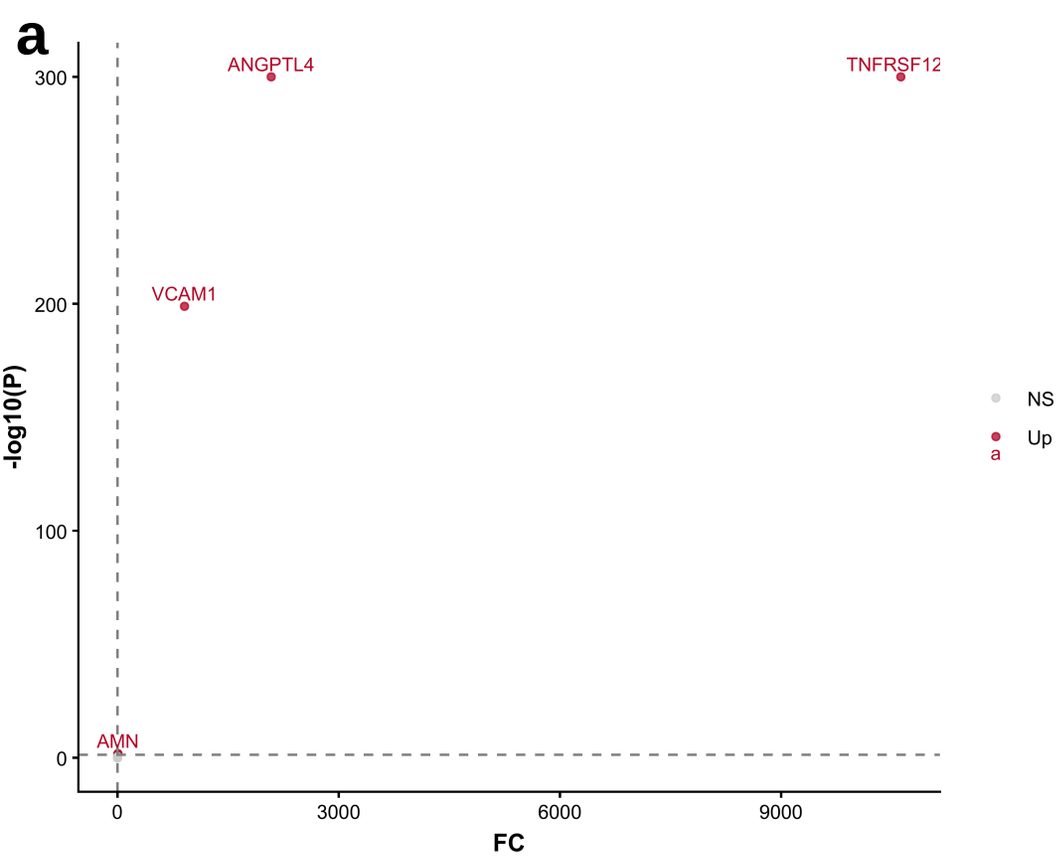

a
Innate
Starvation
mTORC2Actin
ROS
mito_lysis
Module score
Diploid
Malignant
b
UMAP_1
UMAP_2
Low
High
c
Representative genes
Identity
High
Low
Features
STAT1
ISG15
ATF4
DDIT3
EIF2AK3
HMOX1
SOD2
PRDX3
d
Functional network of the high mito_lysis-like state
response to tumor necrosis factor
intrinsic apoptotic signaling pathway
protein folding
response to unfolded protein
avg_log2FC
Gene count
e
KEGG network of the high mito_lysis-like state
TNF signaling pathway
NF-kappa B signaling pathway
IL-17 signaling pathway
Protein processing in endoplasmic reticulum
Gene count
avg_log2FC

