

Supplementary Table S1

A list of top 10 dysregulated mRNAs by 24-hour Δ -9-THC exposure. Those indicating inf in the Log2 Fold Change column had zero value in control, suggesting that they were activated by THC exposure and may serve as biomarkers of THC exposure in bronchial cells.

Downregulated					Upregulated				
Concentration		Gene symbol	Log2 Fold change	Q Value	Concentration		Gene symbol	Log2 Fold change	Q Value
800	1	MCRIP1	-4.58684	0.001878	800	1	ABR	4.92421	0.004818
	2	SSBP1	-4.53692	0.001878		2	FAM20C	4.37887	0.001878
	3	GFUS	-3.81228	0.001878		3	SLCO5A1	4.13916	0.001878
	4	MED18	-3.44421	0.030653		4	MMP1	3.81462	0.001878
	5	GBA	-3.39334	0.001878		5	ATF6B	3.5628	0.001878
	6	TADA2A	-3.37367	0.004818		6	SLC25A6	3.50842	0.001878
	7	TAF9	-3.36146	0.017186		7	NEDD8	3.39449	0.001878
	8	SLC16A1	-3.06372	0.001878		8	IL1RL1	3.18243	0.001878
	9	MRPS12	-3.06178	0.001878		9	C1RL	3.07876	0.014481
	10	SGPP1	-3.02411	0.008371		10	BRD2	3.0684	0.001878
1000	1	SLC39A4	-4.7043	0.006095	1000	1	MT1G	inf	0.001878
	2	GBA	-4.31396	0.001878		2	MMP1	6.28529	0.001878
	3	MCRIP1	-4.02778	0.001878		3	IL1RL1	6.12073	0.001878
	4	RPS25	-3.86789	0.001878		4	KLHDC7B	4.59062	0.008371
	5	FAN1	-3.76331	0.017186		5	LCN2	4.29486	0.001878
	6	PCK2	-3.67426	0.003423		6	RAD17	4.2562	0.011499
	7	GFUS	-3.54866	0.001878		7	HSPA6	3.95743	0.001878
	8	SLC25A24	-3.39671	0.006095		8	NEDD8	3.85935	0.001878
	9	EIF3K	-3.00309	0.001878		9	HMOX1	3.54616	0.001878
	10	DDT	-2.98129	0.001878		10	ZNF469	3.49049	0.001878
1200	1	SLC39A4	-5.29575	0.012503	1200	1	CDC42EP5	inf	0.001878
	2	ATOH8	-4.461	0.001878		2	MT1G	inf	0.001878
	3	NDUFS3	-3.81763	0.001878		3	RN7SKP11	inf	0.001878
	4	TNNI2	-3.42941	0.009452		4	MMP1	7.01104	0.001878
	5	ECH1	-3.37068	0.001878		5	IL1RL1	6.57479	0.001878
	6	DHRS4	-3.36445	0.004818		6	LCN2	4.88431	0.001878
	7	PEG10	-3.11481	0.001878		7	HSPA6	4.42459	0.001878
	8	PCDH18	-3.04253	0.001878		8	KLHDC7B	4.29577	0.012503
	9	TAF9	-3.01899	0.022339		9	NCF2	4.12027	0.004818
	10	RPL7A	-3.00786	0.001878		10	HMOX1	4.07414	0.001878
1500	1	SLC39A4	-4.36553	0.001878	1500	1	LOC646938	inf	0.026199
	2	GFUS	-4.0102	0.001878		2	TNKS2-AS1	inf	0.018979
	3	MTCO2P12	-3.50199	0.02154		3	RPS27P9	inf	0.017186
	4	SYT8	-3.24789	0.001878		4	MT1G	inf	0.001878
	5	SURF2	-3.19974	0.009452		5	SPRR1B	inf	0.001878
	6	KIFC1	-3.17516	0.001878		6	RPS18	8.50609	0.022339
	7	LY6E	-2.93844	0.001878		7	HSPA6	7.77894	0.001878
	8	ANKRD2	-2.81355	0.011499		8	MMP1	5.43214	0.001878
	9	SLC25A24	-2.74909	0.001878		9	HSPA1B	5.16909	0.001878
	10	TNNI2	-2.68063	0.001878		10	HMOX1	4.82331	0.001878

