

Supporting Information

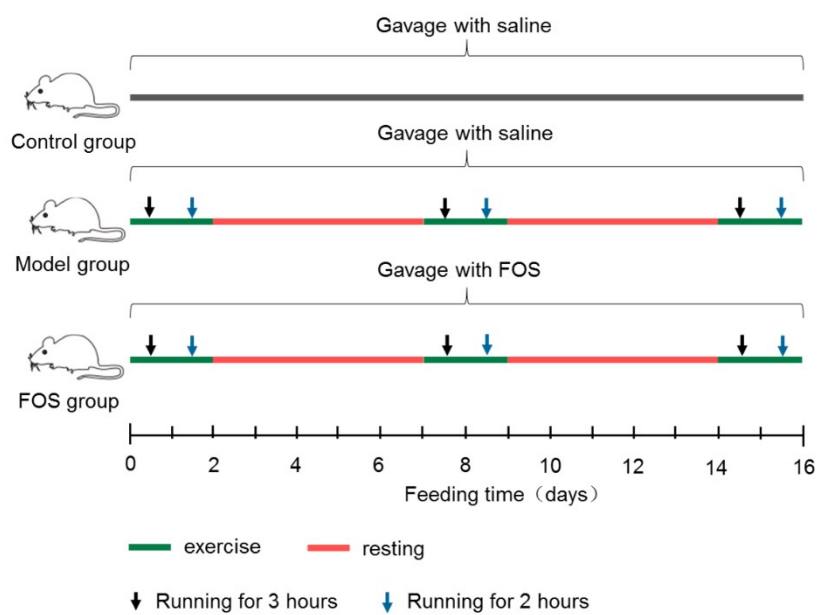


Fig. S1 Schematic illustration of the exercise protocol and feeding strategies.

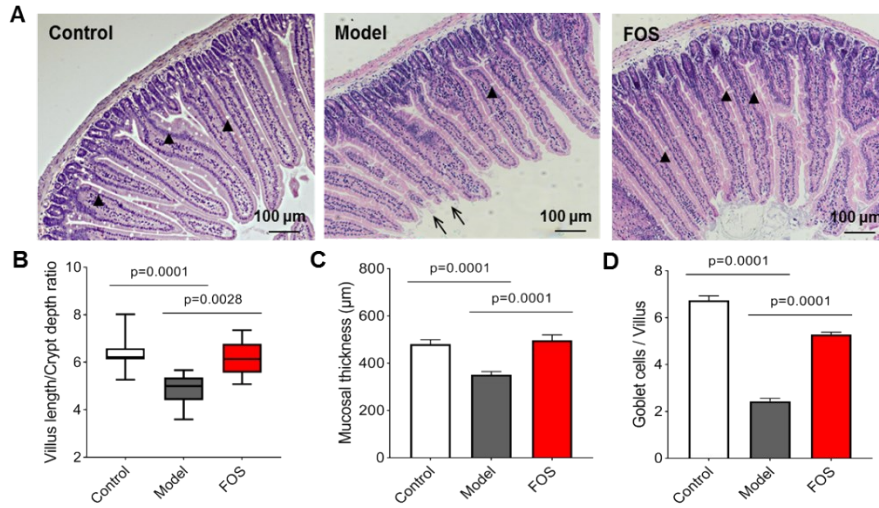


Fig. S2 FOS improved small intestinal epithelium structure in mice under stress. (A) Histology. (B) Villus length/crypt depth ratio. (C) Mucosal thickness. (D) Goblet cells/villus. Data are means \pm SEM (n = 8). Statistical comparisons between two groups were performed using t-test. Note the presence of goblet cells (\blacktriangle), which were distended by pale basophilic secretion. Note some villi with sloughed tips (\blacktriangledown).

