

Papalex CUL3 Analysis

2023-02-21

Goal

The aim of this report is to replicate the results of Papalex et al's pathway enrichment analysis.

```
# Load packages.
library(Seurat)

## Attaching SeuratObject

library(SeuratData)

## -- Installed datasets ----- SeuratData v0.2.2 --
## v thp1.eccite 3.1.5

## ----- Key -----

## v Dataset loaded successfully
## > Dataset built with a newer version of Seurat than installed
## (?) Unknown version of Seurat installed

library(ggplot2)
library(patchwork)
library(scales)
library(dplyr)

## 
## Attaching package: 'dplyr'

## The following objects are masked from 'package:stats':
## 
##     filter, lag

## The following objects are masked from 'package:base':
## 
##     intersect, setdiff, setequal, union

library(reshape2)
library(mixtools)

## mixtools package, version 2.0.0, Released 2022-12-04
## This package is based upon work supported by the National Science Foundation under Grant No. SES-051
```

```

library(stringr)
library(enrichR)

## Welcome to enrichR
## Checking connection ...

## Enrichr ... Connection is Live!
## FlyEnrichr ... Connection is available!
## WormEnrichr ... Connection is available!
## YeastEnrichr ... Connection is available!
## FishEnrichr ... Connection is available!
## OxEnrichr ... Connection is available!

library(kableExtra)

##
## Attaching package: 'kableExtra'
##
## The following object is masked from 'package:dplyr':
##
##     group_rows

```

Download Data

```

# Download dataset using SeuratData.
options(timeout = 1000)
InstallData(ds = "thp1.eccite")

## Warning: The following packages are already installed and will not be
## reinstalled: thp1.eccite

# Setup custom theme for plotting.
custom_theme <- theme(
  plot.title = element_text(size=16, hjust = 0.5),
  legend.key.size = unit(0.7, "cm"),
  legend.text = element_text(size = 14))

# Load object.
eccite <- LoadData(ds = "thp1.eccite")

```

Normalize and plot UMAP

```

# Normalize protein.
eccite <- NormalizeData(
  object = eccite,
  assay = "ADT",
  normalization.method = "CLR",
  margin = 2)

