

Fn_HGFcell

Zhilong Jia

12 June, 2018

18 July, 2018

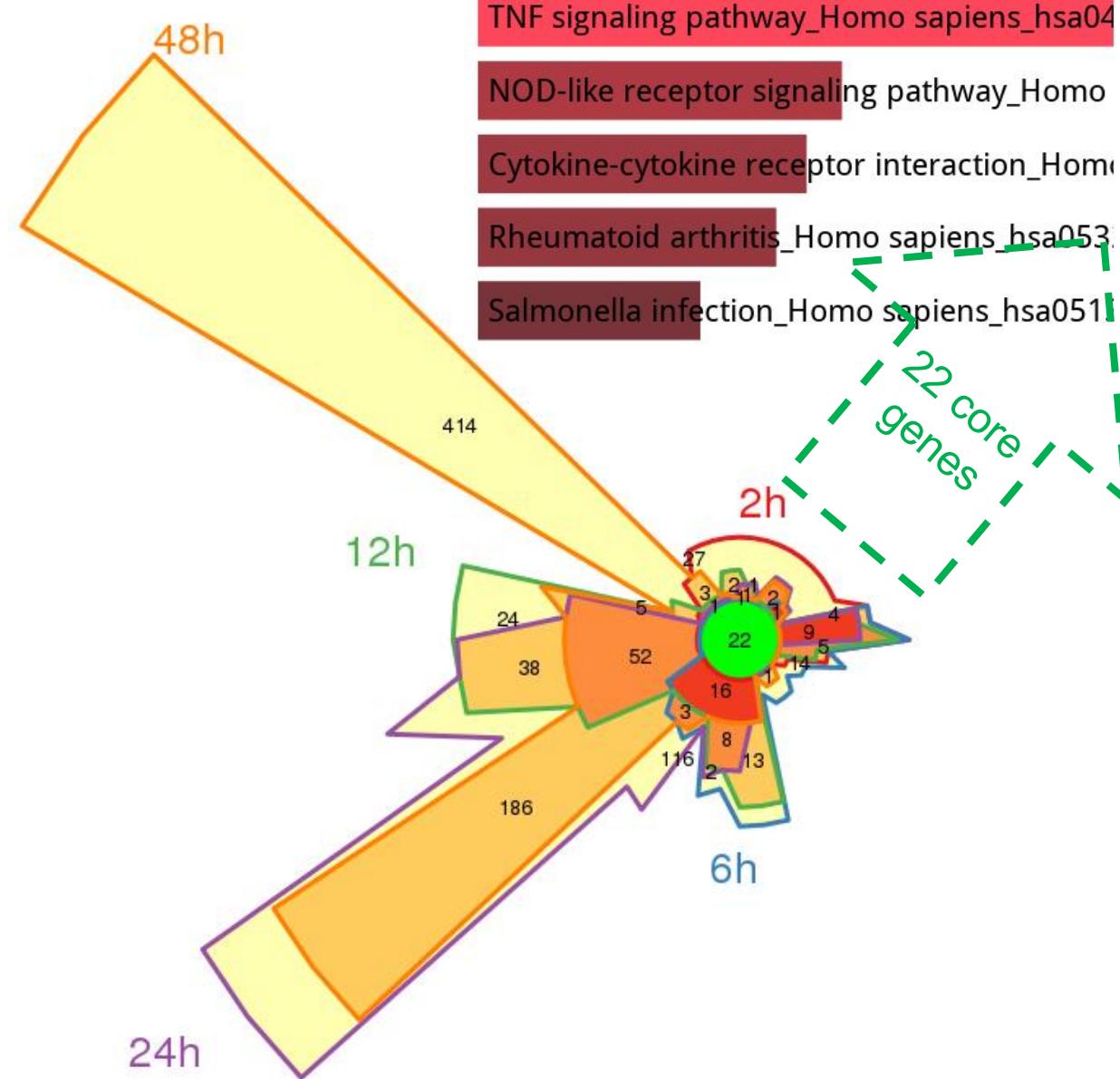
7 Aug, 2018

Data Description and Proposal

Group	0h	2h	6h	12h	24h	48h
ctrl (C)	(BCDEF)0	(BCDEF)2C	(BCDEF)6C	(BCDEF)12C	(BCDEF)24C	(BCDEF)48C
FN (F)		(BCDEF)2F	(BCDEF)6F	<u>(BCDE)12F</u>	(BCDEF)24F	(BCDEF)48F

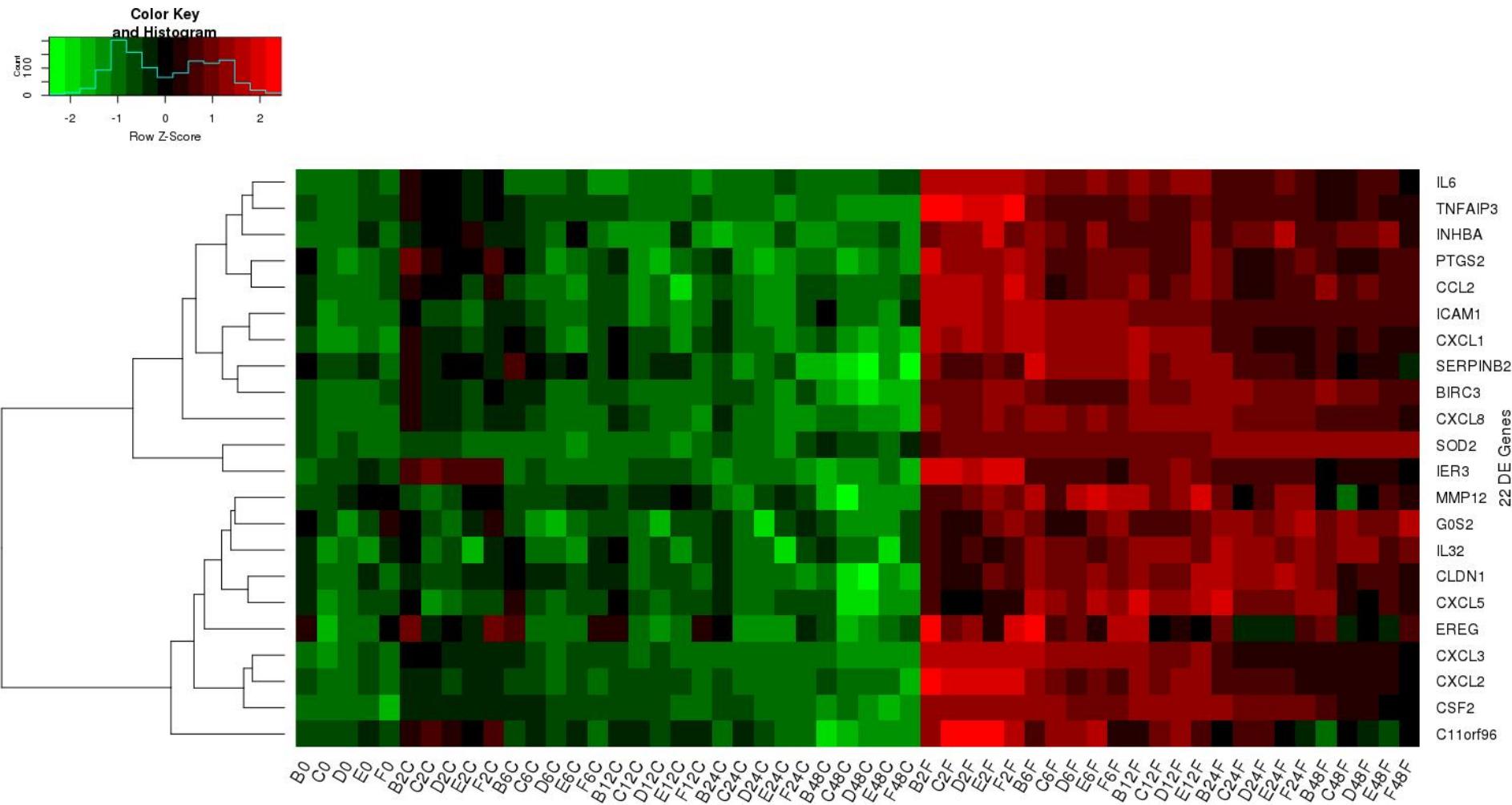
- **DEA at each timepoint (2, 6, 12, 24, 48h)**
 - ChowRuskey plot
 - PCA, heatmap of unioned DEGs
 - pathway & GO analysis
 - pathway & GO analysis of ChowRuskey set
 - **Changes of pathway enrichment (GSEA) via time**
- **time series analysis**
 - PCA, heatmap, pathway & GO analysis of ChowRuskey set and per time span
- **co-expression analysis**
 - cogena/clusterProfiler pathway/GO analysis, drug repositioning analysis
- Enrichment analysis for 24h only

ChowRuskey plot of DEA for each timepoint

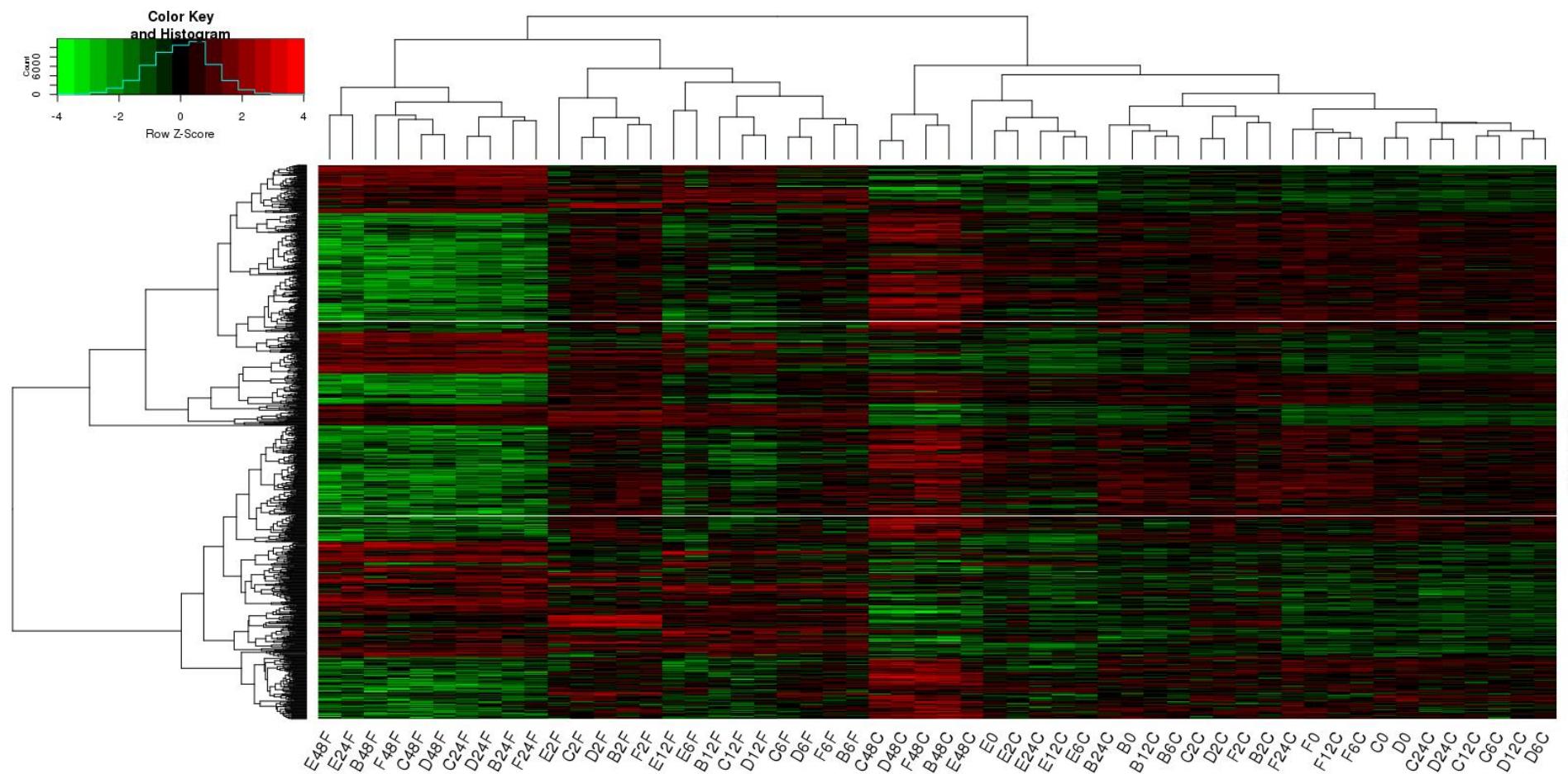


1	SYMBOL	GENENAME
2	BIRC3	baculoviral IAP repeat containing 3
3	C11orf96	chromosome 11 open reading frame 96
4	CCL2	C-C motif chemokine ligand 2
5	CLDN1	claudin 1
6	CSF2	colony stimulating factor 2
7	CXCL1	C-X-C motif chemokine ligand 1
8	CXCL2	C-X-C motif chemokine ligand 2
9	CXCL3	C-X-C motif chemokine ligand 3
10	CXCL5	C-X-C motif chemokine ligand 5
11	CXCL8	C-X-C motif chemokine ligand 8
12	EREG	epiregulin
13	GOS2	G0/G1 switch 2
14	ICAM1	intercellular adhesion molecule 1
15	IER3	immediate early response 3
16	IL32	interleukin 32
17	IL6	interleukin 6
18	INHBA	inhibin beta A subunit
19	MMP12	matrix metallopeptidase 12
20	PTGS2	prostaglandin-endoperoxide synthase 2
21	SERPINB	serpin family B member 2
22	SOD2	superoxide dismutase 2
23	TNFAIP3	TNF alpha induced protein 3