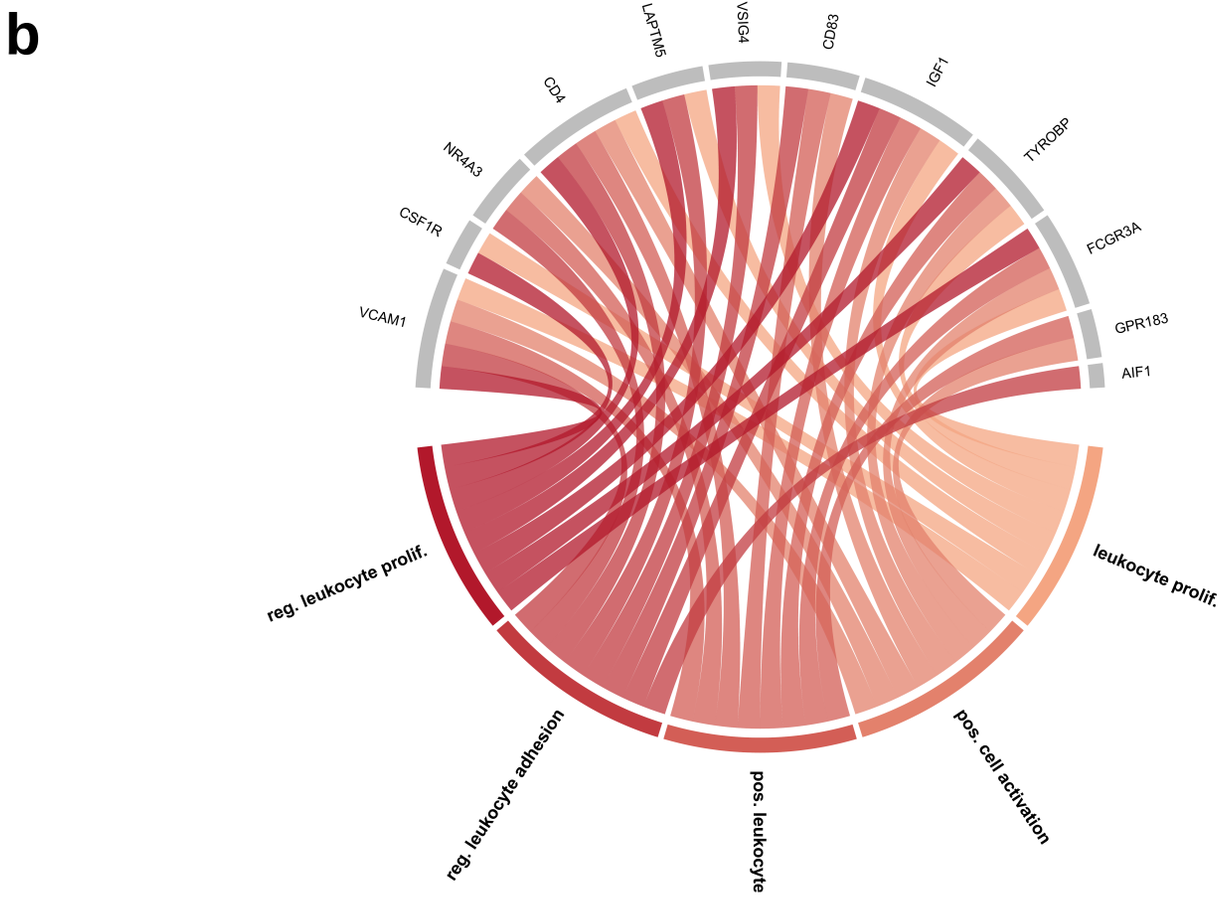

a
ICAM1
PTGS2
IL1RN
ANXA1
ITGAM
IL1A
TNFSF12
MMP9
CXCL3
HLA-A
CXCL16
APOE
0.1225
0.1250
0.1275
0.1300
0.1325
AUPR corrected
Key
Other