```

```

## Normalizing across cells

# Prepare RNA assay for dimensionality reduction:
# Normalize data, find variable features and scale data.
DefaultAssay(object = eccite) <- 'RNA'
eccite <- NormalizeData(object = eccite) %>% FindVariableFeatures() %>% ScaleData()

## Centering and scaling data matrix

# Run Principle Component Analysis (PCA) to reduce the dimensionality of the data.
eccite <- RunPCA(object = eccite)

## PC_ 1
## Positive: BIRC5, TOP2A, CDC20, MKI67, CENPF, TPX2, CDKN3, UBE2C, CKS1B, NUF2
##           CCNA2, NUSAP1, KIAAO101, CENPA, HMGB2, SGOL1, TYMS, STMN1, MYBL2, GTSE1
##           ASPM, H2AFZ, CDCA2, HMMR, CDCA8, KIF2C, CKAP2L, PTTG1, MND1, UBE2T
## Negative: FTH1, FCER1G, NEAT1, SOD2, FTL, MAFB, BTG1, NPC2, CTSL, CTSC
##            CTSB, SLC31A2, CHI3L1, FAM26F, TNFSF13B, GBP5, PLAUR, EVL, GK, ASAHI
##            HLA-DRB1, HLA-DRA, SPP1, SCPEP1, CD74, SAT1, GBP1, SLAMF7, WARS, SDS
## PC_ 2
## Positive: HYOU1, PDIA4, HSPA5, SDF2L1, MEI1, MANF, DNAJB9, NUCB2, TRIB3, WIPI1
##           CRELD2, HSP90B1, MSTO1, SLC39A14, HERPUD1, ALDH1L2, DERL3, VIMP, SEC11C, SERP1
##           PPAPDC1B, CDK2AP2, OSTC, DNAJB11, ERO1LB, SEC61G, SYVN1, TMED2, DNAJC3, PYCR1
## Negative: HSPA8, KIAAO101, TYMS, MKI67, FCER1G, CHI3L1, ACTG1, TOP2A, MYBL2, HSP90AA1
##            CCNA2, BIRC5, CLSPN, PKMYT1, NPC2, NUSAP1, HMGN2, ZWINT, CENPF, H2AFZ
##            TMEM106C, CENPW, TUBA1B, STMN1, CTSC, ASF1B, CDCA5, HMGA1, RRM2, GTSE1
## PC_ 3
## Positive: CDKN1A, ATF5, WARS, PLEK, CXCL10, IL1RN, SOD2, FAM26F, SLC31A2, GBP1
##           IDO1, SLAMF7, GK, HLA-DRA, ISG20, ICAM1, CD274, CCL2, ATF3, GBP5
##           CCL8, CD74, MTHFD2, IL8, FCER1G, GCH1, TNFSF13B, IL4I1, GLUL, RALA
## Negative: QPRT, S100A4, RPLPO, S100A6, ZFP36L2, ALOX5AP, SORL1, ANTXR1, C1orf162, VCAN
##            GLIPR1, CD1D, ID1, CAPN2, ID2, TGFBR1, RGS16, TKT, ITM2C, CDKN2C
##            HSPB1, ACTG1, CORO1A, SMYD3, ID3, RPSA, ALDH2, FOS, AZU1, THYN1
## PC_ 4
## Positive: RMDN3, GCHFR, GRN, DNASE2, WARS, SCCPDH, PSME2, LIPG, CTSD, HLA-DRB1
##           C19orf59, TSPO, HLA-DRB5, LTA4H, HLA-A, IFI30, AGT, GBP5, CEBPE, APOC1
##           GLUL, MARC1, CD74, CD1D, PPARG, ALOX5AP, CLDN23, CD68, S100A8, PLIN2
## Negative: CCL2, IGFBP3, PEA15, CCL3, NFKBIA, MMP9, CCL4, CCL5, POU2F2, IL1B
##            MARCKSL1, CXCL11, MX2, RGS1, CXCL9, USP18, PDPN, SPP1, CLEC5A, E2F1
##            TGFBR1, CKB, RUNX3, PTPN14, SMYD3, TGFB1, CCL8, TESC, GINS2, PNRC1
## PC_ 5
## Positive: FTL, FABP5, PLIN2, CSTB, CTSD, CD36, FTH1, HMGA1, SPOCD1, RMDN3
##           APOC1, DDT4L, AGPAT9, CDK4, MSR1, E2F1, SRM, GCHFR, GINS2, CLDN23
##           TOMM40, RND3, NCF2, FAM111B, DTL, APOE, STRA13, IL8, SLC11A1, CHCHD10
## Negative: TNFSF10, NCF1, PSMB9, CXCL11, CXCL10, IFI27, TMEM176B, RARRES3, TMEM176A, NFKBIA
##            IL32, SOCS1, IFITM1, GBP1, CCNB1, PLK1, HMMR, PNRC1, PSME2, RGS16
##            MY01G, CD74, ISG20, TNFSF13B, CXCL9, TMEM50B, CDC20, IFIT2, PTTG1, GLIPR1

# Run Uniform Manifold Approximation and Projection (UMAP) to visualize clustering in 2-D.
eccite <- RunUMAP(object = eccite, dims = 1:40)

## Warning: The default method for RunUMAP has changed from calling Python UMAP via reticulate to the R