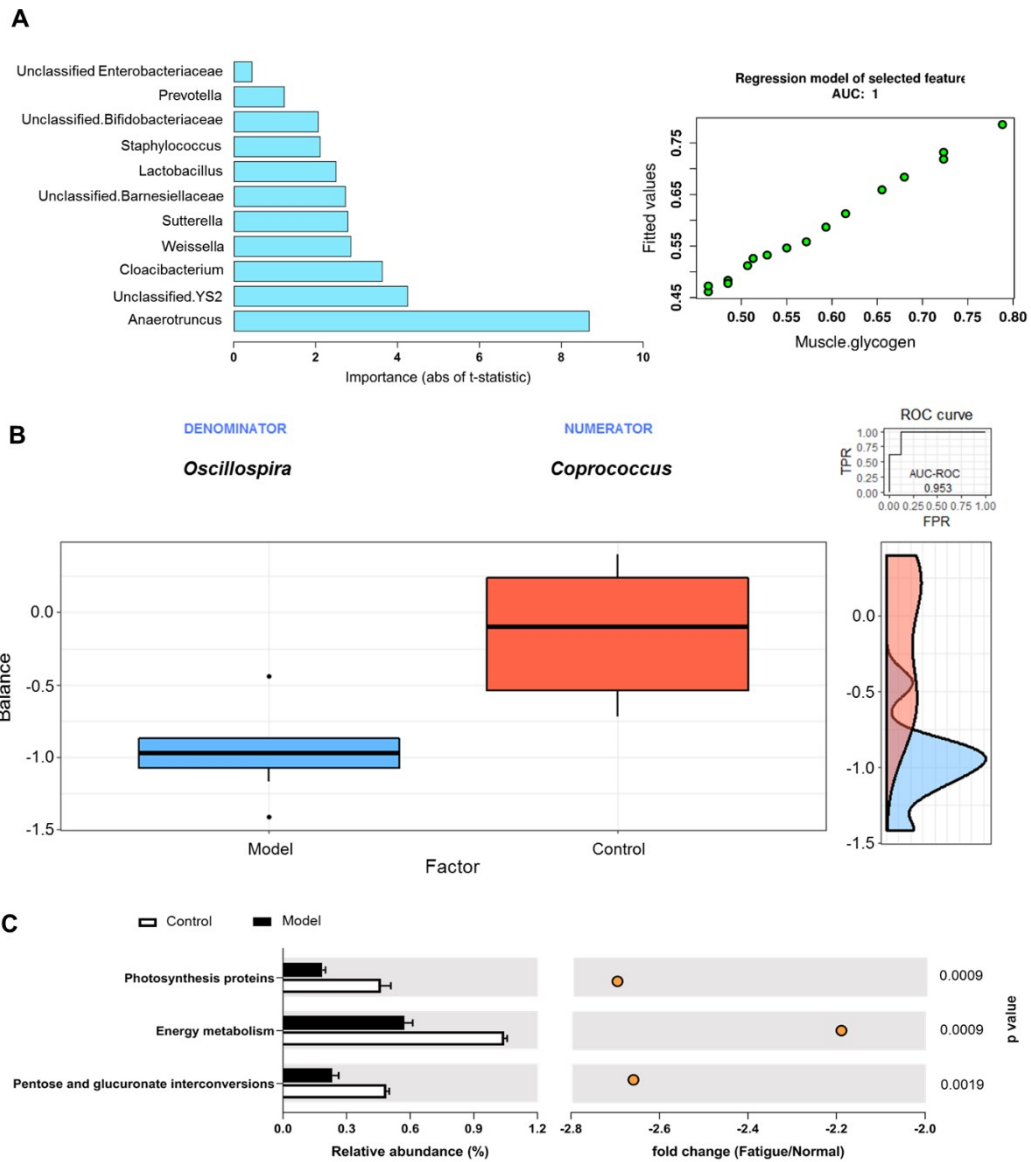


Fig. S3 (A) LASSO regularized regression investigated the correlation of microbial communities and muscle glycogen levels between Control and Model groups. (B) Boxplot of the proposed balance scores to distinguish individuals from Control and Model groups. (C) Significantly different KEGG pathways between Control and Model groups that were identified with Wilcoxon test and ANCOM analysis ($p < 0.05$).

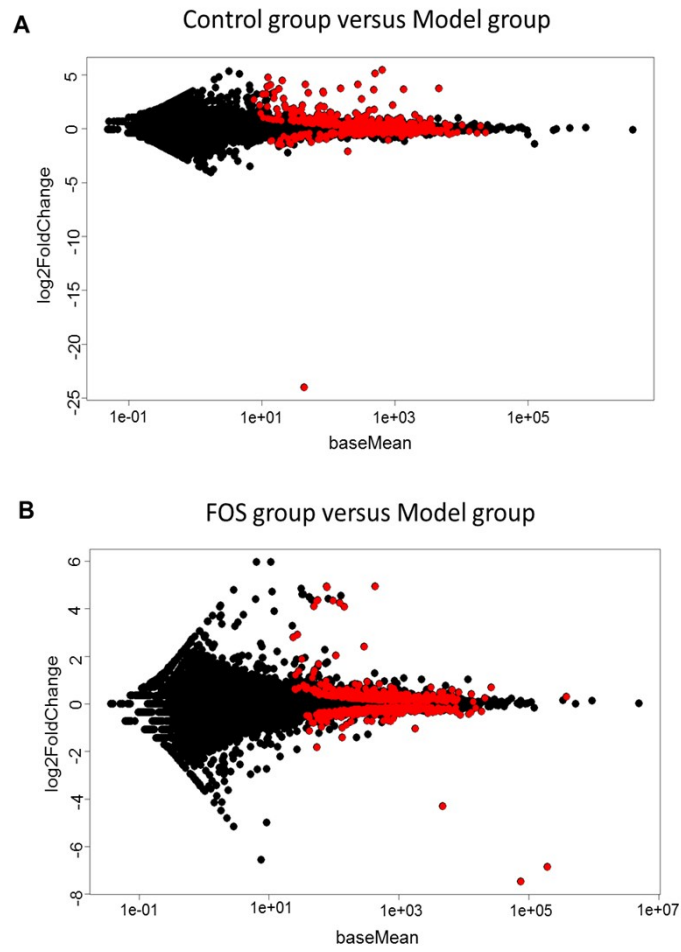


Fig. S4 MAplot indicating differentially expressed genes (DEGs) (Red dots) and non- differentially expressed genes (Black dots).

