Supplementary Information

Single-cell RNA-sequencing of peripheral blood mononuclear cells reveals widespread, context-specific gene expression regulation upon pathogenic exposure.

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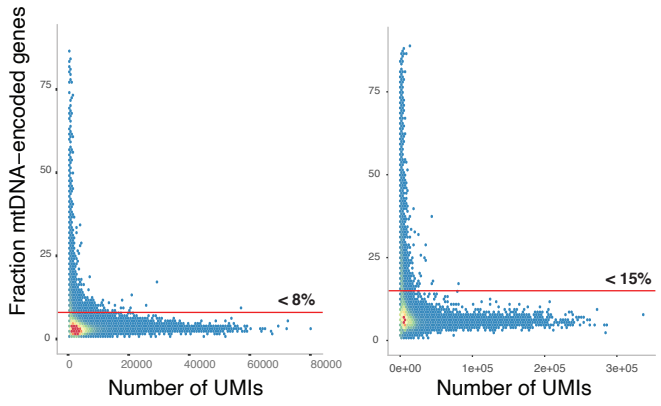
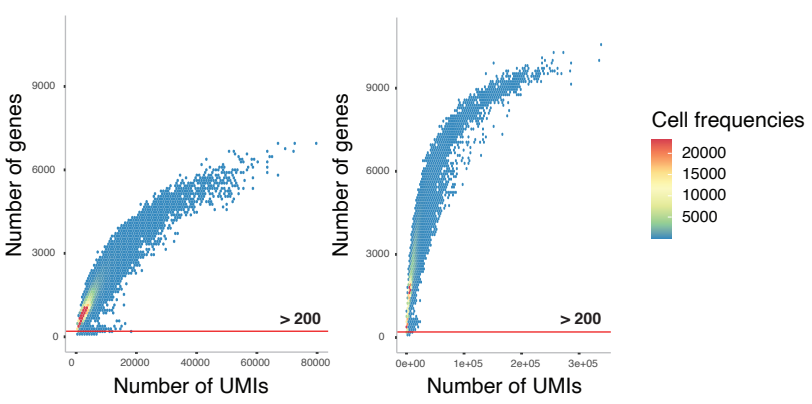
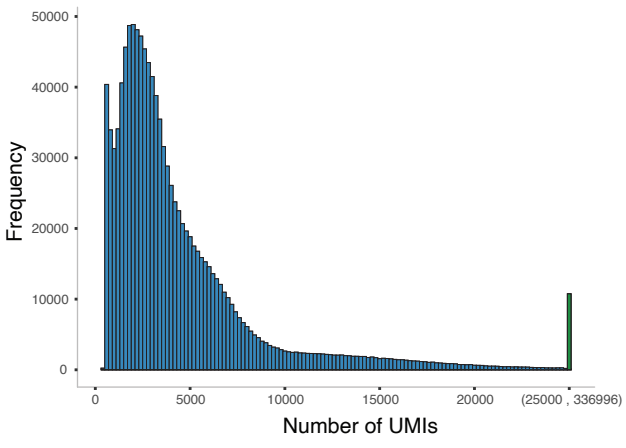
a


V2
V3
Fraction mtDNA−encoded genes
< 8%
< 15%
Number of UMIs
Number of UMIs

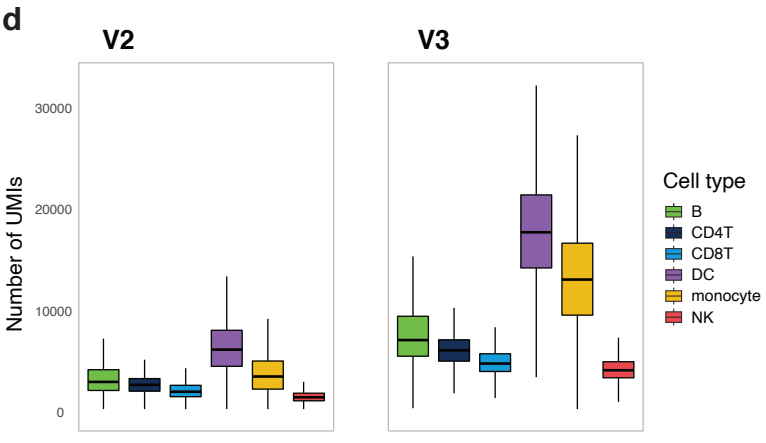
b


V2
V3
Number of genes
> 200
> 200
Number of UMIs
Number of UMIs
Cell frequencies
20000
15000
10000
5000

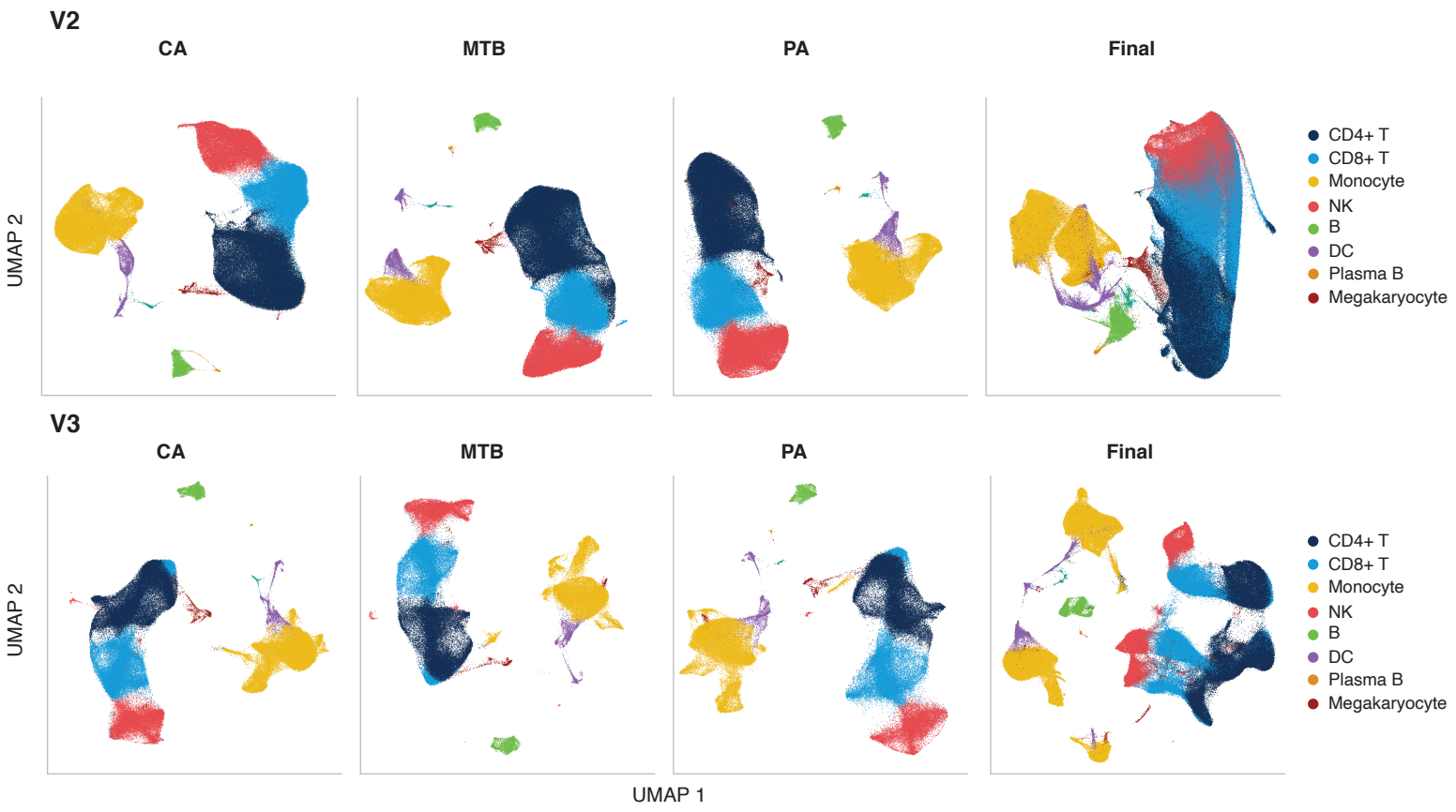
c


Frequency
Number of UMIs
(25000 , 336996)