```

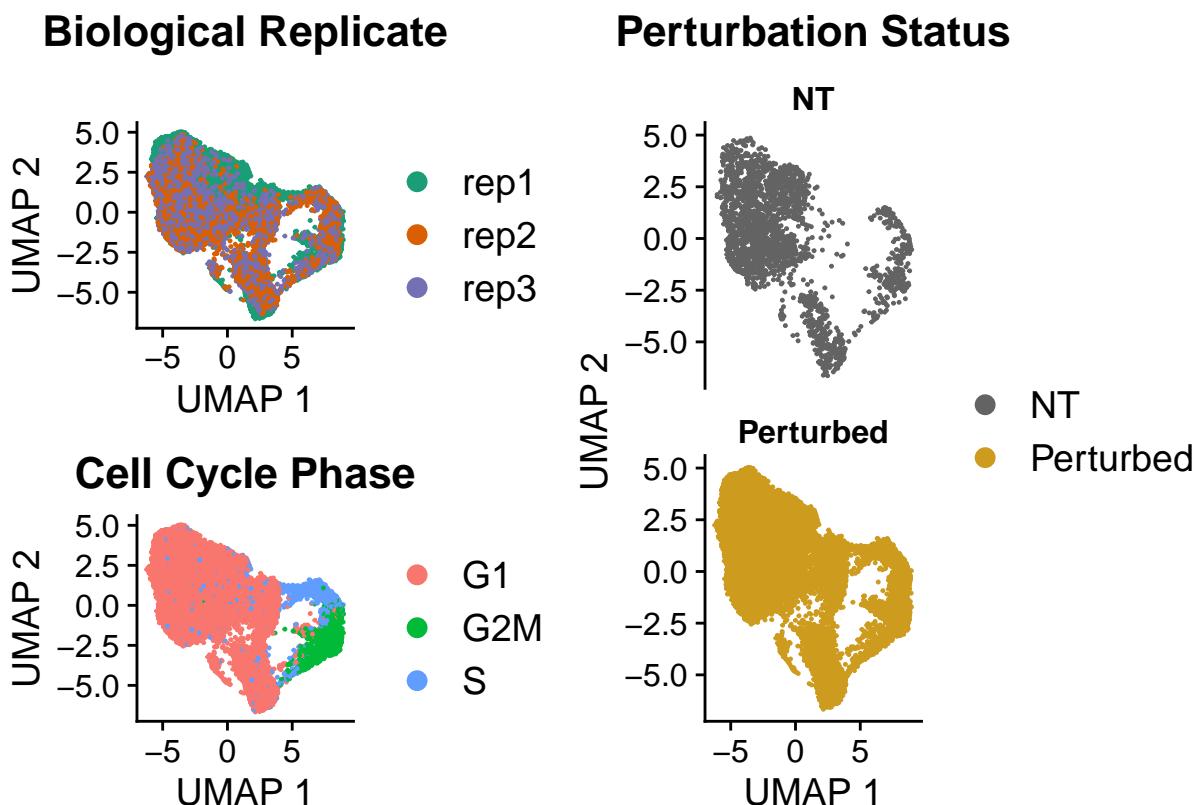
```
p2 <- DimPlot(
  object = eccite,
  group.by = 'Phase',
  label = F, pt.size = 0.2,
  reduction = "umap", repel = T) +
  ggtitle("Cell Cycle Phase") +
  ylab("UMAP 2") +
  xlab("UMAP 1") +
  custom_theme
```

```

p3 <- DimPlot(
  object = eccite,
  group.by = "crispr",
  pt.size = 0.2,
  reduction = "umap",
  split.by = "crispr",
  ncol = 1,
  cols = c("grey39","goldenrod3")) +
  ggtitle("Perturbation Status") +
  ylab("UMAP 2") +
  xlab("UMAP 1") +
  custom_theme

# Visualize plots.
((p1 / p2 + plot_layout(guides = 'auto')) | p3 )

```



Remove technical factors

```

# Calculate perturbation signature (PRTB).
eccite<- CalcPerturbSig(
  object = eccite,
  assay = "RNA",

```

```

slot = "data",
gd.class ="gene",
nt.cell.class = "NT",
reduction = "pca",
ndims = 40,
num.neighbors = 20,
split.by = "replicate",
new.assay.name = "PRTB")

```

```

## Processing rep1

## Processing rep3

## Processing rep2

# Prepare PRTB assay for dimensionality reduction:
# Normalize data, find variable features and center data.
DefaultAssay(object = eccite) <- 'PRTB'

# Use variable features from RNA assay.
VariableFeatures(object = eccite) <- VariableFeatures(object = eccite[["RNA"]])
eccite <- ScaleData(object = eccite, do.scale = F, do.center = T)