Supplementary Figure S1

A

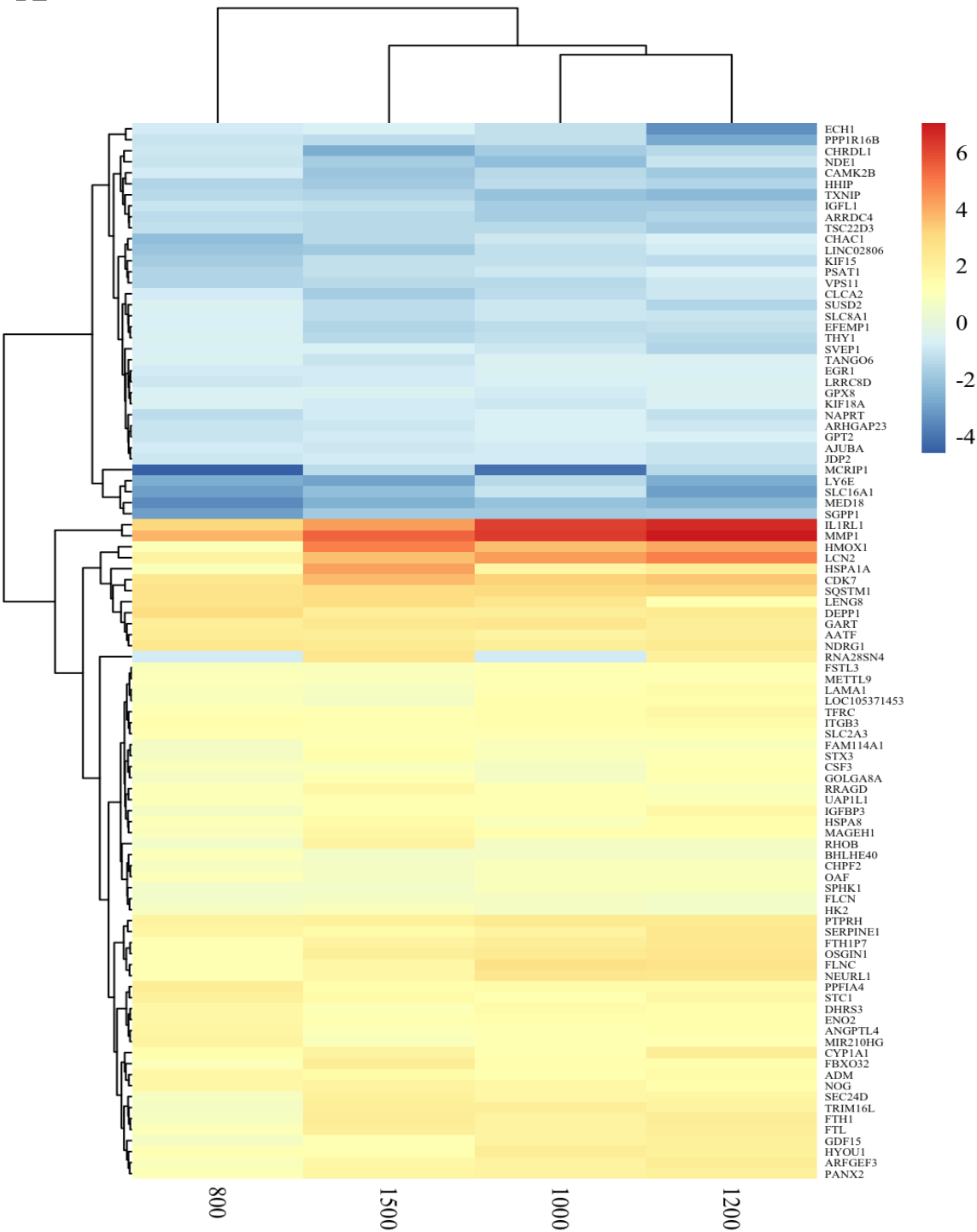


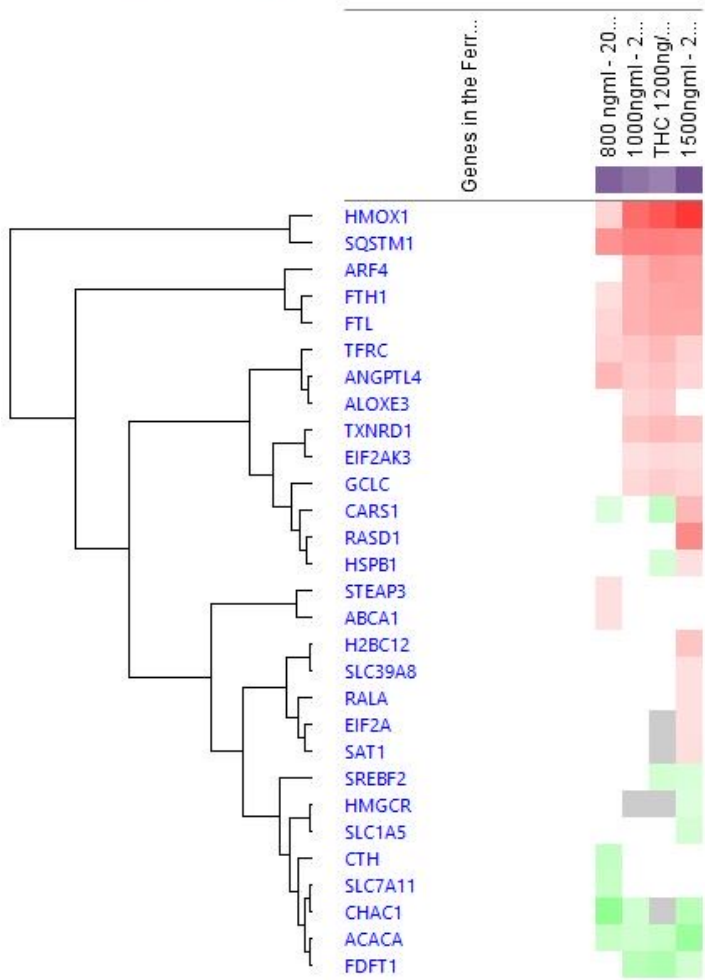
Figure S1. (A) Global alteration of gene expression profiles in BEAS-2B cells associated with all treatment groups of Δ -9-THC compared to the vehicle

B. Genes in various pathways

Ferroptosis-related genes

Analysis Comparison 1

Expr Log Ratio
-4.537 4.924



NRF2-related genes

Analysis Comparison 1

Expr Log Ratio
-4.537 4.924

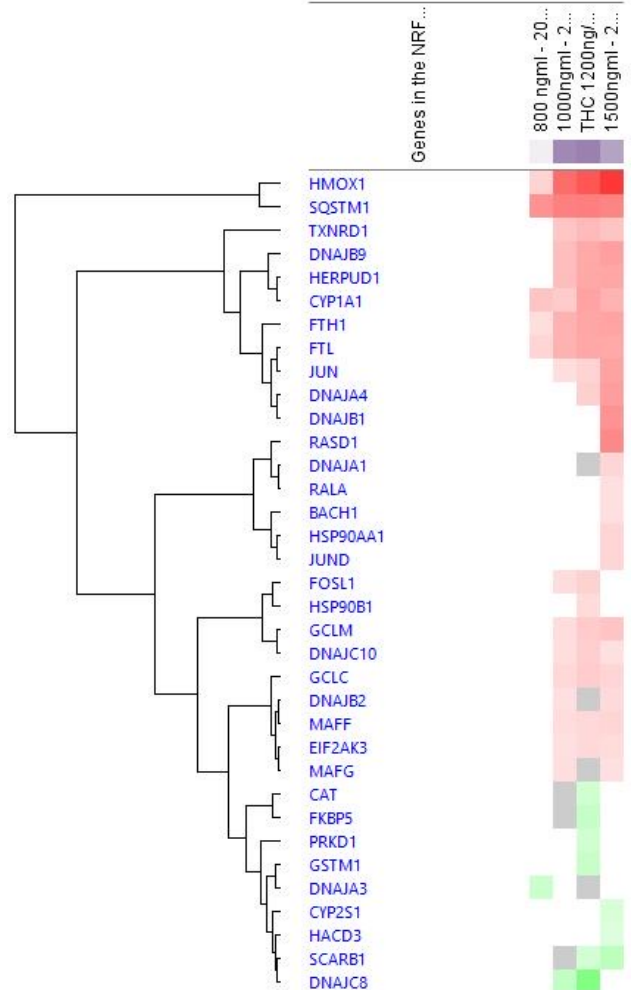


Figure S1. (B) Expression pattern of genes in the RNAseq database of THC-exposed BEAS-2B cells. A. A heatmap showing differentially regulated genes (upregulated and downregulated) in all treatment groups (FDR < 0.1). B. Ferroptosis and NRF-related genes differentially expressed in THC-exposed cells. Data suggest that THC can cause alterations in the expression of genes involved in ferroptosis and NRF-2 pathway.