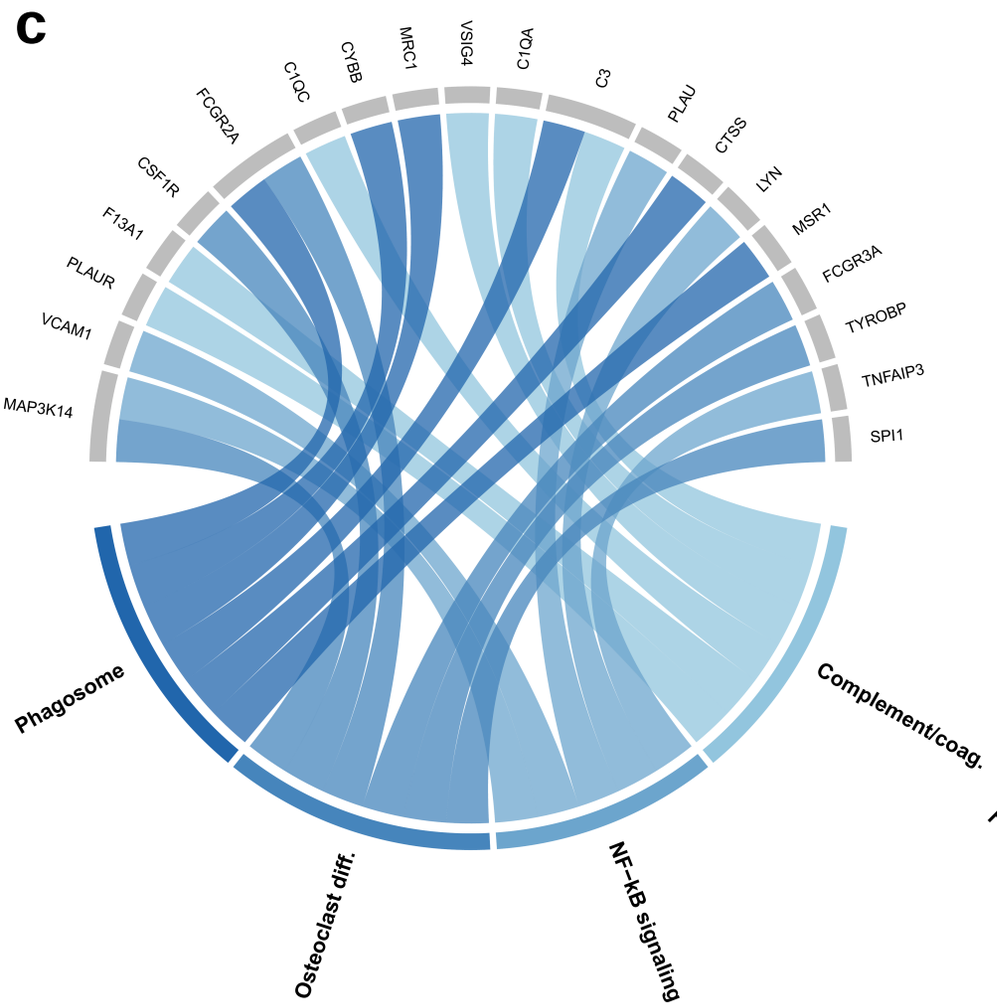

b
Tumor_like_epithelial
Tubular_epithelial_like_transport
Tubular_epithelial_like_PT
T_IL7R_memory_naive_like
T/NK_cytotoxic
Plasma_cell_like
Myeloid_like
Fibroblast_or_SMC_like
Epithelial_or_Tubular_candidate
Epithelial_like_tumor_candidate
Endothelial_like
Endothelial
CollectingDuct_Intercalated_like
CD8_T_cytotoxic_exhaustion_like
B_cell_like
TNFSF12
IL1A
CXCL2
PTGS2
IL1RN
2.0
1.5
1.0
0.5
0.0
0%
20%
40%
60%