```

```

## Centering data matrix

# Run PCA to reduce the dimensionality of the data.
eccite <- RunPCA(object = eccite, reduction.key = 'prtbpca', reduction.name = 'prtbpca')

## Warning: Keys should be one or more alphanumeric characters followed by an
## underscore, setting key from prtbpca to prtbpca_

## Warning: All keys should be one or more alphanumeric characters followed by an
## underscore '_', setting key to prtbpca_

## prtbpca_1
## Positive: SPP1, S100A4, RPLPO, VCAN, ZFP36L1, TREM2, TGFB1, CAPN2, TGFBI, LGALS1
##           RPSA, SORL1, FSCN1, CSF1R, YWHAH, LMNA, RPS2, ADORA3, HSPB1, CORO1A
##           ID2, MMP9, VAT1, GLO1, COL6A1, AP1S2, NFKBIA, MGST3, APOE, IL8
## Negative: CD74, HLA-DRA, CXCL10, WARS, GBP5, GBP1, IFI27, HLA-DRB1, FAM26F, PSMB9
##           HLA-DRB5, IL18BP, PSME2, SOCS1, HLA-DPA1, HLA-DQB1, SOD2, IFITM1, NCF1, S100A8
##           HLA-A, GLUL, CTSL, CD70, FCGR1B, HLA-DMA, HLA-DPB1, FCER1G, LY6E, CHI3L1
## prtbpca_2
## Positive: CXCL10, CXCL11, CXCL9, GBP1, SOCS1, GBP5, SOD2, TNFSF13B, CCL2, IFIT3
##           IL32, MX1, GYPC, IL18BP, ISG20, WARS, TNFSF10, IDO1, LY6E, IFI27
##           RSAD2, BAZ1A, FAM26F, IFIT2, GCH1, CD274, USP18, FTH1, TMEM176A, H1F0
## Negative: S100A8, S100A9, ALOX5AP, S100A4, SPP1, CTSD, C19orf59, S100A6, GRN, APOC1
##           TREM2, CHI3L1, S100A10, ANXA2, GLO1, CALR, PPIB, TSPO, TIMP1, HLA-DRB5
##           IL8, SRGN, PLAUR, VIM, DNASE2, FABP5, LGALS1, HLA-DRB1, FN1, FCER1G
## prtbpca_3
## Positive: CXCL10, CCL2, CXCL11, S100A9, S100A8, ALOX5AP, ISG15, CXCL9, IFI6, MX1
##           LY6E, CCL8, CYP1B1, S100A10, IL32, MARCKSL1, NFKBIA, GLO1, AP1S2, IFITM1

```



```

## Warning: All keys should be one or more alphanumeric characters followed by an
## underscore '_', setting key to prtbumap_

# Generate plots to check if clustering is driven by biological replicate ID,
# cell cycle phase or target gene class.
q1 <- DimPlot(
  object = eccite,
  group.by = 'replicate',
  reduction = 'prtbumap',
  pt.size = 0.2, cols = "Dark2", label = F, repel = T) +
  scale_color_brewer(palette = "Dark2") +
  ggtitle("Biological Replicate") +
  ylab("UMAP 2") +
  xlab("UMAP 1") +
  custom_theme

## Scale for colour is already present.
## Adding another scale for colour, which will replace the existing scale.

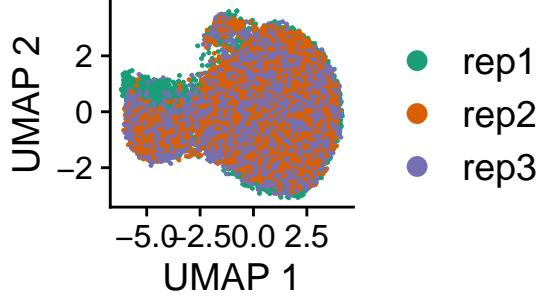
q2 <- DimPlot(
  object = eccite,
  group.by = 'Phase',
  reduction = 'prtbumap',
  pt.size = 0.2, label = F, repel = T) +
  ggtitle("Cell Cycle Phase") +
  ylab("UMAP 2") +
  xlab("UMAP 1") +
  custom_theme

q3 <- DimPlot(
  object = eccite,
  group.by = 'crispr',
  reduction = 'prtbumap',
  split.by = "crispr",
  ncol = 1,
  pt.size = 0.2,
  cols = c("grey39","goldenrod3")) +
  ggtitle("Perturbation Status") +
  ylab("UMAP 2") +
  xlab("UMAP 1") +
  custom_theme

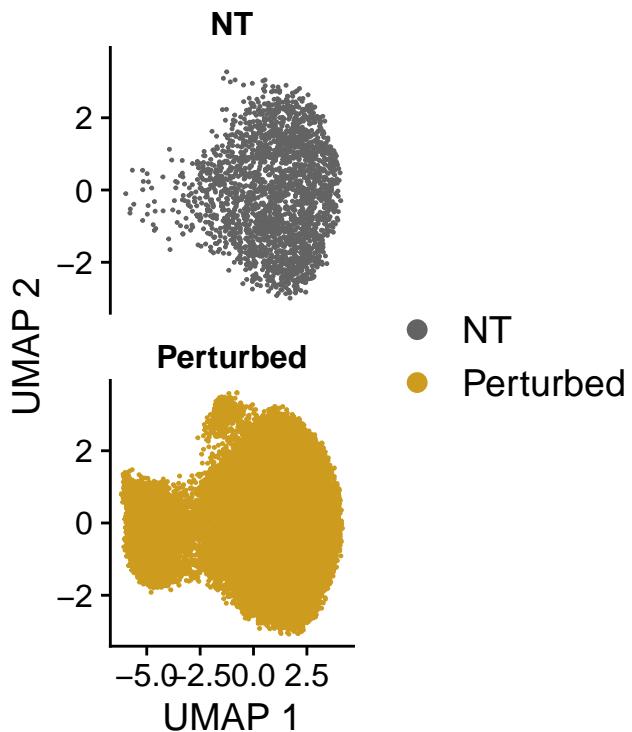
# Visualize plots.
(q1 / q2 + plot_layout(guides = 'auto') | q3)