Supplementary Figure S2A

Enrichment FDR	Pathway Genes	Fold Enrichment	Pathway
0.002451271	33	138.1575758	Fructose and mannose metabolism
0.013422149	109	41.82752294	HIF-1 signaling pathway
0.019724723	5	455.92	Neomycin, kanamycin and gentamicin biosynthesis
0.033274529	246	18.53333333	Shigellosis
0.047199405	20	113.98	Glycosaminoglycan biosynthesis
0.049466222	67	34.0238806	Glycolysis / Gluconeogenesis
0.049466222	31	73.53548387	Galactose metabolism
0.049466222	35	65.13142857	Starch and sucrose metabolism
0.049466222	49	46.52244898	Amino sugar and nucleotide sugar metabolism
0.049466222	1527	4.478585462	Metabolic pathways
0.049466222	37	61.61081081	Biosynthesis of nucleotide sugars
0.049466222	72	31.66111111	Mitophagy
0.049466222	46	49.55652174	Type II diabetes mellitus
0.049466222	47	48.50212766	Carbohydrate digestion and absorption
0.049466222	57	39.99298246	Legionellosis
0.049466222	67	34.0238806	Acute myeloid leukemia
0.049466222	70	32.56571429	Central carbon metabolism in cancer
0.064529653	100	22.796	AGE-RAGE signaling pathway in diabetic complications
0.069418479	115	19.8226087	Carbon metabolism
0.069418479	120	18.99666667	AMPK signaling pathway
0.070635514	131	17.40152672	FoxO signaling pathway
0.070635514	141	16.16737589	Autophagy
0.070635514	137	16.63941606	Insulin signaling pathway
0.074356038	162	14.07160494	JAK-STAT signaling pathway
0.074356038	161	14.15900621	MicroRNAs in cancer
0.100994457	232	9.825862069	Thermogenesis

Figure S2. (A) Upregulated gene associated Pathways enrichment in BEAS-2B cells exposed to delta-9 THC *in vitro*. Metabolic pathways were the most dysregulated pathways followed by immune and one carbon metabolism pathways.

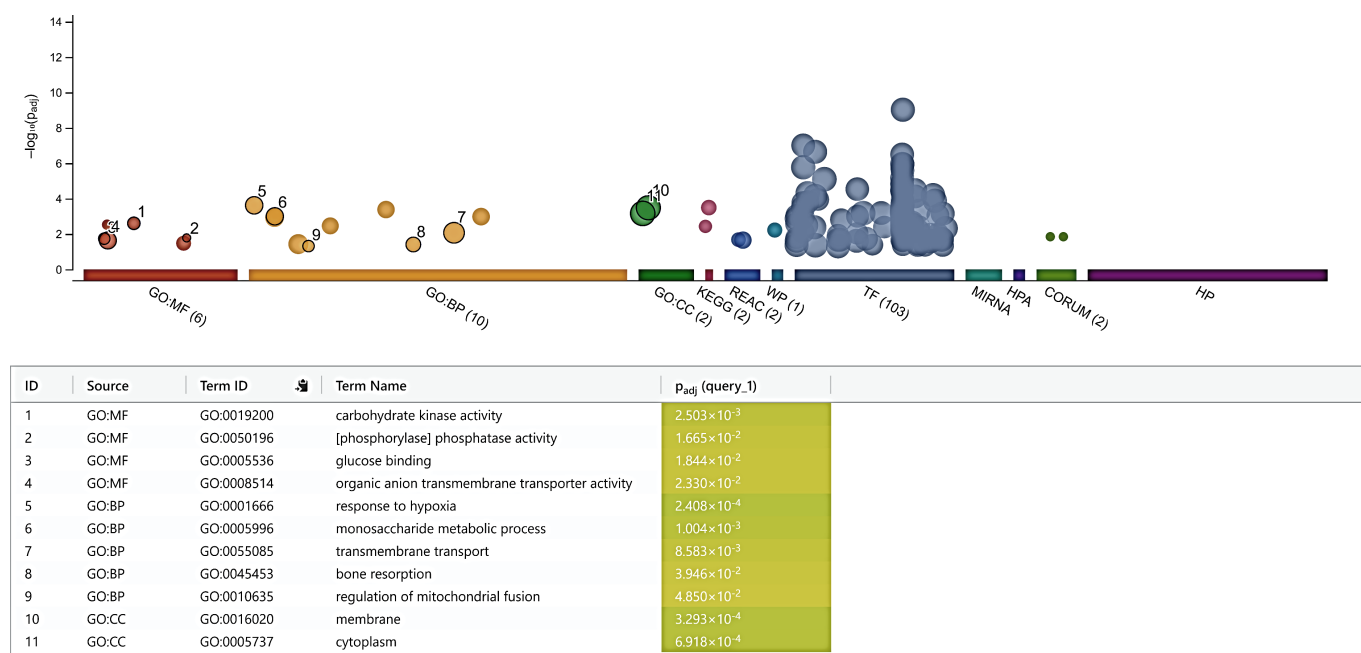
Supplementary Figure S2B

Enrichment FDR	Pathway Genes	Fold Enrichment	Pathway
1.28E-06	75	93.5220513	Biosynthesis of amino acids
0.000293	115	45.7444816	Carbon metabolism
0.0009831	37	94.7858628	Alanine, aspartate and glutamate metabolism
0.0009831	40	87.6769231	Glycine, serine and threonine metabolism
0.0037203	1527	5.74177623	Metabolic pathways
0.0303011	22	79.7062937	Arginine biosynthesis
0.0303011	19	92.291498	2-Oxocarboxylic acid metabolism
0.0408464	34	51.5746606	RNA polymerase
0.0500746	50	35.0707692	Cysteine and methionine metabolism
0.0500746	57	30.7638327	Glutathione metabolism
0.0500746	61	28.7465322	Arachidonic acid metabolism
0.0500746	63	27.8339438	Cytosolic DNA-sensing pathway
0.0548541	75	23.3805128	Thyroid hormone synthesis
0.1030885	155	11.3131514	Biosynthesis of cofactors
0.1826455	306	5.73051785	Huntington disease