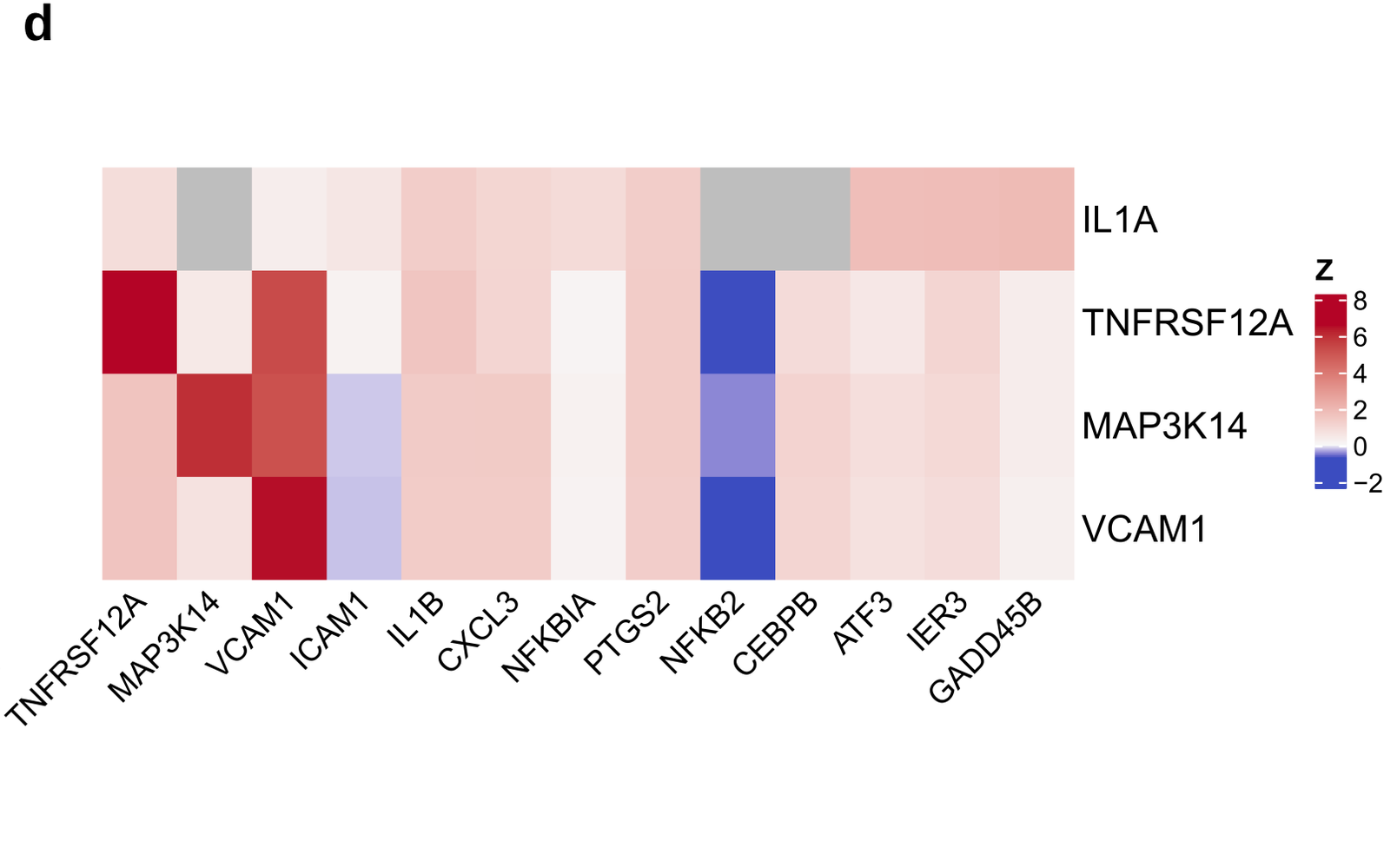

c
High
Low
20%
40%
60%
2.0
1.6
1.2
0.8
TNFRSF12A
IL1R1
IL1RAP
CXCR1
CXCR2
PTGER2
PTGER4
d
TNFSF12
IL1A
1.6
1.2
0.8
0.4
0.002
0.003
0.004
0.005
FOS
BHLHE40
NFKB2
HSP90AB1
GADD45B
JUN
CAT
ATF3
CDKN1A
CEBPB
TNFRSF12A
IER3
CCL2
MAP3K14
PTGS2
HMOX1
TRIB1
VCAM1
CXCL1
SOD2
NFKBIA
CXCL3
CXCL8
IL1B
ICAM1

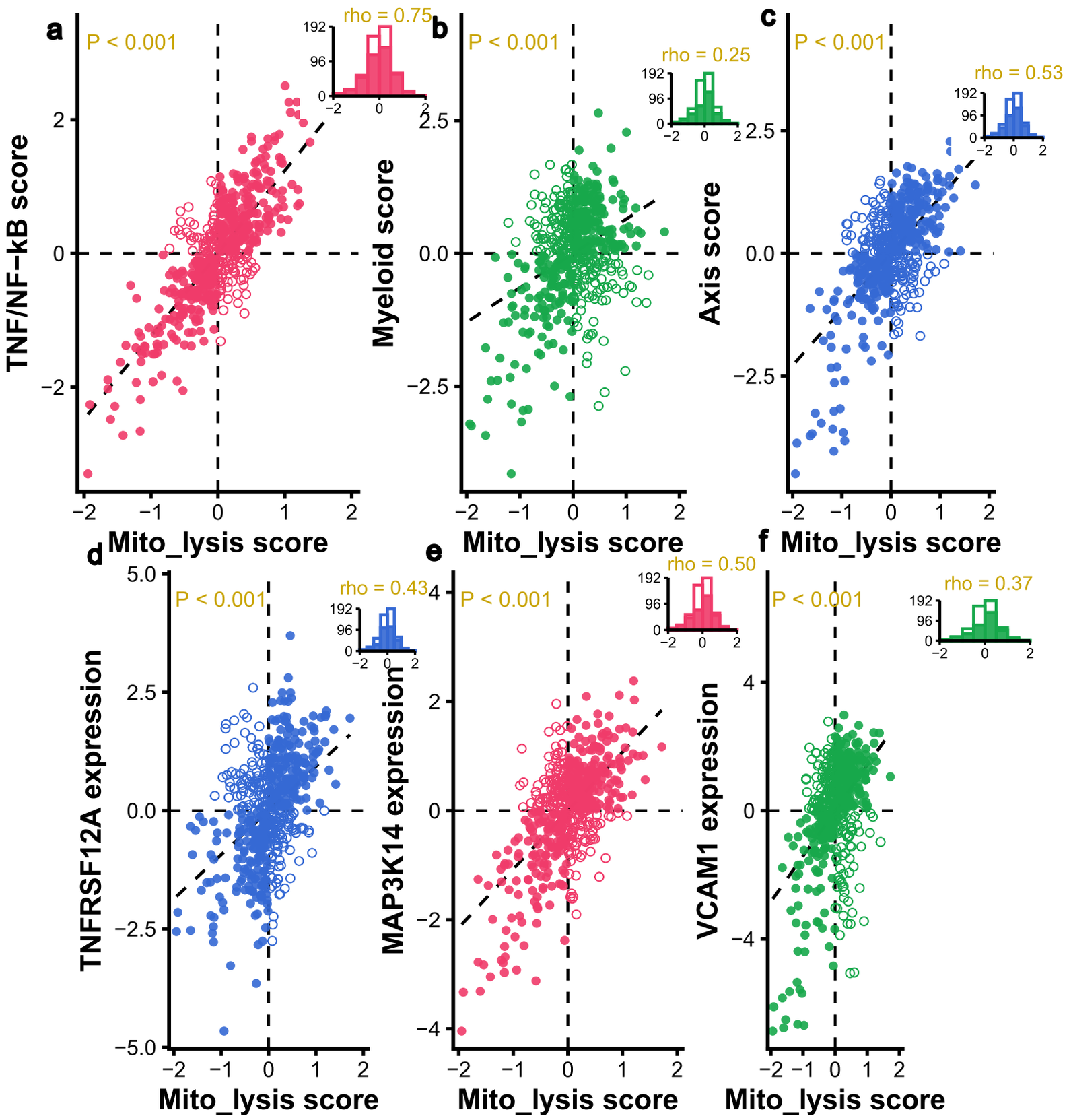

e
Predicted ligand-target links converging on the high mito_lysis program
avg_log2FC
IL1A
TNFSF12
0.005
0.004
0.003
0.002
0.001
0
avg_log2FC
1.6
0.4
CAT
VCAM1
CCL2
PTGS2
SOD2
JUN
ICAM1
IL1B
CXCL3
CXCL1
NFKBIA
HMOX1
CXCL8
FOS
CDKN1A
MAP3K14
NFKB2
TNFRSF12A
CEBPB
TRIB1
HSP90AB1
BHLHE40
ATF3
IER3
GADD45B