```

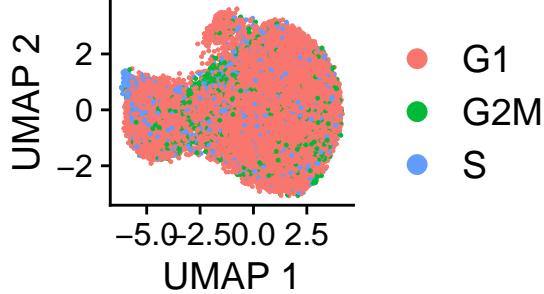
Biological Replicate



Perturbation Status



Cell Cycle Phase



Run mixscape

```
# Run mixscape.
eccite <- RunMixscape(
  object = eccite,
  assay = "PRTB",
  slot = "scale.data",
  labels = "gene",
  nt.class.name = "NT",
  min.de.genes = 5,
  iter.num = 10,
  de.assay = "RNA",
  verbose = F,
  prtb.type = "KO")

## Warning in FindMarkers.default(object = data.use, slot = data.slot, counts =
## counts, : No features pass logfc.threshold threshold; returning empty
## data.frame

## number of iterations= 95
## number of iterations= 187
## number of iterations= 172
```

```

## number of iterations= 18
## number of iterations= 6
## number of iterations= 18
## number of iterations= 11
## number of iterations= 11
## number of iterations= 59
## number of iterations= 43
## number of iterations= 42
## number of iterations= 19
## number of iterations= 12
## number of iterations= 12
## number of iterations= 23
## number of iterations= 19
## number of iterations= 19
## number of iterations= 51
## number of iterations= 51
## number of iterations= 51
## number of iterations= 36
## number of iterations= 26
## number of iterations= 25
## number of iterations= 20
## number of iterations= 12
## number of iterations= 12
## number of iterations= 17
## number of iterations= 15
## number of iterations= 14
## number of iterations= 13
## number of iterations= 73
## number of iterations= 46
## number of iterations= 41

# Calculate percentage of KO cells for all target gene classes.
df <- prop.table(table(eccite$mixscape_class.global, eccite$NT),2)

df2 <- reshape2::melt(df)
df2$Var2 <- as.character(df2$Var2)
test <- df2[which(df2$Var1 == "KO"),]
test <- test[order(test$value, decreasing = T),]
new.levels <- test$Var2
df2$Var2 <- factor(df2$Var2, levels = new.levels )
df2$Var1 <- factor(df2$Var1, levels = c("NT", "NP", "KO"))
df2$gene <- sapply(as.character(df2$Var2), function(x) strsplit(x, split = "g")[[1]][1])
df2$guide_number <- sapply(as.character(df2$Var2),
                           function(x) strsplit(x, split = "g")[[1]][2])
df3 <- df2[-c(which(df2$gene == "NT")),]

p1 <- ggplot(df3, aes(x = guide_number, y = value*100, fill= Var1)) +
  geom_bar(stat= "identity") +
  theme_classic()+
  scale_fill_manual(values = c("grey49", "grey79","coral1")) +
  ylab("% of cells") +
  xlab("sgRNA")

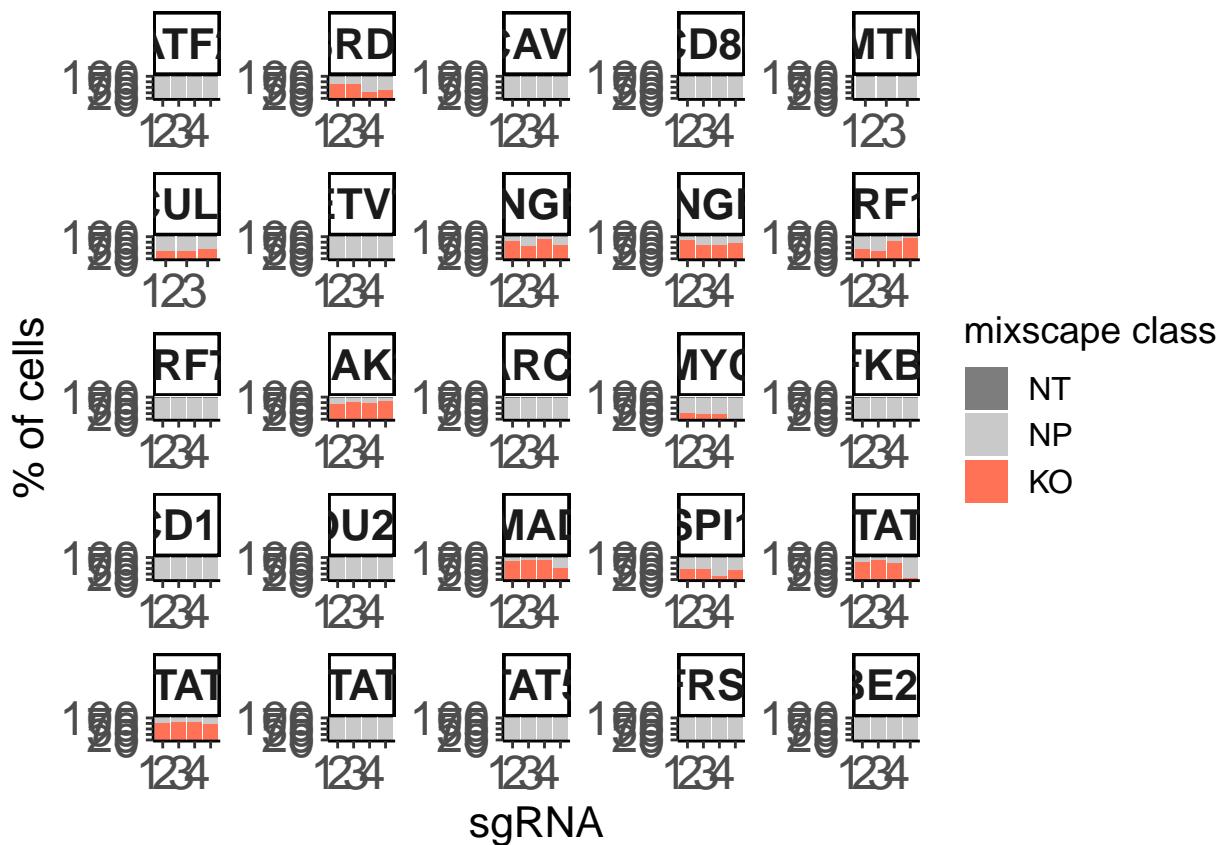
p1 + theme(axis.text.x = element_text(size = 18, hjust = 1),