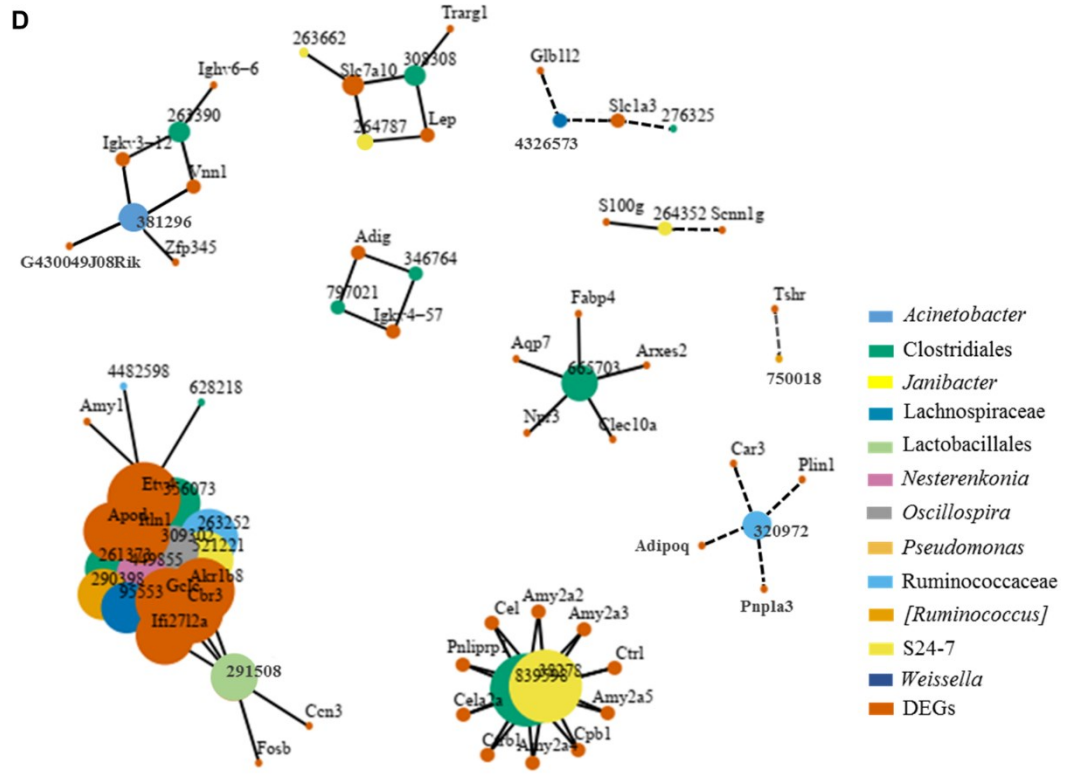
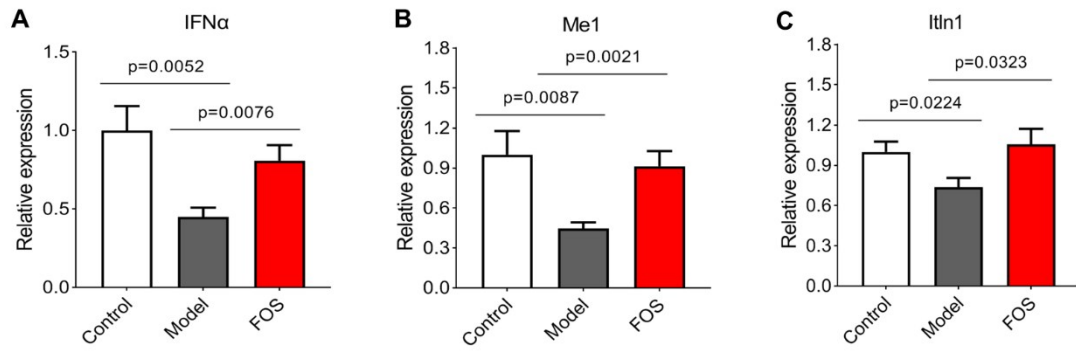


Fig. S5 Relative mRNA expression of (A) IFN α , (B) Me1 and (C) Itln1. Data are means \pm SEM (n = 8). Statistical comparisons between two groups were performed using t-test. (D) Pearson's correlation ($|r| > 0.8$ and $p < 0.05$) between the expression of colonic genes and the abundance of gut microbiota in FOS group. Solid lines indicate positive correlations, while dashed lines indicate negative correlations.