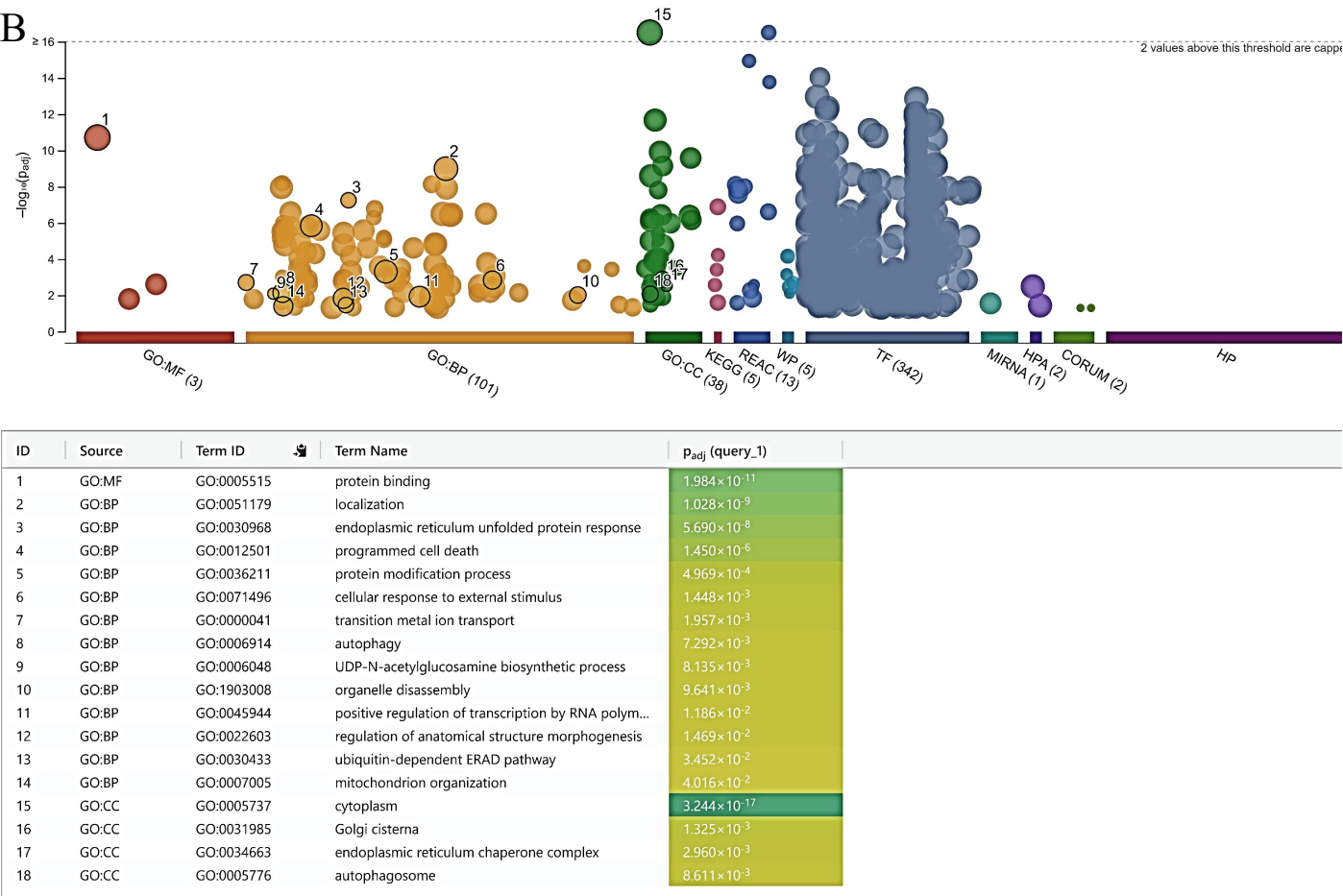
Figure S2. (B) Downregulated gene associated Pathways enrichment in BEAS-2B cells exposed to delta-9 THC *in vitro*. Metabolic pathways were the most dysregulated pathways followed by immune and one carbon metabolism pathways.