```

```

axis.text.y = element_text(size = 18),
axis.title = element_text(size = 16),
strip.text = element_text(size=16, face = "bold")) +
facet_wrap(vars(gene), ncol = 5, scales = "free") +
labs(fill = "mixscape class") +theme(legend.title = element_text(size = 14),
legend.text = element_text(size = 12))

```



Perform Marker Gene Analysis/Pathway Enrichment Analysis Ordered by Log Fold Change

Papalex et reports 5 major pathways in CUL3 KO cells. Nuclear Receptors Meta-Pathway,NRF2 pathway,Phytochemical activity on NRF2 transcriptional activation,TYROBP causal network ,and complement system activation. We see pvalues that are approximately the same. However, we do see that the pathway “Phytochemical activity on NRF2 transcriptional activation” is ranked ahead of “TYROBP causal network” in this analysis whereas according to paplexi et al, the realtive pvalue rank should be flipped between these two pathways.

```
CUL3_marker = FindMarkers(eccite,ident.1 = 'CUL3 KO',ident.2 = 'NT',
assay = 'RNA',only.pos = T)
```

```
## For a more efficient implementation of the Wilcoxon Rank Sum Test,
## (default method for FindMarkers) please install the limma package
```

```

## -----
## install.packages('BiocManager')
## BiocManager::install('limma')
## -----
## After installation of limma, Seurat will automatically use the more
## efficient implementation (no further action necessary).
## This message will be shown once per session

CUL3_marker$avg_log2FC = signif(CUL3_marker$avg_log2FC, digits=2)
CUL3_marker$p_val = signif(CUL3_marker$p_val, digits=2)

# get top 300 genes by log fold change
top = 300
CUL3_top = rownames(CUL3_marker)[order(CUL3_marker$avg_log2FC, decreasing = T)[1:top]]
# run pathway enrichment analysis
pathways = enrichr(CUL3_top, databases = 'WikiPathway_2021_Human')

## Uploading data to Enrichr... Done.
## Querying WikiPathway_2021_Human... Done.
## Parsing results... Done.

# get term and pvalue (using subset truncates pvalues for some reason)
pathways = cbind(pathways$WikiPathway_2021_Human$Term,
                  pathways$WikiPathway_2021_Human$Adjusted.P.value)[1:50,]

pathways[,2] = signif(as.numeric(pathways[,2]), digits=2)
# make table
results = kable(pathways, booktabs = TRUE, linesep = "",
                 caption = "Pathway Enrichment Analysis With Top 300 Genes by Log Fold Change")
kable_styling(results, position = "center", latex_options = "scale_down")