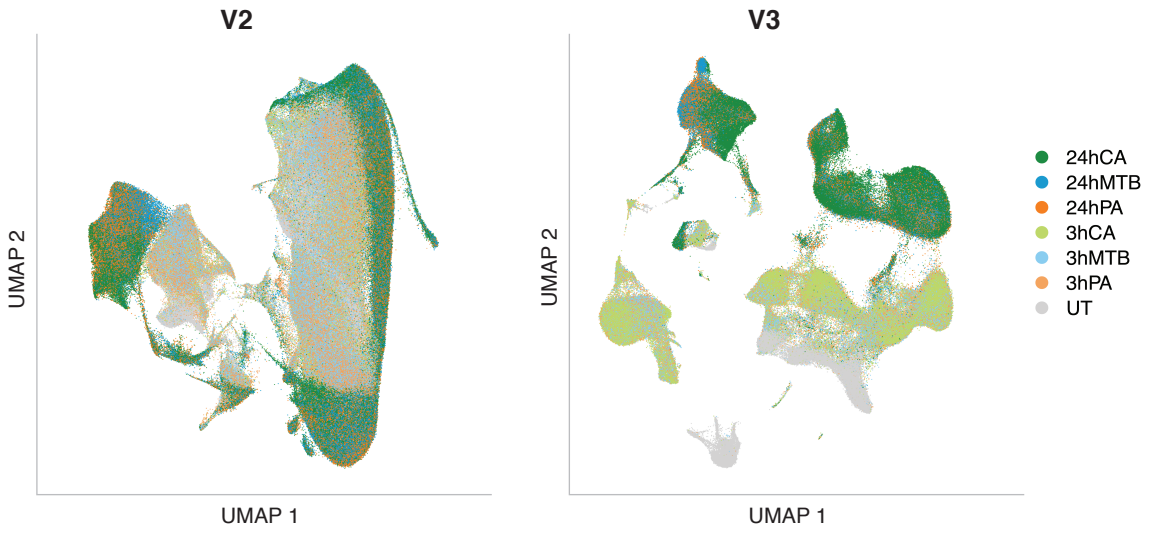
d


V2
V3
Number of UMIs
Cell type
B
CD4T
CD8T
DC
monocyte
NK

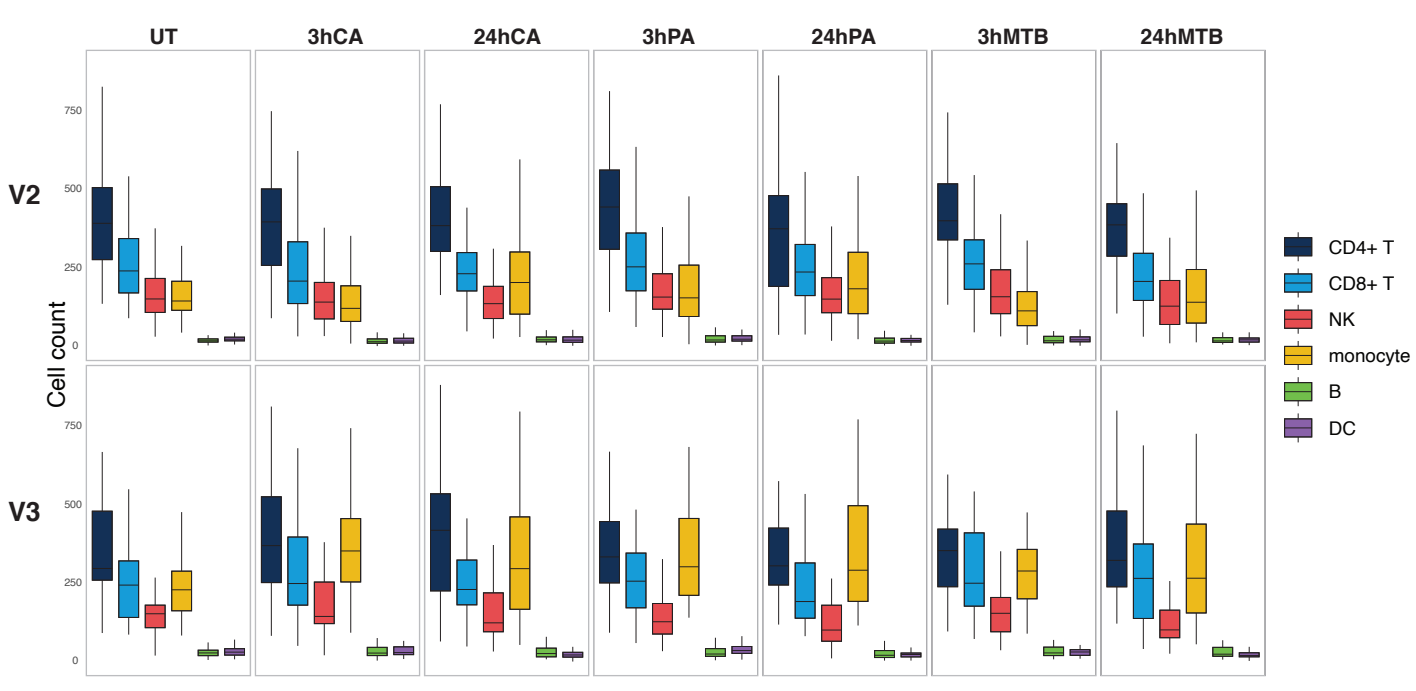
e


V2
CA
MTB
PA
Final
V3
UMAP 2
UMAP 1
CD4+ T
CD8+ T
Monocyte
NK
B
DC
Plasma B
Megakaryocyte

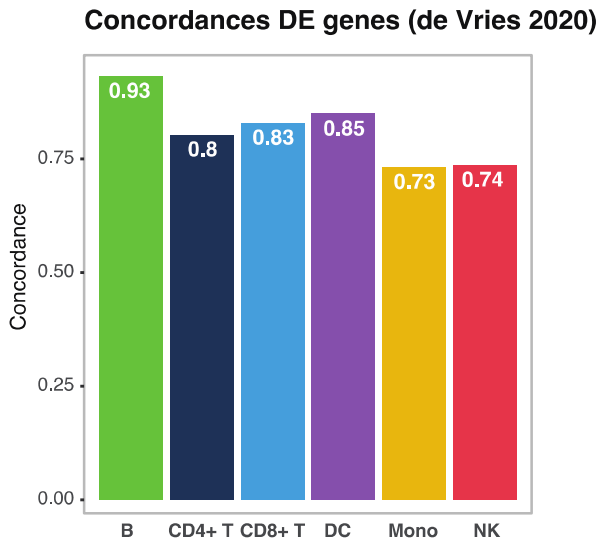
f


V2
V3
UMAP 2
UMAP 1
24hCA
24hMTB
24hPA
3hCA
3hMTB
3hPA
UT

g


UT
3hCA
24hCA
3hPA
24hPA
3hMTB
24hMTB
V2
V3
Cell count
CD4+ T
CD8+ T
NK
monocyte
B
DC

Supplementary Figure 1. Dataset characteristics
a. *The proportion of mitochondrial genes per cell (y-axis) against the number of unique molecular identifiers (UMIs) per cell (x-axis), split per scRNA-seq library chemistry (v2 or v3). Cell density is indicated by color in each graph, going from blue to red for low to high cell numbers, respectively. The red line indicates the QC threshold used for removing cells.* ***b.*** *Number of expressed genes versus number of UMIs per cell. Cell density is indicated by color in each graph, going from blue to red for low to high cell numbers, respectively. The red line indicates the QC threshold used for removing cells with a low number of expressed genes.* ***c.*** *Distribution of the number of UMIs observed per cell (combining v2 and v3 chemistry). Note that the rightest bin (green) is larger than the other ones.* ***d.*** *Boxplot (showing median, 25th and 75th percentile, and 1.5 x the interquartile range) of the observed number of UMIs per cell, split by cell type and library chemistry.* ***e.*** *The UMAP plots per stimulation and library chemistry. Each dot represents a single-cell and the color indicates the assigned cell type.* ***f.*** *The integrated UMAP per chemistry where all cells are combined.* ***g.*** *Boxplots (showing median, 25th and 75th percentile, and 1.5 x the interquartile range) representing the cell type proportions per individual, split by stimulation-timepoint combination and chemistry. Colors represent the cell types. The number of individuals and cells included in each analysis can be found in the Source Data file.*



Supplementary Figure 2. Concordance differential expression results with literature
Bar plot showing the concordance of the identified differentially expressed (DE) genes in this study (as shown in ***Supplementary Data 5****) with those identified in de Vries et al. 2020. Each bar represents a different cell type. The number of individuals and cells included in each analysis can be found in the Source Data file.*