Supplementary Figure S3

A



B



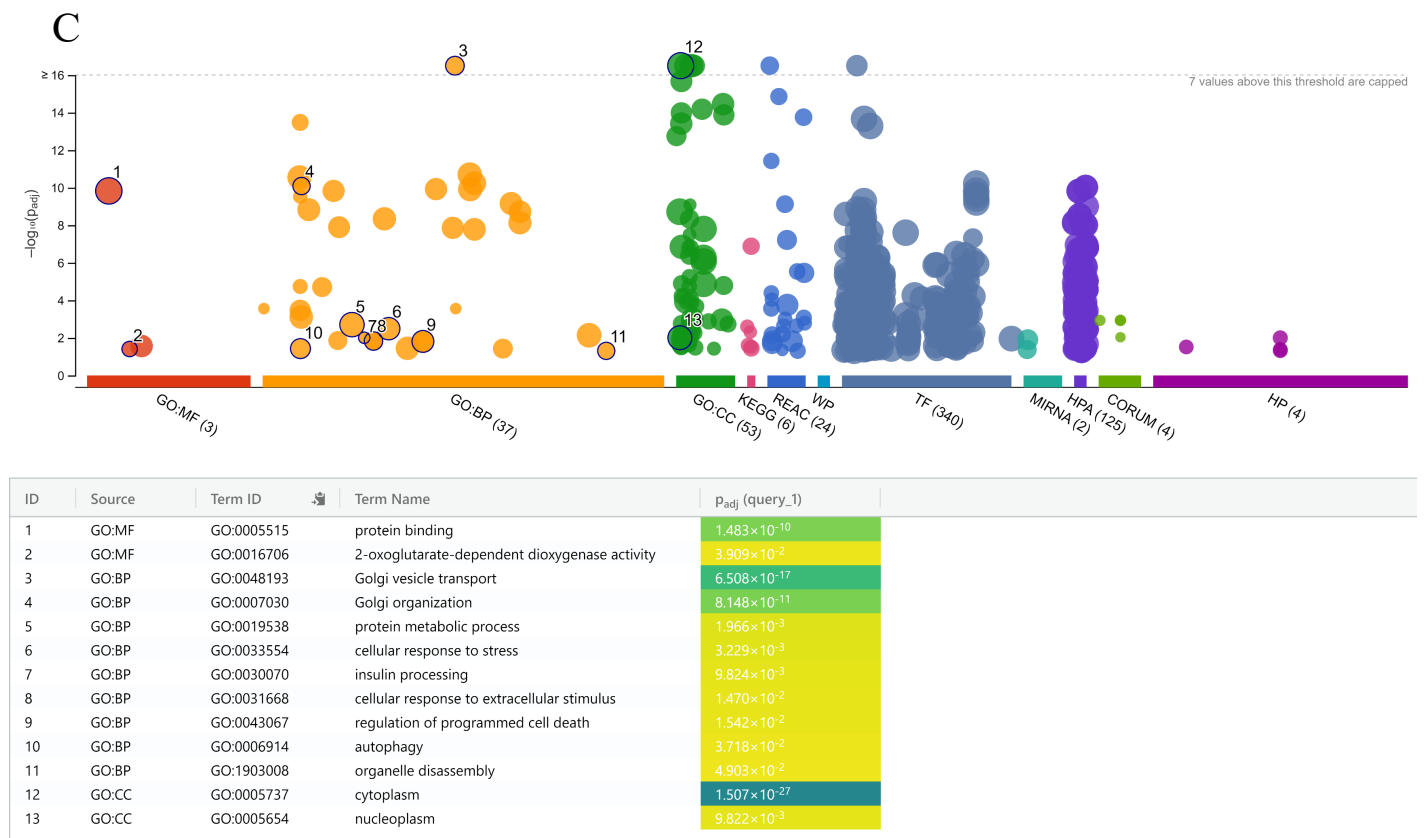
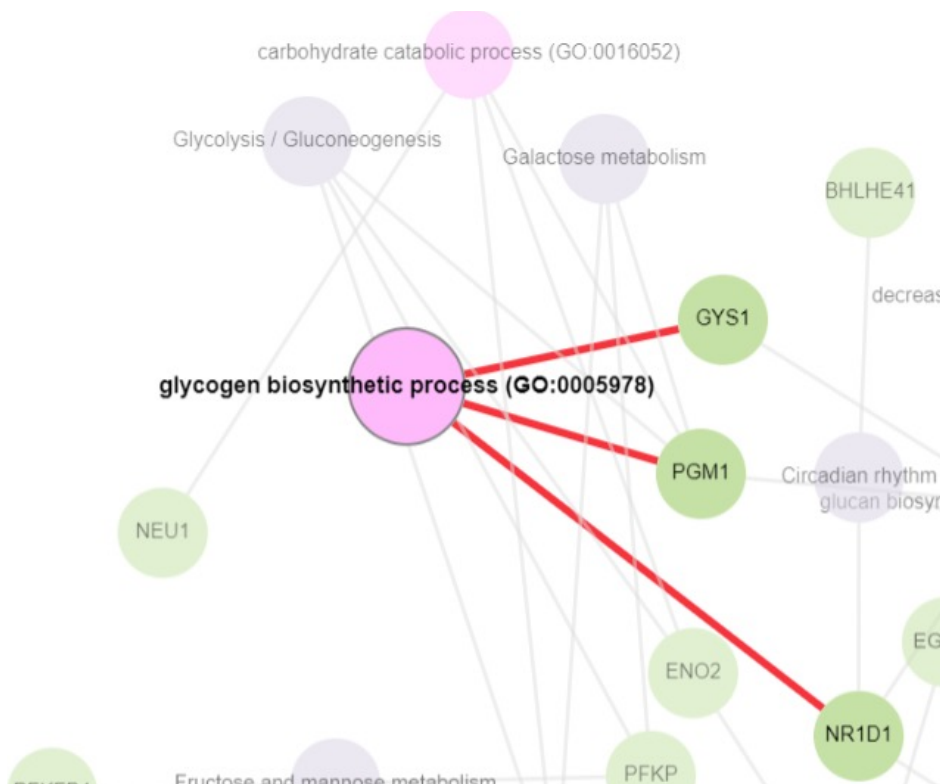


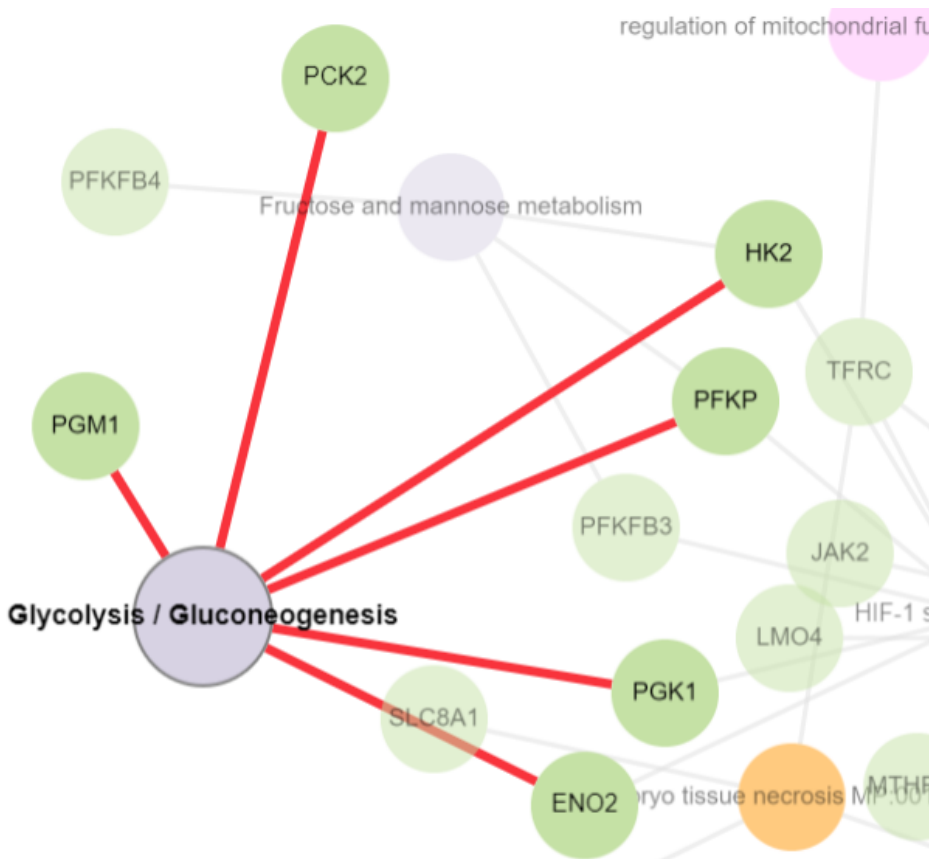
Figure S3. The GO terms represented by the genes dysregulated by THC exposure *in vitro*.