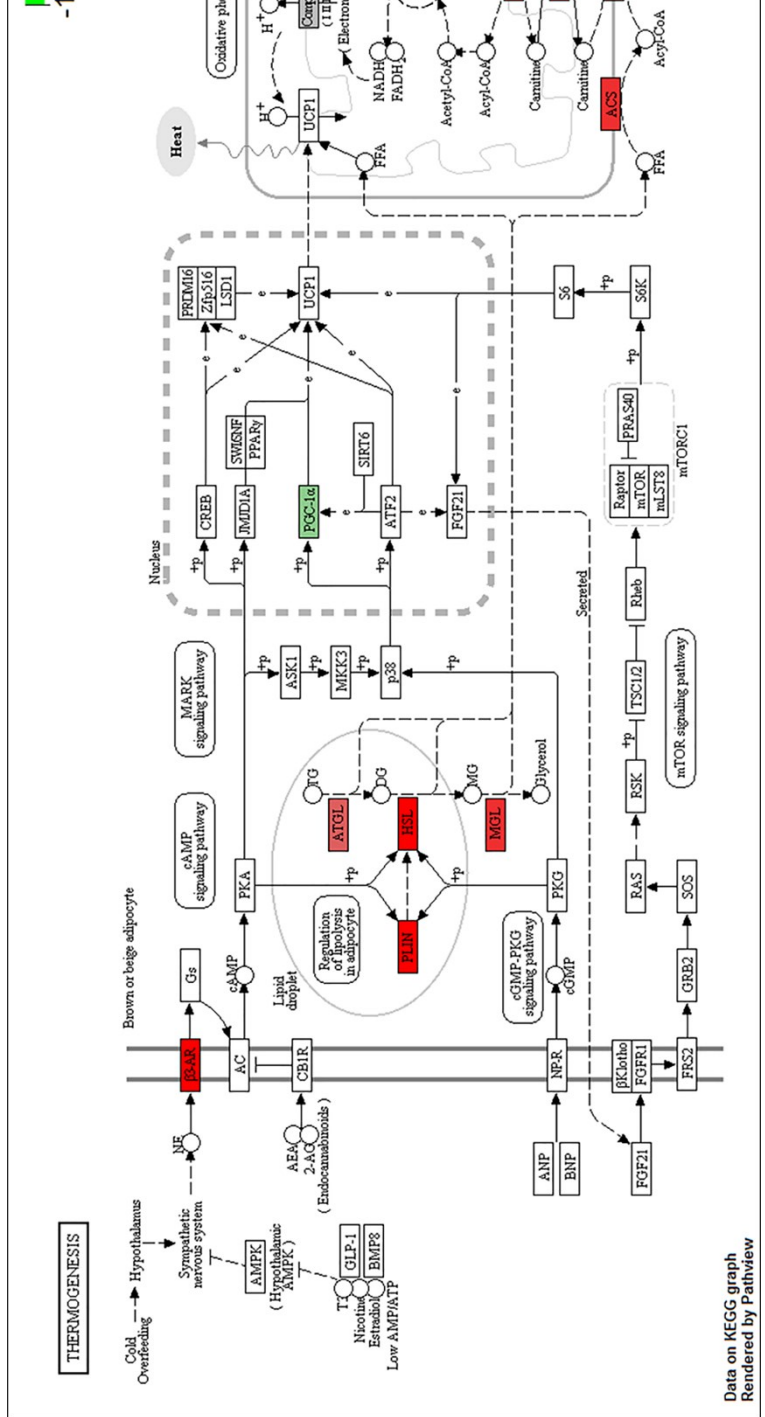


Fig. S6 The pathview map of “Thermogenesis” according to KEGG enrichment results between Model and FOS groups.

Fig. S7 The relative abundance of *Parabacteroides*. Data are means \pm SEM (n = 8).

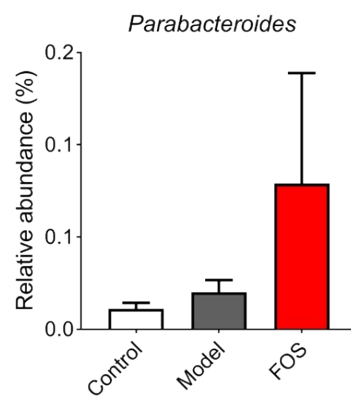


Table S1 Primer sequences for RT-PCR amplification.

Gene	Forward (5'-3')	Reverse (5'-3')
Me1	AATTCCTACGTGTTCCCTGG	ATCCTAGCTGTTGCGTTACTG
IFN α	GATGGATCCCTCCTAGACTCATTCTG	GGCTGTGTTTCTTCTCTCTCAGGAAC
Itln1	CACGAAGAATGGTGTTCATC	AGACCCAAAGGTGTTGTAG
Occludin	ACGGTGCCATAGAATGAGATGTTG	CAGCTAGTTGTTTCATTTCTGCACC
ZO-1	GAGCAGGCTTTGGAGGAGAC	AGCTGCTGAACAGCAAAAGC
NLRP6	AGCTGAGAACGCTGTGTCG	AACTTGGGAACCCCGAAGC
Muc2	CACACAGCGGCCTTTCTCAT	ACCCTCCTCCTACCACATTG
IL-18	ACTGTACAACCGCAGTAATACGG	AGTGAACATTACAGATTTA
β -actin	CAGGCATTGCTGACAGGATG	TGCTGATCCACATCTGCTGG

Table S2 Significantly changed gut microbial enzymes between Control and Model groups according to ANCOM and Wilcoxon test.