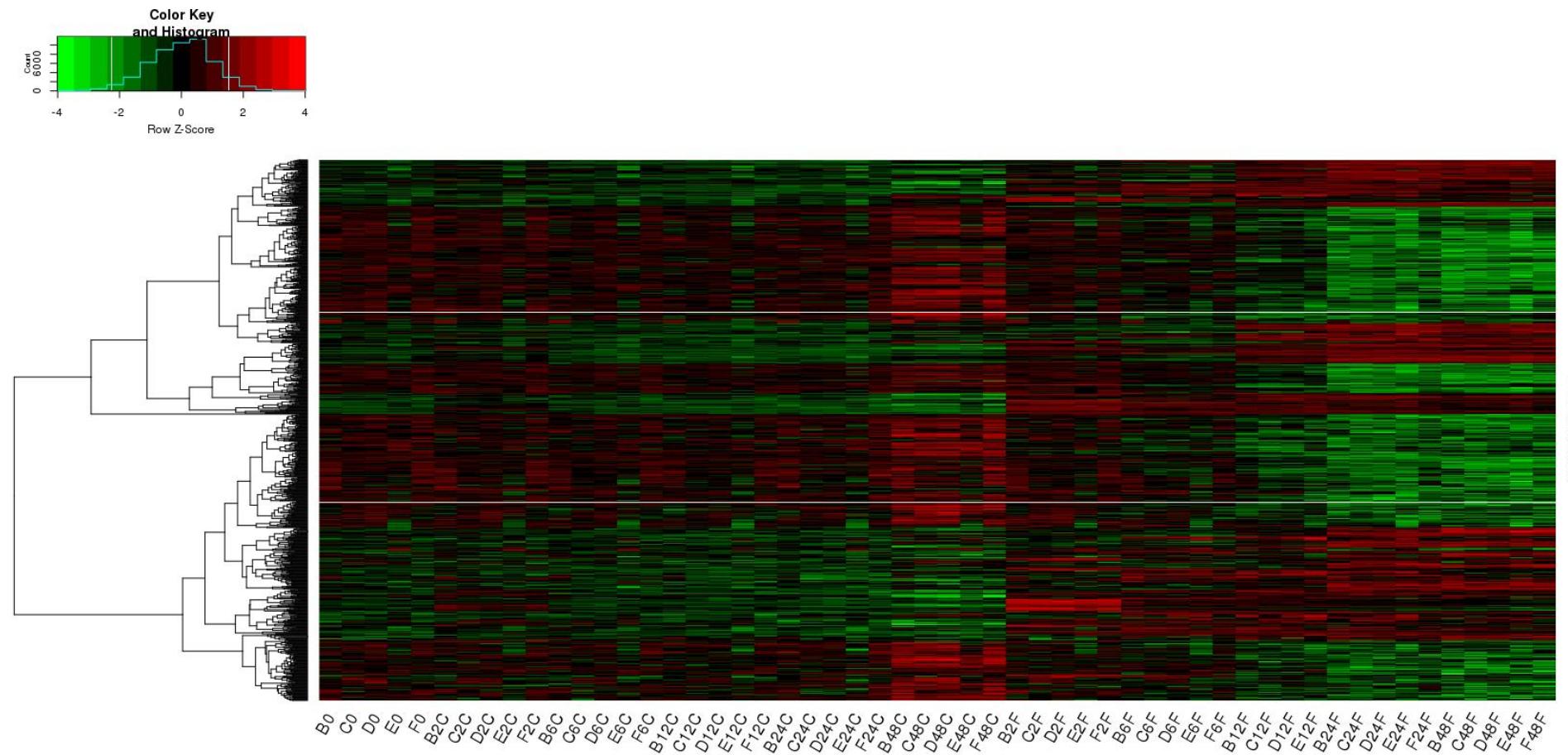
heatmap (Colv=F) of 22 core genes



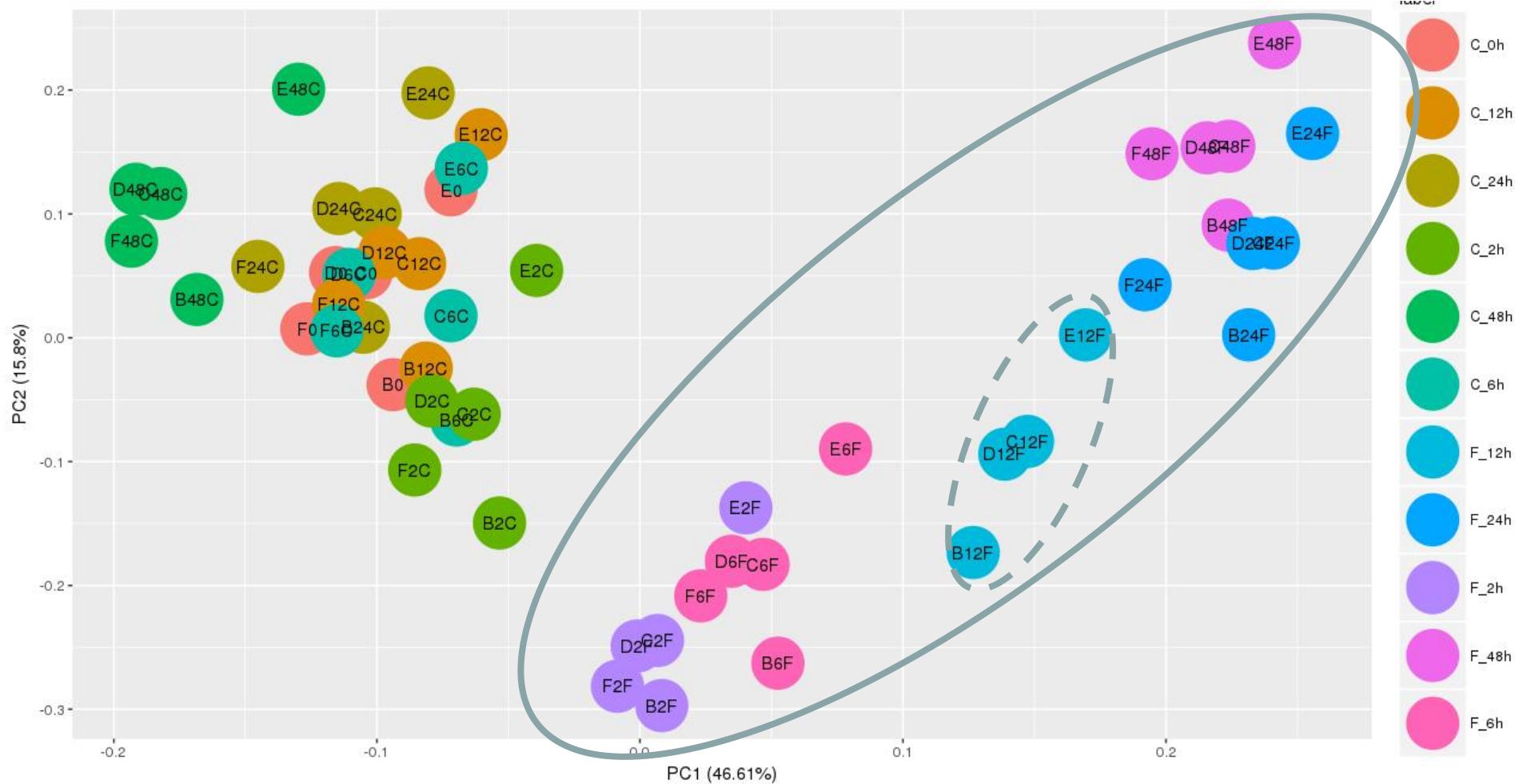
heatmap (Colv=T) of united genes



heatmap (Colv=F) of united genes

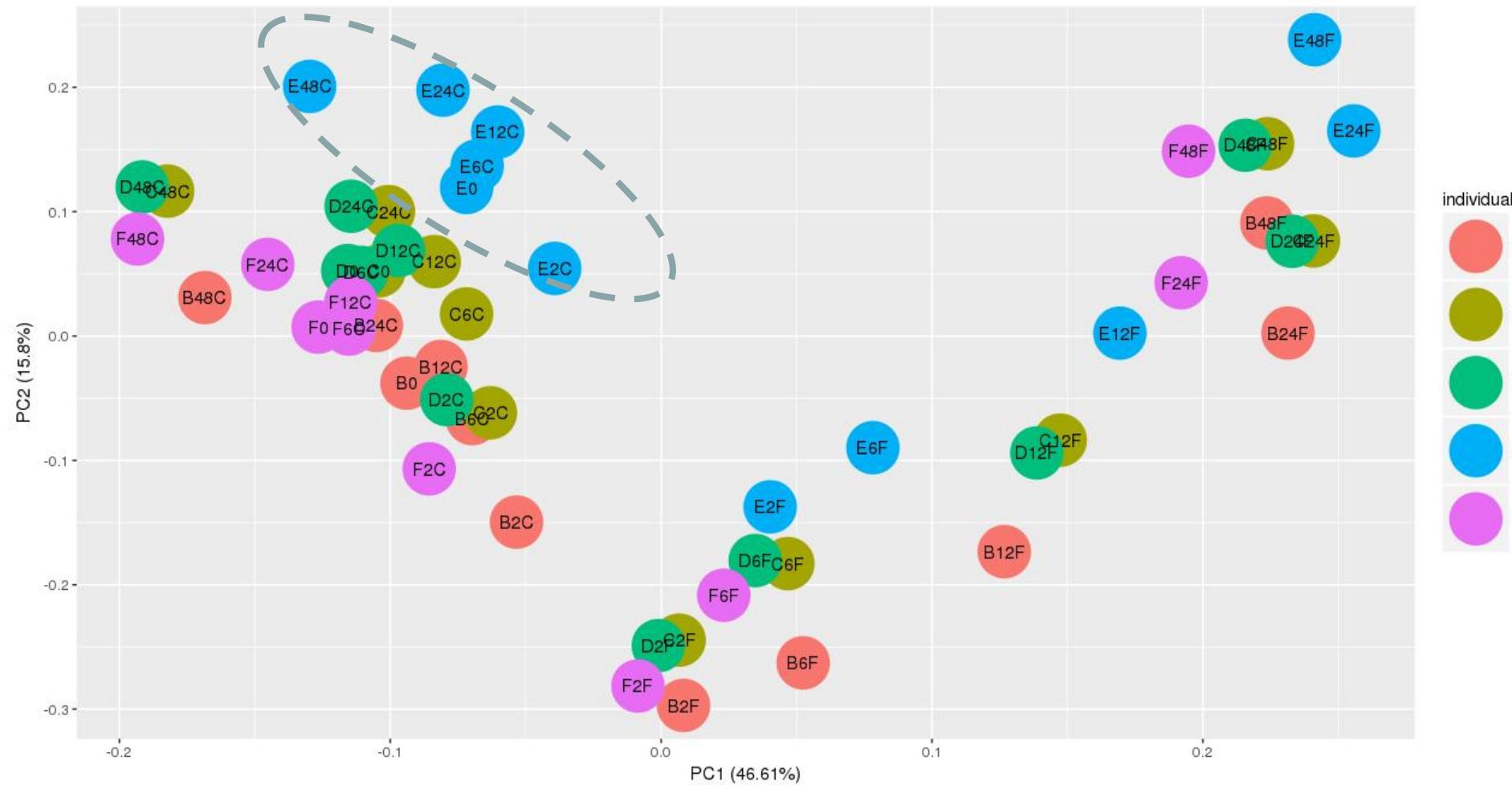


PCA of united DEGs from each timepoint



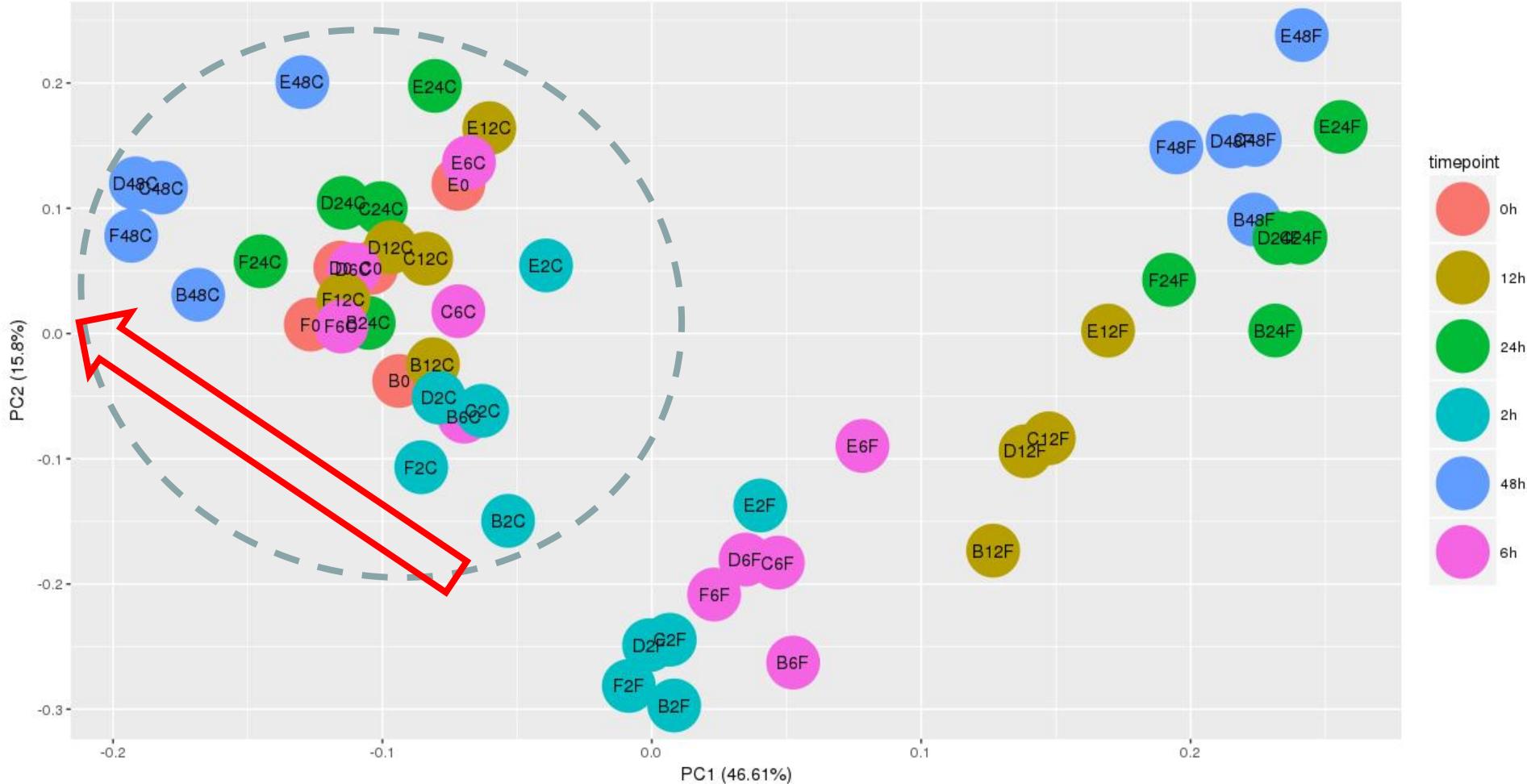
Cs and Fs, Fs from different timepoints can be clearly separated; while the ctrl group are individual-specific (next slide).

PCA of unioned DEGs from each timepoint



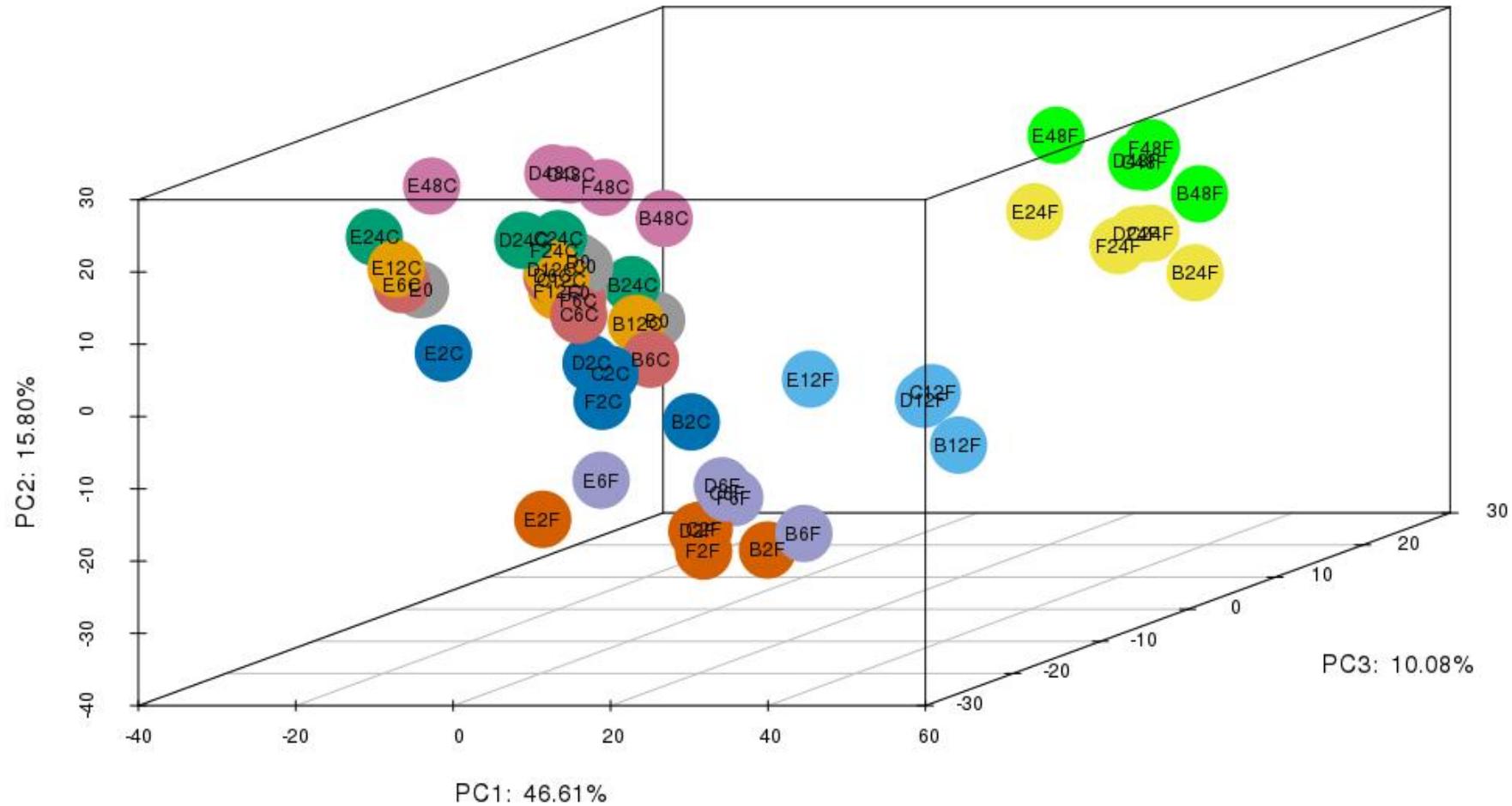
The ctrl group are individual-specific, representing no significant changes over time, compared with the Fn (next slide).

PCA of unioned DEGs from each timepoint

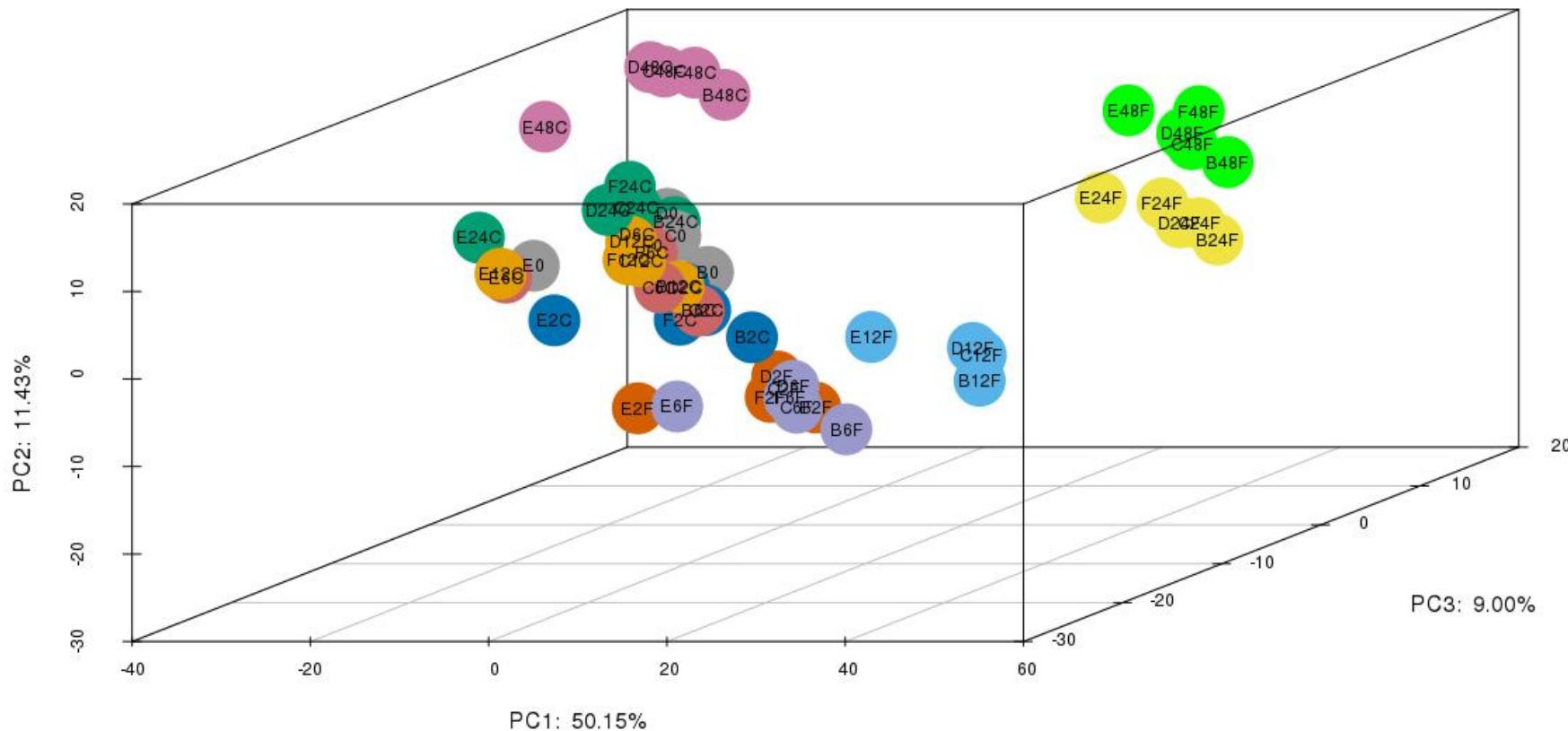


The ctrl group has no significant changes over time, compared with the Fn.

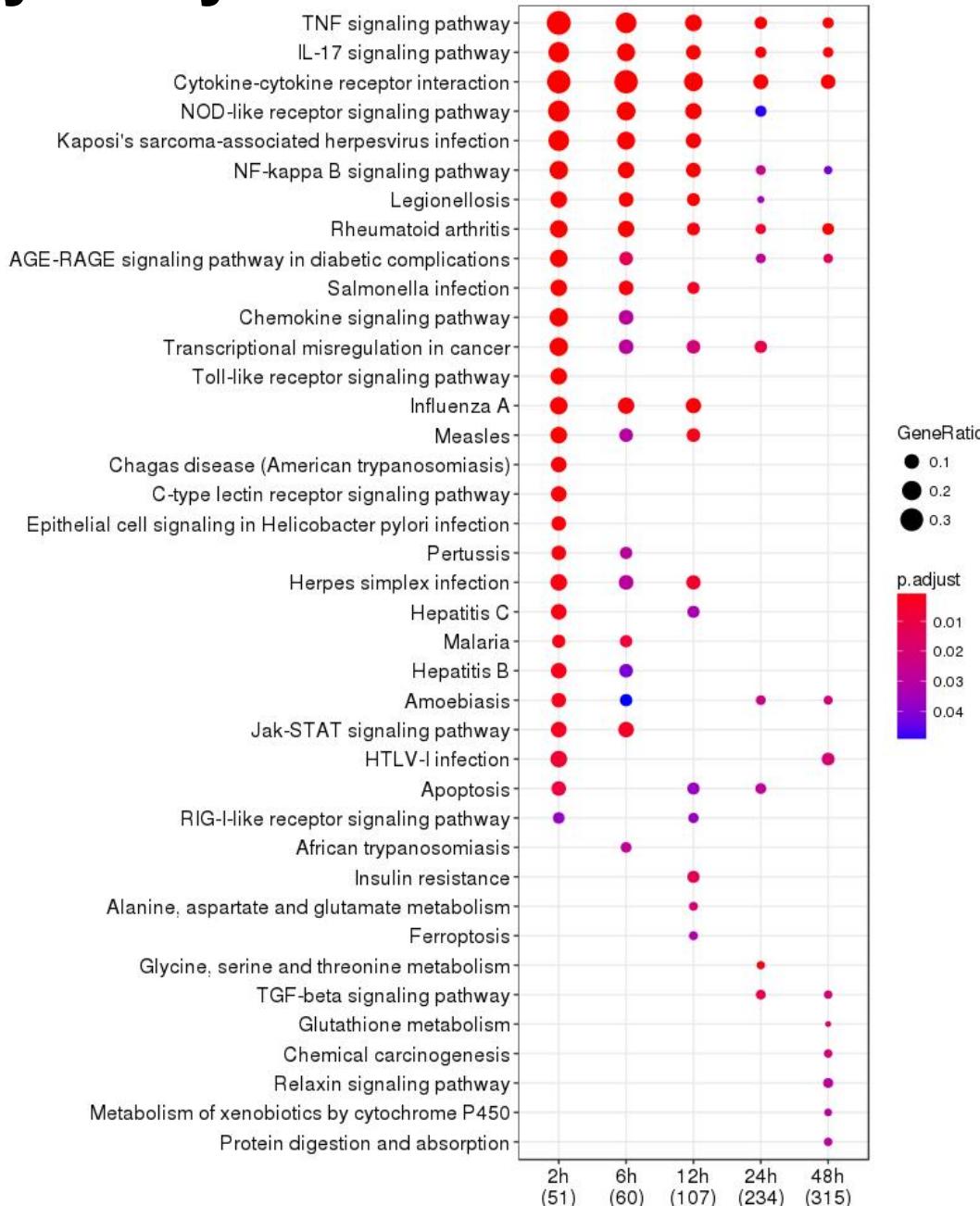
3D-PCA of unioned DEGs from each timepoint



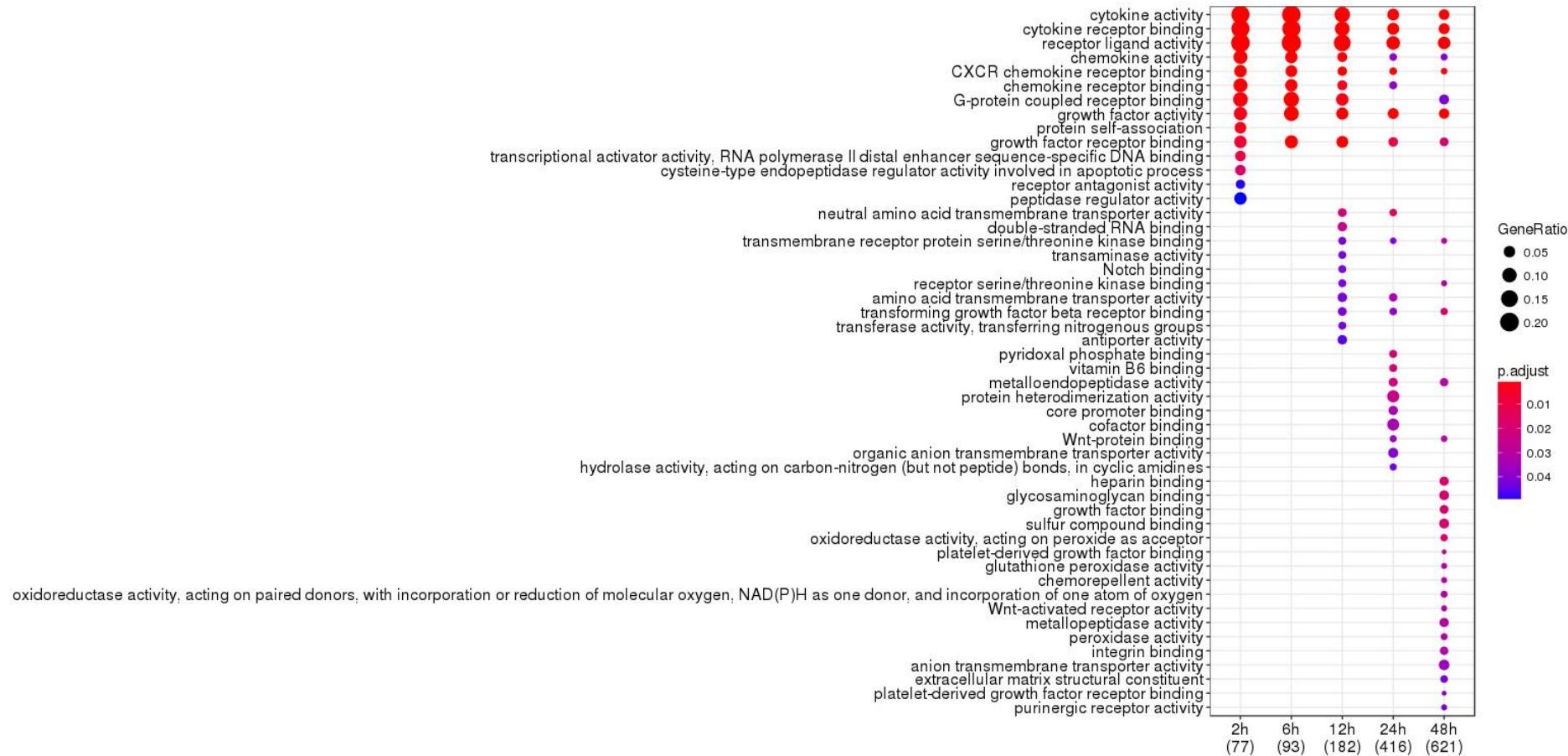
3D-PCA (scaled) of unioned DEGs from each timepoint



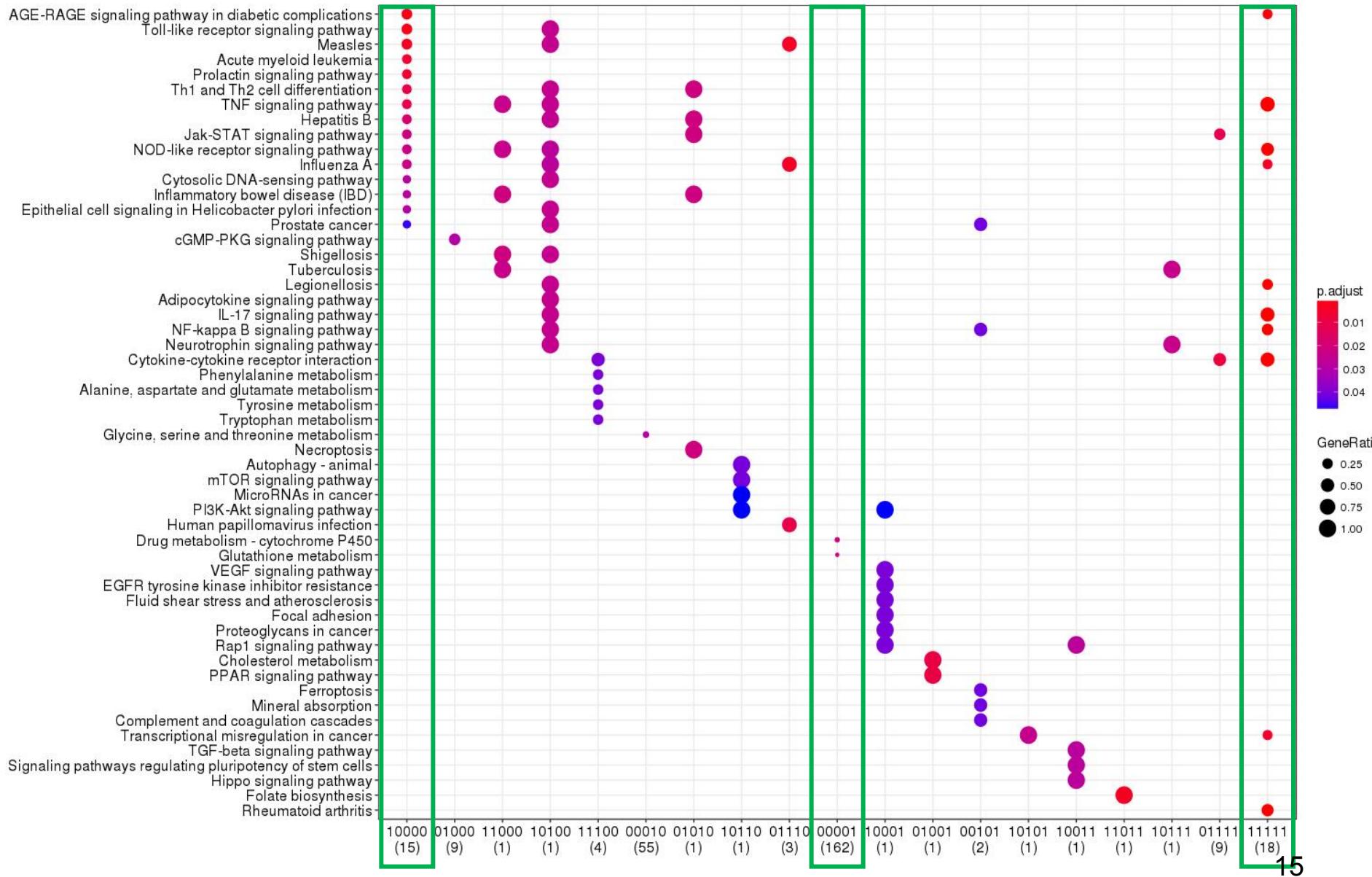
Pathway analysis of DEGs at each timepoint