```

Perform Marker Gene Analysis/Pathway Enrichment Analysis By Pvalue

```

# get top 300 genes by log fold change
top = 300
CUL3_top = rownames(CUL3_marker)[order(CUL3_marker$p_val, decreasing = F)[1:top]]
# run pathway enrichment analysis
pathways = enrichr(CUL3_top, databases = 'WikiPathway_2021_Human')

## Uploading data to Enrichr... Done.
## Querying WikiPathway_2021_Human... Done.
## Parsing results... Done.

# get term and pvalue (using subset truncates pvalues for some reason)
pathways = cbind(pathways$WikiPathway_2021_Human$Term,
                  pathways$WikiPathway_2021_Human$Adjusted.P.value)[1:50,]
pathways[,2] = signif(as.numeric(pathways[,2]), digits=2)

```

Table 1: Pathway Enrichment Analysis With Top 300 Genes by Log Fold Change

Nuclear Receptors Meta-Pathway WP2882	1.2e-19
IL-18 signaling pathway WP4754	2.7e-15
NRF2 pathway WP2884	5.8e-14
Lung fibrosis WP3624	7.7e-10
Spinal Cord Injury WP2431	2.1e-08
Phytochemical activity on NRF2 transcriptional activation WP3	5.9e-08
SARS-CoV-2 innate immunity evasion and cell-specific immune response WP5039	2e-07
Ferroptosis WP4313	3e-07
Selenium Micronutrient Network WP15	3.8e-07
TYROBP causal network in microglia WP3945	8.2e-07
Regulation of toll-like receptor signaling pathway WP1449	8.2e-07
Chemokine signaling pathway WP3929	8.8e-07
NRF2-ARE regulation WP4357	9.4e-07
IL1 and megakaryocytes in obesity WP2865	1.1e-06
Photodynamic therapy-induced NFE2L2 (NRF2) survival signaling WP3612	1.1e-06
Toll-like Receptor Signaling Pathway WP75	1.1e-06
Photodynamic therapy-induced AP-1 survival signaling. WP3611	1.1e-06
p53 transcriptional gene network WP4963	1.2e-06
Senescence and Autophagy in Cancer WP615	1.2e-06
Apoptosis-related network due to altered Notch3 in ovarian cancer WP2864	1.6e-06
Allograft Rejection WP2328	1.7e-06
VEGFA-VEGFR2 Signaling Pathway WP3888	3e-06
Oxidative Stress WP408	8.2e-06
Vitamin D Receptor Pathway WP2877	1.1e-05
Vitamin B12 metabolism WP1533	1.1e-05
Photodynamic therapy-induced NF- κ B survival signaling WP3617	1.1e-05
Pentose Phosphate Metabolism WP134	2.4e-05
Microglia Pathogen Phagocytosis Pathway WP3937	2.5e-05
Oxidative Damage WP3941	2.5e-05
COVID-19 adverse outcome pathway WP4891	2.5e-05
Complement and Coagulation Cascades WP558	2.9e-05
Platelet-mediated interactions with vascular and circulating cells WP4462	4.7e-05
Aryl Hydrocarbon Receptor Netpath WP2586	6e-05
Glucocorticoid Receptor Pathway WP2880	0.00011
Complement system WP2806	0.00017
Kynurenine Pathway and links to Cellular Senescence WP5044	0.00021
Fibrin Complement Receptor 3 Signaling Pathway WP4136	0.00032
Vitamin D-sensitive calcium signaling in depression WP4698	0.00032
Cytokines and Inflammatory Response WP530	0.00037
Folate Metabolism WP176	0.00074
Tryptophan catabolism leading to NAD $^{+}$ production WP4210	0.00074
RANKL/RANK signaling pathway WP2018	0.0016
miRNAs involvement in the immune response in sepsis WP4329	0.0019
Photodynamic therapy-induced HIF-1 survival signaling WP3614	0.0019
Complement Activation WP545	0.0025
Ebstein-Barr virus LMP1 signaling WP262	0.0029
Glutathione metabolism WP100	0.0029
Metabolic reprogramming in colon cancer WP4290	0.0032
NAD Metabolism in Oncogene-Induced Senescence and Mitochondrial Dysfunction-Associated Senescence WP5046	0.0032
Unfolded protein response WP4925	0.0032

```
#make table
results = kable(pathways,booktabs = TRUE, linesep = "",
  caption = "Pathway Enrichment Analysis With Top 300 Genes by Pvalue")
kable_styling(results,position = "center", latex_options = "scale_down")
```