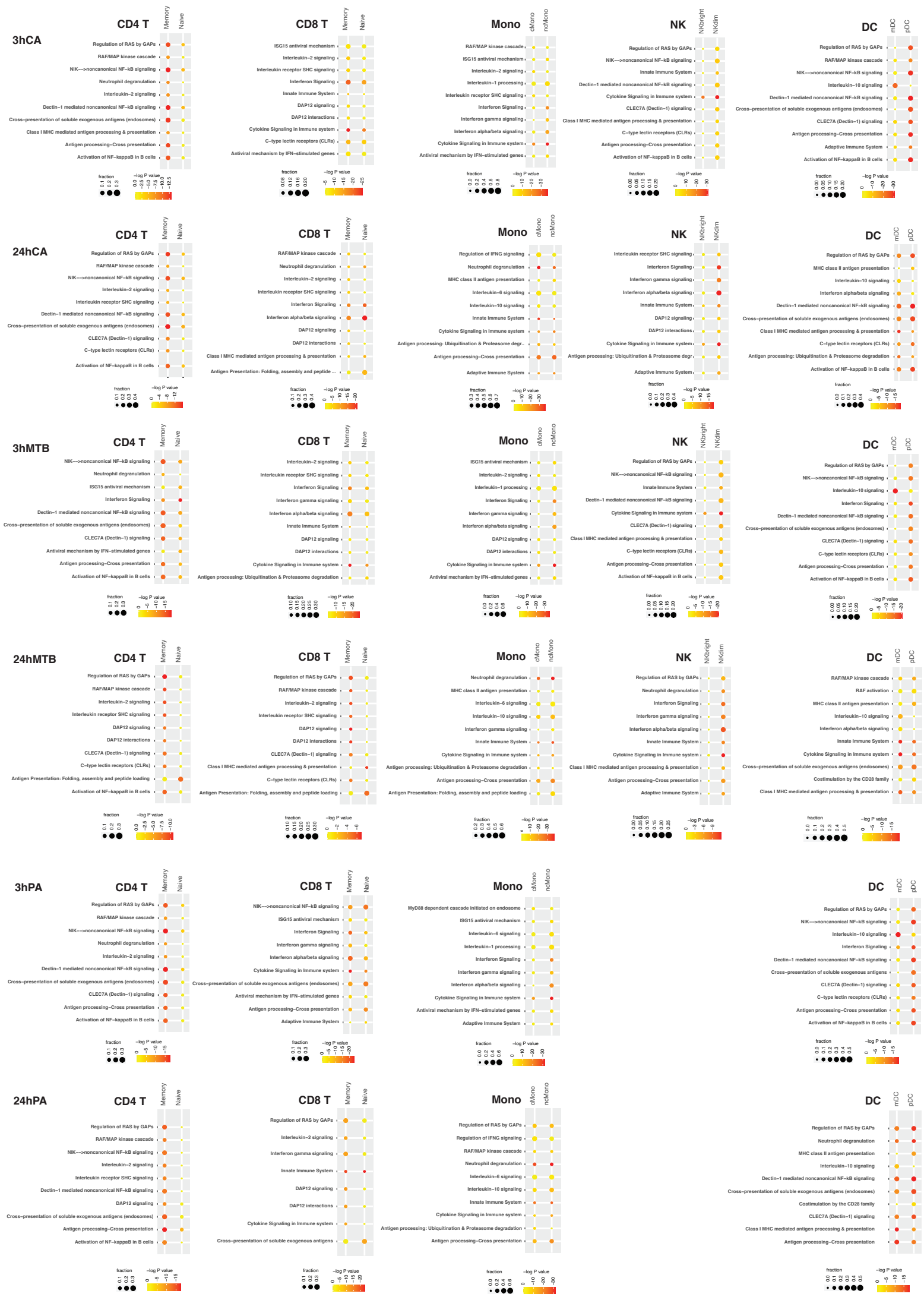
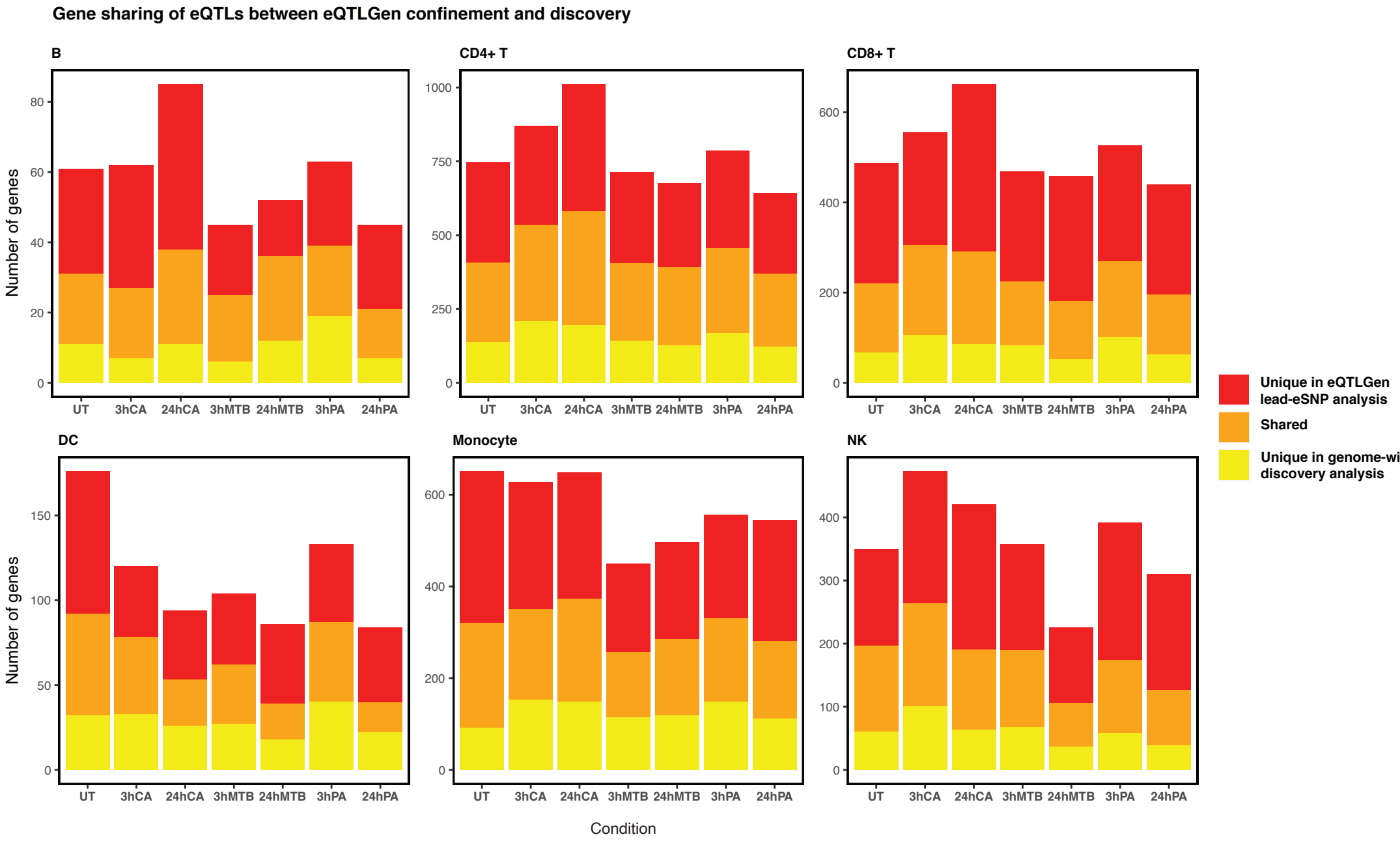