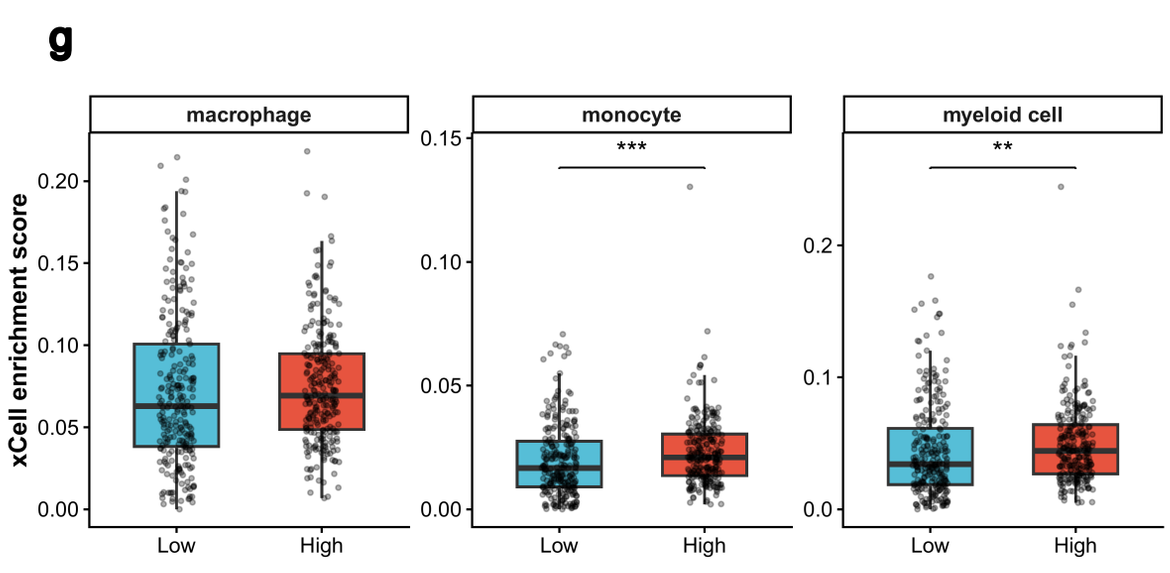

a
ANGPTL4
TNFRSF12
VCAM1
AMN
300
200
100
0
0
3000
6000
9000
FC
-log10(P)
NS
Up
a

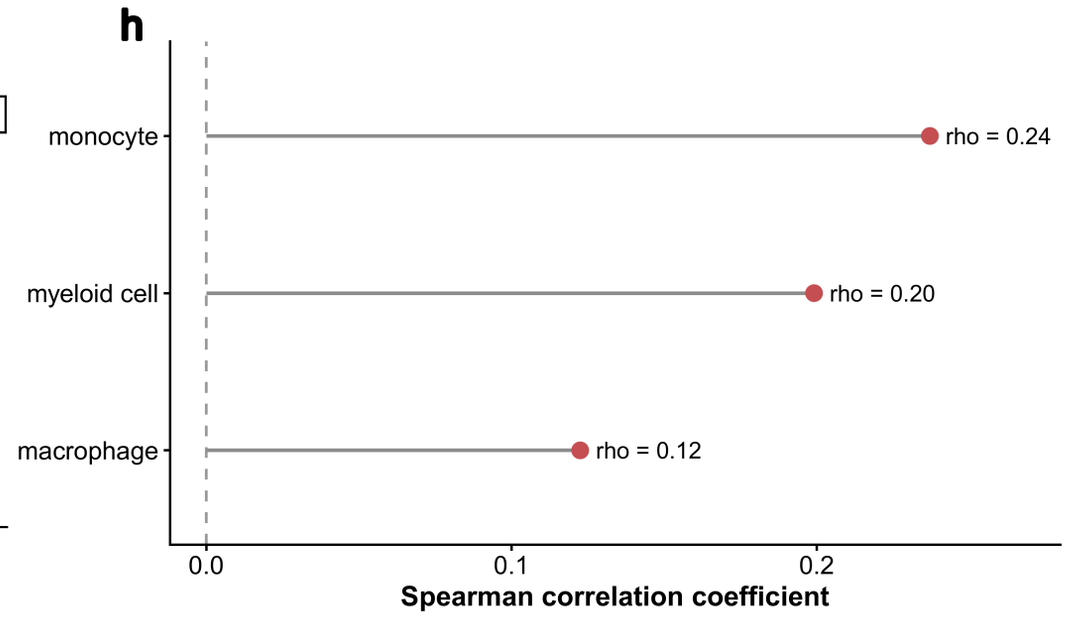

b
LAPTM5
VSIG4
CD83
IGF1
TYROBP
FCGR3A
GPR183
AIF1
CD4
NR4A3
CSF1R
VCAM1
reg. leukocyte prolif.
reg. leukocyte adhesion
pos. leukocyte
pos. cell activation
leukocyte prolif.