GO analysis of DEGs at each timepoint

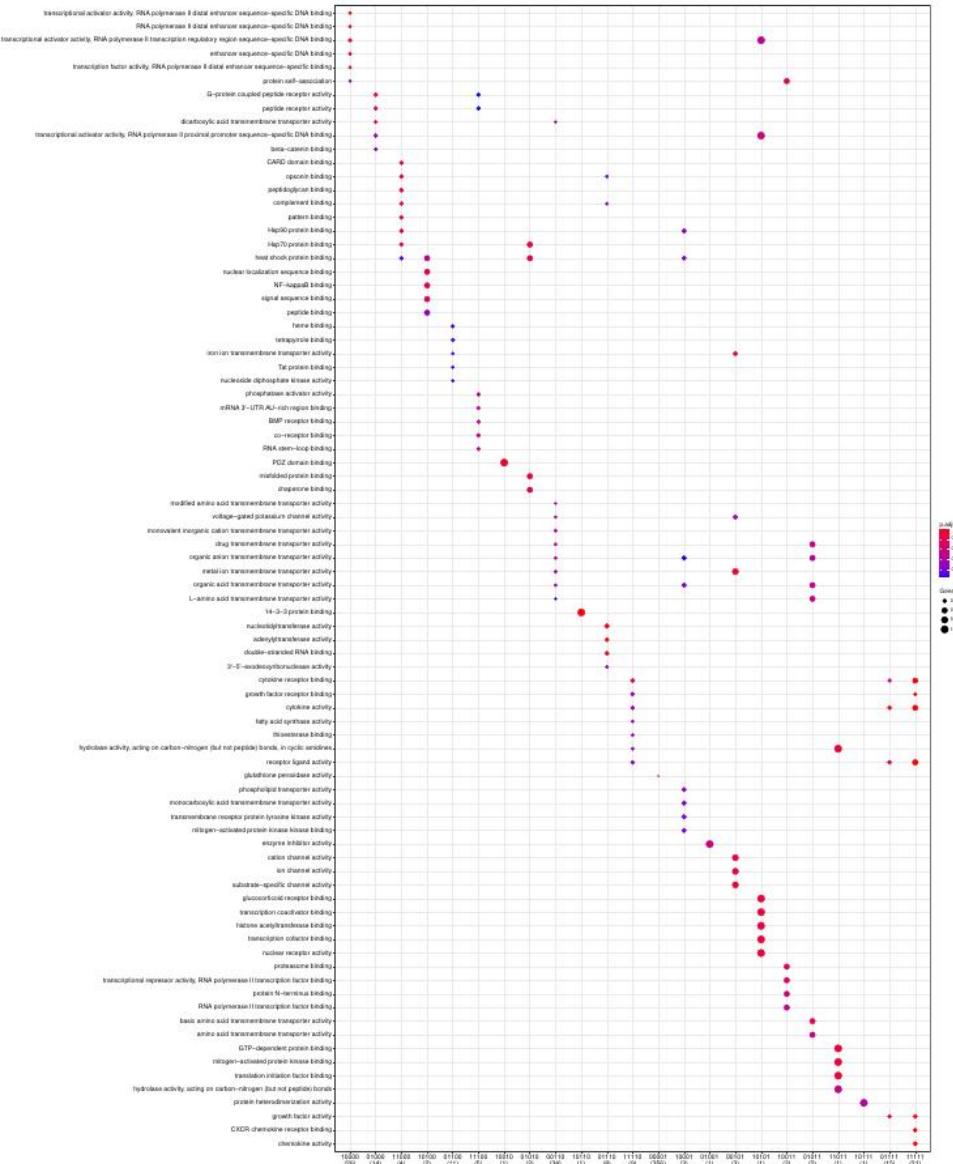


Pathway analysis for each part in ChowRuskey plot

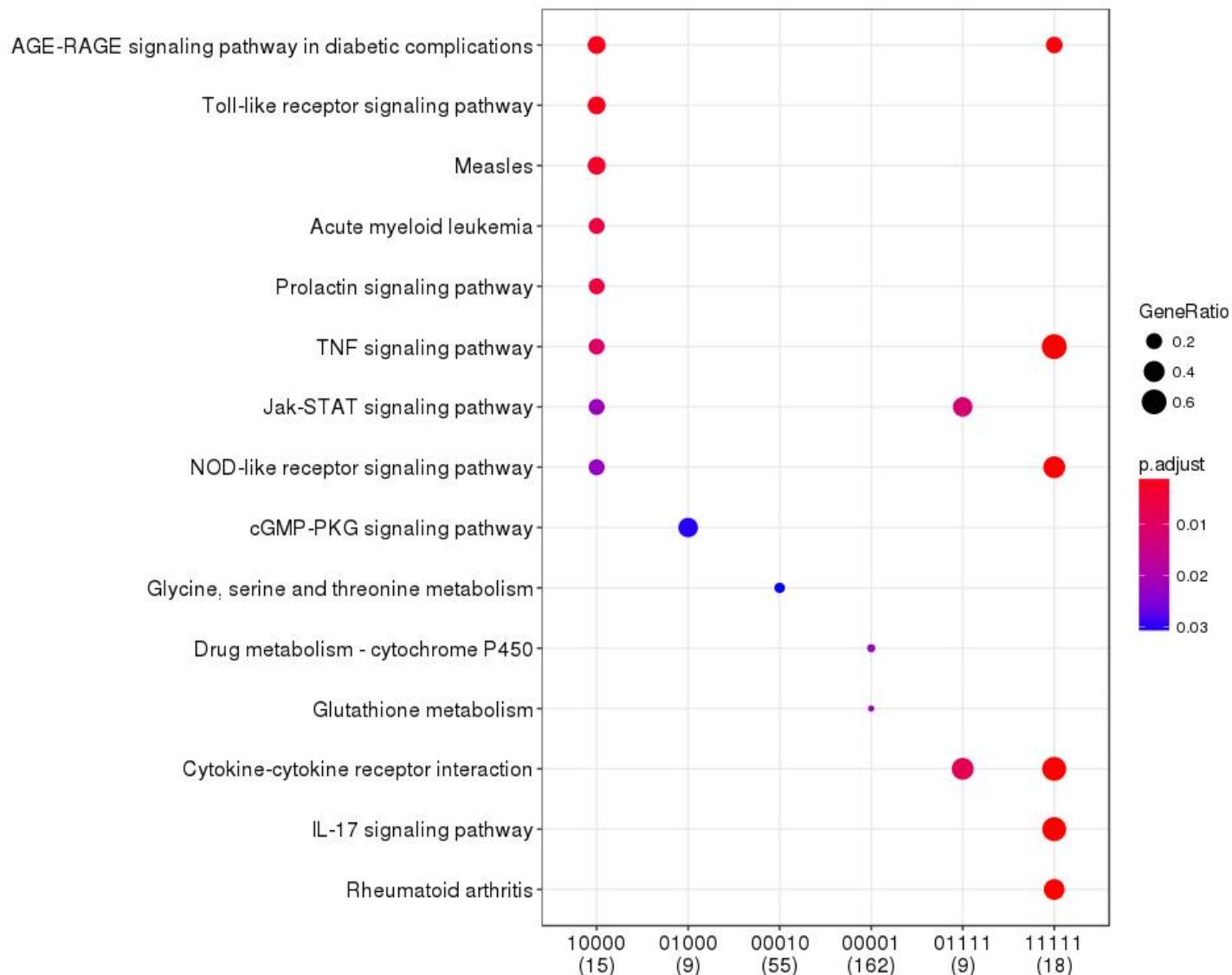


2h, 6h, 12h, 24h, 48h (1: existed; 0: non-existed)

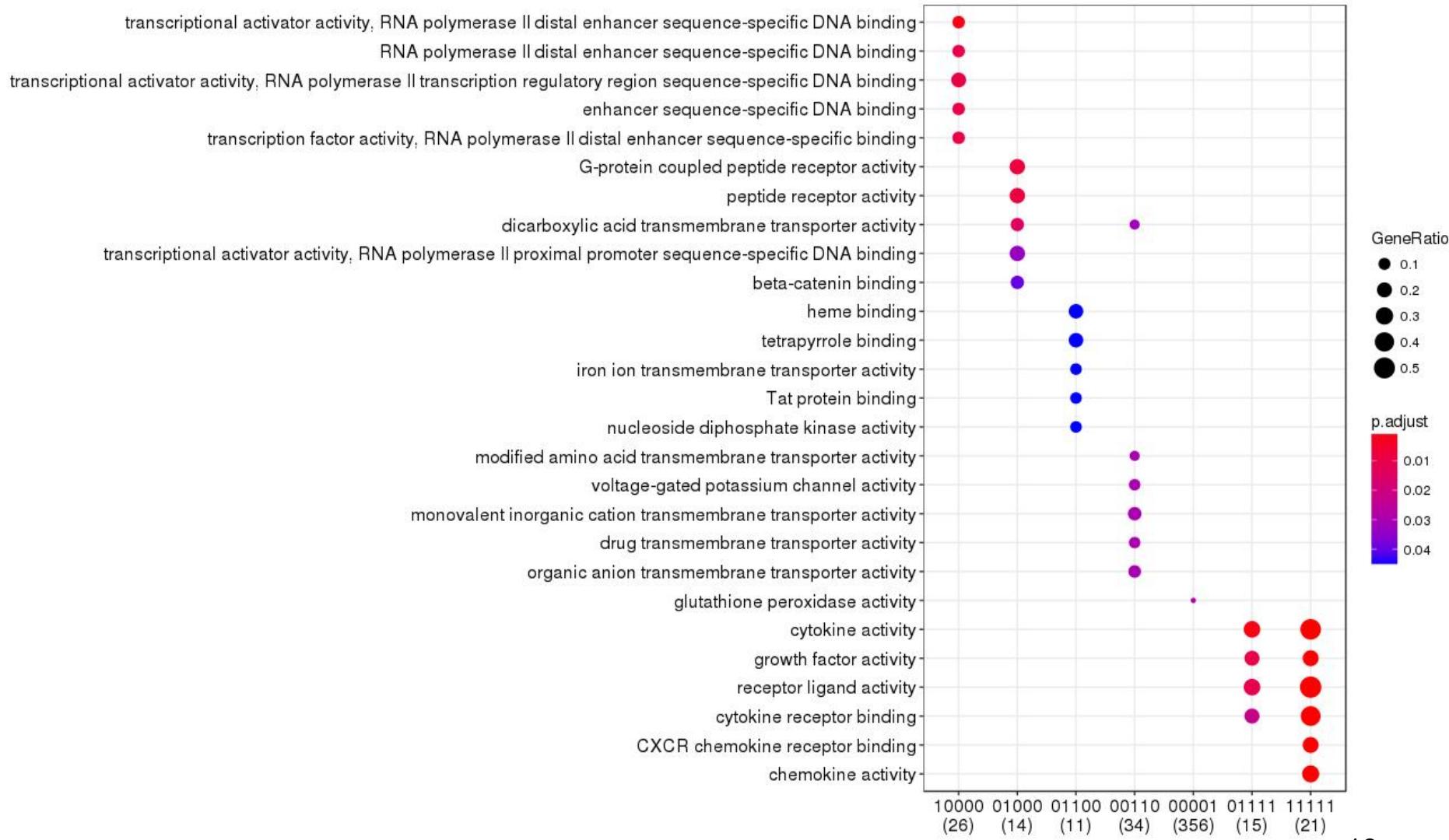
GO analysis for each part in ChowRuskey plot



Pathway analysis for each part in ChowRuskey plot (filtered)



GO analysis for each part in ChowRuskey plot (filtered)

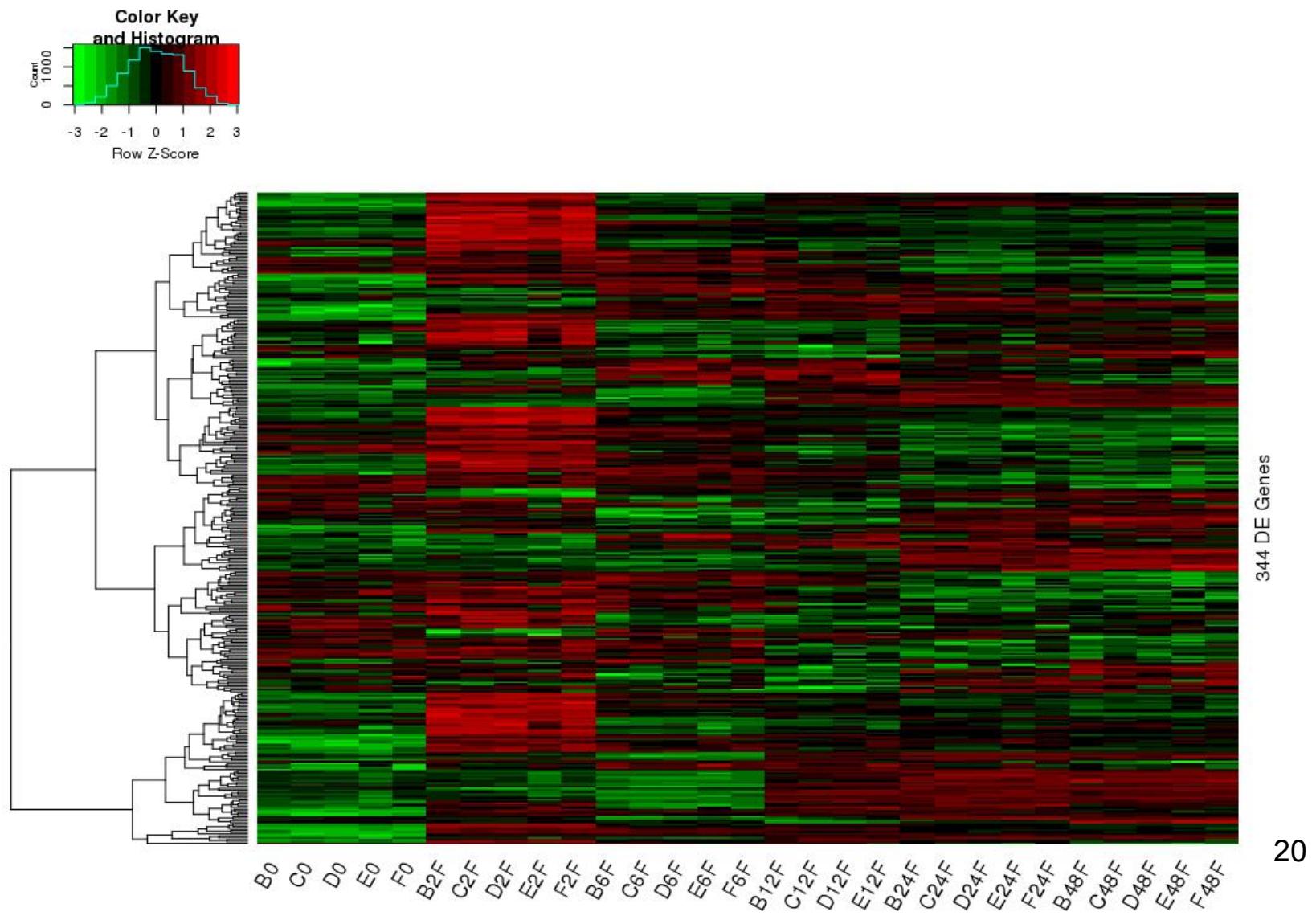


time series analysis

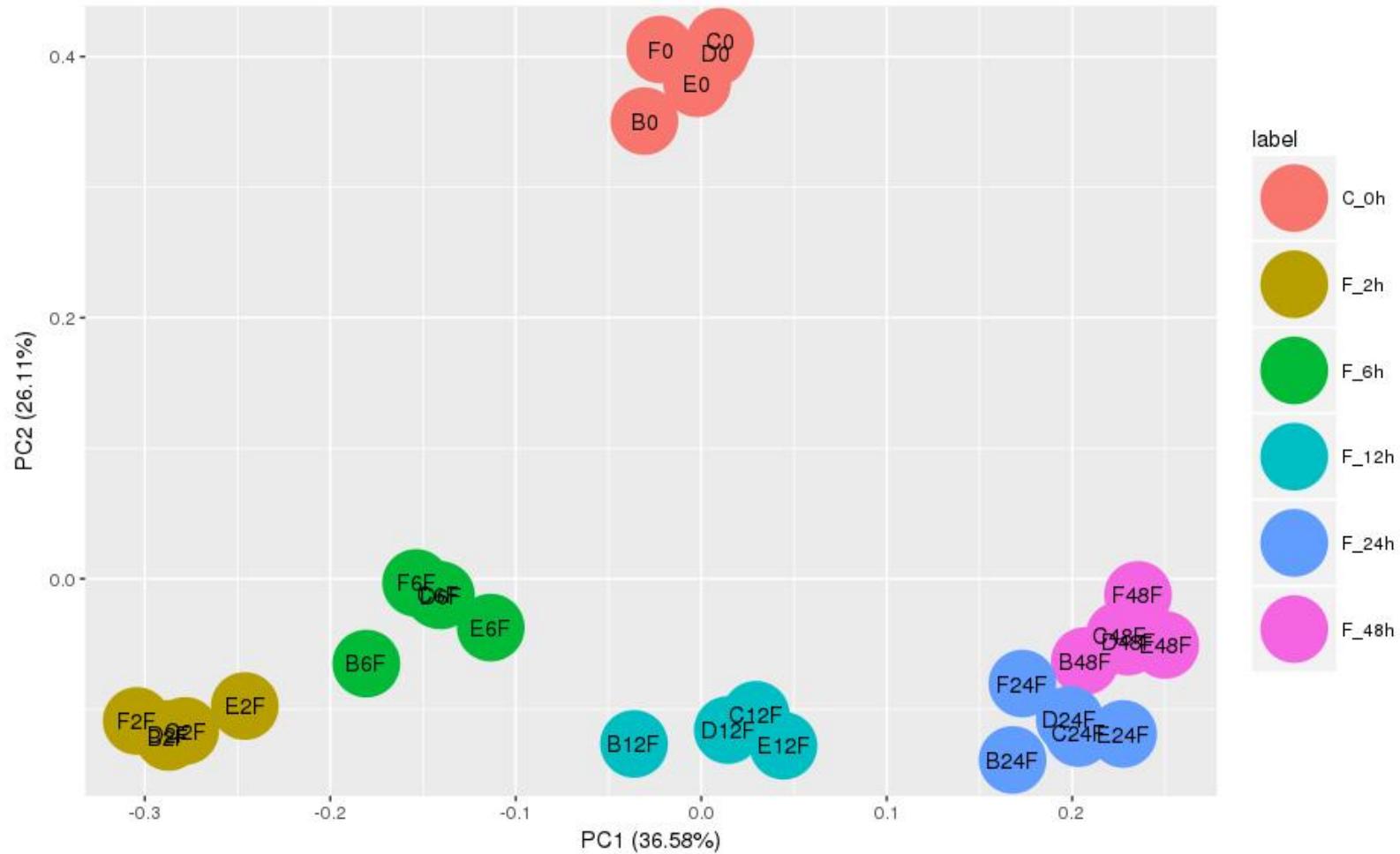
- DEGs from Fn group over time comparsion (F_2h - C_0h, F_6h - F_2h, F_12h - F_6h, F_24h - F_12h, F_48h - F_24h)

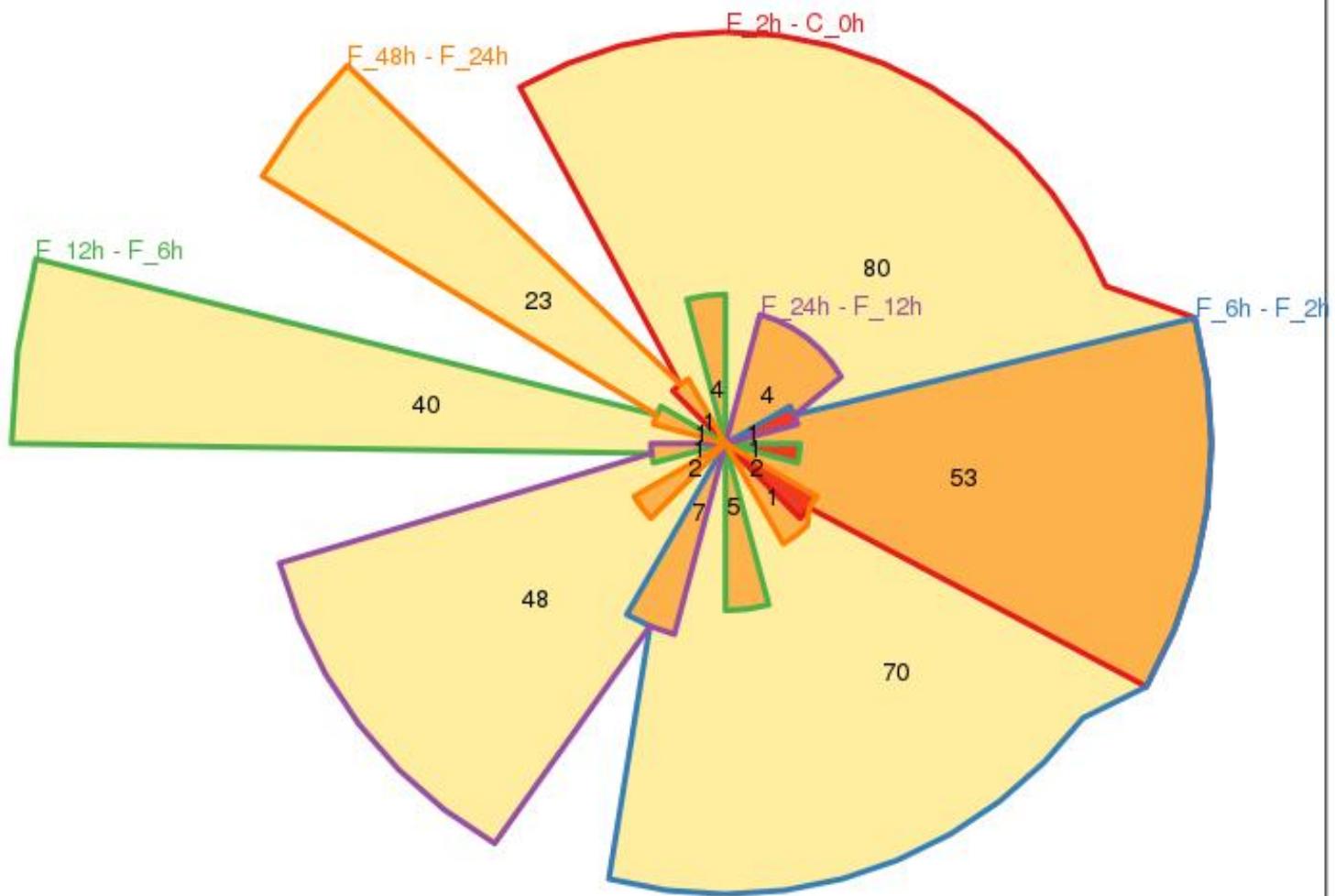
```
sapply(DEA_list$DEG, length)
F_2h - C_0h    F_6h - F_2h   F_12h - F_6h  F_24h - F_12h  F_48h - F_24h
146           140            52             63            30
```

```
> length(union_time_course_DEG)
[1] 846
> length(union_time_indep_DEG)
[1] 971
> length(intersect(union_time_indep_DEG, union_time_course_DEG))
[1] 397
```



PCA





KEGG analysis

AGE-RAGE signaling pathway in diabetic complications



Cytokine-cytokine receptor interaction



NF-kappa B signaling pathway



TNF signaling pathway



Th1 and Th2 cell differentiation



IL-17 signaling pathway



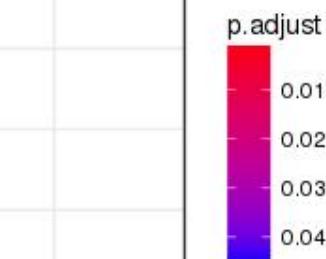
C-type lectin receptor signaling pathway



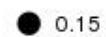
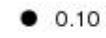
Osteoclast differentiation



Complement and coagulation cascades



GeneRatio



Human papillomavirus infection



Glycosphingolipid biosynthesis - ganglio series



10000
(47)

01000
(32)

11000
(29)