Supplementary Figure S4

A



B



C

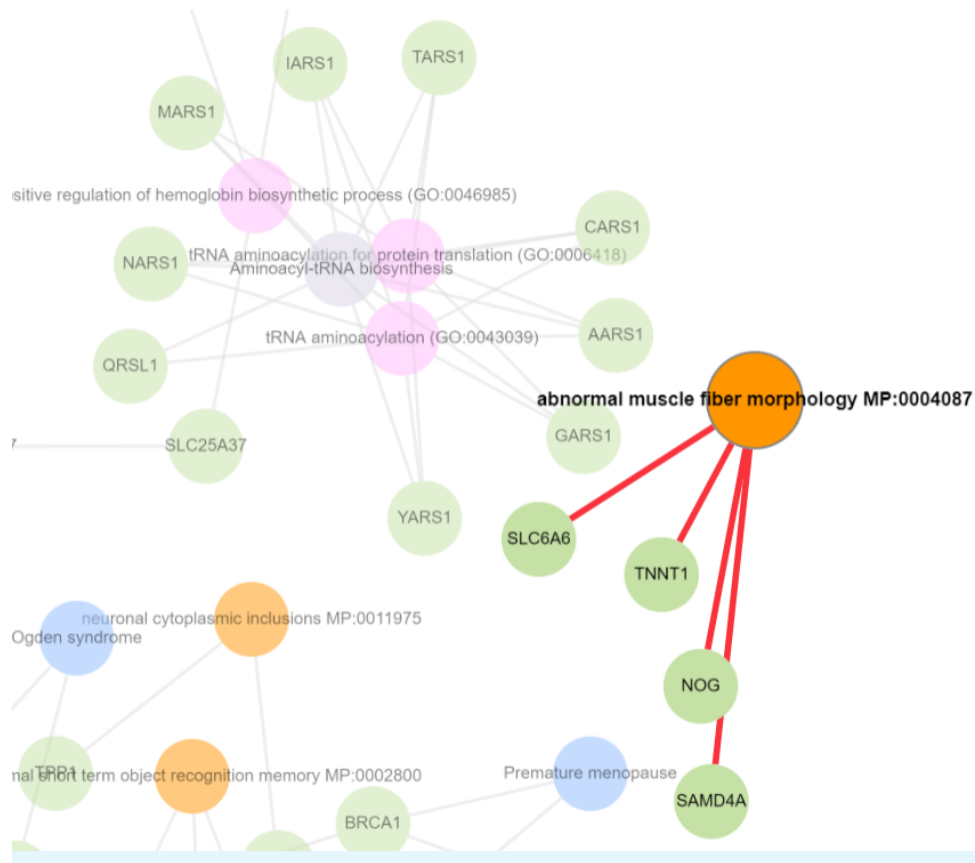


Figure S4. Major biological processes and their associated genes affected by THC exposure (800 ng/mL) *in vitro*.

Supplementary FigureS5



FigureS5. Pathways dysregulated by THC exposure (800 ng/mL) *in vitro*.

Supplementary Figure S6

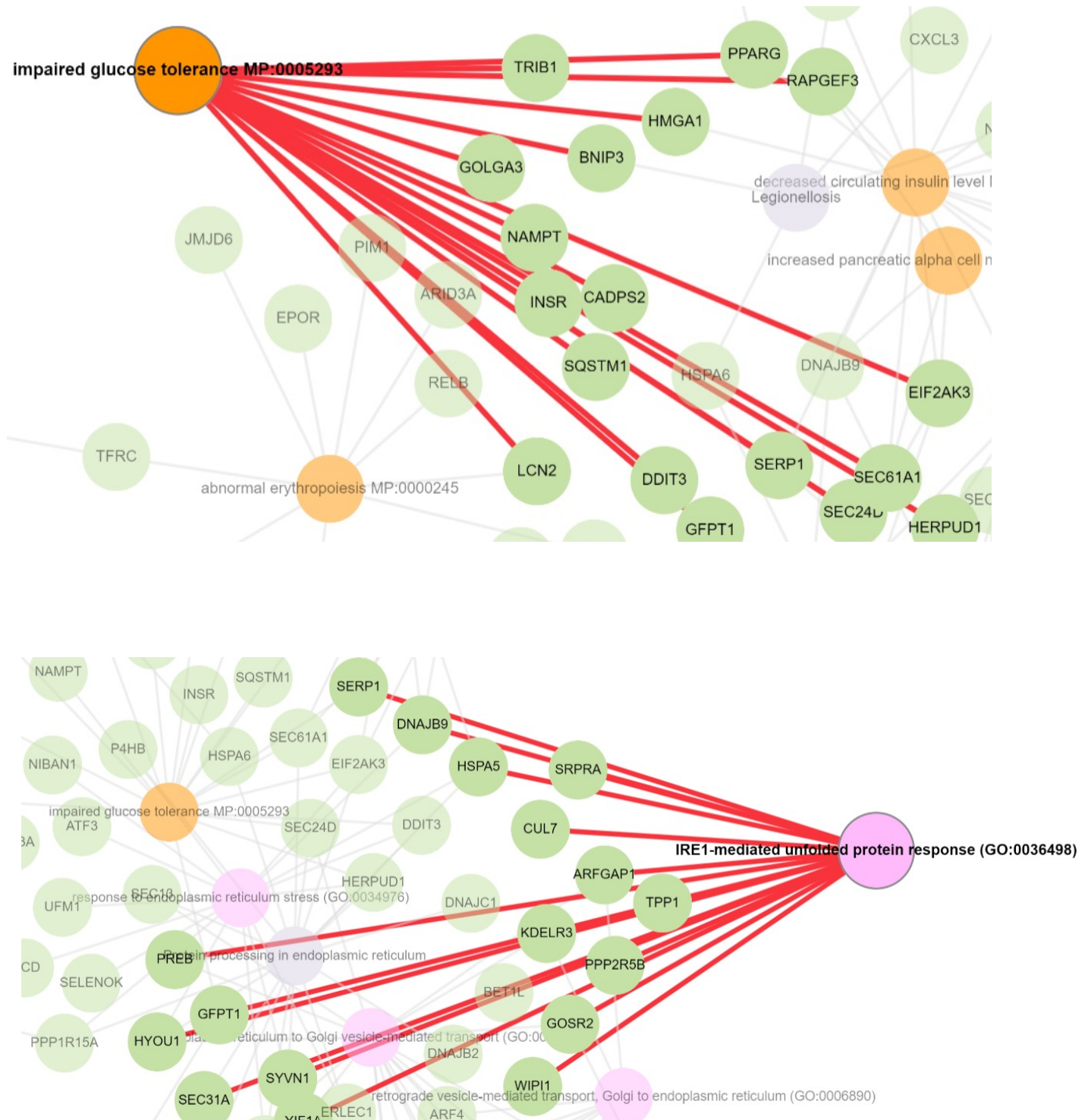


Figure S6. Impaired glucose response and IRE-1 mediated unfolded protein response dysregulated by THC exposure (1000 ng/mL) *in vitro*.