Taxa	KEGG_Description	p-values	Relative abundance		Related KEGG pathways
			Model (%)	Control (%)	
K04041	fructose-1,6-bisphosphatase III [EC:3.1.3.11]	0.001	0.017±0.001	0.047±0.004	ko00010 Glycolysis / Gluconeogenesis; ko00030 Pentose phosphate pathway
K06152	gluconate 2-dehydrogenase gamma chain [EC:1.1.1.99.3]	0.001	0.014±0.001	0.036±0.003	ko00030 Pentose phosphate pathway
K00925	acetate kinase [EC:2.7.2.1]	0.003	0.116±0.002	0.082±0.004	ko00620 Pyruvate metabolism
K01835	phosphoglucomutase [EC:5.4.2.2]	0.003	0.097±0.005	0.063±0.004	ko00010 Glycolysis / Gluconeogenesis; ko00030 Pentose phosphate pathway
K02110	F-type H ⁺ -transporting ATPase subunit c	0.016	0.011±0.001	0.007±0.001	ko00190 Oxidative phosphorylation
K01693	imidazoleglycerol-phosphate dehydratase [EC:4.2.1.19]	0.031	0.023±0.001	0.024±0.001	ko00340 Histidine metabolism
K00603	glutamate formiminotransferase / 5-formyltetrahydrofolate cyclo-ligase [EC:2.1.2.5 6.3.3.2]	0.035	0.026±0.003	0.035±0.004	ko00341 Histidine metabolism
K03498	trk system potassium uptake protein	0.04	0.128±0.004	0.141±0.006	
K02495	oxygen-independent coproporphyrinogen III oxidase [EC:1.3.98.3]	0.045	0.114±0.004	0.125±0.006	ko00860 Porphyrin and chlorophyll metabolism
K00705	4-alpha-glucanotransferase [EC:2.4.1.25]	0.046	0.163±0.016	0.110±0.008	ko00500 Starch and sucrose metabolism
K14155	cysteine-S-conjugate beta-lyase [EC:4.4.1.13]	0.046	0.116±0.005	0.133±0.007	ko00270 Cysteine and methionine metabolism
K09816	zinc transport system permease protein	0.046	0.069±0.003	0.079±0.005	ko02010 ABC transporters

Table S3 Significantly different expressed genes (DEGs) for colonic transcriptome (Control group versus Model group).

GeneID	FoldChange	pvalue	padj	Symbol	Name
ENSMUSG00000094306	0.000	0.000	0.000	Gm24924	predicted gene, 24924
ENSMUSG00000029816	0.228	0.000	0.020	GpnmB	glycoprotein (transmembrane) nmb family with sequence similarity 220, member A
ENSMUSG00000083012	0.347	0.001	0.036	Fam220a	triggering receptor expressed on myeloid cells 2 CD300 molecule like family member B
ENSMUSG00000023992	0.369	0.001	0.024	Trem2	FBJ osteosarcoma oncogene B
ENSMUSG00000063193	0.373	0.001	0.027	Cd300b	apolipoprotein D
ENSMUSG00000003545	0.408	0.001	0.041	Fosb	hexokinase 3
ENSMUSG00000022548	0.413	0.000	0.000	Apod	dipeptidase 2
ENSMUSG00000025877	0.455	0.002	0.042	Hk3	C-type lectin
ENSMUSG00000053687	0.464	0.000	0.004	Dpep2	domain family 10, member A cellular
ENSMUSG00000000318	0.483	0.001	0.033	Clec10a	communication network factor 3
ENSMUSG00000037362	0.486	0.000	0.001	Ccn3	ets variant 4
ENSMUSG00000017724	0.4946	0.000	0.012	Etv4	peroxiredoxin like 2A
ENSMUSG00000021792	2.003	0.000	0.000	Prx12a	RIKEN cDNA F730043M19 gene
ENSMUSG00000052125	2.025	0.001	0.041	F730043M19Rik	RIKEN cDNA G430049J08 gene
ENSMUSG00000096528	2.088	0.000	0.000	G430049J08Rik	transferrin aldo-keto
ENSMUSG00000032554	2.171	0.000	0.004	Trf	reductase family 1, member B8
ENSMUSG00000029762	2.180	0.000	0.005	Akr1b8	neuronatin
ENSMUSG00000067786	2.341	0.000	0.001	Nnat	gasdermin C4
ENSMUSG00000055748	2.347	0.000	0.017	Gsdmc4	carbonyl
ENSMUSG00000022947	2.360	0.000	0.002	Cbr3	

ENSMUSG00000021069	2.401	0.000	0.000	Pygl	reductase 3 liver glycogen phosphorylase
ENSMUSG00000032350	2.402	0.000	0.005	Gclc	glutamate- cysteine ligase, catalytic subunit
ENSMUSG00000003123	2.416	0.000	0.000	Lipe	lipase, hormone sensitive
ENSMUSG000000094117	2.464	0.001	0.036	Igkv3-12	immunoglobulin kappa variable 3- 12
ENSMUSG00000005360	2.474	0.000	0.000	Slc1a3	solute carrier family 1 (glial high affinity glutamate transporter), member 3
ENSMUSG00000029417	2.477	0.000	0.002	Cxcl9	chemokine (C-X- C motif) ligand 9
ENSMUSG00000037440	2.487	0.000	0.000	Vnn1	vanin 1
ENSMUSG00000028427	2.633	0.000	0.000	Aqp7	aquaporin 7
ENSMUSG00000032418	2.708	0.000	0.000	Me1	malic enzyme 1, NADP(+)- dependent, cytosolic
ENSMUSG00000047182	2.728	0.000	0.020	Irs3	insulin receptor substrate 3
ENSMUSG00000079017	2.737	0.000	0.000	Ifi2712a	interferon, alpha- inducible protein 27 like 2A
ENSMUSG00000074195	2.843	0.000	0.011	Clca4b	chloride channel accessory 4B adipocyte-related
ENSMUSG00000048040	3.082	0.000	0.000	Arxes2	X-chromosome expressed sequence 2
ENSMUSG00000038209	3.157	0.000	0.008	Itln1	intelectin 1 (galactofuranose binding)
ENSMUSG00000040808	3.356	0.001	0.034	S100g	S100 calcium binding protein G trafficking
ENSMUSG00000046275	3.386	0.000	0.000	Trarg1	regulator of GLUT4