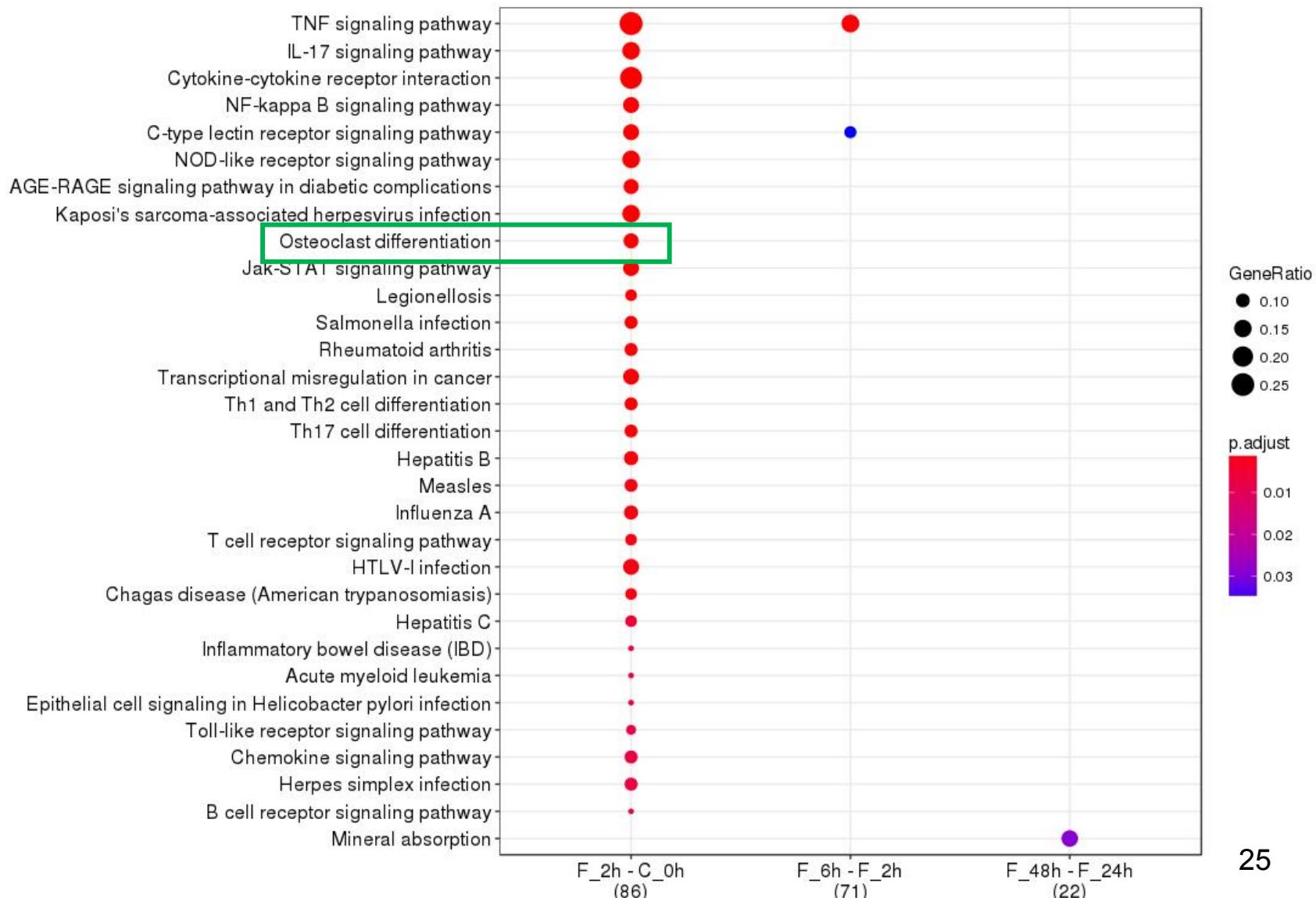
00010
(24)

F_2h - C_0h, F_6h - F_2h, F_12h - F_6h, F_24h - F_12h, F_48h - F_24h²³

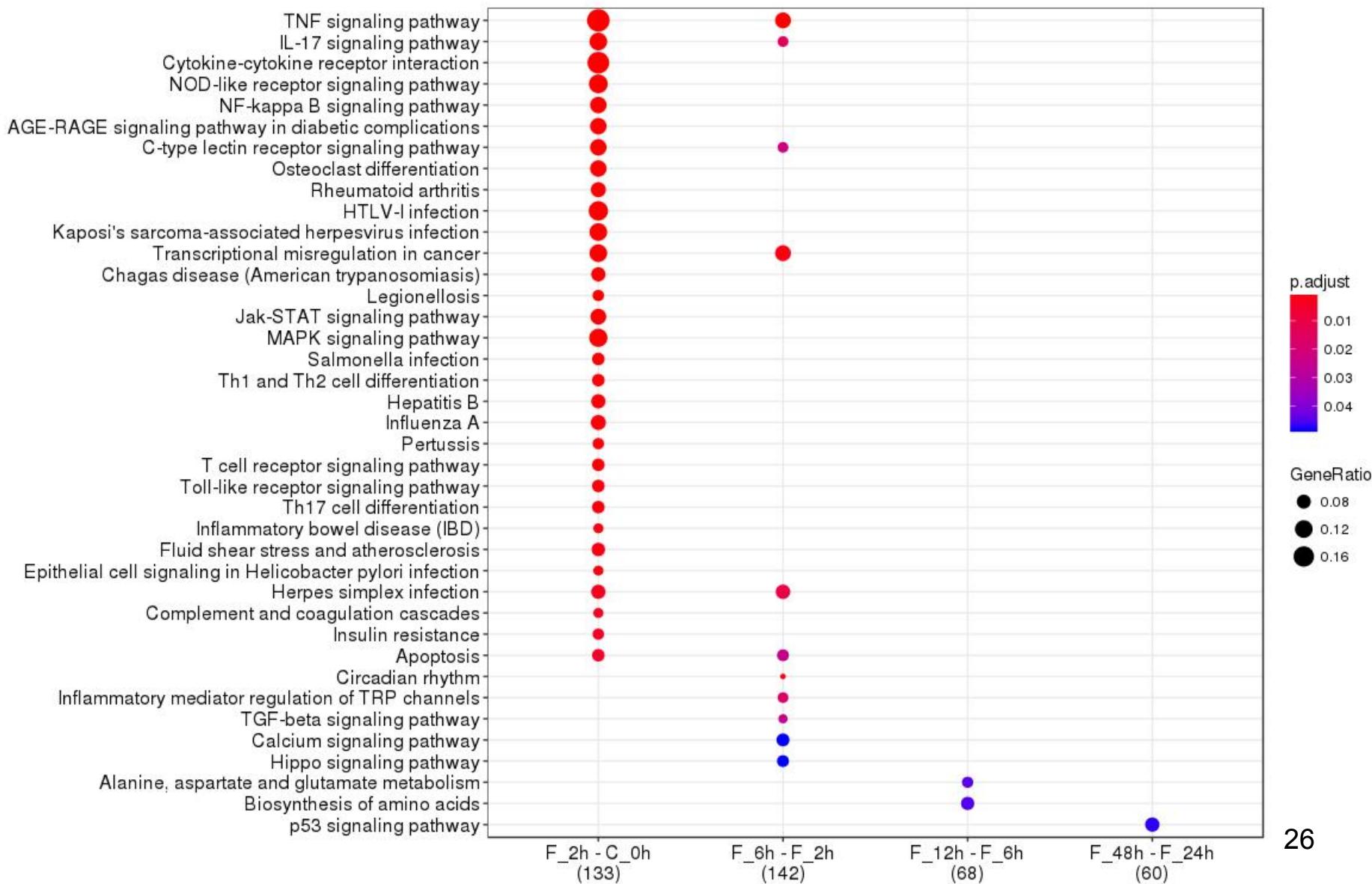
GO analysis



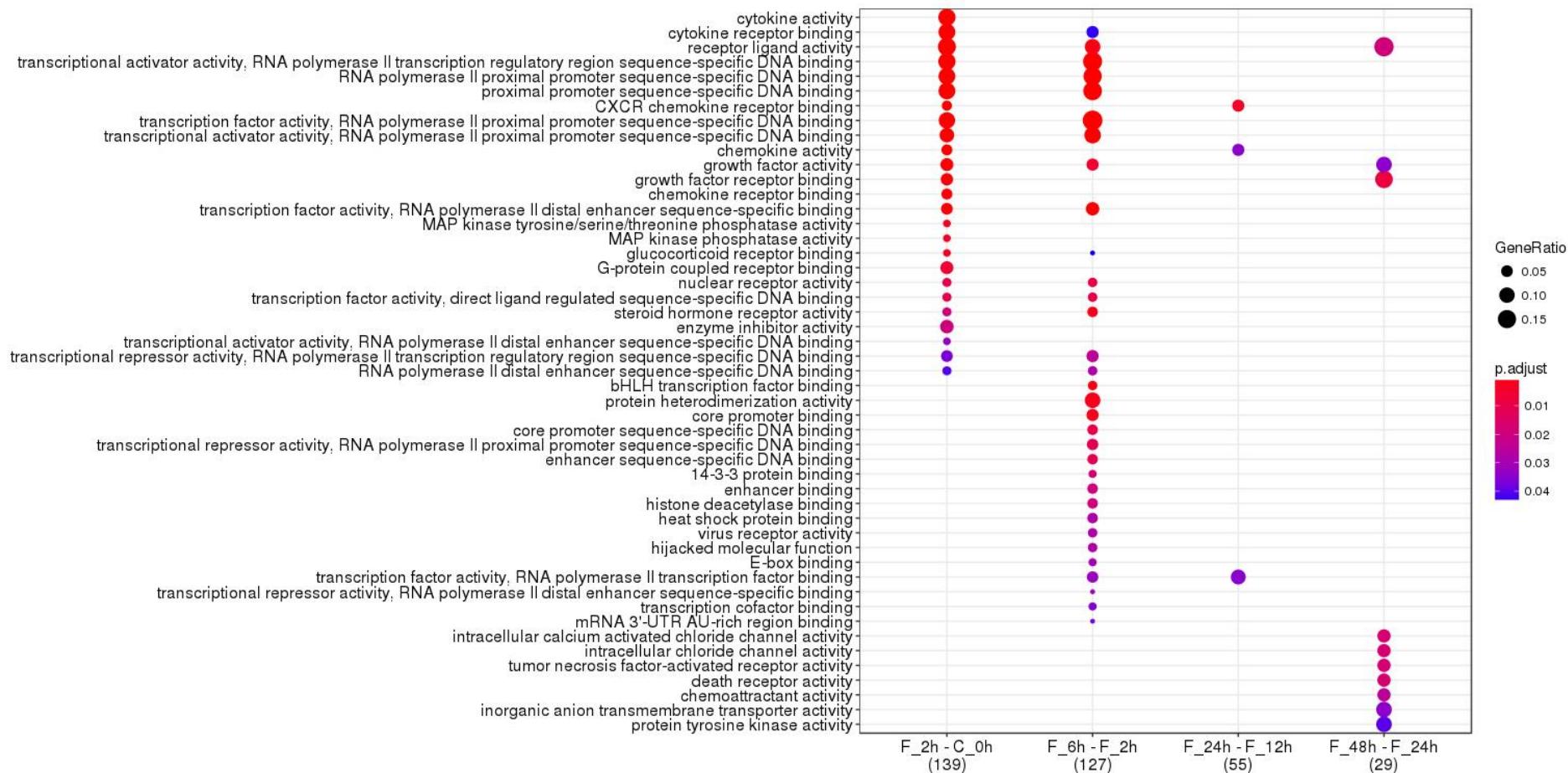
KEGG analysis for time-course DEG ($\log FC \geq 2$)



KEGG analysis for time-course DEG ($\log FC \geq 1.5$)



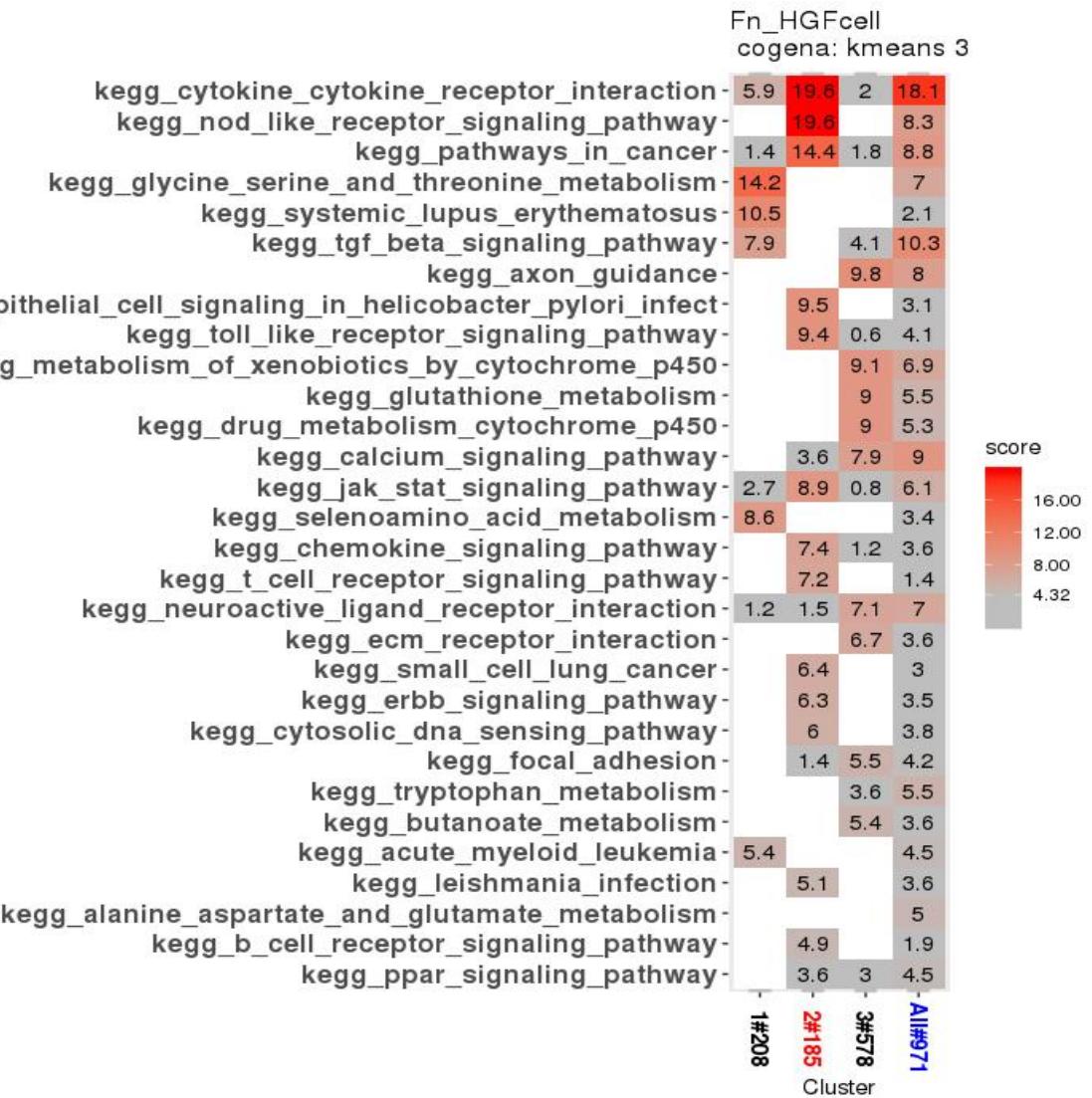
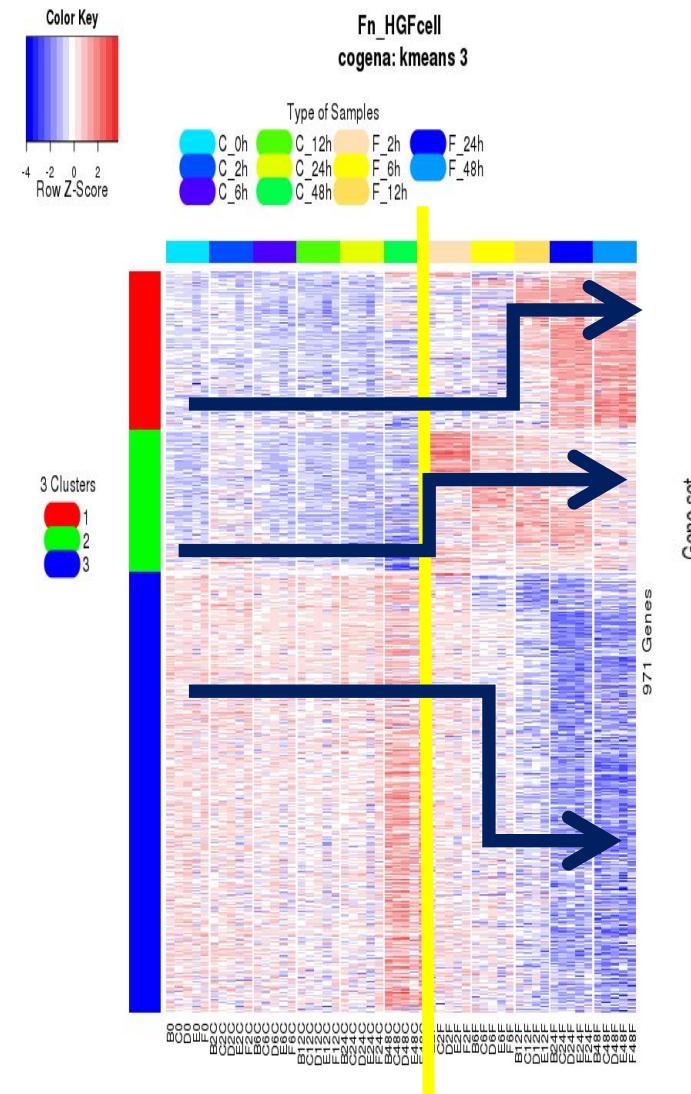
GO analysis for time-course DEG



co-expression analysis

- cogena analysis
 - co-expression analysis
 - KEGG/GO pathway analysis
 - GO BP and MF analysis for cluster 2/1

cogena co-expression and KEGG analysis



C1: up after 12h; C2: up immediately; C3: down after 12h

enriched KEGG pathways

C1 (up after 12h):

- kegg_glycine_serine_and_threonine_metabolism
- kegg_systemic_lupus_erythematosus
- kegg_tgf_beta_signaling_pathway
- kegg_selenoamino_acid_metabolism

C2 (up immediately):

- kegg_cytokine_cytokine_receptor_interaction
- kegg_nod_like_receptor_signaling_pathway
- kegg_pathways_in_cancer
- kegg_toll_like_receptor_signaling_pathway
- kegg_epithelial_cell_signaling_in_helicobacter_pylori_infect
- kegg_toll_like_receptor_signaling_pathway
- kegg_jak_stat_signaling_pathway
- kegg_chemokine_signaling_pathway
- kegg_t_cell_receptor_signaling_pathway
- kegg_small_cell_lung_cancer
- kegg_erbb_signaling_pathway
- kegg_cytosolic_dna_sensing_pathway

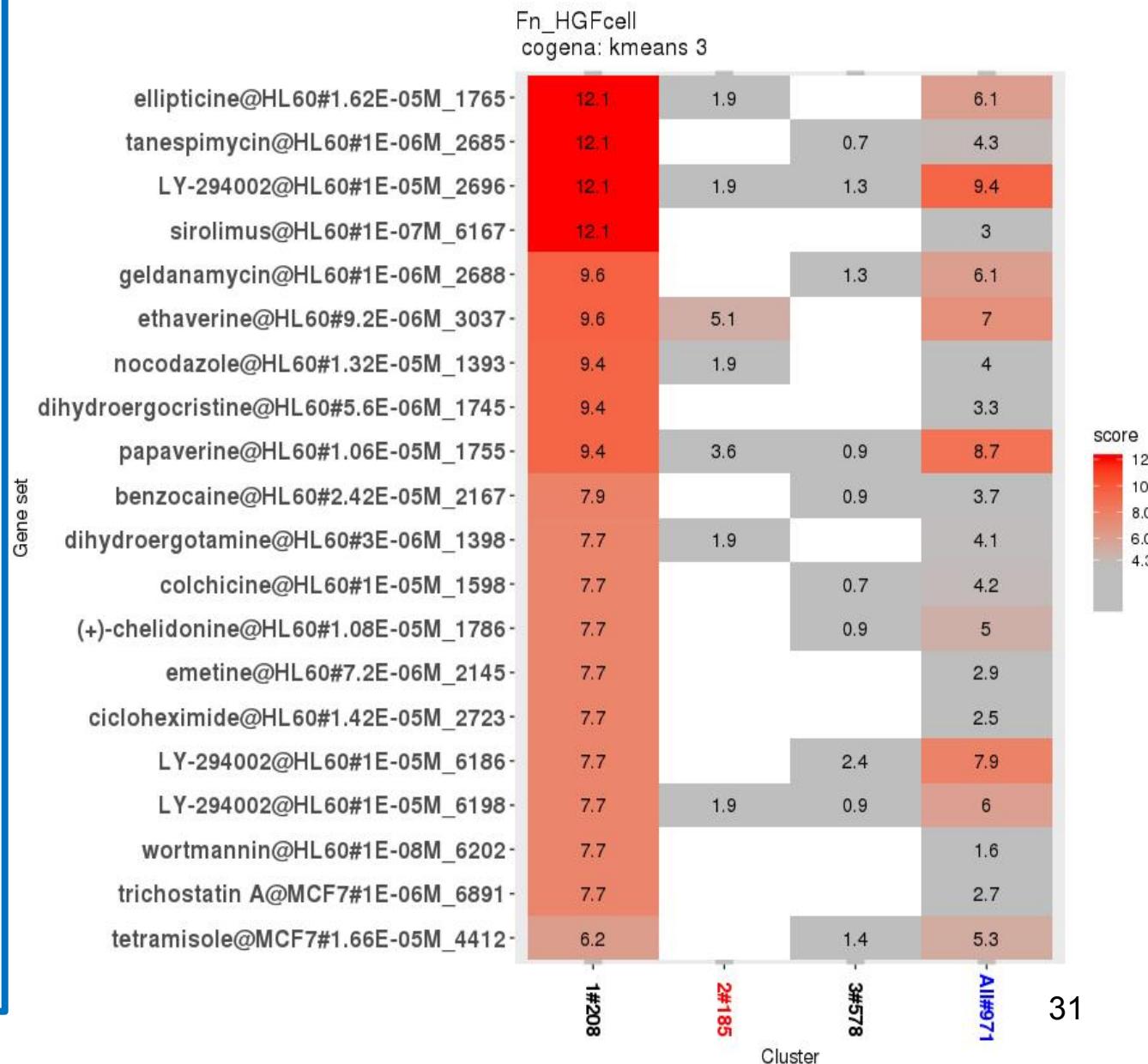
C3 (down after 12h):

- kegg_axon_guidance
- kegg_metabolism_of_xenobiotics_by_cytochrome_p450
- kegg_glutathione_metabolism
- kegg_drug_metabolism_cytochrome_p45
- kegg_calcium_signaling_pathway
- kegg_neuroactive_ligand_receptor_interaction
- kegg_ecm_receptor_interaction

- **TGF betas** cause the transcription of mRNAs involved in **apoptosis, extracellular matrix neogenesis and immunosuppression**.
- The **ErbB** family of receptor tyrosine kinases (RTKs) couples binding of extracellular growth factor ligands to intracellular signaling pathways regulating diverse biologic responses, including **proliferation, differentiation, cell motility³⁰, and survival**.

Drug repositioning (C1+CMapDn)

tanespimycin,
Geldanamycin: Hsp90 inhibitor; antibiotics.
trichostatin: antifungal antibiotic.
Etravirine: treating HIV
Sirolimus: immunosuppressant, inhibits activation of T cells and B cells by reducing their sensitivity to interleukin-2 (IL-2) through mTOR inhibition.
wortmannin, LY-294002: PI3K inhibitor, also inhibit other PI3K-related enzymes such as mTOR, DNA-PKcs, some phosphatidylinositol 4-kinases, myosin light chain kinase (MLCK) and MAPK at high concentrations.



Drug repositioning (C2+CMapDn)

Adriamycin:抗肿瘤抗生素

ciclosporin:

immunosuppressant.

Tacrolimus:

immunosuppressant, inhibiting the production of interleukin-2, a molecule that promotes the development and proliferation of T cells, which are vital to the body's learned (or adaptive) immune response.

Rimexolone: a

glucocorticoid steroid used to treat inflammation in the eye .