Table 2: Pathway Enrichment Analysis With Top 300 Genes by Pvalue

Nuclear Receptors Meta-Pathway WP2882	5.4e-14
NRF2 pathway WP2884	1.2e-11
IL-18 signaling pathway WP4754	3e-09
TYROBP causal network in microglia WP3945	2.1e-06
Phytochemical activity on NRF2 transcriptional activation WP3	3e-06
SARS-CoV-2 innate immunity evasion and cell-specific immune response WP5039	3e-06
Selenium Micronutrient Network WP15	4.8e-06
Ferroptosis WP4313	4.8e-06
Oxidative Damage WP3941	4.8e-06
Complement system WP2806	8.3e-06
Lung fibrosis WP3624	1.3e-05
Senescence and Autophagy in Cancer WP615	1.6e-05
NRF2-ARE regulation WP4357	2.5e-05
Apoptosis-related network due to altered Notch3 in ovarian cancer WP2864	2.8e-05
Photodynamic therapy-induced NFE2L2 (NRF2) survival signaling WP3612	2.8e-05
Regulation of toll-like receptor signaling pathway WP1449	2.9e-05
COVID-19 adverse outcome pathway WP4891	4.2e-05
Toll-like Receptor Signaling Pathway WP75	6.9e-05
Aryl Hydrocarbon Receptor Netpath WP2586	9.9e-05
p53 transcriptional gene network WP4963	0.00013
Oxidative Stress WP408	0.00015
Spinal Cord Injury WP2431	0.00019
Photodynamic therapy-induced NF-kB survival signaling WP3617	0.00019
Complement Activation WP545	0.00024
Type II interferon signaling (IFNG) WP619	0.00025
Kynurene Pathway and links to Cellular Senescence WP5044	0.00028
Complement and Coagulation Cascades WP558	0.00033
Microglia Pathogen Phagocytosis Pathway WP3937	0.00035
Vitamin D-sensitive calcium signaling in depression WP4698	0.00038
Fibrin Complement Receptor 3 Signaling Pathway WP4136	0.00038
Chemokine signaling pathway WP3929	0.00045
Allograft Rejection WP2328	0.00065
Aryl Hydrocarbon Receptor Pathway WP2873	0.00067
Folate Metabolism WP176	0.00083
Vitamin B12 metabolism WP1533	0.001
Platelet-mediated interactions with vascular and circulating cells WP4462	0.001
Pentose Phosphate Metabolism WP134	0.0011
Adipogenesis WP236	0.0015
Overview of leukocyte-intrinsic Hippo pathway functions WP4542	0.0015
RANKL/RANK signaling pathway WP2018	0.0015
miRNAs involvement in the immune response in sepsis WP4329	0.0019
FGF23 signaling in hypophosphatemic rickets and related disorders WP4790	0.0025
Glutathione metabolism WP100	0.003
Sphingolipid Metabolism (general overview) WP4725	0.0033
IL1 and megakaryocytes in obesity WP2865	0.0033
NAD Metabolism in Oncogene-Induced Senescence and Mitochondrial Dysfunction-Associated Senescence WP5046	0.0033
TNF-alpha signaling pathway WP231	0.0036
Sphingolipid Metabolism (integrated pathway) WP4726	0.0037
Cytokines and Inflammatory Response WP530	0.0042
Non-genomic actions of 1,25 dihydroxyvitamin D3 WP4341	0.005