3hCA
CD4 T
Memory
Naive
Regulation of RAS by GAPs
RAF/MAP kinase cascade
NIK−>noncanonical NF−kB signaling
Neutrophil degranulation
Interleukin−2 signaling
Dectin−1 mediated noncanonical NF−kB signaling
Cross−presentation of soluble exogenous antigens (endosomes)
Class I MHC mediated antigen processing & presentation
Antigen processing−Cross presentation
Activation of NF−kappaB in B cells
CD8 T
Memory
Naive
ISG15 antiviral mechanism
Interleukin−2 signaling
Interleukin receptor SHC signaling
Interferon Signaling
Innate Immune System
DAP12 signaling
DAP12 interactions
Cytokine Signaling in Immune system
C−type lectin receptors (CLRs)
Antiviral mechanism by IFN−stimulated genes
Mono
cMono
ncMono
RAF/MAP kinase cascade
ISG15 antiviral mechanism
Interleukin−2 signaling
Interleukin−1 processing
Interleukin receptor SHC signaling
Interferon Signaling
Interferon gamma signaling
Interferon alpha/beta signaling
Cytokine Signaling in Immune system
Antiviral mechanism by IFN−stimulated genes
NK
NKbright
NKdim
Regulation of RAS by GAPs
NIK−>noncanonical NF−kB signaling
Innate Immune System
Dectin−1 mediated noncanonical NF−kB signaling
Cytokine Signaling in Immune system
CLEC7A (Dectin−1) signaling
Class I MHC mediated antigen processing & presentation
C−type lectin receptors (CLRs)
Antigen processing−Cross presentation
Activation of NF−kappaB in B cells
DC
mDC
pDC
Regulation of RAS by GAPs
RAF/MAP kinase cascade
NIK−>noncanonical NF−kB signaling
Interleukin−10 signaling
Dectin−1 mediated noncanonical NF−kB signaling
Cross−presentation of soluble exogenous antigens (endosomes)
CLEC7A (Dectin−1) signaling
Antigen processing−Cross presentation
Adaptive Immune System
Activation of NF−kappaB in B cells
fraction
−log P value
24hCA
CD4 T
Memory
Naive
Regulation of RAS by GAPs
RAF/MAP kinase cascade
NIK−>noncanonical NF−kB signaling
Interleukin−2 signaling
Interleukin receptor SHC signaling
Dectin−1 mediated noncanonical NF−kB signaling
Cross−presentation of soluble exogenous antigens (endosomes)
CLEC7A (Dectin−1) signaling
C−type lectin receptors (CLRs)
Activation of NF−kappaB in B cells
CD8 T
Memory
Naive
RAF/MAP kinase cascade
Neutrophil degranulation
Interleukin−2 signaling
Interleukin receptor SHC signaling
Interferon Signaling
Interferon alpha/beta signaling
DAP12 signaling
DAP12 interactions
Class I MHC mediated antigen processing & presentation
Antigen Presentation: Folding, assembly and peptide ...
Mono
cMono
ncMono
Regulation of IFNG signaling
Neutrophil degranulation
MHC class II antigen presentation
Interleukin−6 signaling
Interleukin−10 signaling
Innate Immune System
Cytokine Signaling in Immune system
Antigen processing: Ubiquitination & Proteasome degr...
Antigen processing−Cross presentation
Adaptive Immune System
NK
NKbright
NKdim
Interleukin receptor SHC signaling
Interferon Signaling
Interferon gamma signaling
Interferon alpha/beta signaling
Innate Immune System
DAP12 signaling
DAP12 interactions
Cytokine Signaling in Immune system
Antigen processing: Ubiquitination & Proteasome degr
Adaptive Immune System
DC
mDC
pDC
Regulation of RAS by GAPs
MHC class II antigen presentation
Interleukin−10 signaling
Interferon alpha/beta signaling
Dectin−1 mediated noncanonical NF−kB signaling
Cross−presentation of soluble exogenous antigens (endosomes)
Class I MHC mediated antigen processing & presentation
C−type lectin receptors (CLRs)
Antigen processing: Ubiquitination & Proteasome degradation
Activation of NF−kappaB in B cells
3hMTB
CD4 T
Memory
Naive
NIK−>noncanonical NF−kB signaling
Neutrophil degranulation
ISG15 antiviral mechanism
Interferon Signaling
Dectin−1 mediated noncanonical NF−kB signaling
Cross−presentation of soluble exogenous antigens (endosomes)
CLEC7A (Dectin−1) signaling
Antiviral mechanism by IFN−stimulated genes
Antigen processing−Cross presentation
Activation of NF−kappaB in B cells
CD8 T
Memory
Naive
Interleukin−2 signaling
Interleukin receptor SHC signaling
Interferon Signaling
Interferon gamma signaling
Interferon alpha/beta signaling
Innate Immune System
DAP12 signaling
DAP12 interactions
Cytokine Signaling in Immune system
Antigen processing: Ubiquitination & Proteasome degradation
Mono
cMono
ncMono
ISG15 antiviral mechanism
Interleukin−2 signaling
Interleukin−1 processing
Interferon Signaling
Interferon gamma signaling
Interferon alpha/beta signaling
DAP12 signaling
DAP12 interactions
Cytokine Signaling in Immune system
Antiviral mechanism by IFN−stimulated genes
NK
NKbright
NKdim
Regulation of RAS by GAPs
NIK−>noncanonical NF−kB signaling
Innate Immune System
Dectin−1 mediated noncanonical NF−kB signaling
Cytokine Signaling in Immune system
CLEC7A (Dectin−1) signaling
Class I MHC mediated antigen processing & presentation
C−type lectin receptors (CLRs)
Antigen processing−Cross presentation
Activation of NF−kappaB in B cells
DC
mDC
pDC
Regulation of RAS by GAPs
NIK−>noncanonical NF−kB signaling
Interleukin−10 signaling
Interferon Signaling
Dectin−1 mediated noncanonical NF−kB signaling
Cross−presentation of soluble exogenous antigens (endosomes)
CLEC7A (Dectin−1) signaling
C−type lectin receptors (CLRs)
Antigen processing−Cross presentation
Activation of NF−kappaB in B cells
24hMTB
CD4 T
Memory
Naive
Regulation of RAS by GAPs
RAF/MAP kinase cascade
Interleukin−2 signaling
Interleukin receptor SHC signaling
DAP12 signaling
DAP12 interactions
CLEC7A (Dectin−1) signaling
C−type lectin receptors (CLRs)
Antigen Presentation: Folding, assembly and peptide loading
Activation of NF−kappaB in B cells
CD8 T
Memory
Naive
Regulation of RAS by GAPs
RAF/MAP kinase cascade
Interleukin−2 signaling
Interleukin receptor SHC signaling
DAP12 signaling
DAP12 interactions
CLEC7A (Dectin−1) signaling
Class I MHC mediated antigen processing & presentation
C−type lectin receptors (CLRs)
Antigen Presentation: Folding, assembly and peptide loading
Mono
cMono
ncMono
Neutrophil degranulation
MHC class II antigen presentation
Interleukin−6 signaling
Interleukin−10 signaling
Interferon gamma signaling
Innate Immune System
Cytokine Signaling in Immune system
Antigen processing: Ubiquitination & Proteasome degradation
Antigen processing−Cross presentation
Antigen Presentation: Folding, assembly and peptide loading
NK
NKbright
NKdim
Regulation of RAS by GAPs
Neutrophil degranulation
Interferon Signaling
Interferon gamma signaling
Interferon alpha/beta signaling
Innate Immune System
Cytokine Signaling in Immune system
Class I MHC mediated antigen processing & presentation
Antigen processing−Cross presentation
Adaptive Immune System
DC
mDC
pDC
RAF/MAP kinase cascade
RAF activation
MHC class II antigen presentation
Interleukin−10 signaling
Interferon alpha/beta signaling
Innate Immune System
Cytokine Signaling in Immune system
Cross−presentation of soluble exogenous antigens (endosomes)
Costimulation by the CD28 family
Class I MHC mediated antigen processing & presentation
3hPA
CD4 T
Memory
Naive
Regulation of RAS by GAPs
RAF/MAP kinase cascade
NIK−>noncanonical NF−kB signaling
Neutrophil degranulation
Interleukin−2 signaling
Dectin−1 mediated noncanonical NF−kB signaling
Cross−presentation of soluble exogenous antigens (endosomes)
CLEC7A (Dectin−1) signaling
Antigen processing−Cross presentation
Activation of NF−kappaB in B cells
CD8 T
Memory
Naive
NIK−>noncanonical NF−kB signaling
ISG15 antiviral mechanism
Interferon Signaling
Interferon gamma signaling
Interferon alpha/beta signaling
Cytokine Signaling in Immune system
Cross−presentation of soluble exogenous antigens (endosomes)
Antiviral mechanism by IFN−stimulated genes
Antigen processing−Cross presentation
Adaptive Immune System
Mono
cMono
ncMono
MyD88 dependent cascade initiated on endosome
ISG15 antiviral mechanism
Interleukin−6 signaling
Interleukin−1 processing
Interferon Signaling
Interferon gamma signaling
Interferon alpha/beta signaling
Cytokine Signaling in Immune system
Antiviral mechanism by IFN−stimulated genes
Adaptive Immune System
DC
mDC
pDC
Regulation of RAS by GAPs
NIK−>noncanonical NF−kB signaling
Interleukin−10 signaling
Interferon Signaling
Dectin−1 mediated noncanonical NF−kB signaling
Cross−presentation of soluble exogenous antigens
CLEC7A (Dectin−1) signaling
C−type lectin receptors (CLRs)
Antigen processing−Cross presentation
Activation of NF−kappaB in B cells
24hPA
CD4 T
Memory
Naive
Regulation of RAS by GAPs
RAF/MAP kinase cascade
NIK−>noncanonical NF−kB signaling
Interleukin−2 signaling
Interleukin receptor SHC signaling
Dectin−1 mediated noncanonical NF−kB signaling
DAP12 signaling
Cross−presentation of soluble exogenous antigens (endosomes)
Antigen processing−Cross presentation
Activation of NF−kappaB in B cells
CD8 T
Memory
Naive
Regulation of RAS by GAPs
Interleukin−2 signaling
Interferon gamma signaling
Innate Immune System
DAP12 signaling
DAP12 interactions
Cytokine Signaling in Immune system
Cross−presentation of soluble exogenous antigens
Mono
cMono
ncMono
Regulation of RAS by GAPs
Regulation of IFNG signaling
RAF/MAP kinase cascade
Neutrophil degranulation
Interleukin−6 signaling
Interleukin−10 signaling
Innate Immune System
Cytokine Signaling in Immune system
Antigen processing: Ubiquitination & Proteasome degradation
Antigen processing−Cross presentation
DC
mDC
pDC
Regulation of RAS by GAPs
Neutrophil degranulation
MHC class II antigen presentation
Interleukin−10 signaling
Dectin−1 mediated noncanonical NF−kB signaling
Cross−presentation of soluble exogenous antigens (endosomes)
Costimulation by the CD28 family
CLEC7A (Dectin−1) signaling
Class I MHC mediated antigen processing & presentation
Antigen processing−Cross presentation
fraction
−log P value