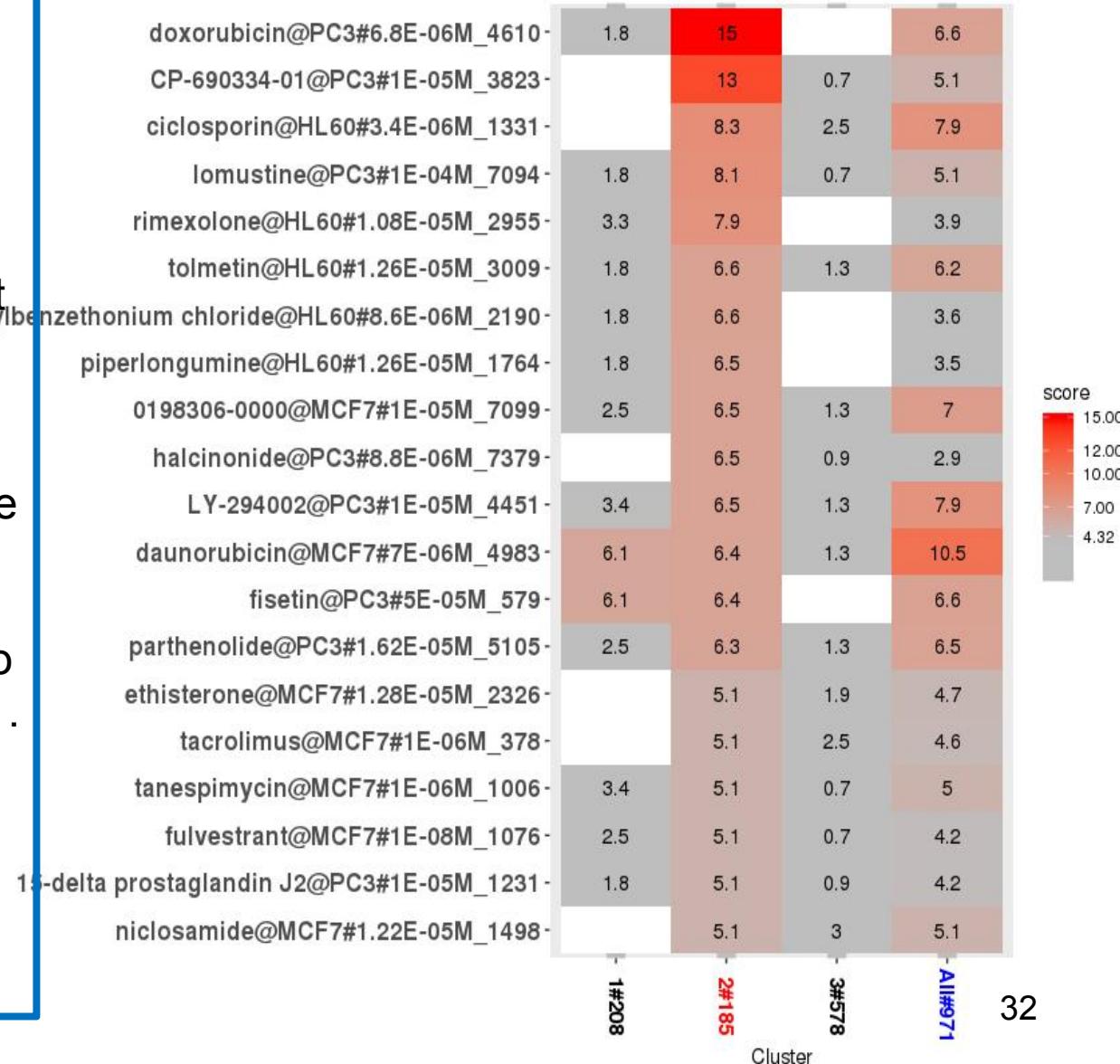
tolmetin: non-steroidal anti-inflammatory drug.

tanespimycin,

methylbenzethonium chloride: antiseptic.

ref Wikipedia

Fn_HGFcell
cogena: kmeans 3



Drug repositioning (C3+CMapUp)

Rifabutin is an antibiotic used to treat tuberculosis and prevent and treat *Mycobacterium avium* complex.

Trichostatin: an antifungal antibiotic.

Zalcitabine: treatment of HIV/AIDS.

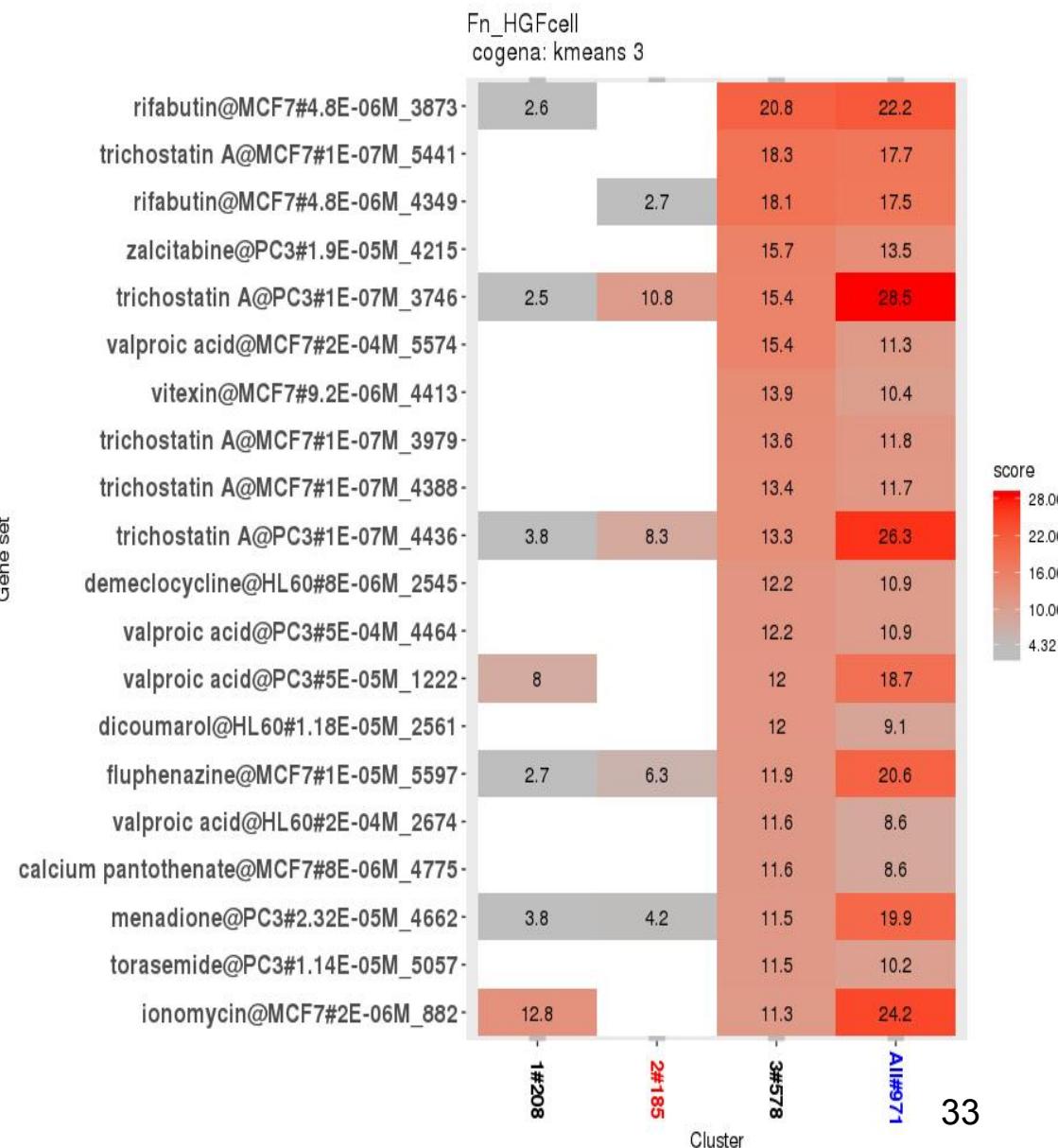
demeclacycline: treat various types of bacterial infections.

Pantothenic acid, also called vitamin B5, synthesize and metabolize proteins, carbohydrates, and fats.

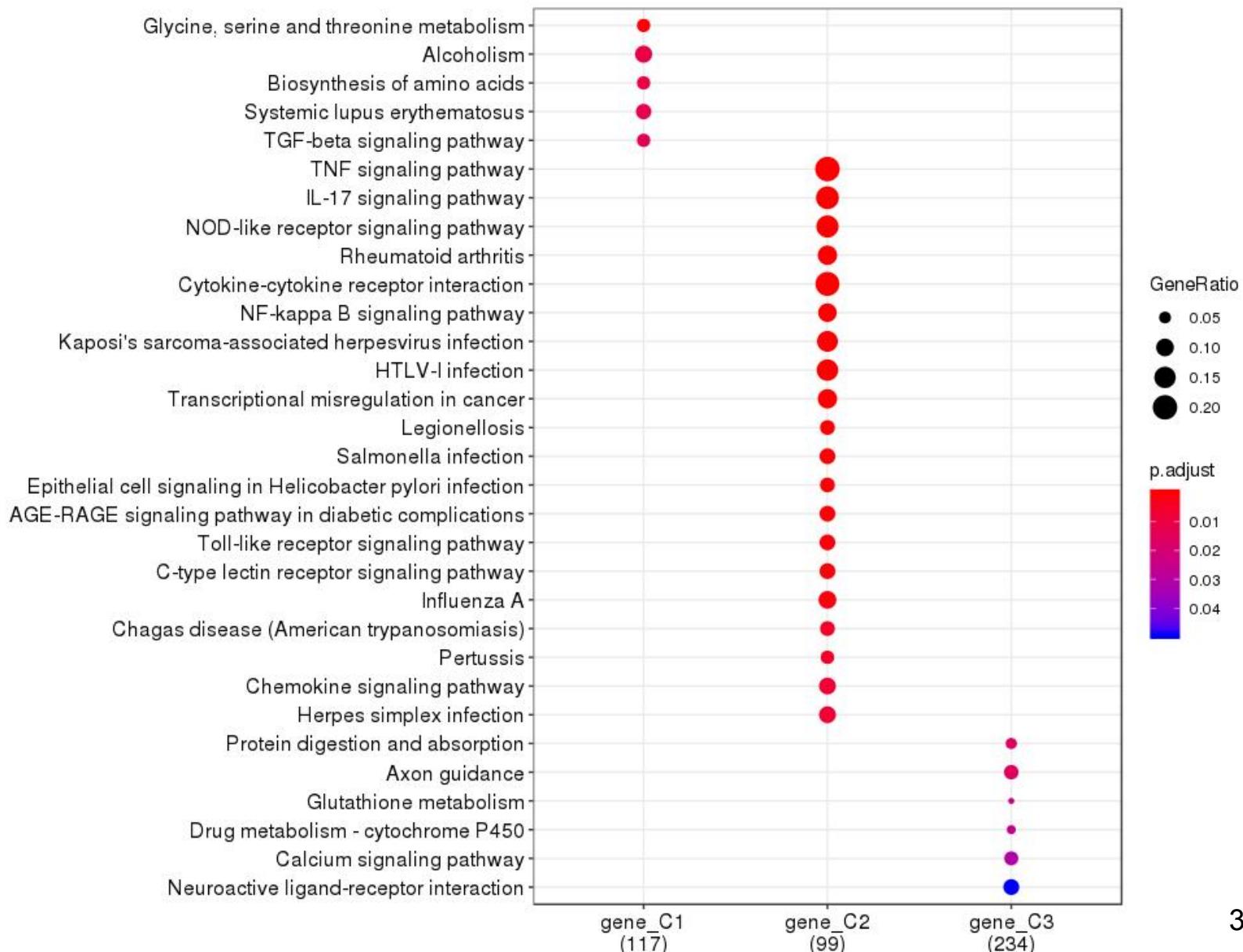
Menadione: occasionally used as a nutritional supplement in animal feed because of its vitamin K activity.

Ionomycin is an ionophore produced by the bacterium *Streptomyces conglobatus*. It is used in research to raise the intracellular level of calcium (Ca^{2+}) and as a research tool to understand Ca^{2+} transport across biological membranes. It is also used to stimulate the intracellular production of the following cytokines; interferon, perforin, IL-2, and IL-4 - usually in conjunction with PMA. These cytokines are important in the inflammatory response.