					(SLC2A4) 1
					N-
ENSMUSG00000048142	3.419	0.000	0.000	Nat8l	acetyltransferase
					8-like
					patatin-like
ENSMUSG00000041653	3.510	0.000	0.005	Pnpla3	phospholipase
					domain containing
					3
ENSMUSG00000031722	3.667	0.001	0.027	Hp	haptoglobin
					carbonic
ENSMUSG00000031373	3.765	0.000	0.000	Car5b	anhydrase 5b,
					mitochondrial
					tissue inhibitor of
ENSMUSG00000030317	3.776	0.000	0.000	Timp4	metalloproteinase
					4
					ATP-binding
ENSMUSG00000055782	4.012	0.000	0.000	Abcd2	cassette, sub-
					family D (ALD),
					member 2
					serine (or
					cysteine)
ENSMUSG00000066361	4.165	0.000	0.000	Serpina3c	peptidase
					inhibitor, clade A,
					member 3C
ENSMUSG00000022206	4.271	0.000	0.001	Npr3	natriuretic peptide
					receptor 3
ENSMUSG00000031489	4.424	0.000	0.000	Adrb3	adrenergic
					receptor, beta 3
					melanocortin 2
ENSMUSG00000039956	4.453	0.001	0.022	Mrap	receptor accessory
					protein
ENSMUSG00000074264	4.463	0.000	0.000	Amy1	amylase 1,
					salivary
					fatty acid binding
ENSMUSG00000062515	4.466	0.000	0.000	Fabp4	protein 4,
					adipocyte
					ankyrin repeat and
ENSMUSG00000074771	6.532	0.000	0.000	Ankef1	EF-hand domain
					containing 1
					cell death-
ENSMUSG00000030278	6.650	0.000	0.000	Cidec	inducing DFFA-
					like effector c
					solute carrier
ENSMUSG00000020264	6.852	0.000	0.000	Slc36a2	family 36

					(proton/amino acid symporter), member 2
ENSMUSG00000040564	7.055	0.000	0.000	Apoc1	apolipoprotein C-I
ENSMUSG00000044405	9.226	0.000	0.000	Adig	adipogenin thyroid stimulating hormone receptor
ENSMUSG00000020963	9.384	0.000	0.000	Tshr	
ENSMUSG00000030546	9.833	0.000	0.001	Plin1	perilipin 1
ENSMUSG00000036395	10.045	0.000	0.000	Glb112	galactosidase, beta 1-like 2
ENSMUSG00000043122	10.267	0.000	0.000	A530016L24Rik	RIKEN cDNA A530016L24 gene
ENSMUSG00000035686	10.641	0.000	0.000	Thrsp	thyroid hormone responsive
ENSMUSG00000005413	12.033	0.000	0.000	Hmox1	heme oxygenase 1
ENSMUSG00000027559	12.599	0.000	0.000	Car3	carbonic anhydrase 3 solute carrier family 7 (cationic amino acid transporter, y+ system), member 10
ENSMUSG00000030495	12.672	0.000	0.000	Slc7a10	
ENSMUSG00000037071	12.987	0.000	0.000	Scd1	stearoyl-Coenzyme A desaturase 1
ENSMUSG00000078087	13.281	0.000	0.010	Rps1211	ribosomal protein S12-like 1
ENSMUSG00000074268	14.780	0.000	0.020	Amy2a5	amylase 2a5
ENSMUSG00000093931	14.780	0.000	0.020	Amy2a3	amylase 2a3
ENSMUSG00000096569	14.780	0.000	0.020	Amy2a2	amylase 2a2
ENSMUSG00000096770	14.780	0.000	0.020	Amy2a4	amylase 2a4
ENSMUSG00000039196	16.377	0.000	0.000	Orm1	orosomuroid 1 adiponectin, C1Q and collagen domain containing
ENSMUSG00000022878	16.878	0.000	0.000	Adipoq	
ENSMUSG00000012705	17.042	0.000	0.000	Retn	resistin
ENSMUSG00000059201	21.707	0.000	0.029	Lep	leptin
ENSMUSG00000002588	26.790	0.000	0.000	Pon1	paraoxonase 1
ENSMUSG00000061780	34.820	0.000	0.000	Cfd	complement factor D (adipsin)
ENSMUSG00000025479	43.444	0.000	0.000	Cyp2e1	cytochrome P450, family 2,

subfamily e,
polypeptide 1

Table S4 Significantly different expressed genes (DEGs) for colonic transcriptome (FOS group versus Model group).