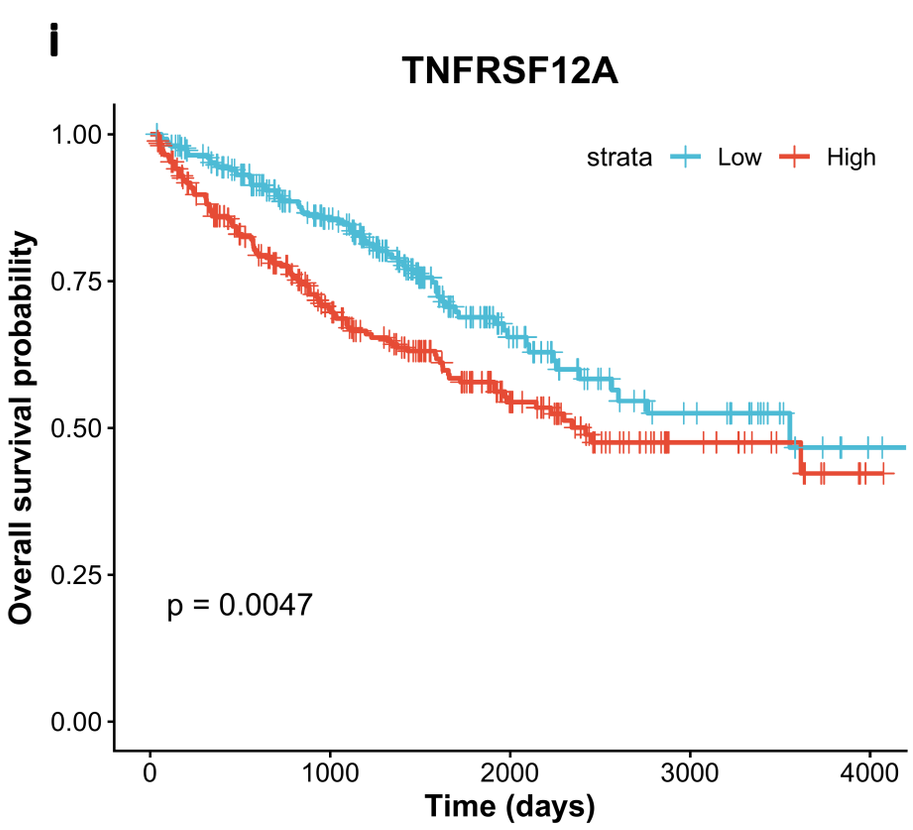

c
FCGR2A
C1QC
CYBB
MRC1
VSIG4
C1QA
C3
PLAU
CTSS
LYN
MSR1
FCGR3A
TYROBP
TNFAIP3
SPI1
CSF1R
F13A1
PLAUR
VCAM1
MAP3K14
Phagosome
Osteoclast diff.
NF−kB signaling
Complement/coag.

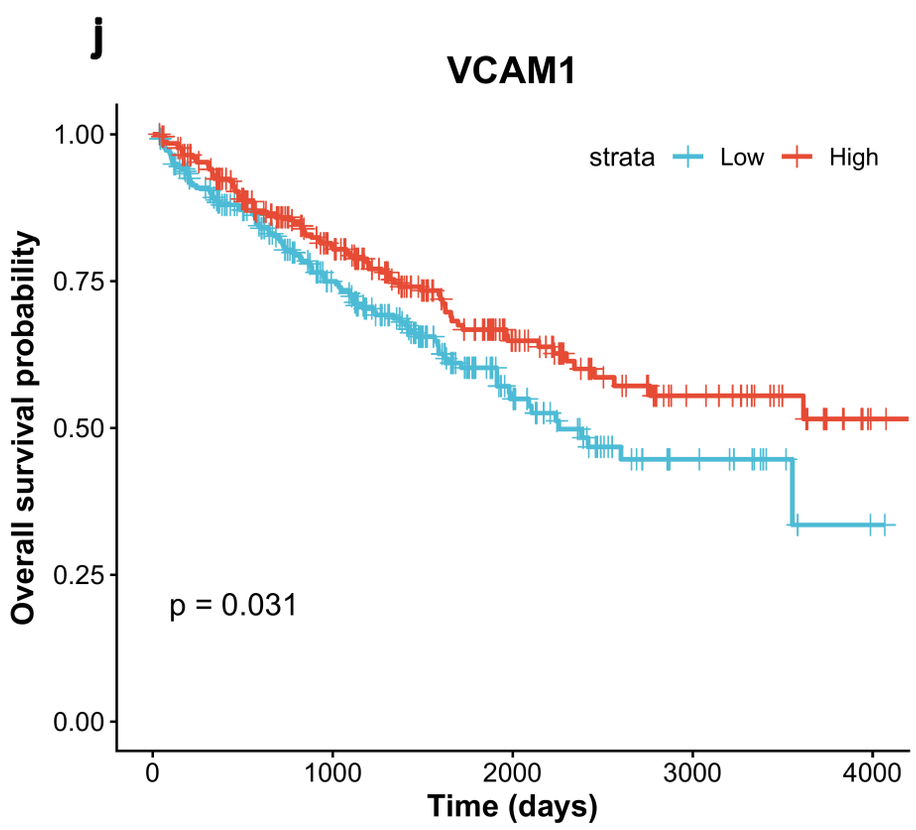

d
IL1A
TNFRSF12A
MAP3K14
VCAM1
z
8
6
4
2
0
−2
TNFRSF12A
MAP3K14
VCAM1
ICAM1
IL1B
CXCL3
NFKBIA
PTGS2
NFKB2
CEBPB
ATF3
IER3
GADD45B