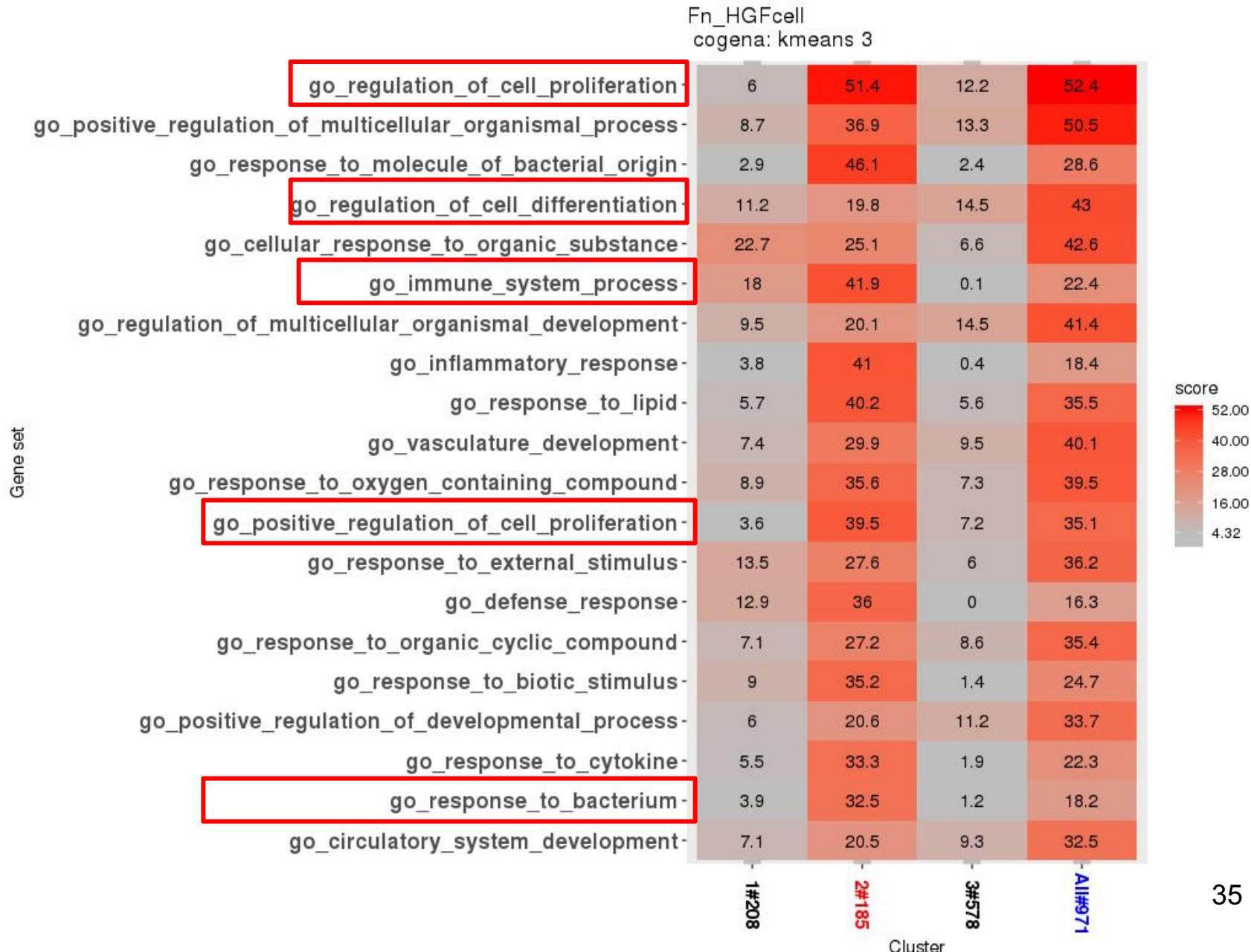
ref Wikipedia



enriched KEGG pathways by compareCluster

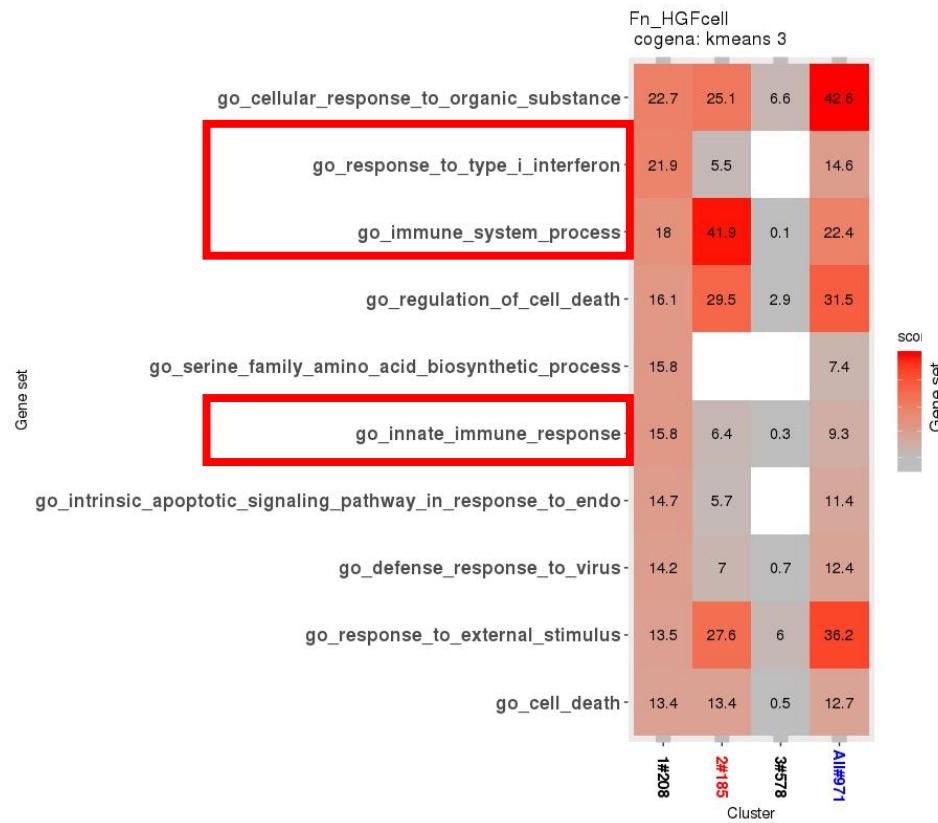


cogena co-expression and GO analysis

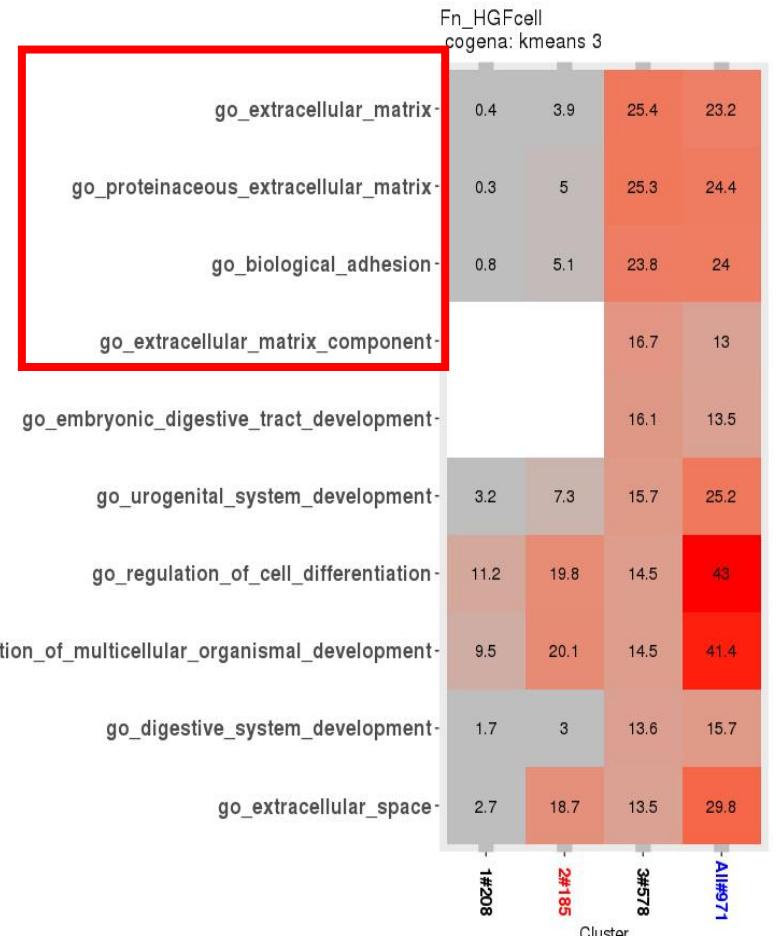


cogena co-expression and GO analysis

Gene set

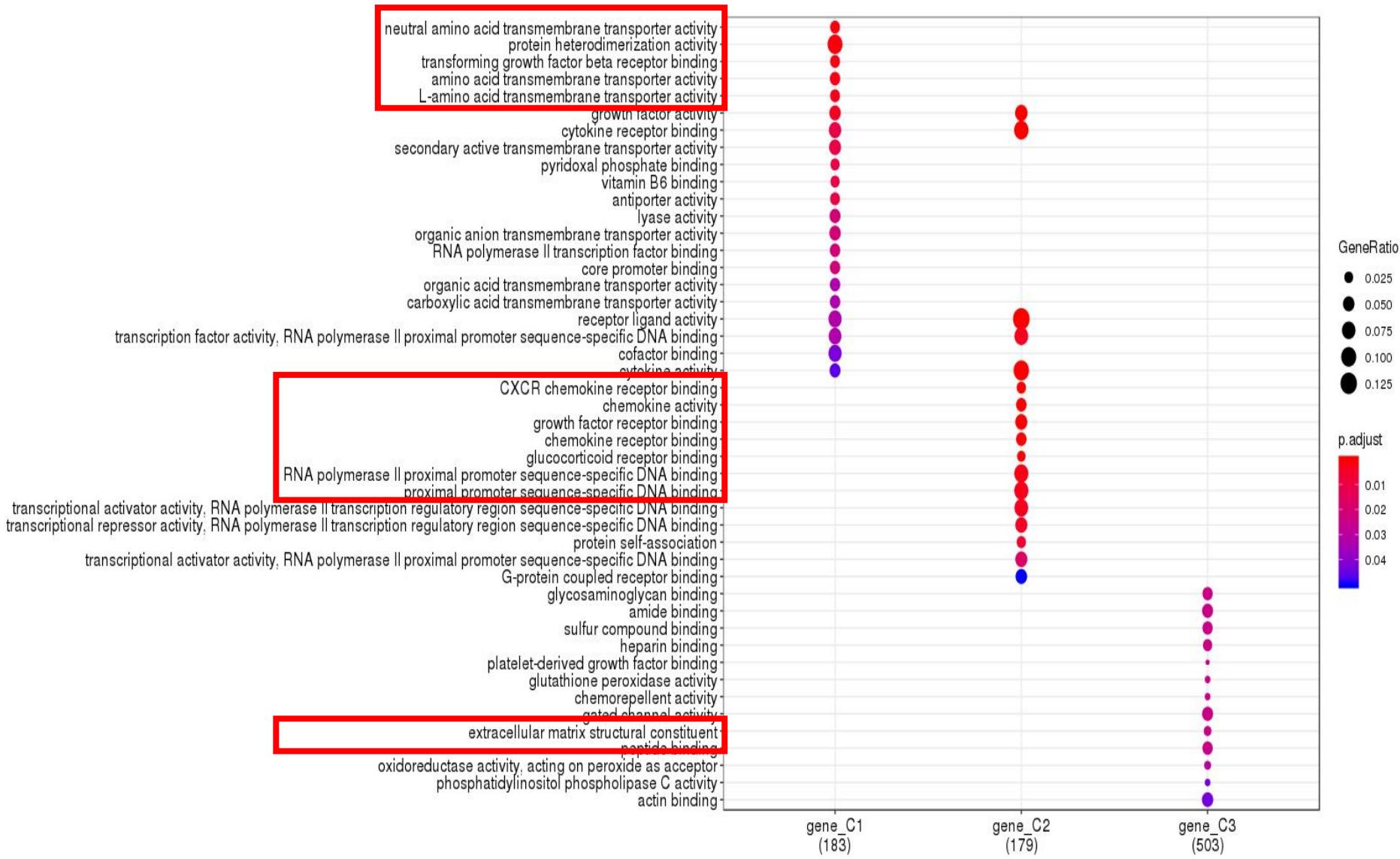


ranked by C1

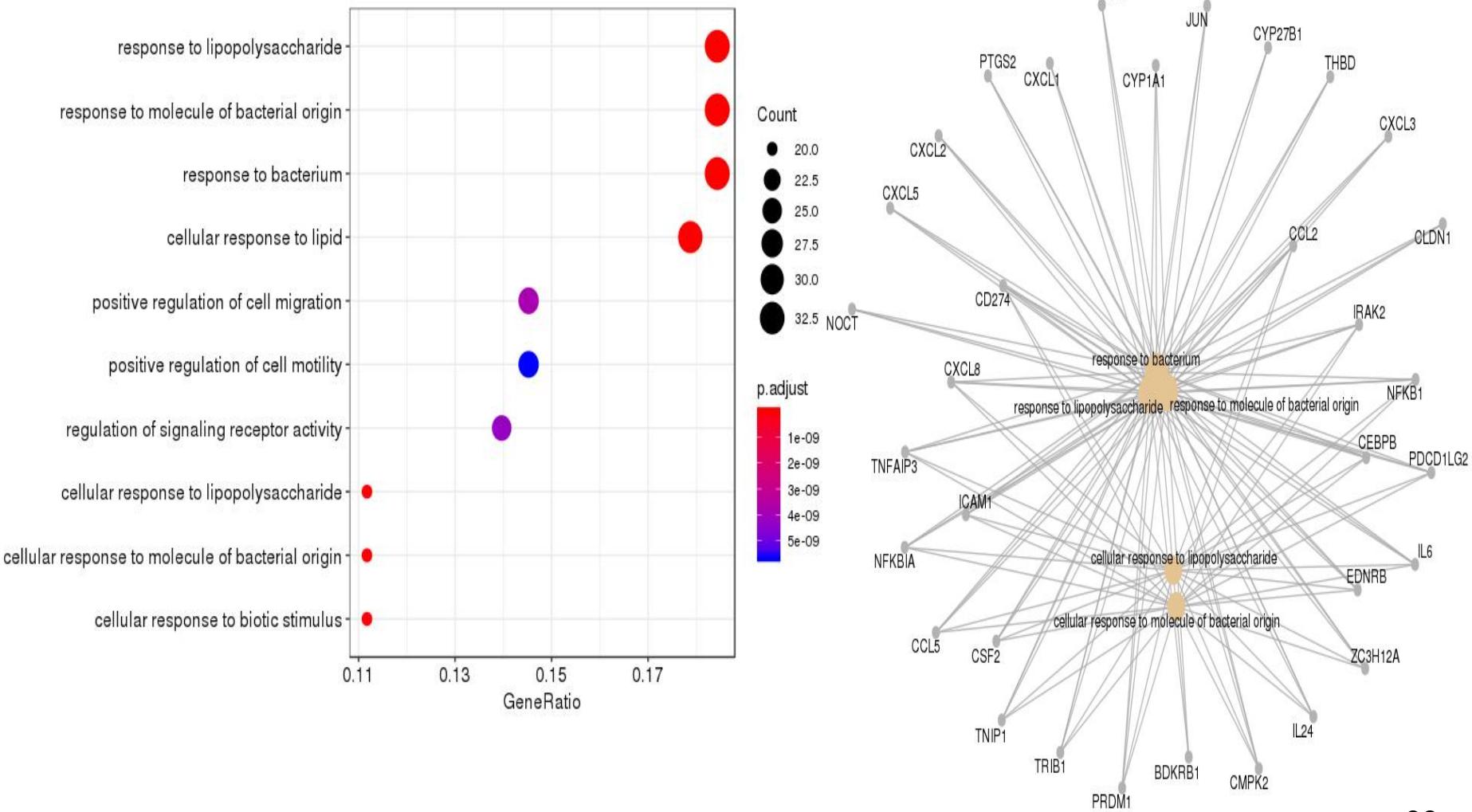


ranked by C3

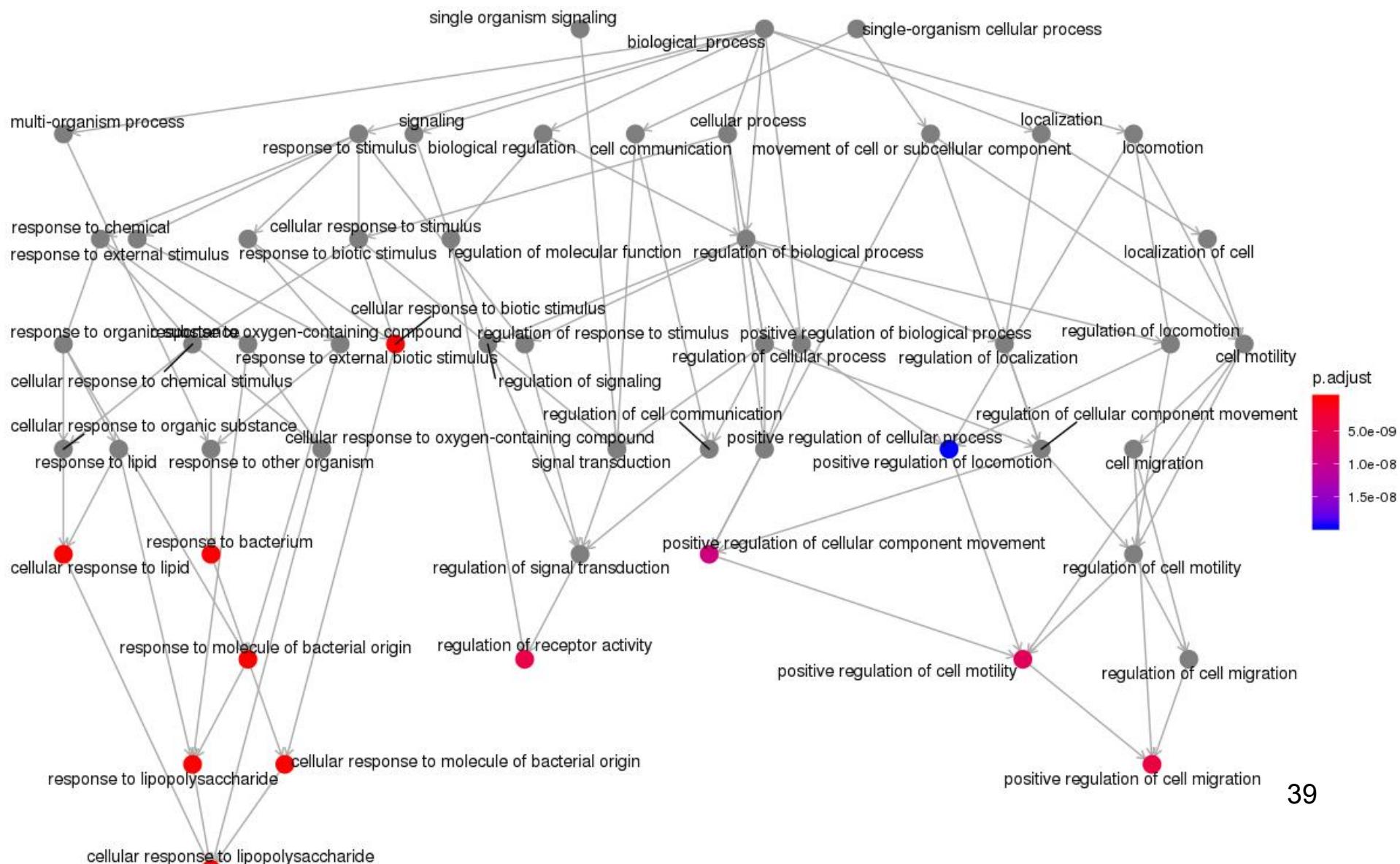
GO analysis based on ClusterProfiler



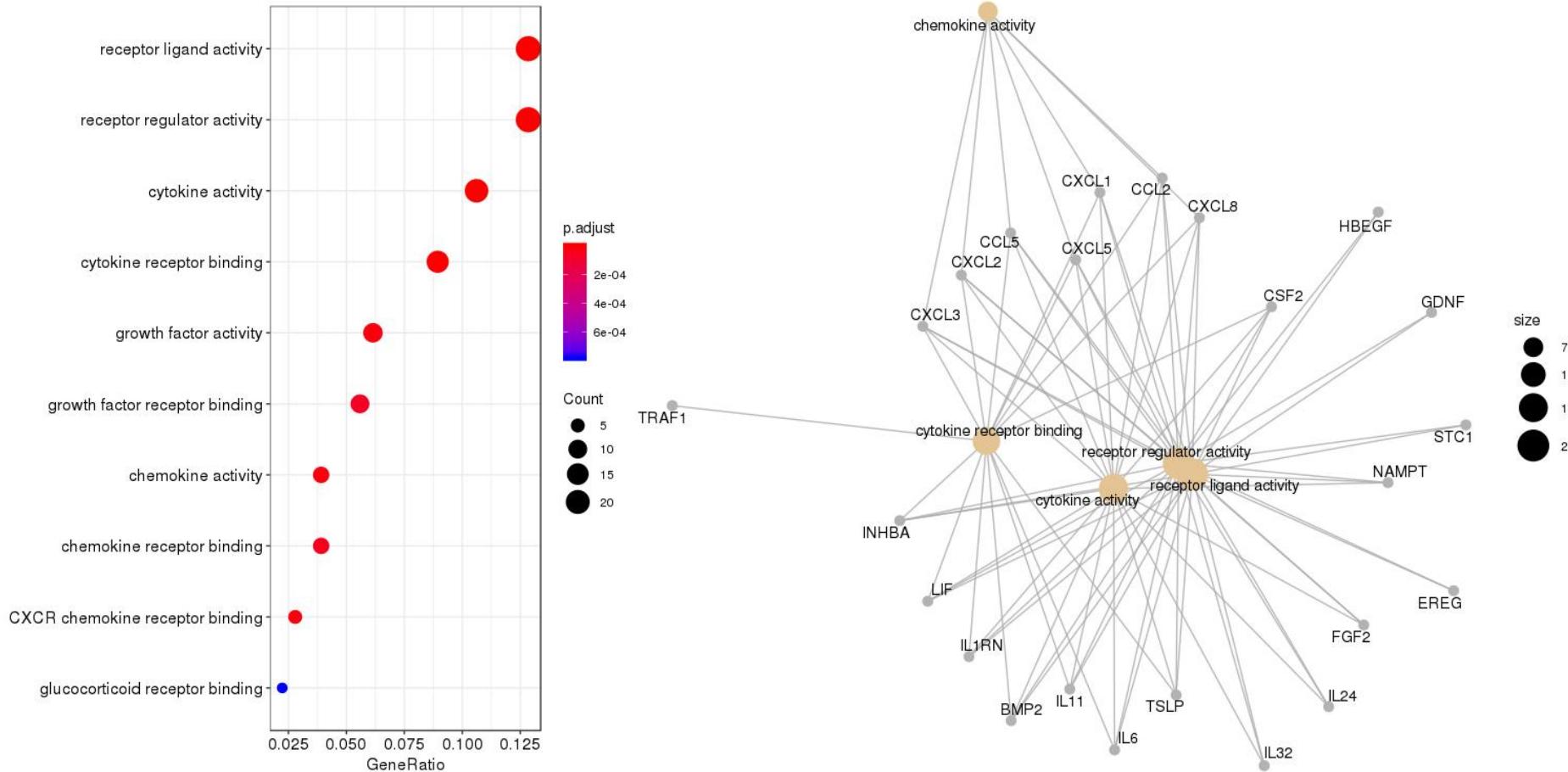
GO BP analysis for cluster2



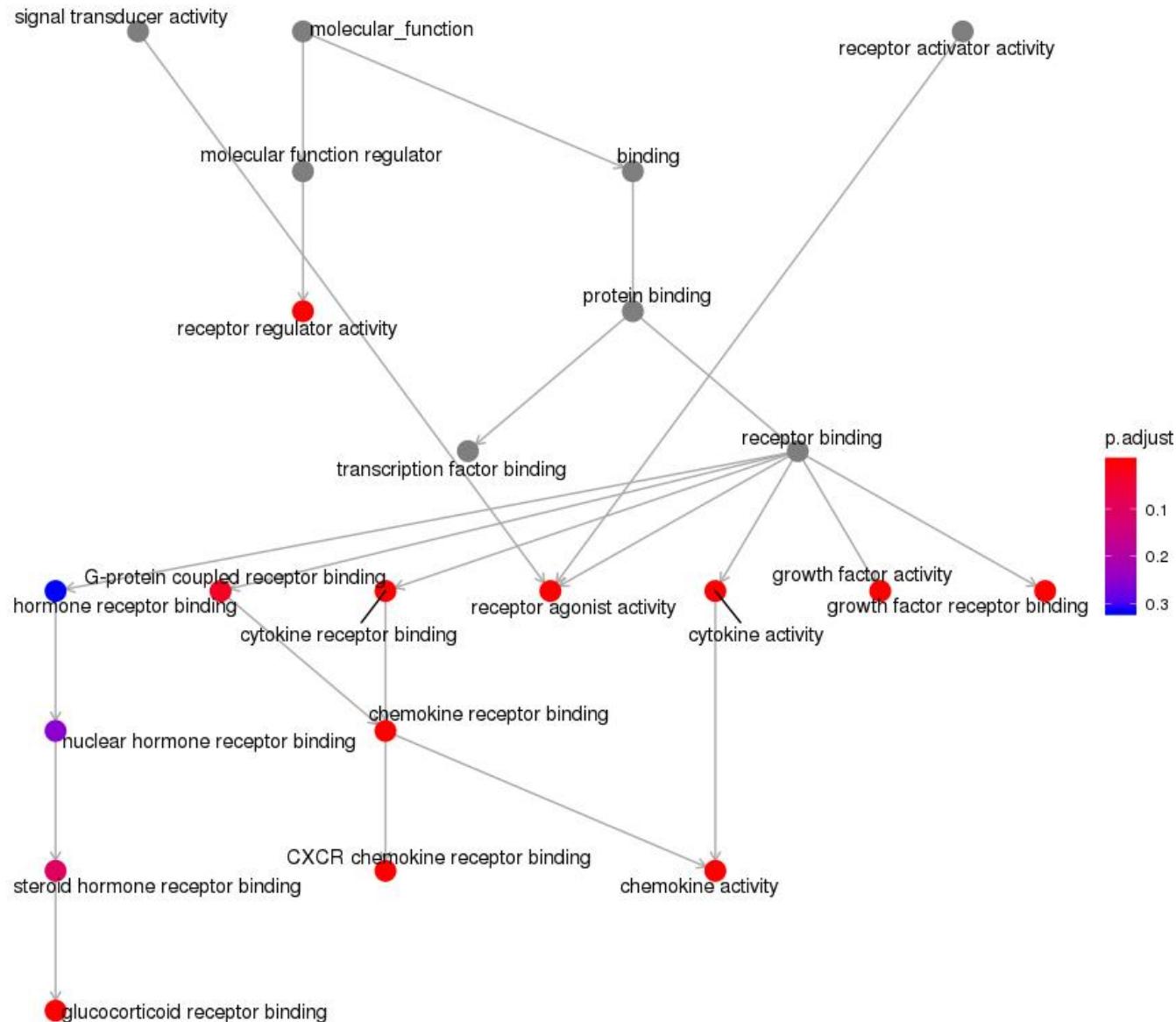
GO BP analysis for cluster2



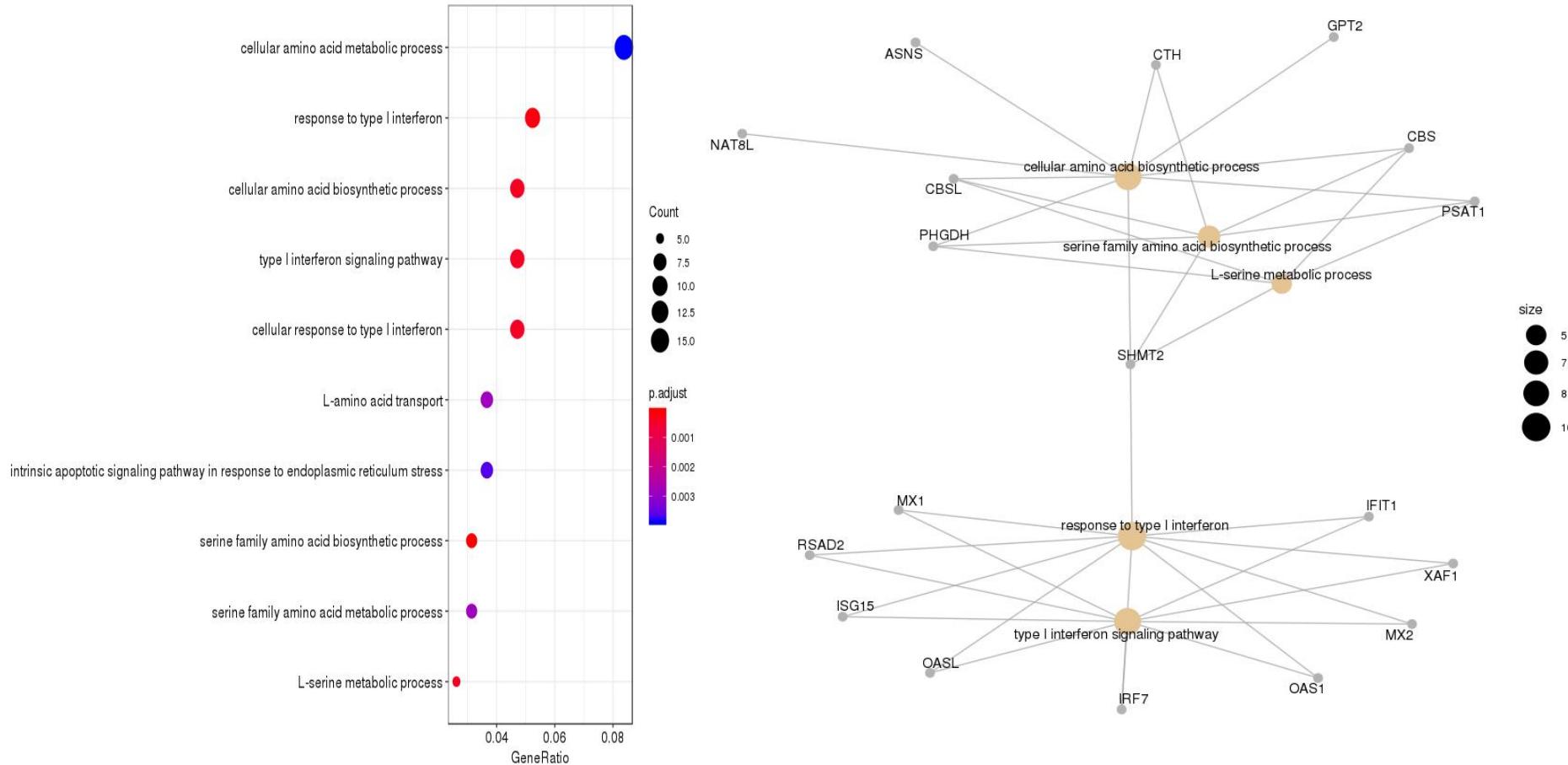
GO MF analysis for cluster2



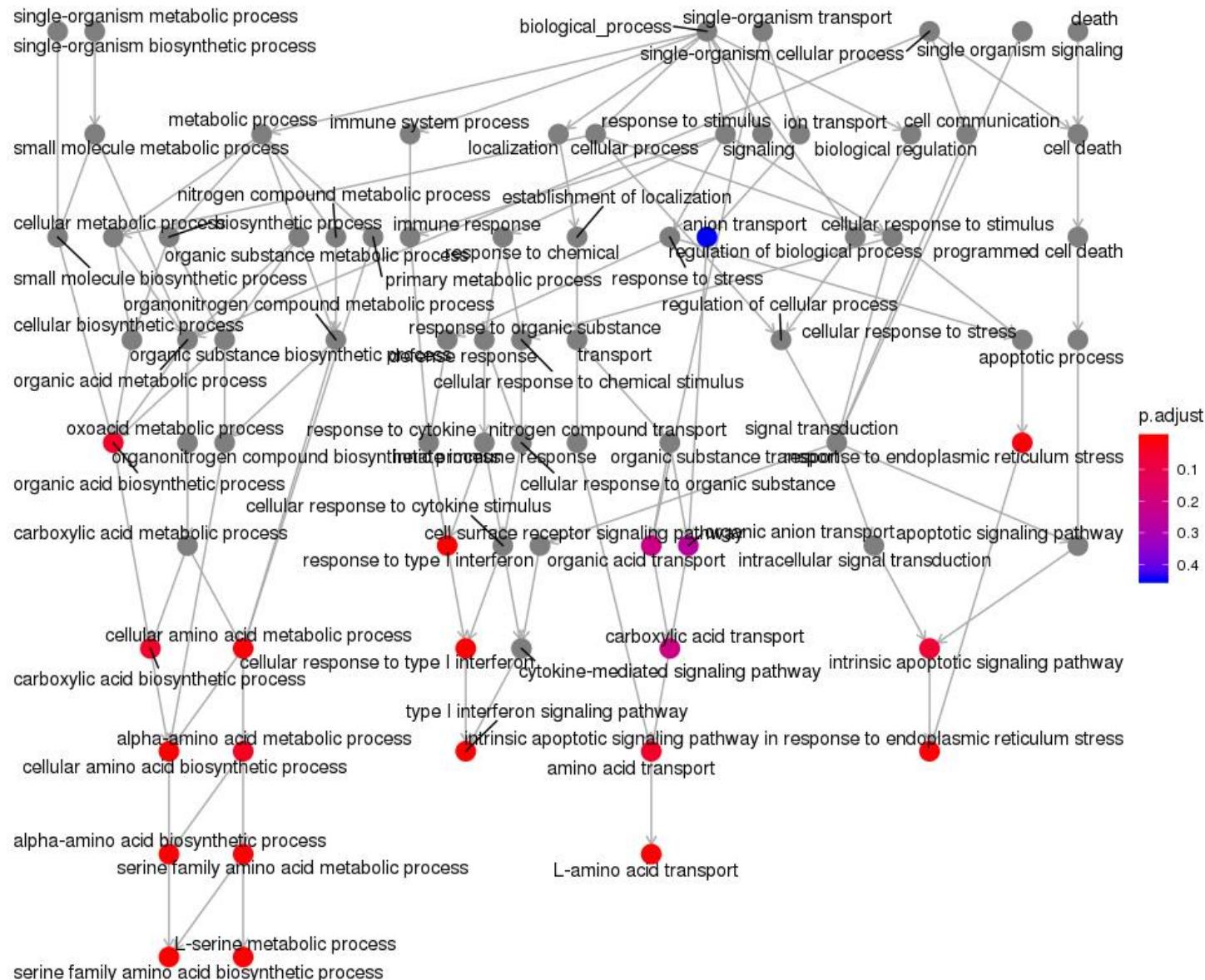
GO MF analysis for cluster2



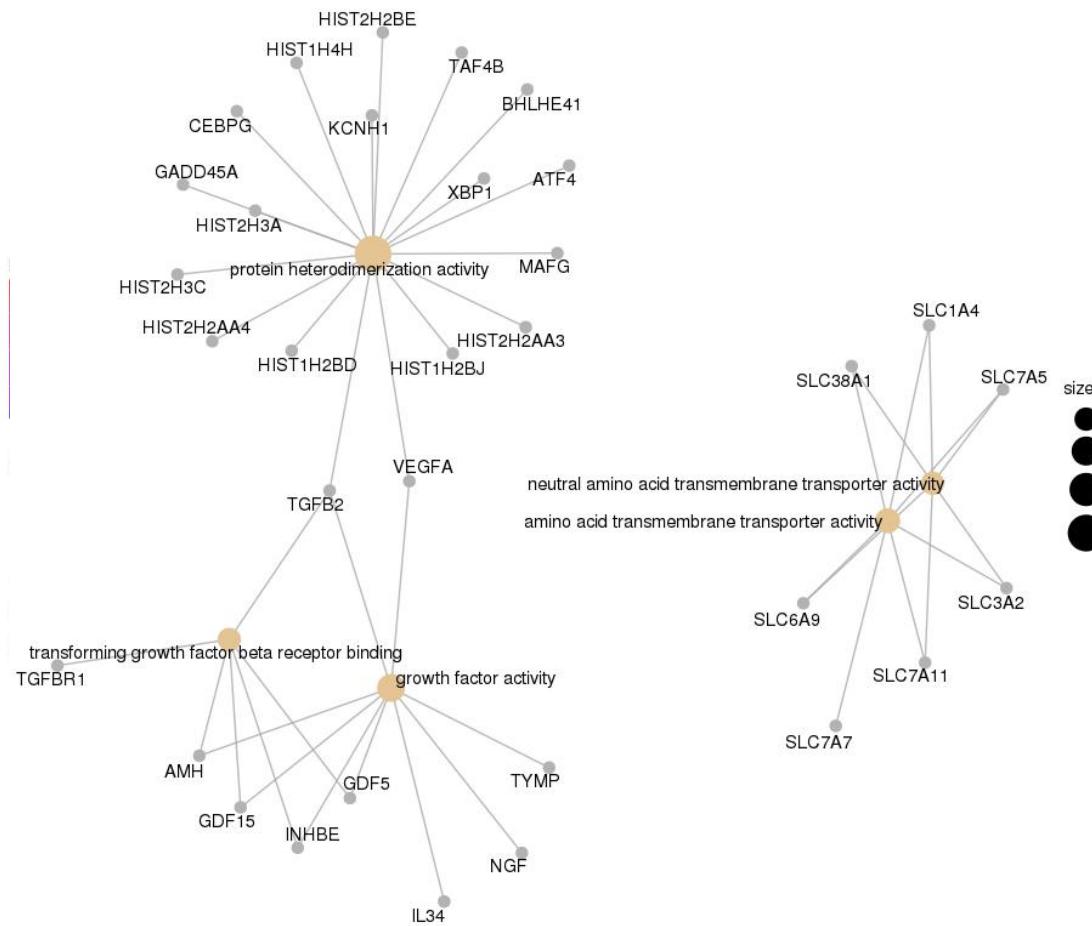
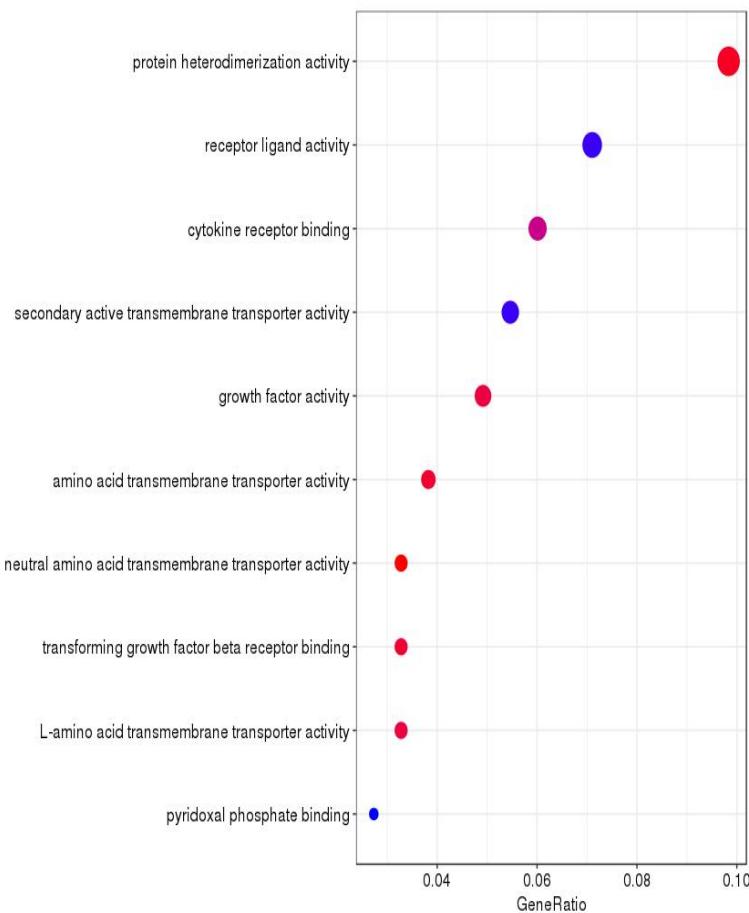
GO BP analysis for cluster1