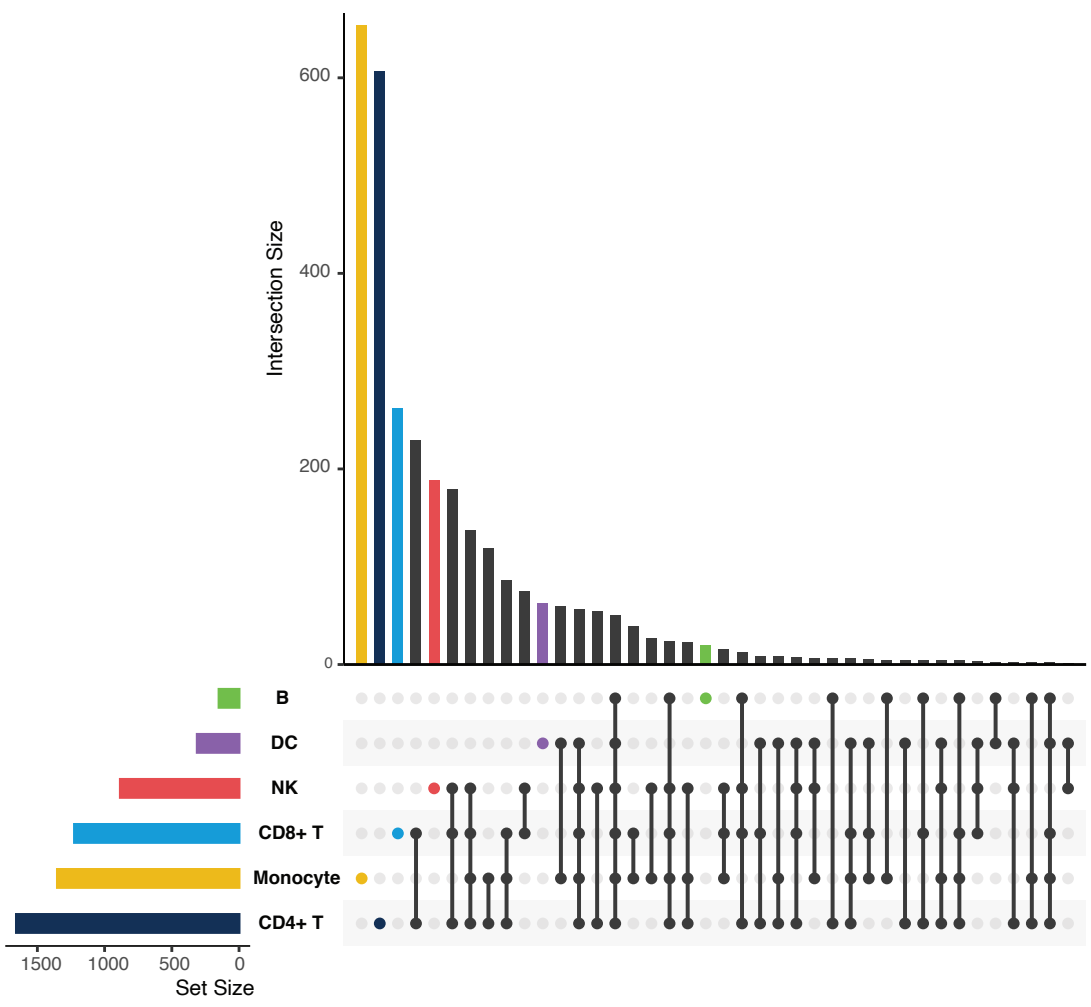
Figure S3. Most differentially enriched pathways in the subcell types

Dotplots of the 10 most enriched pathways with the largest difference in significance between both subcell types, split by subcell type and pathogen stimulation (a complete overview of the enriched pathways can be found in ***Table S6****). When subcell type classification provided too few cells or could not be confidently made, no results are shown for that pathogen stimulation. The color indicates the log10 transformed FDR p-value, the size of the dot represents the fraction of DE genes that were found in the total list of genes for the pathway. The number of individuals and cells included in each analysis can be found in the Source Data file.*

a


Gene sharing of eQTLs between eQTLGen confinement and discovery
B
CD4+ T
CD8+ T
DC
Monocyte
NK
Number of genes
UT
3hCA
24hCA
3hMTB
24hMTB
3hPA
24hPA
Condition
Unique in eQTLGen lead-eSNP analysis
Shared
Unique in genome-wide discovery analysis

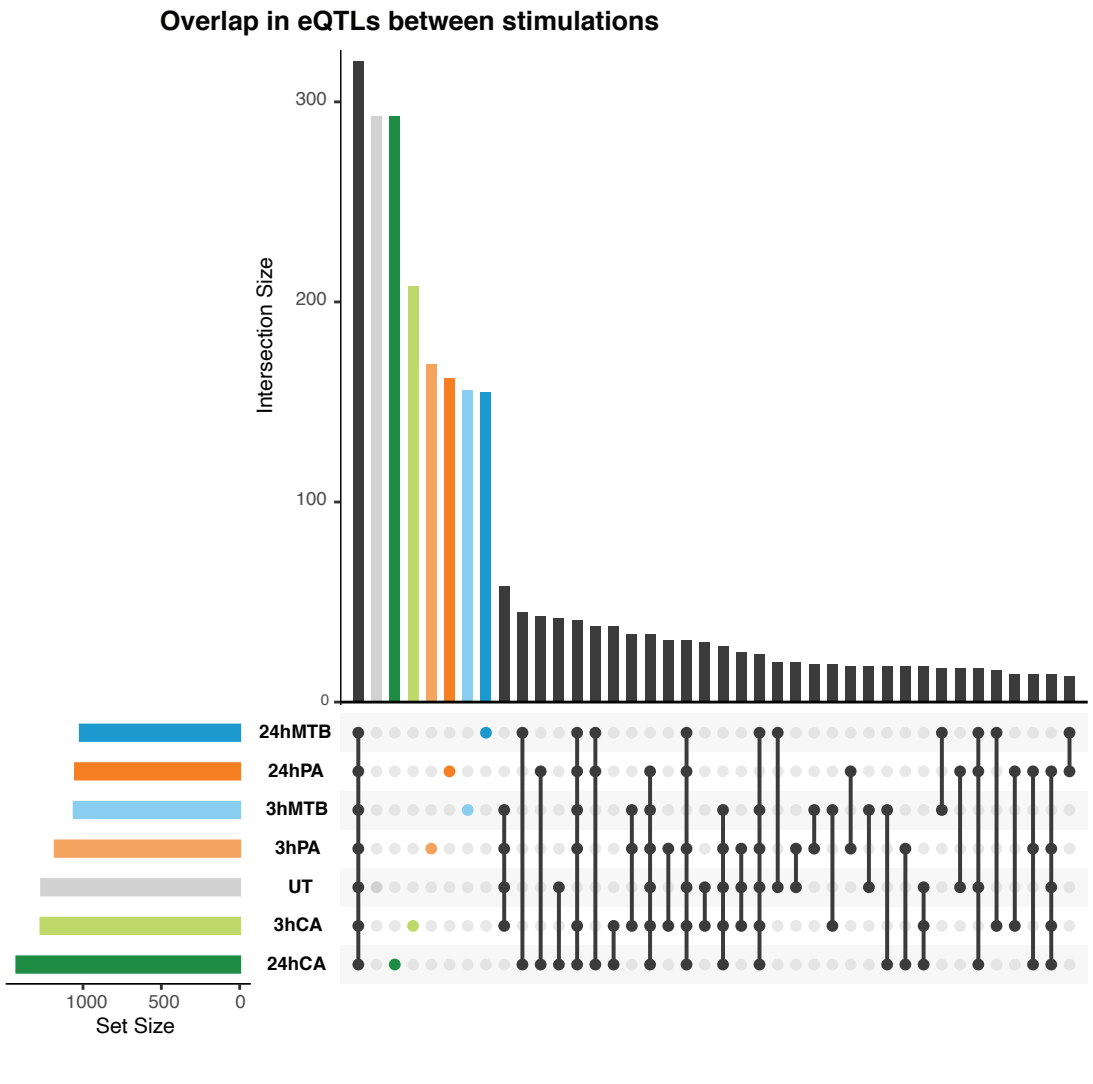
b


Overlap in eQTLs between cell types
Intersection Size
Set Size
B
DC
NK
CD8+ T
Monocyte
CD4+ T

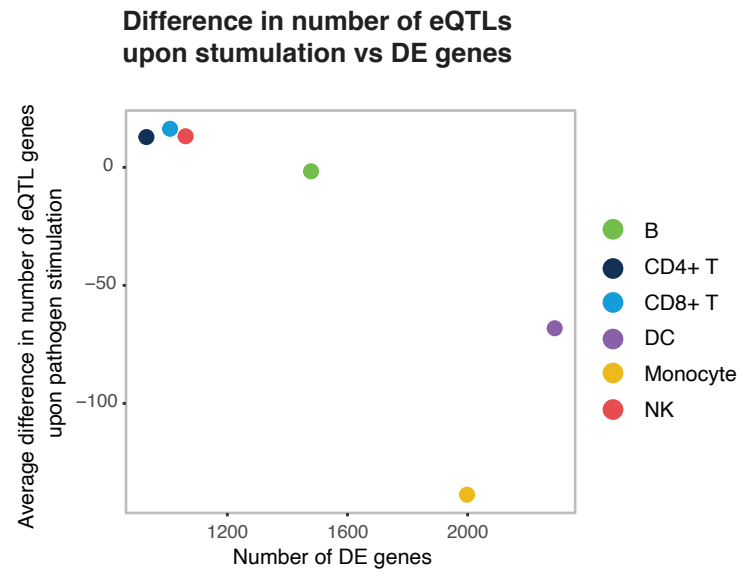
c


CD4+ T
CD4 Naive
CD4 Memory
463
133
123
558
502
6
222
CD8+ T
CD8 Naive
CD8 Memory
466
19
41
118
621
3
139
DC
mDC
pDC
52
108
127
42
34
29
NK
NKdim
NKbright
76
122
701
58
2
8
Monocyte
ncMono
cMono
334
79
106
367
571
4
141