Supplementary Figure S7

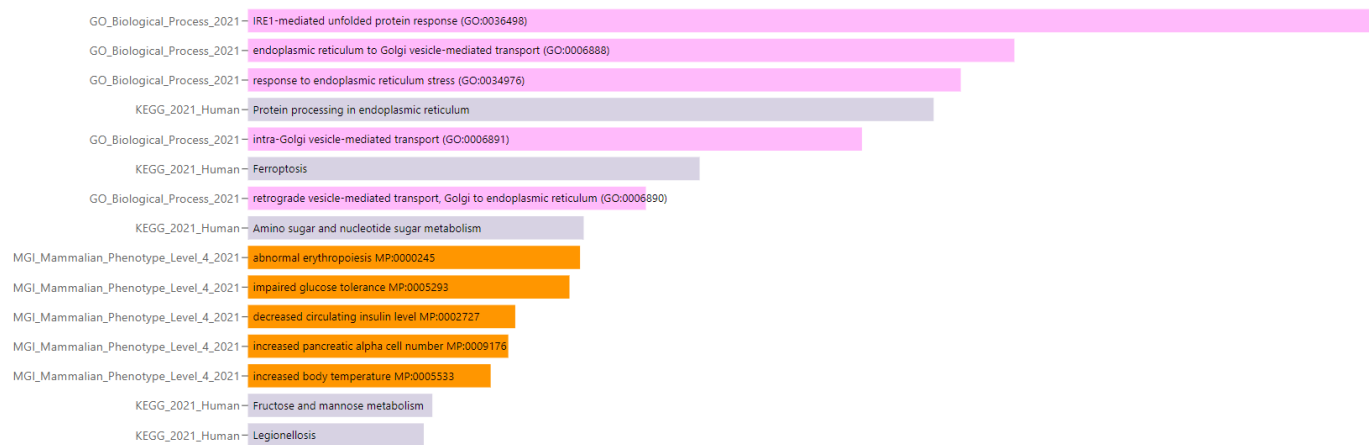


Figure S7. Pathways dysregulated by THC exposure (1000 ng/mL) *in vitro*.

Supplementary Figure S8

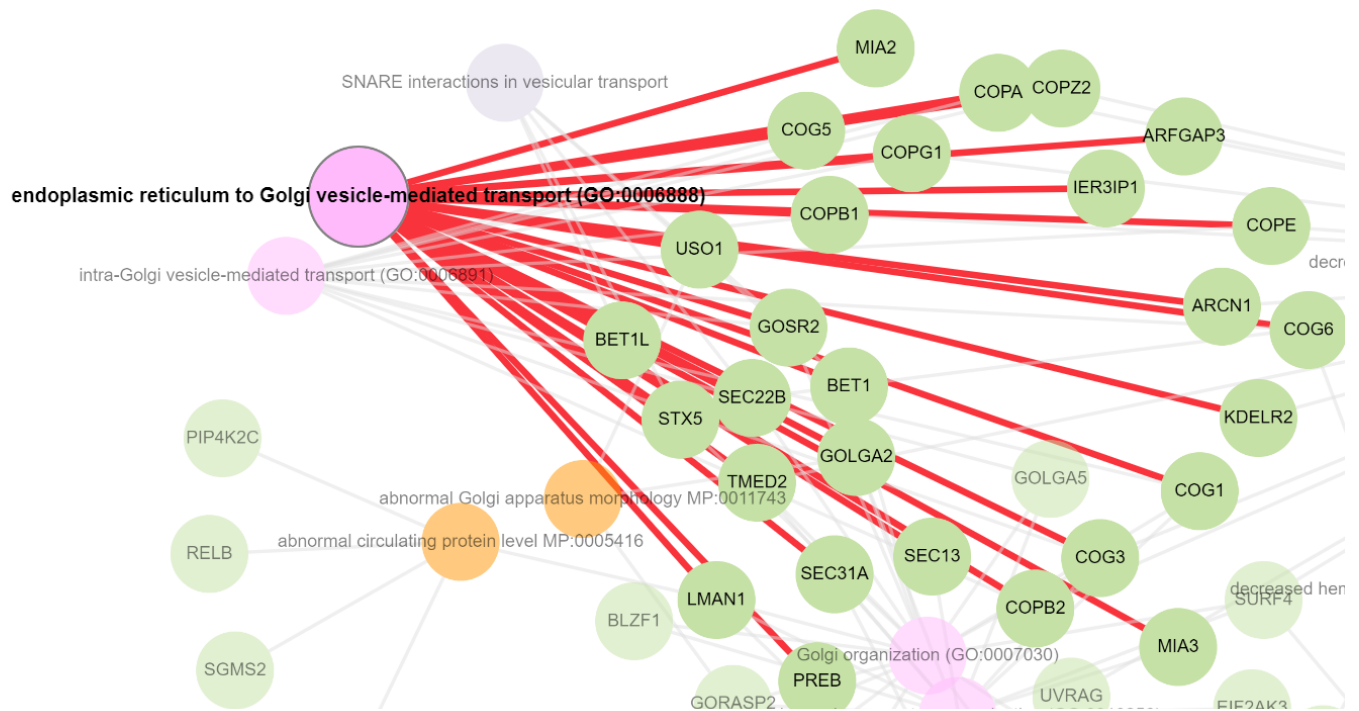


Figure S8. Genes most significantly dysregulated by THC exposure (1200 ng/mL) *in vitro*.