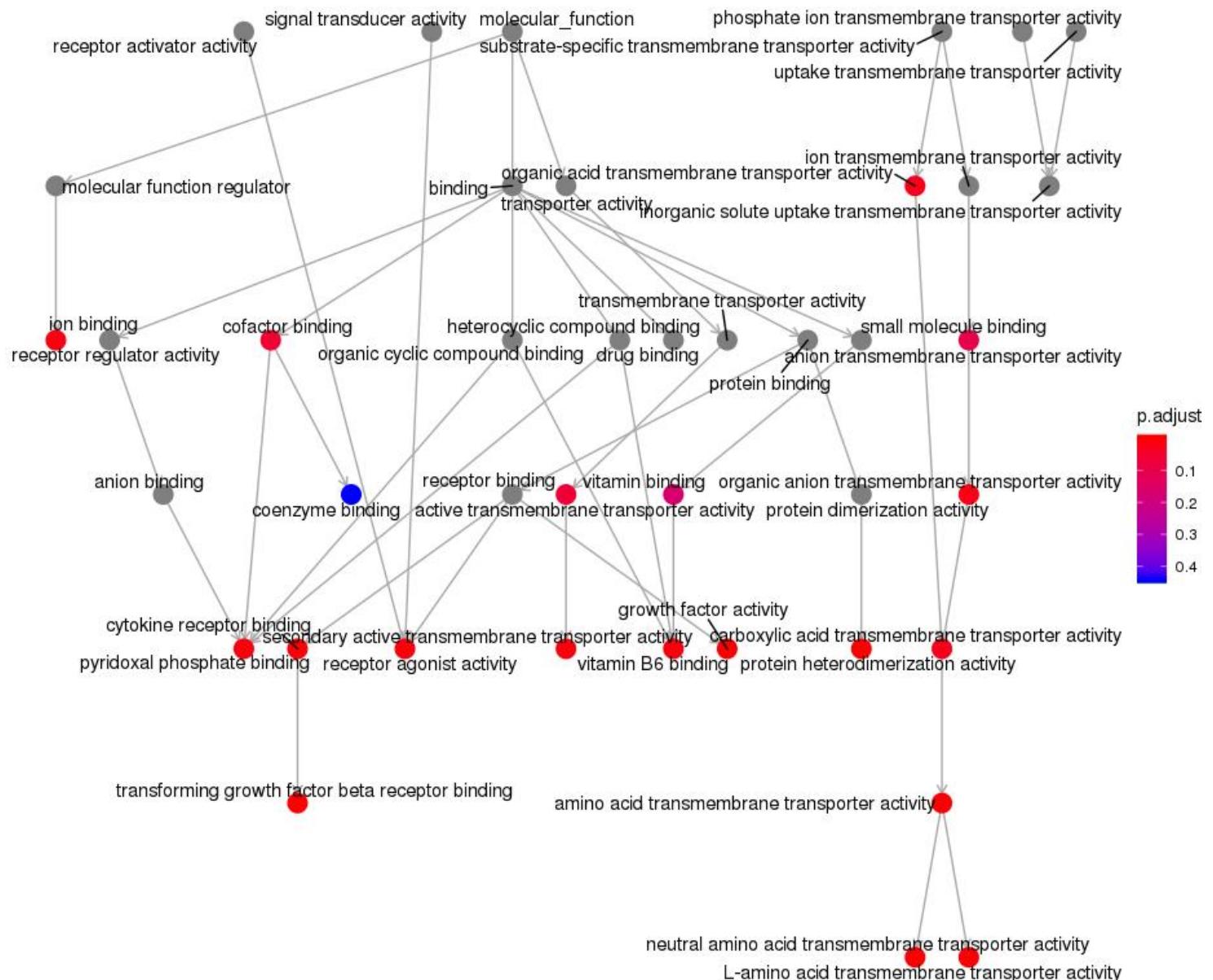
GO BP analysis for cluster1



GO MF analysis for cluster1



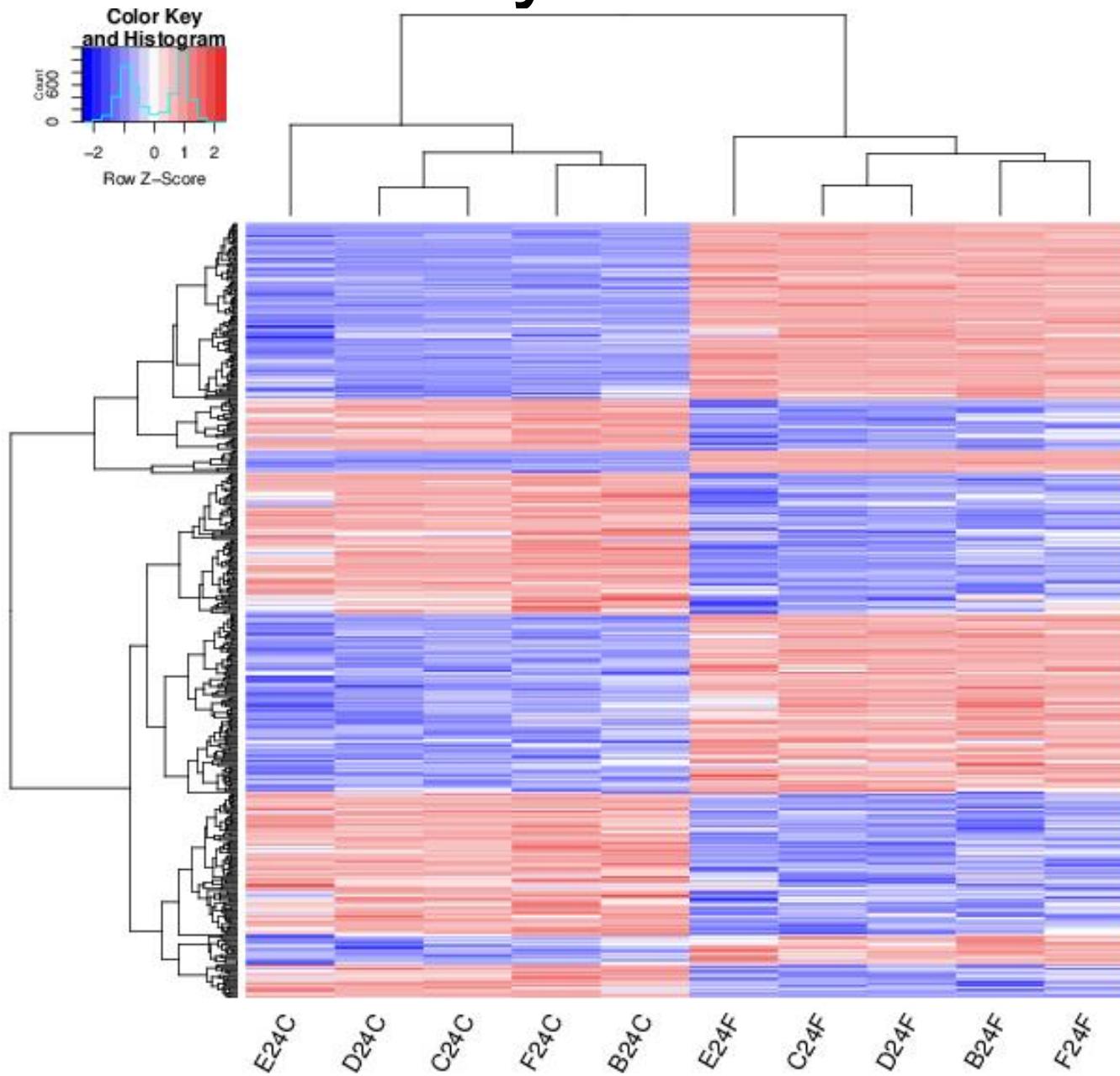
GO MF analysis for cluster1



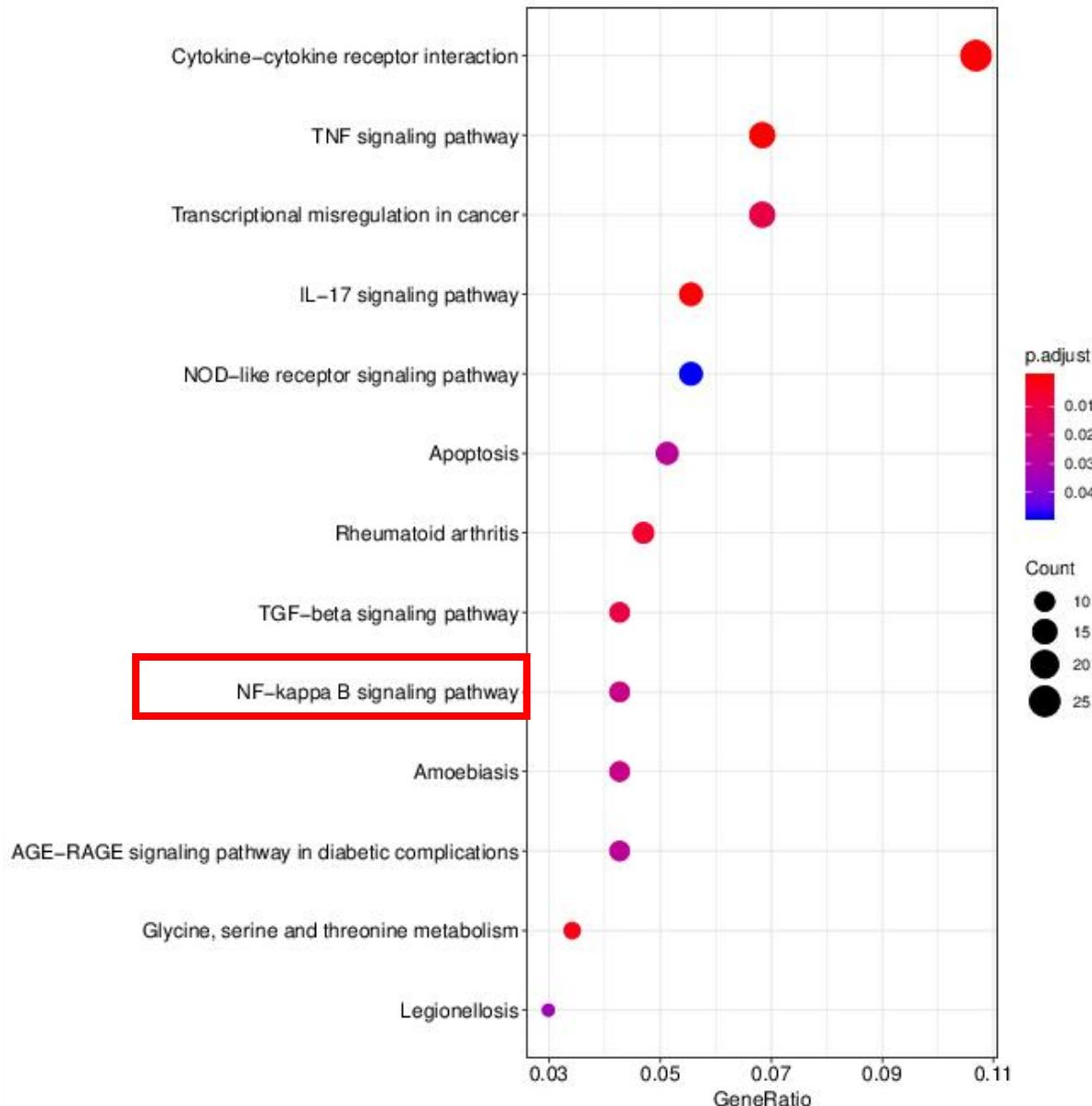
Enrichment analysis for 24h only

- heatmap
- Pathway analysis (KEGG, MSigDB_C2, GSEA)
- GO analysis (BP, MF)
- cogena analysis
 - heatmap
 - pathway