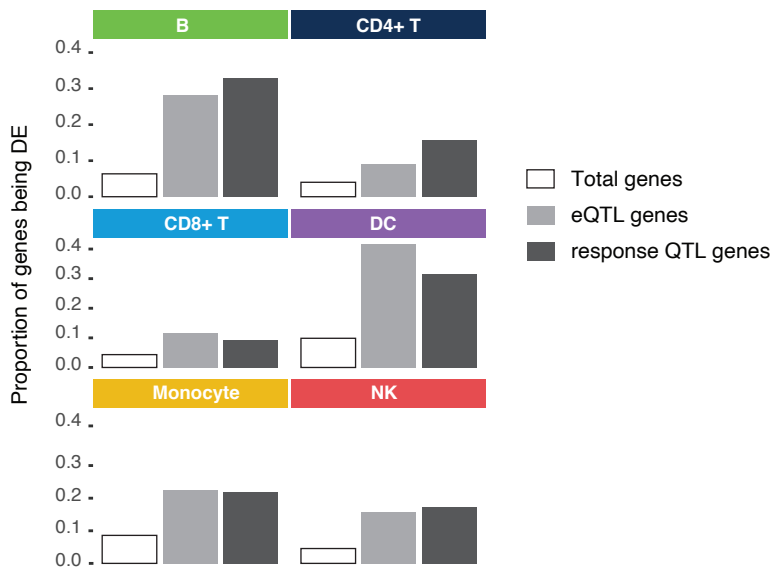
d


Overlap in eQTLs between stimulations
Intersection Size
Set Size
24hMTB
24hPA
3hMTB
3hPA
UT
3hCA
24hCA

e

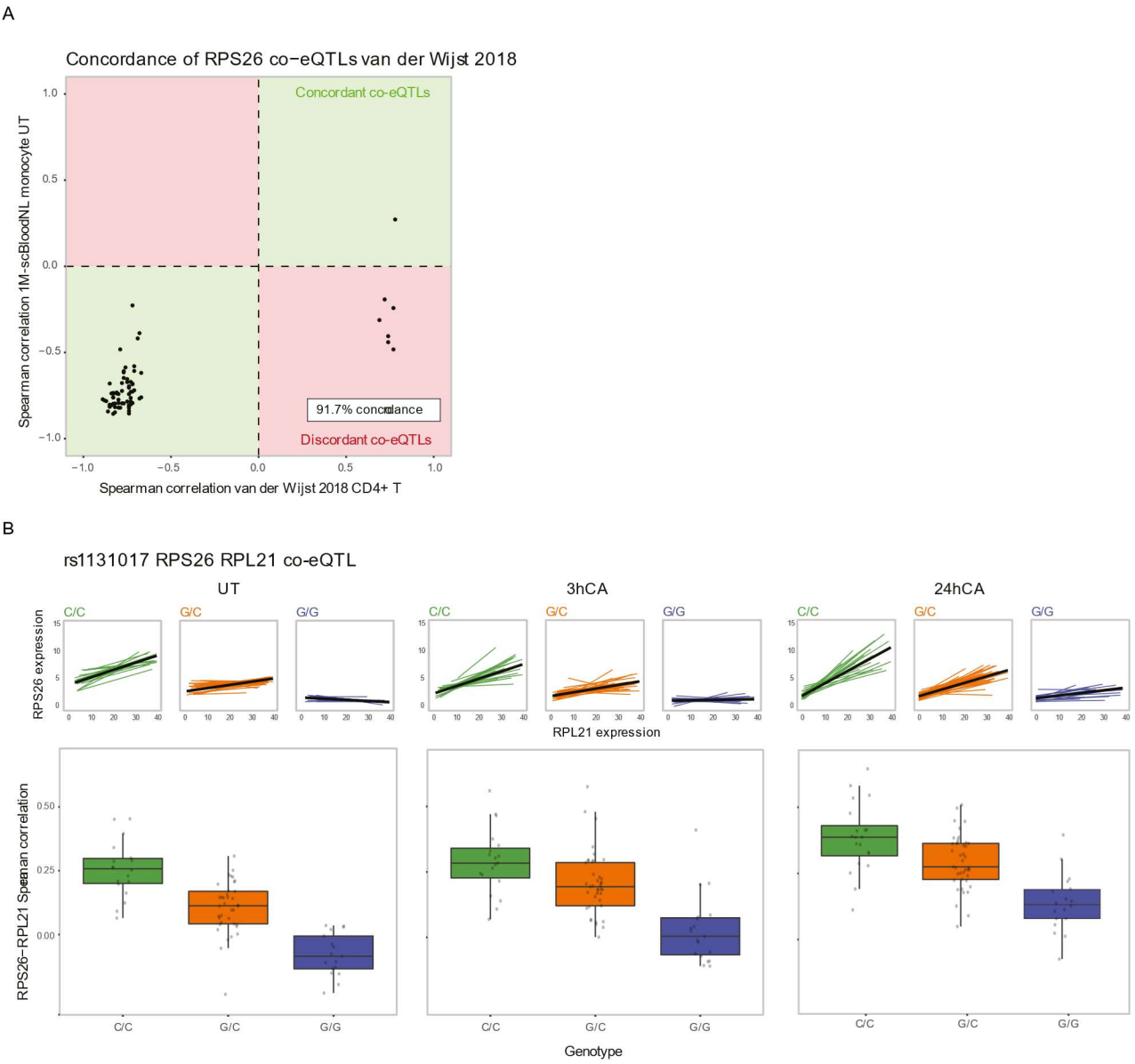

Difference in number of eQTLs upon stumulation vs DE genes
Average difference in number of eQTL genes upon pathogen stimulation
Number of DE genes
B
CD4+ T
CD8+ T
DC
Monocyte
NK

f


Proportion of genes found as differentially expressed
Proportion of genes being DE
B
CD4+ T
CD8+ T
DC
Monocyte
NK
Total genes
eQTL genes
response QTL genes

Supplementary Figure 4. eQTL characteristics

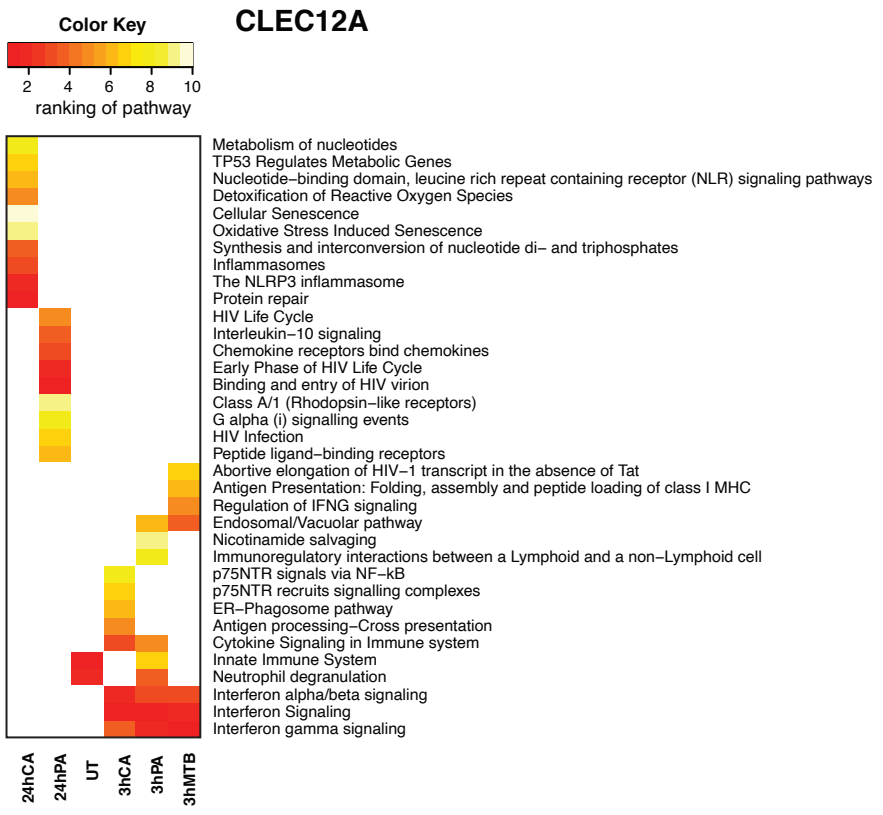
a. *Stacked bar plots showing the total number of unique eQTL genes per stimulation-timepoint combination within the eQTLGen lead-eSNP confined eQTL analysis (**Supplementary Data 7**) and the genome-wide cis-eQTL discovery analysis (**Supplementary Data 8**). The red color shows eQTL genes that were uniquely identified in the eQTLGen lead-eSNP confined analysis, orange is shared across both analyses and yellow shows eQTL genes that are unique to the genome-wide cis-eQTL discovery analysis.* ***b.*** *Overlap of eQTL effects between cell types. Each bar represents the number of eQTLs found for that group, which is indicated by the dots underneath the bar. Colored bars show eQTLs that are unique to one group and black bars are a combination of different groups.* ***c.*** *Venn diagrams that show the overlap in identified eQTL genes (in the eQTLGen-confined eQTL analysis) for each major cell type and their two corresponding subcell types.* ***d.*** *Overlap of eQTL effects between stimulation-timepoint combinations. Each bar represents the number of eQTLs found for that group, which is indicated by the dots underneath the bar. Colored bars show eQTLs that are unique to one group and black bars are a combination of different groups.* ***e.*** *Dot plot showing the difference in number of identified eQTLs upon stimulation (y-axis) compared to the number of DE genes (x-axis). Each dot represents a different cell type, shown by the color.* ***f.*** *Bar plots showing the proportion of genes that were identified as DE (**Supplementary Data 5**) per cell type. The three bars represent the complete set of tested genes (white), the complete set of genes with at least one eQTL (gray, **Supplementary Data 7**) and the complete set of genes with at least one response QTL (dark gray, **Supplementary Data 9**). The number of individuals and cells included in each analysis can be found in the Source Data file.*