Supplementary Figure S9

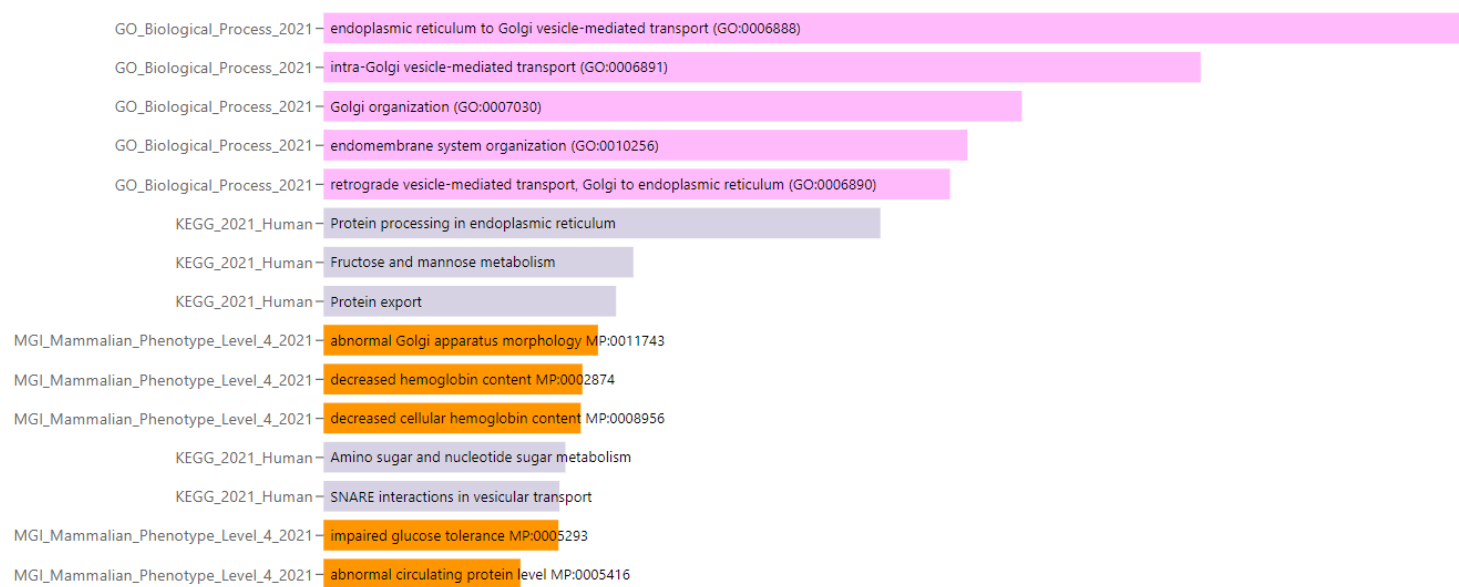


Figure S9. Pathways dysregulated by THC exposure (1200 ng/mL) *in vitro*.

Supplementary Figure S10

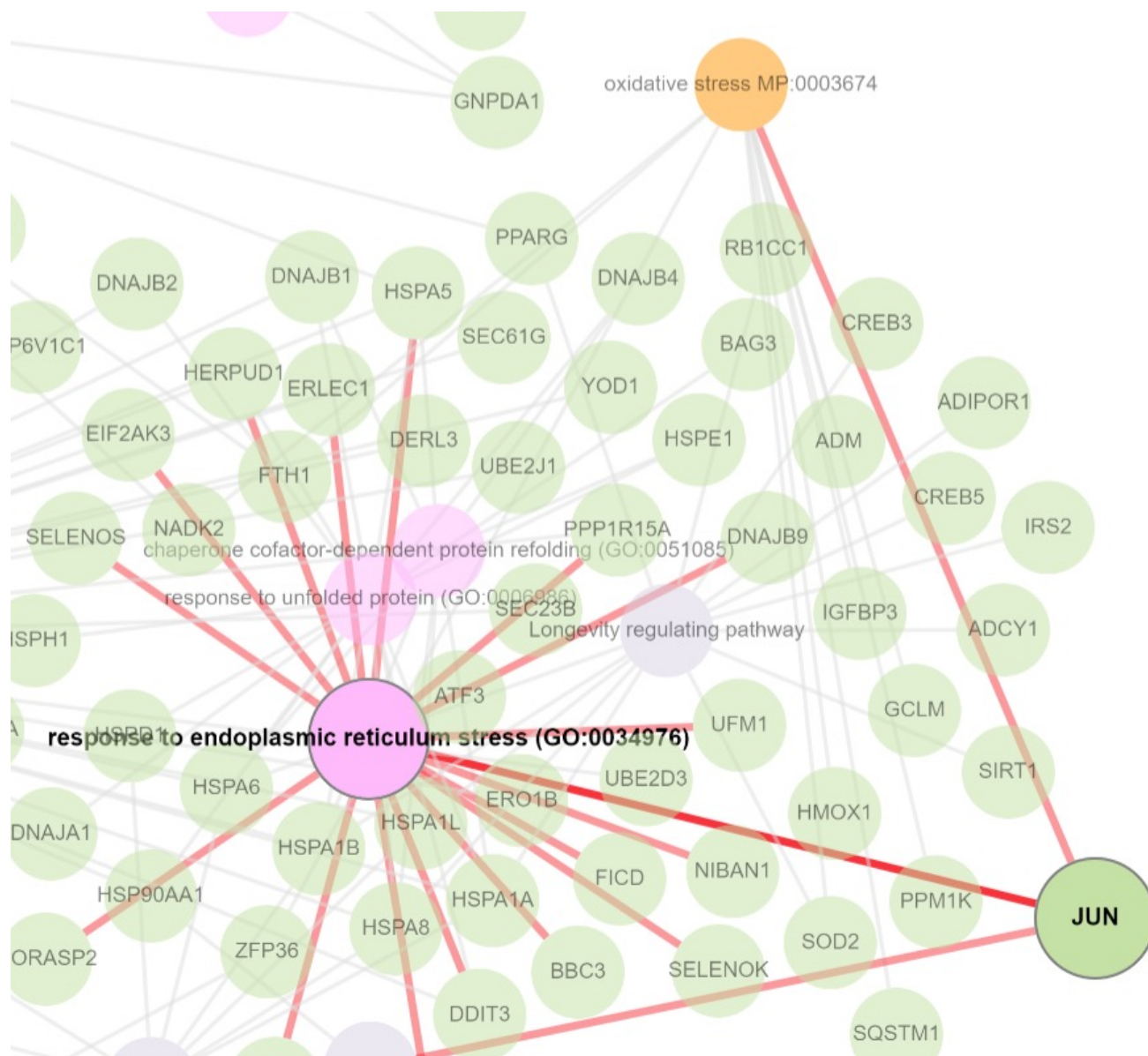


Figure S10. Pathways dysregulated by THC exposure (1500 ng/mL) *in vitro*.