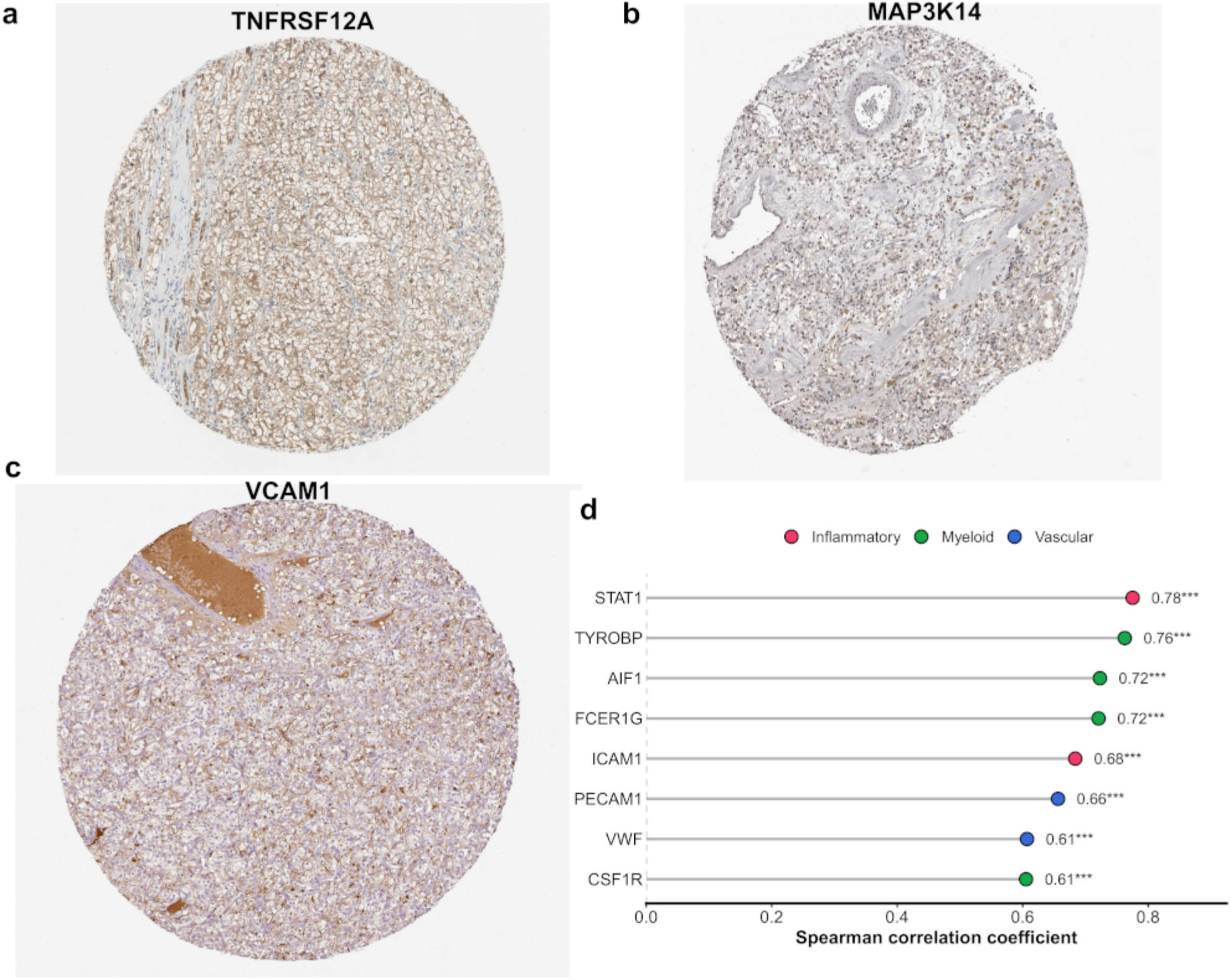

a
P < 0.001
rho = 0.75
TNF/NF−kB score
b
P < 0.001
rho = 0.25
Myeloid score
c
P < 0.001
rho = 0.53
Axis score
d
Mito_lysis score
P < 0.001
rho = 0.43
TNFRSF12A expression
e
Mito_lysis score
P < 0.001
rho = 0.50
MAP3K14 expression
f
Mito_lysis score
P < 0.001
rho = 0.37
VCAM1 expression
Mito_lysis score