GeneID	FoldChange	pvalue	padj	Symbol	Name
ENSMUSG00000035202	0.006	0.000	0.000	Lars2	leucyl-tRNA synthetase, mitochondrial
ENSMUSG00000098178	0.009	0.000	0.000	Gm42418	predicted gene, 42418
ENSMUSG00000089855	0.051	0.000	0.000		
ENSMUSG00000065820	0.283	0.000	0.000	Gm26316	predicted gene, 26316
ENSMUSG00000065087	0.376	0.000	0.000	Snord22	small nucleolar RNA, C/D box 22
ENSMUSG00000000216	0.455	0.002	0.037	Scnn1g	sodium channel, nonvoltage-gated 1 gamma
ENSMUSG00000019970	0.485	0.001	0.023	Sgk1	serum/glucocorticoid regulated kinase 1
ENSMUSG00000044330	0.496	0.000	0.000	Gm9790	predicted gene 9790
ENSMUSG00000095865	2.148	0.002	0.037	Gm13237	predicted gene 13237
ENSMUSG00000095554	2.323	0.003	0.046	Ighv1-16	immunoglobulin heavy variable 1-16
ENSMUSG00000076680	2.462	0.000	0.009	Ighv6-6	immunoglobulin heavy variable 6-6
ENSMUSG00000097854	2.589	0.001	0.021	Gm26602	predicted gene, 26602
ENSMUSG00000074506	2.660	0.000	0.001	Gm10705	predicted gene 10705
ENSMUSG00000074731	3.188	0.000	0.000	Zfp345	zinc finger protein 345
ENSMUSG00000076556	3.683	0.000	0.000	Igkv4-57	immunoglobulin kappa variable 4-57
ENSMUSG00000047370	4.104	0.000	0.004	Gm7367	predicted pseudogene 7367
ENSMUSG00000005413	5.300	0.001	0.019	Hmox1	heme oxygenase 1
ENSMUSG00000031896	6.945	0.001	0.022	Ctrl	chymotrypsin-like ribosomal protein
ENSMUSG00000067575	7.459	0.000	0.011	Rpl35a-ps3	L35A, pseudogene 3
ENSMUSG00000083424	7.459	0.000	0.011	Rpl35a-ps4	ribosomal protein 35A, pseudogene 4
ENSMUSG00000094664	7.459	0.000	0.011	Rpl35a-ps6	ribosomal protein L35A, pseudogene 6
ENSMUSG00000066724	16.795	0.001	0.026	Gm10175	predicted gene

					10175
ENSMUSG00000042179	17.198	0.000	0.011	Pnliprp1	pancreatic lipase related protein 1
ENSMUSG00000031957	18.918	0.002	0.036	Ctrb1	chymotrypsinogen B1
ENSMUSG00000058579	19.996	0.002	0.040	Cela2a	chymotrypsin-like elastase family, member 2A
ENSMUSG00000026818	20.356	0.000	0.011	Cel	carboxyl ester lipase
ENSMUSG00000011463	20.379	0.001	0.025	Cpb1	carboxypeptidase B1 (tissue)
ENSMUSG00000074268	29.831	0.002	0.030	Amy2a5	amylase 2a5
ENSMUSG00000093931	30.457	0.001	0.028	Amy2a3	amylase 2a3
ENSMUSG00000096569	30.457	0.001	0.028	Amy2a2	amylase 2a2
ENSMUSG00000096770	30.457	0.001	0.028	Amy2a4	amylase 2a4
ENSMUSG00000078087	30.601	0.000	0.000	Rps1211	ribosomal protein S12-like 1

Table S5 Significant GO enrichment results for colonic transcriptome (Control group versus Model group).