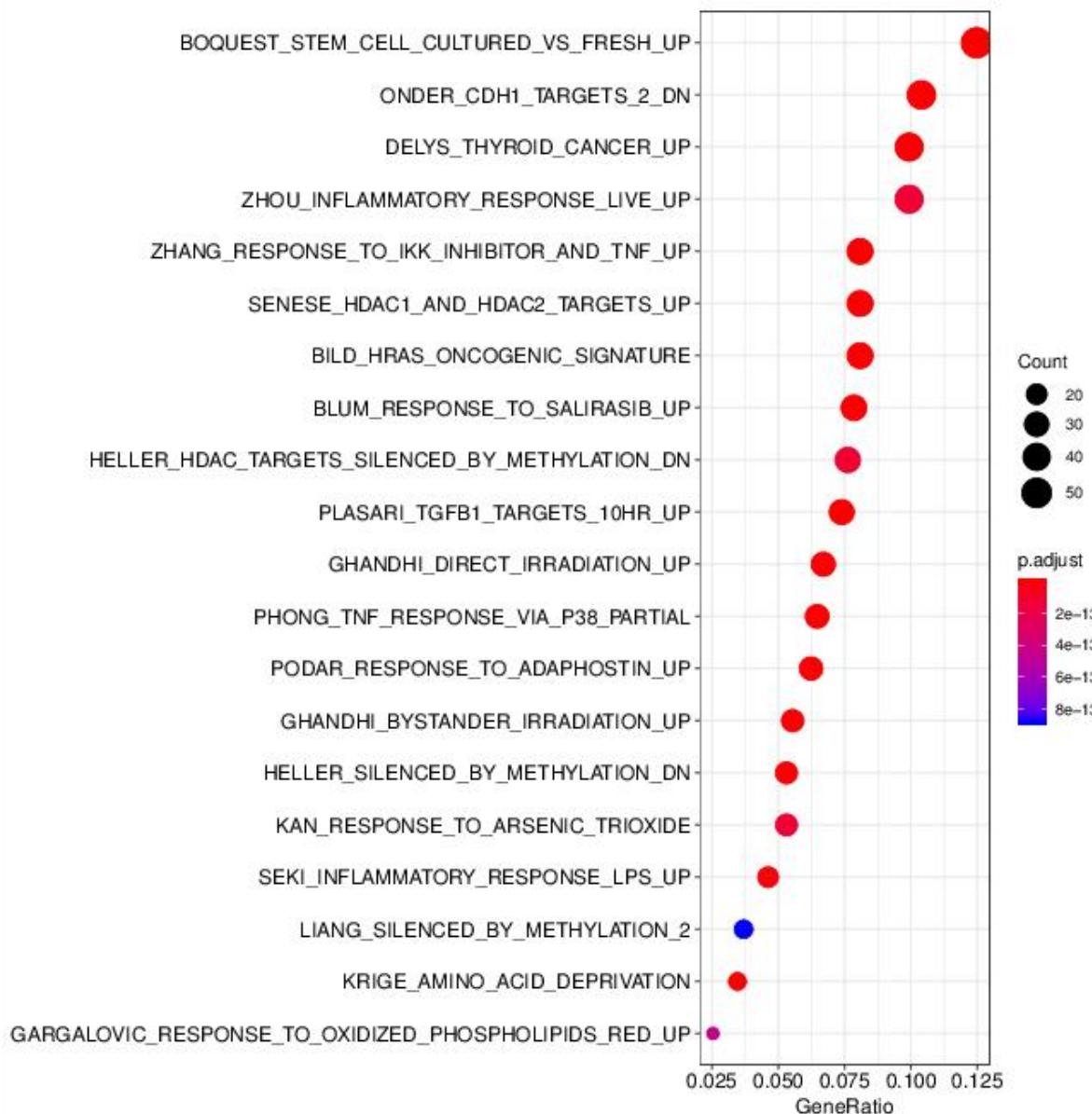
Analysis at 12h



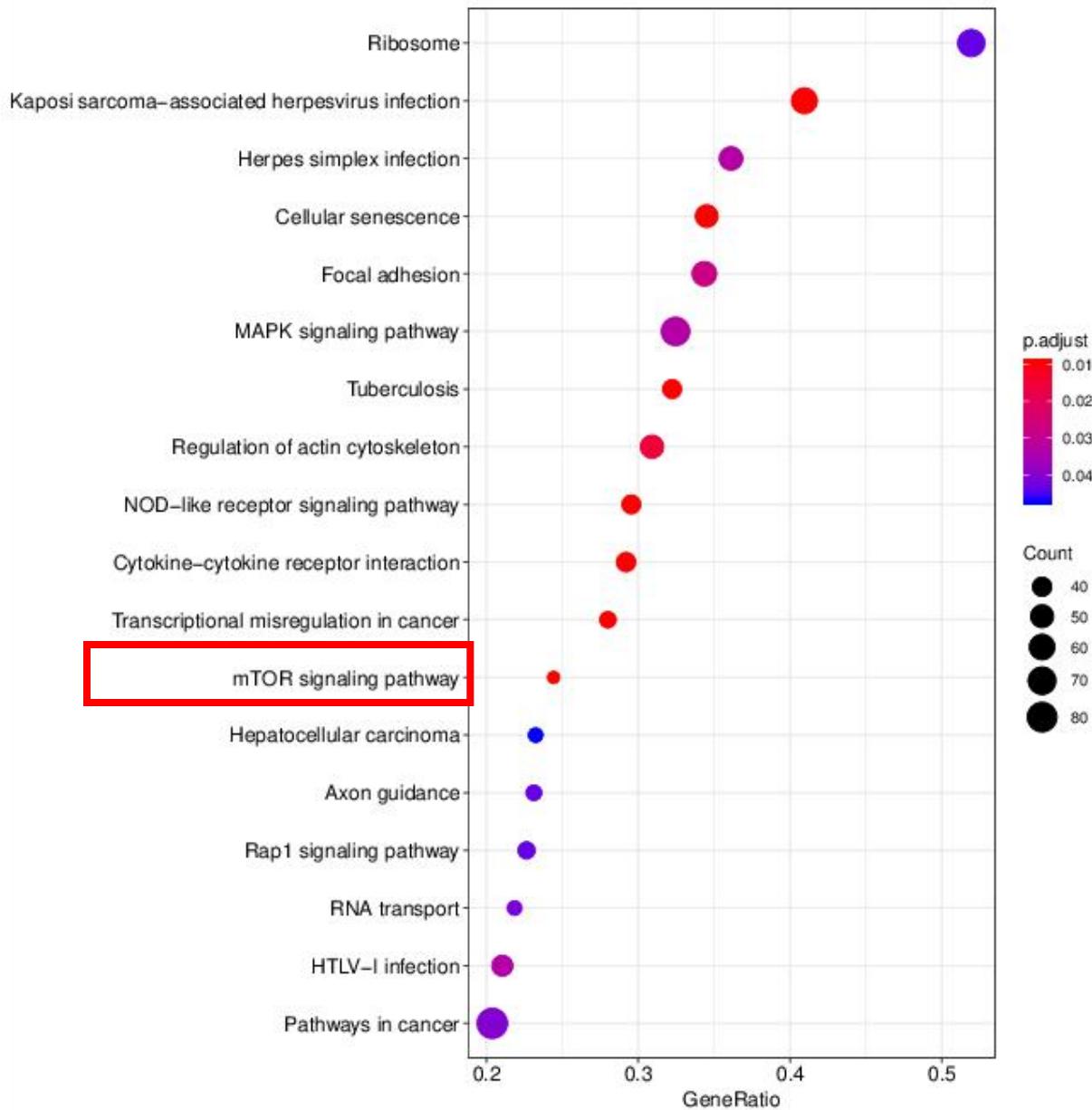
KEGG



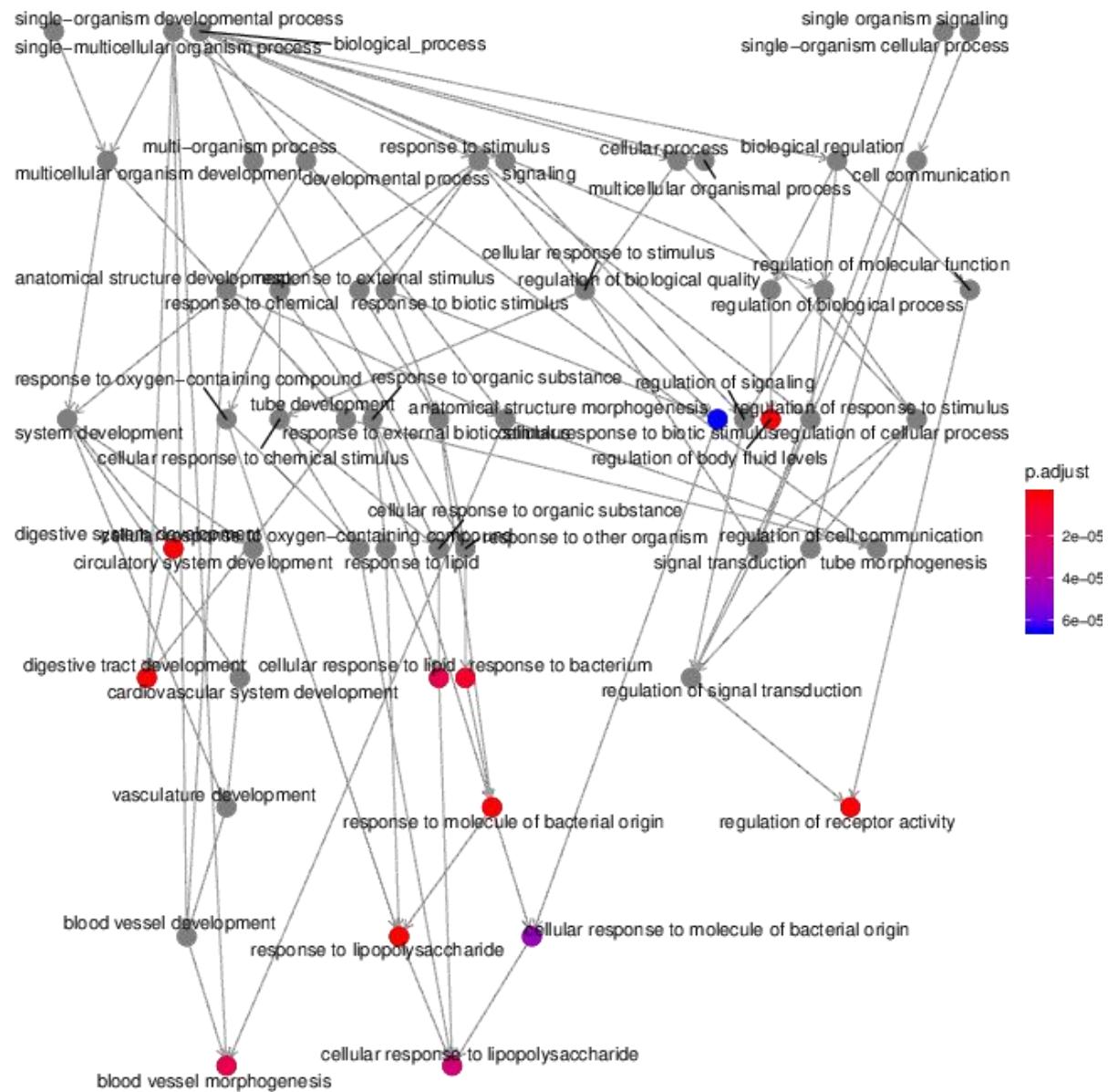
C2_all_pathway



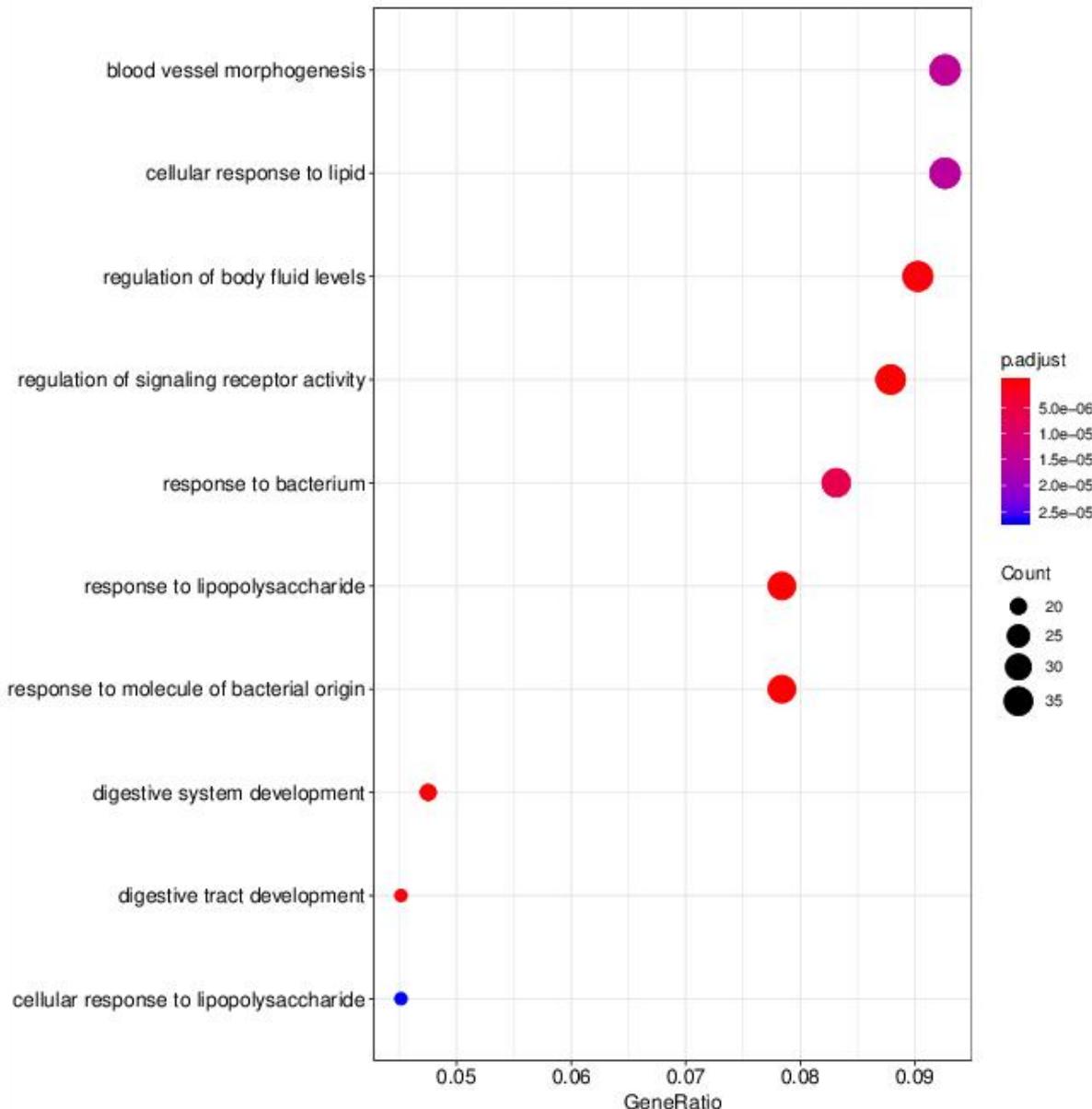
GSE analysis



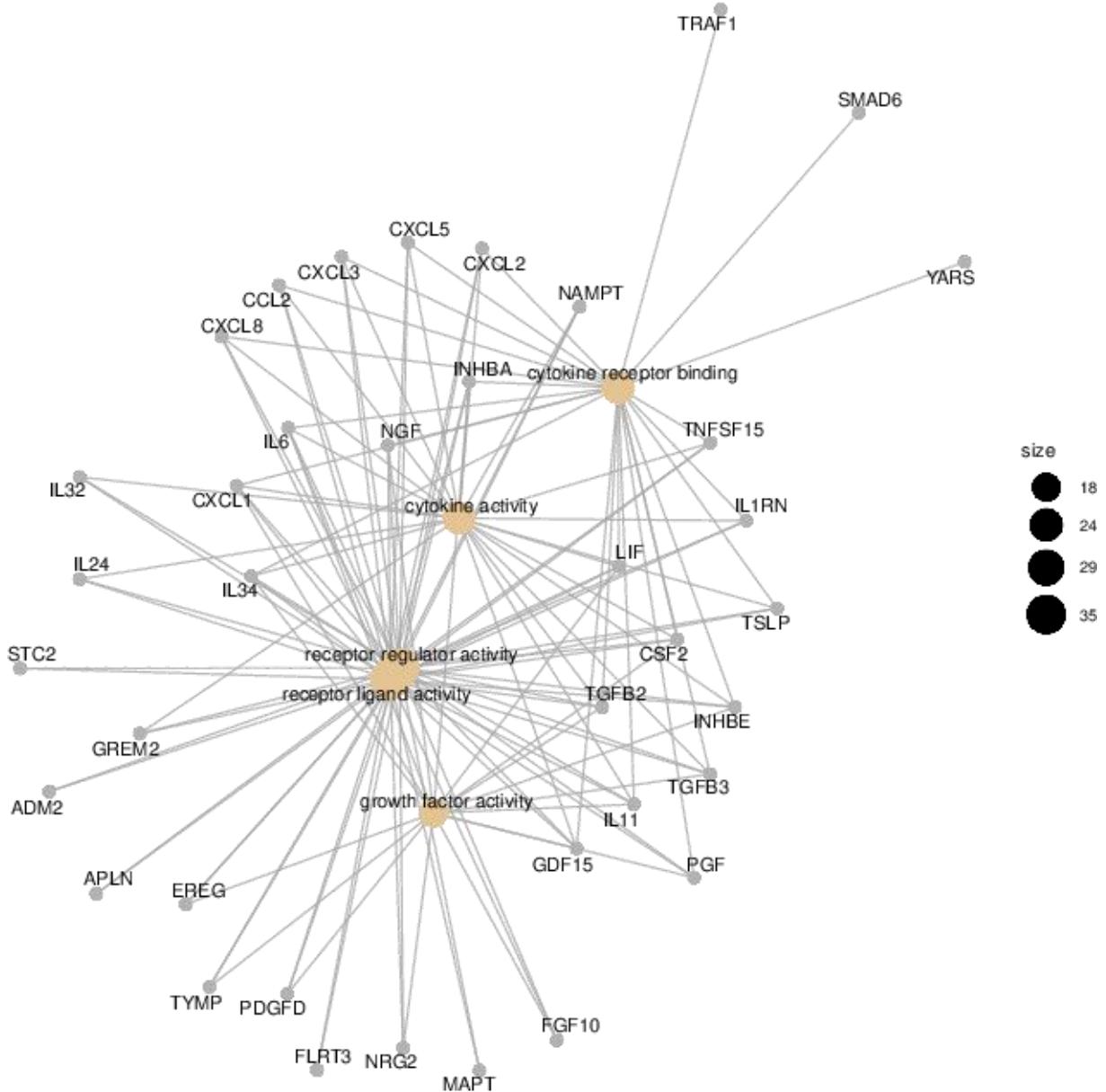
GO_bp



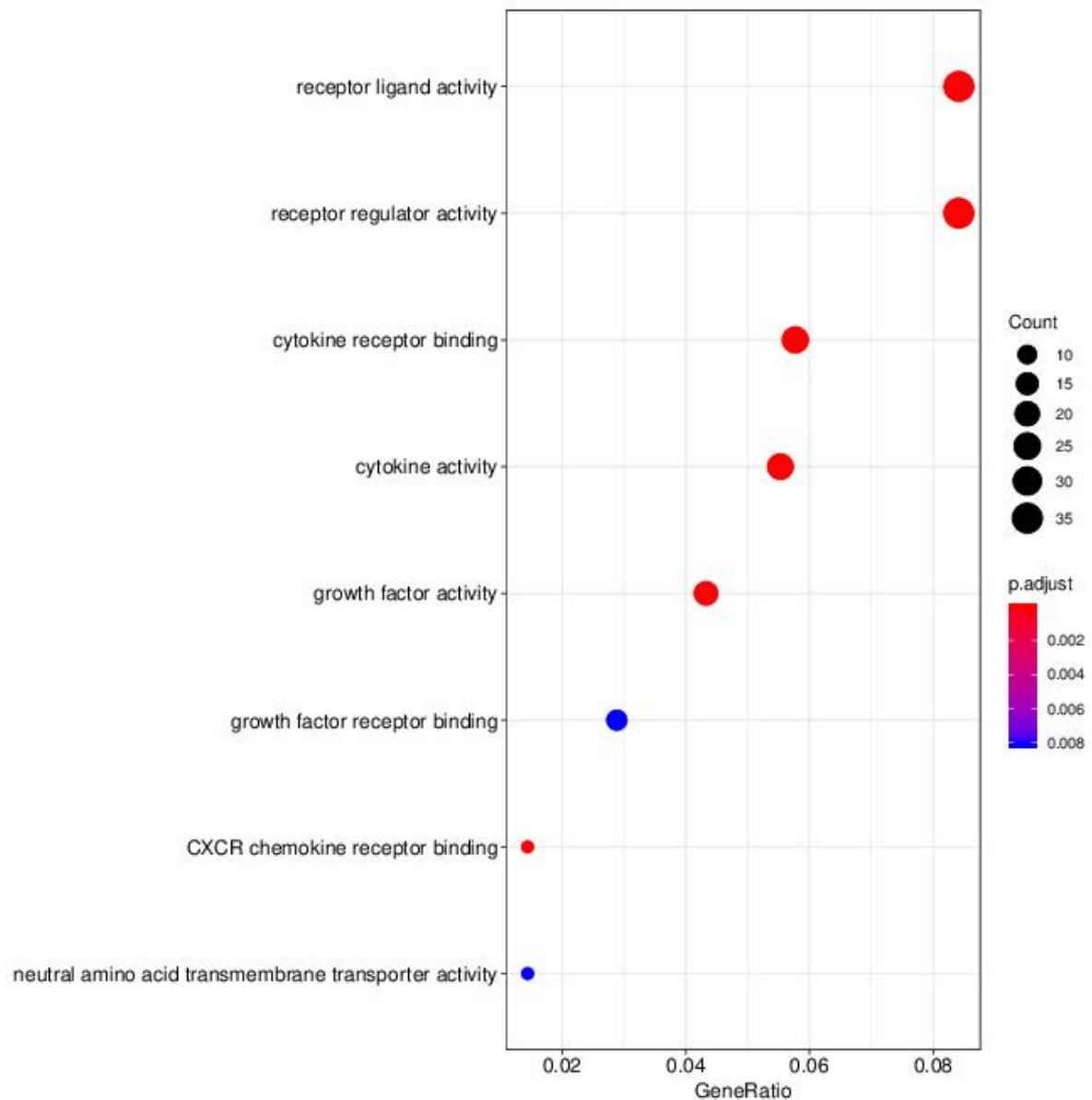
GO_bp



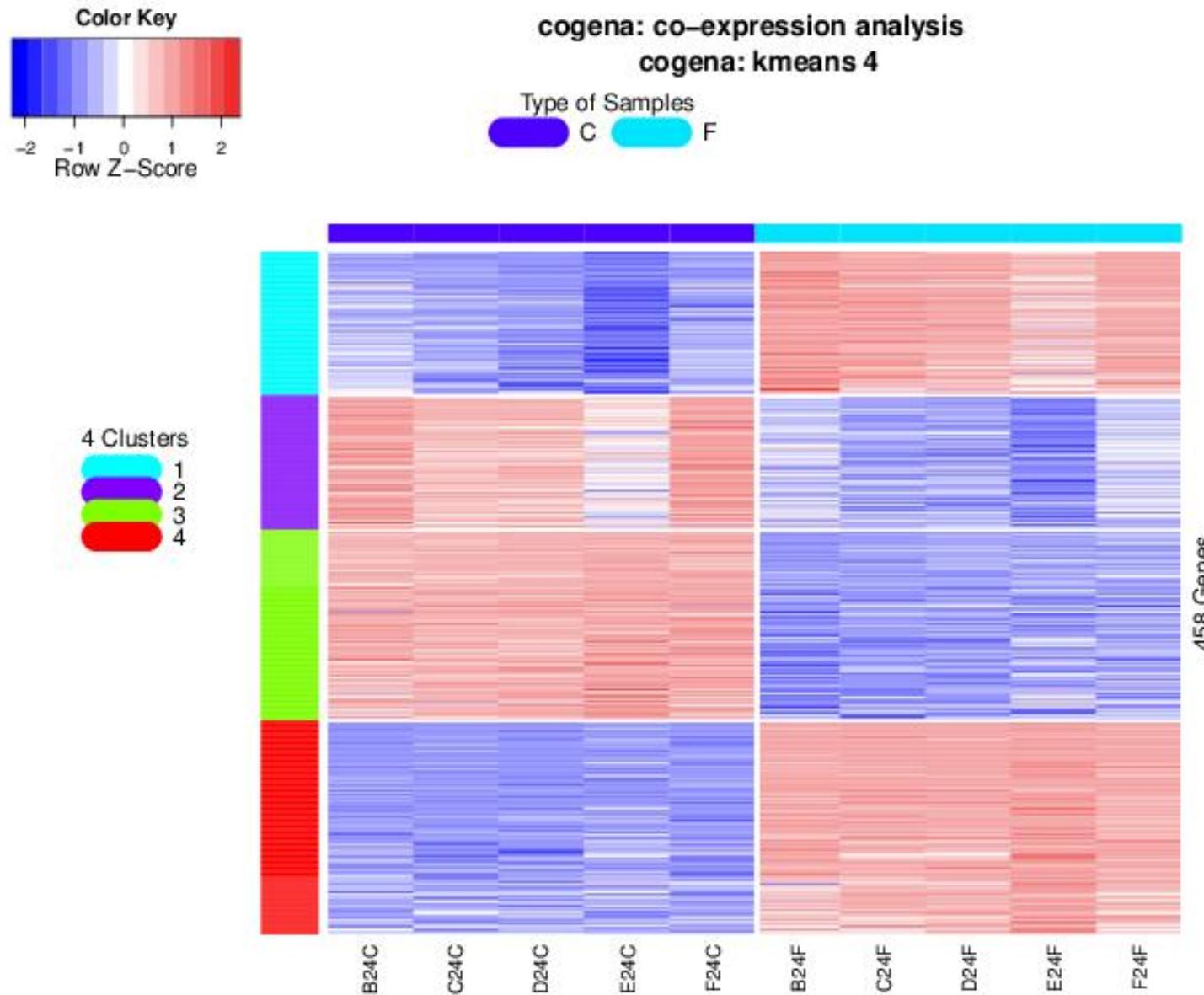
GO_MF



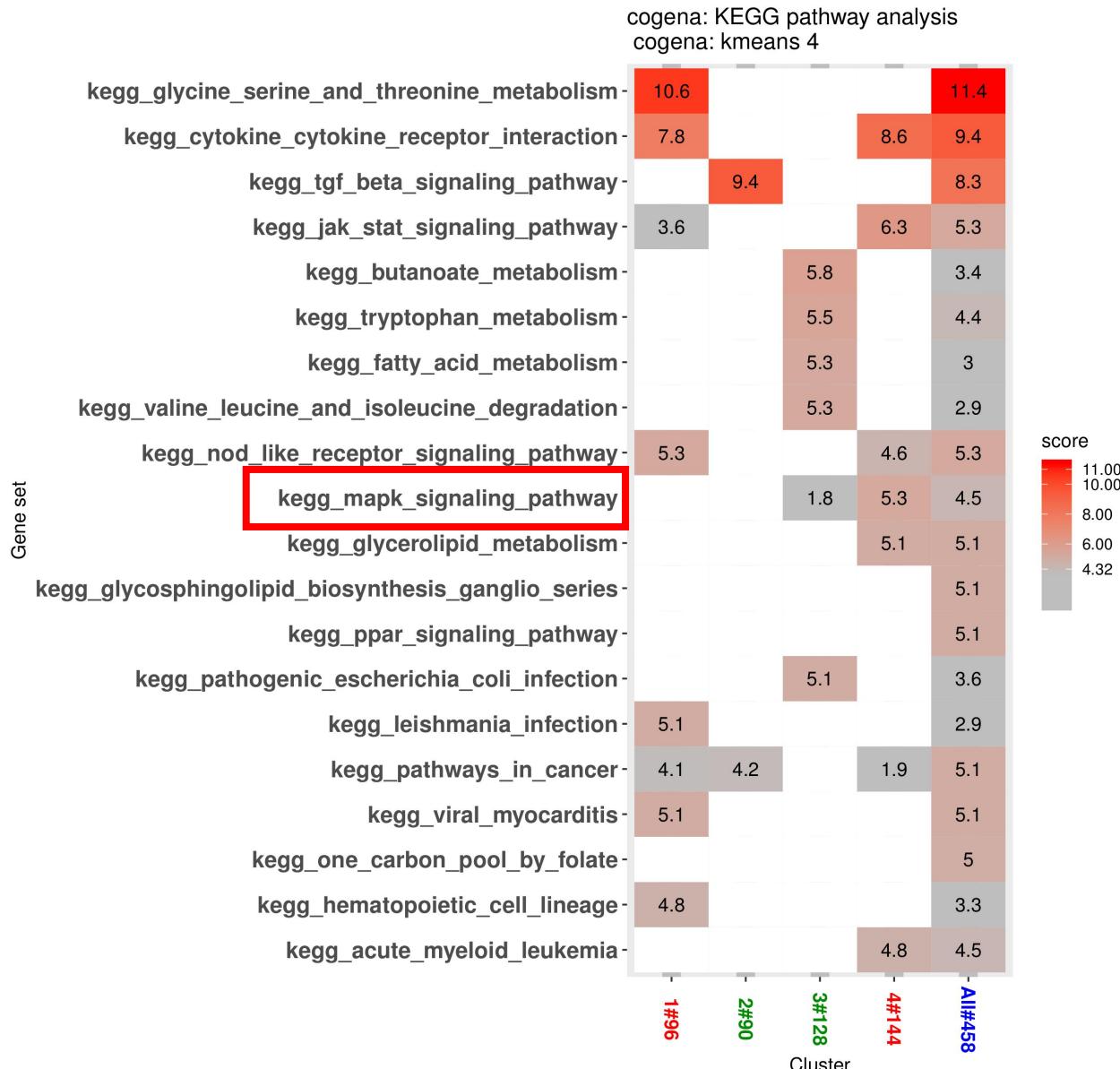
GO_MF



cogena_heatmap



cogena_pathway

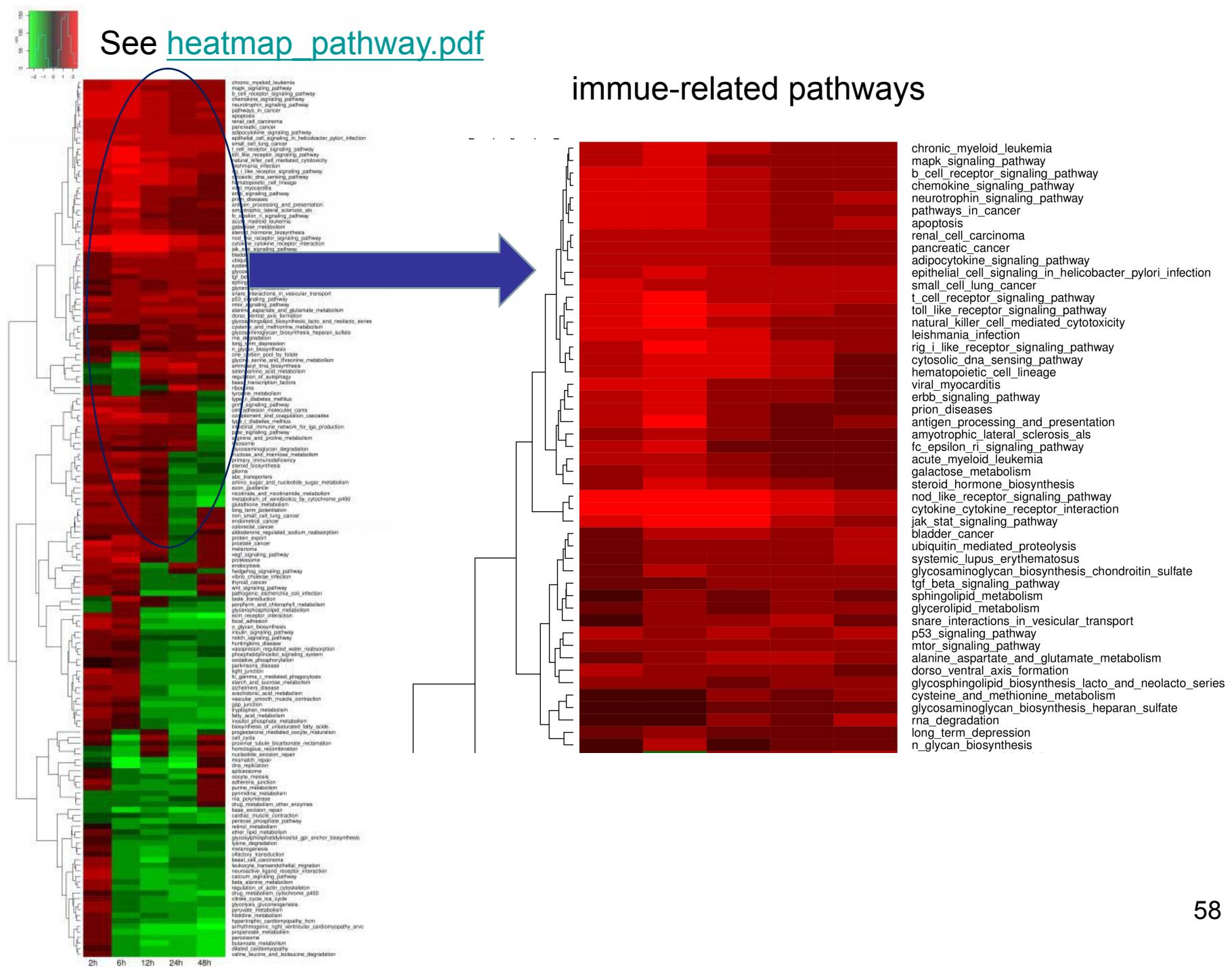


Changes of pathway enrichment (GSEA) via time

- using time-indep data (t-statistic)
- GSEA
- enriched (up or down-) pathways for up or down-regulated genes per timepoint
- heatmap

See [heatmap_pathway.pdf](#)

immune-related pathways



See [heatmap_pathway.pdf](#)

metabolite-related pathways