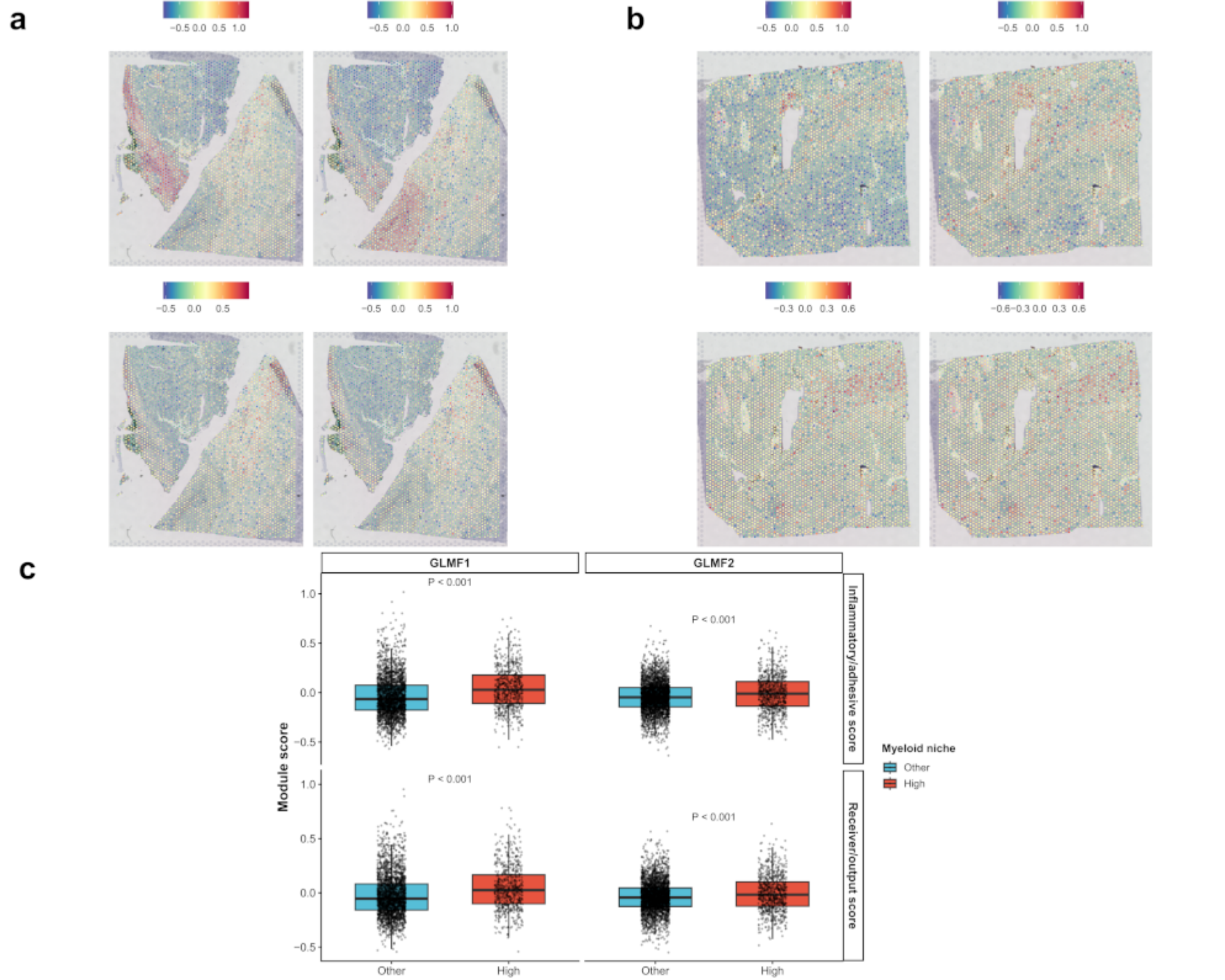

g
macrophage
monocyte
myeloid cell
***
**
xCell enrichment score
Low
High


h
monocyte
myeloid cell
macrophage
rho = 0.24
rho = 0.20
rho = 0.12
Spearman correlation coefficient


i
TNFRSF12A
strata Low High
Overall survival probability
p = 0.0047
Time (days)
Number at risk
257 168 56 23 2
258 137 61 17 1
0 1000 2000 3000 4000
Time (days)


j
VCAM1
strata Low High
Overall survival probability
p = 0.031
Time (days)
Number at risk
257 147 50 14 1
258 158 67 26 2
0 1000 2000 3000 4000
Time (days)


a
TNFRSF12A
b
MAP3K14
c
VCAM1
d
Inflammatory
Myeloid
Vascular
STAT1
TYROBP
AIF1
FCER1G
ICAM1
PECAM1
VWF
CSF1R
0.78***
0.76***
0.72***
0.72***
0.68***
0.66***
0.61***
0.61***
0.0
0.2
0.4
0.6
0.8
Spearman correlation coefficient


a
b
c
−0.5 0.0 0.5 1.0
−0.5 0.0 0.5
−0.3 0.0 0.3 0.6
−0.6 −0.3 0.0 0.3 0.6
GLMF1
GLMF2
P < 0.001
Inflammatory/adhesive score
Receiver/output score
Module score
1.0
0.5
0.0
−0.5
Other
High
Myeloid niche