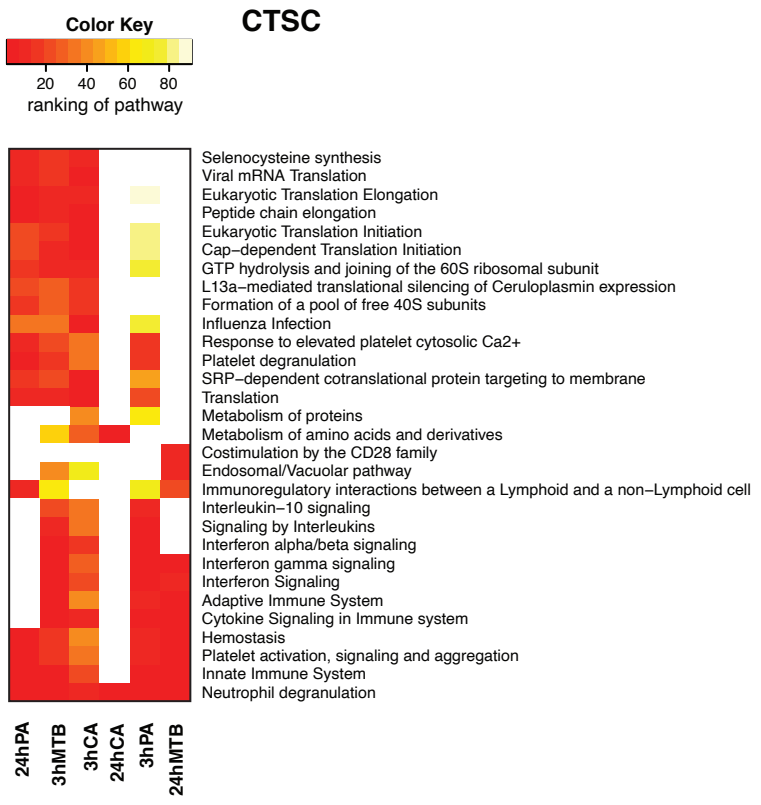
Supplementary Figure 5. RPS26 co-expression QTLs

a. *Concordance plot comparing Spearman correlations of RPS26 co-expression QTLs in CD4+ T cells from van der Wijst et al. 2018 (x-axis) compared to RPS26 co-expression QTLs in monocytes in the untreated condition of this study. Each dot represents a different co-expression QTL. Dots in green quadrants are concordant and dots in red quadrants are discordant.* ***b.*** *The co-expression QTL of RPS26 and RPL21, mediated by rs1131018, across different stimulation-timepoint combinations (meta-analysis p for the UT 1.21x10^{-31}, 3h CA 4.72x10^{-24}, 24h CA 1.28x10^{-5} conditions. Full summary statistics can be found in* ***Supplementary Data 11****). The top graphs show the individual co-expression, with each colored line representing one individual and the black line showing the regression line across all points. Boxplots (showing median, 25th and 75th percentile, and 1.5 x the interquartile range) representing the Spearman correlations per individual, split by genotype group. Each dot represents the Spearman correlation between RPS26 and RPL21 for one individual within that genotype group. Colors represent the three genotype groups for rs1131018. The number of individuals and cells included in each analysis can be found in the Source Data file.*

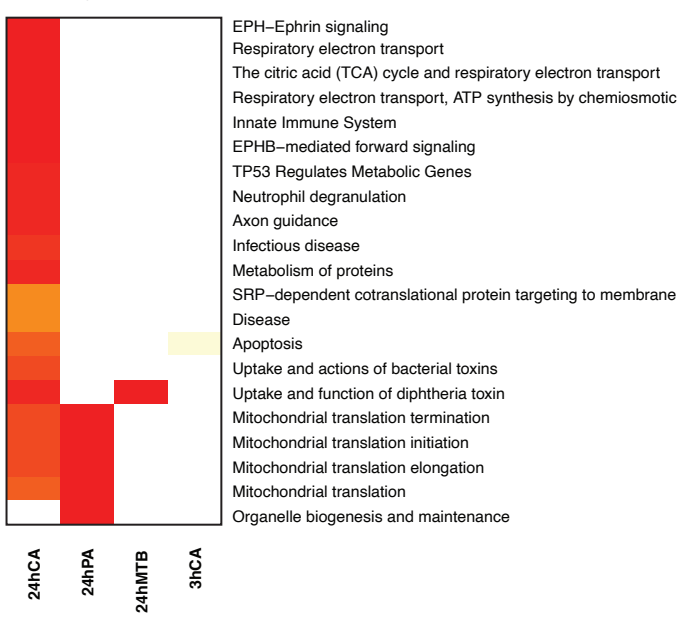
CLEC12A



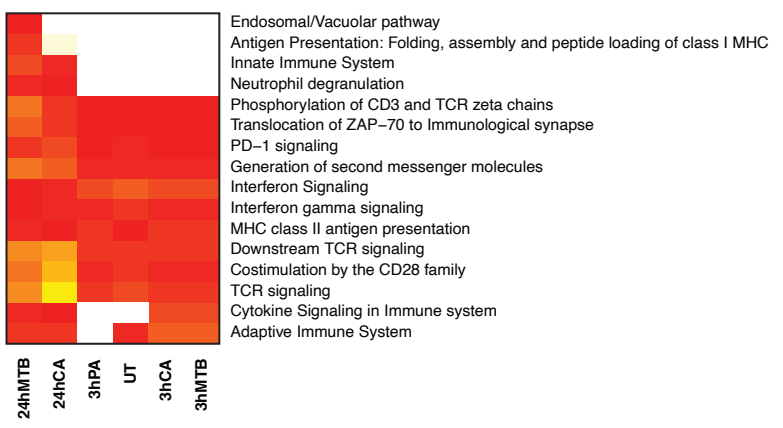
CTSC



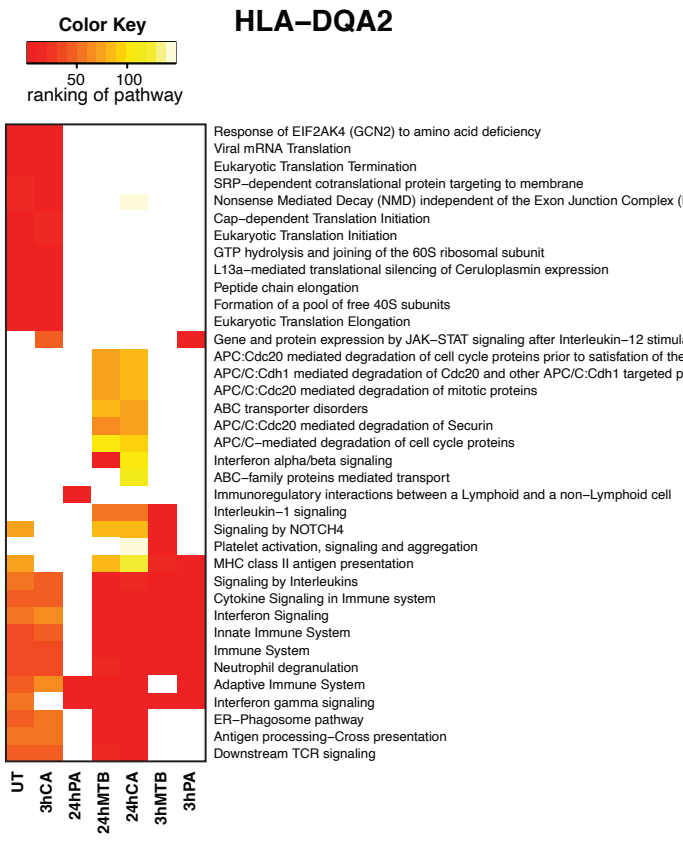
DNAJC15



HLA–DQA1



HLA–DQA2



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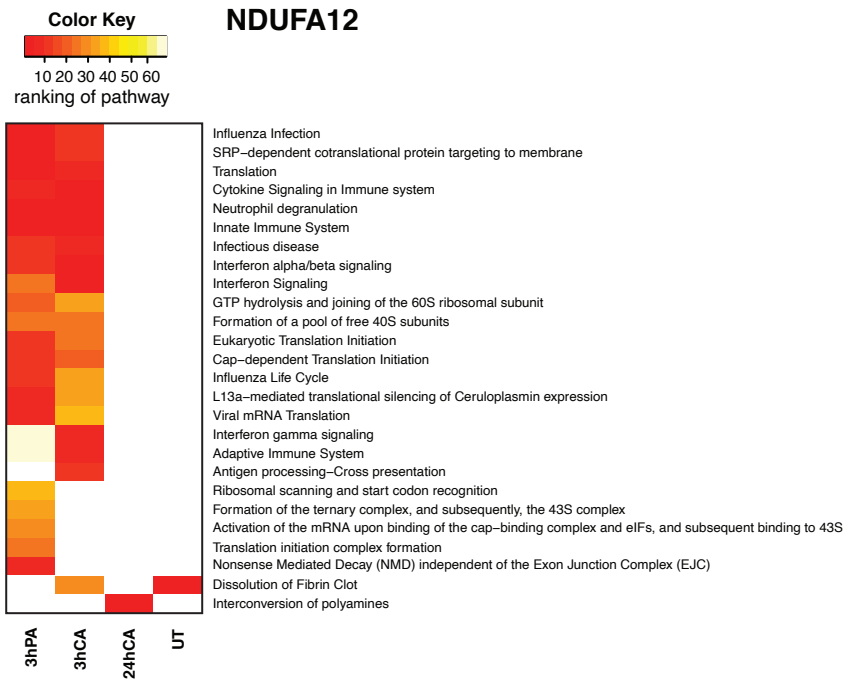
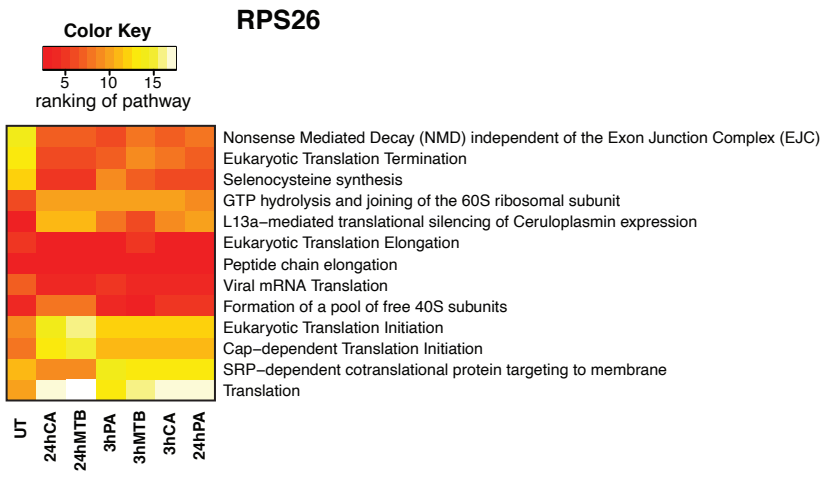


RPS26



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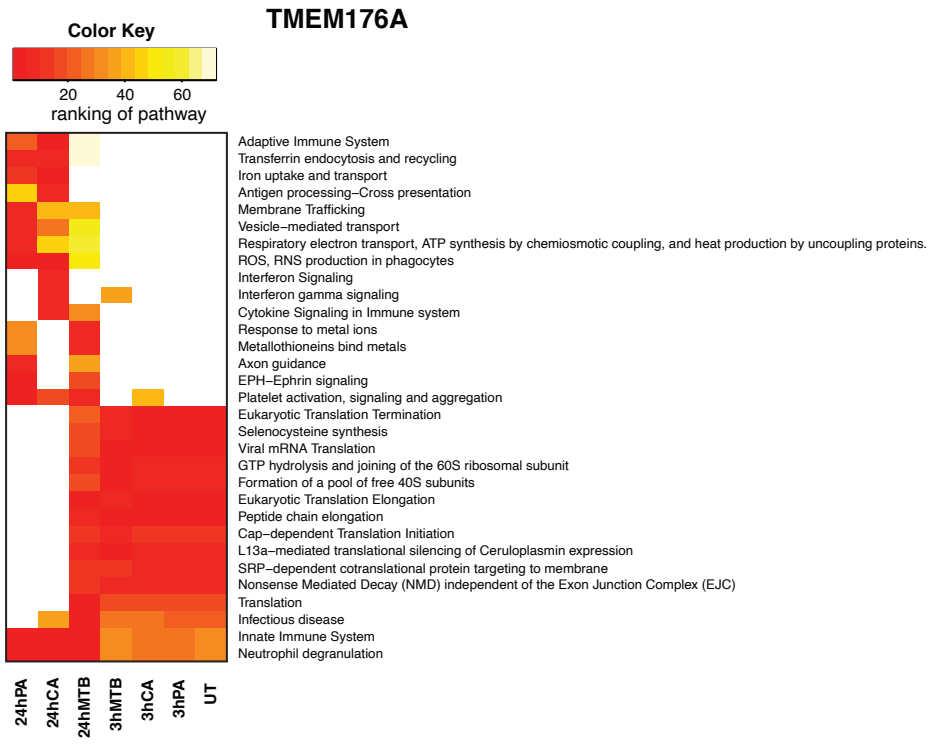

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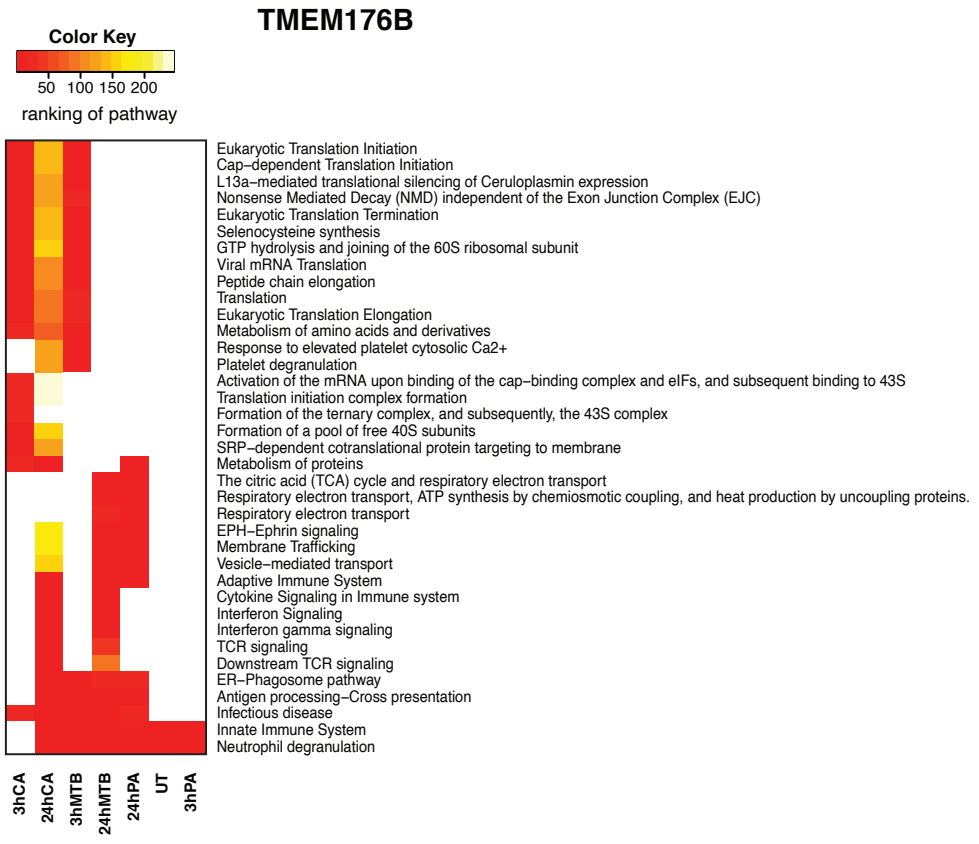

Supplementary Figure 6. Pathway enrichment analysis of co-expression QTL gene sets
Heatmaps showing the enrichment ranks of the pathways associated with the set of co-expressed genes affected by each co-expression QTL gene. Darker colors represent lower ranks, i.e. stronger enrichment, and lighter colors represent higher ranks, i.e. less enrichment. Full summary statistics can be found in ***Supplementary Data 6****. The number of individuals and cells included in each analysis can be found in the Source Data file.*

Supplementary Note 1. Single-cell eQTLGen Consortium

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