ID	Term	Genes	adjust p value	Richfactor	z-score
GO:0005840	ribosome	Apod, Rps14, Rps18, Rpl18, Rps15, Rpl37a, Rpl36, Rps7, Rplp1, Rps5, Rpl19, Rps28, Rps16, Rps4x, Rps19, Rpl23, Rack1, Rpl36a, Rpl7, Rps10, Ppargc1a, Rps20, Rplp0, Rps11, Rps17, Rbm3, Rps3, Rps8	0.000	28/227	1.134
GO:0005778	peroxisomal membrane	Abcd2, Mgst1, Cat, Pxmp4, Acs11, Pxmp2, Cav1	0.005	7/45	1.134
GO:0031903	microbody membrane	Abcd2, Mgst1, Cat, Pxmp4, Acs11, Pxmp2, Cav1	0.005	7/45	1.134
GO:0016324	apical plasma membrane	Scnn1a, Slc9a3, Atp1a1, Amotl1, Enpep, Scnn1b, Trf, Slc23a2, P2ry4, Myo1a, Cav1, Hsp90ab1, S100g, Slc26a3, Muc13, Slc26a2, Birc5, Cd44, Anxa6	0.017	19/317	1.147
GO:0045177	apical part of cell	Scnn1a, Slc9a3, Mgst1, Atp1a1, Pdzd2, Amotl1, Enpep, Scnn1b, Trf, Slc23a2, Iptr3, Ctst, P2ry4, Myo1a, Cav1, Hsp90ab1, S100g, Reep6, Slc26a3, Muc13, Slc26a2, Birc5, Cd44, Anxa6	0.007	24/419	1.225
GO:0034358	plasma lipoprotein particle	Pon1, Apoc1, Lpl, Msr1, Lsr	0.034	5/35	1.342
GO:1990777	lipoprotein particle	Pon1, Apoc1, Lpl, Msr1, Lsr	0.034	5/35	1.342
GO:0032994	protein-lipid complex	Pon1, Apoc1, Lpl, Msr1, Lsr	0.041	5/37	1.342
GO:0044438	microbody part	Abcd2, Hspd1, Mgst1, Cat, Pxmp4, Acs11, Pxmp2, Cav1	0.005	8/61	1.414
GO:0044439	peroxisomal part	Abcd2, Hspd1, Mgst1, Cat, Pxmp4, Acs11, Pxmp2, Cav1	0.005	8/61	1.414
GO:0022625	cytosolic large ribosomal subunit	Rpl18, Rpl37a, Rpl36, Rplp1, Rpl19, Rpl23, Rpl36a, Rpl7, Rplp0	0.001	9/61	1.667
GO:0005777	peroxisome	Abcd2, Idh1, Hspd1, Hsd12, Mgst1, Cat, Pxmp4, Vwa8, Ech1, Ephx2, Acs11, Hsd17b4, Pxmp2, Cav1, Syt7	0.000	15/146	1.807

GO:004257	9	microbody	Abcd2, Idh1, Hspd1, Hsd12, Mgst1, Cat, Pxmp4, Vwa8, Ech1, Ephx2, Acsl1, Hsd17b4, Pxmp2, Cav1, Syt7	0.000	15/146	1.807
GO:001593	4	large ribosomal subunit	Rpl18, Rpl37a, Rpl36, Rplp1, Rpl19, Rpl23, Rpl36a, Rpl7, Rplp0, Rbm3	0.028	10/122	1.897
GO:000575	9	mitochondr ial matrix	Hadha, Hspd1, Hadhb, Etfb, Acadl, Mcl1, Ppif, Acadvl, Etfdh, Pde2a, Cs, Mdh2, Dglucy, Mipep, Acsm3, Trap1, Rps3, Hspe1, Etfb	0.003	19/265	2.065

Table S6 Significant GO enrichment results for colonic transcriptome (FOS group versus Model group).

ID	Term	Genes	adjust p value	Rich-factor	z-score
GO:0000276	mitochondrial proton-transporting ATP synthase complex	Atp5h, Atp5g1, Atp5l	0.039	3/11	1.732
GO:0000313	organellar ribosome	Mrpl32, Mrpl42, Mrpl38, Mrpl58, Mrps15, Mrpl40, Mrps21, Mrps14, Mrps25, Mrps22, Mrps36, Nsun4, Mrps5, Mrpl39	0.000	14/93	2.673
GO:0000314	organellar small ribosomal subunit	Mrpl42, Mrps15, Mrps21, Mrps14, Mrps25, Mrps22, Mrps36, Mrps5	0.000	8/31	2.121
GO:0000315	organellar large ribosomal subunit	Mrpl32, Mrpl42, Mrpl38, Mrpl58, Mrpl40, Nsun4, Mrpl39	0.031	7/60	1.890
GO:0000502	proteasome complex	Psmb2, Psmb6, Psmc3, Psma3, Psme1, Psmc7, Psmc8, Psmd3, Psmd4, Psmd5, Psmd6, Psmd7, Psmd8, Psmd9, Psmd10, Psmd11, Psmd12, Psmd13, Psmd14, Psmd15, Psmd16, Psmd17, Psmd18, Psmd19, Psmd20, Psmd21, Psmd22, Psmd23, Psmd24, Psmd25, Psmd26, Psmd27, Psmd28, Psmd29, Psmd30, Psmd31, Psmd32, Psmd33, Psmd34, Psmd35, Psmd36, Psmd37, Psmd38, Psmd39, Psmd40, Psmd41, Psmd42, Psmd43, Psmd44, Psmd45, Psmd46, Psmd47, Psmd48, Psmd49, Psmd50, Psmd51, Psmd52, Psmd53, Psmd54, Psmd55, Psmd56, Psmd57, Psmd58, Psmd59, Psmd60, Psmd61, Psmd62, Psmd63, Psmd64, Psmd65, Psmd66, Psmd67, Psmd68, Psmd69, Psmd70, Psmd71, Psmd72, Psmd73, Psmd74, Psmd75, Psmd76, Psmd77, Psmd78, Psmd79, Psmd80, Psmd81, Psmd82, Psmd83, Psmd84, Psmd85, Psmd86, Psmd87, Psmd88, Psmd89, Psmd90, Psmd91, Psmd92, Psmd93, Psmd94, Psmd95, Psmd96, Psmd97, Psmd98, Psmd99, Psmd100	0.000	11/66	3.317
GO:0000786	nucleosome	Hist2h3b, Hist2h4, Gylr1, Hist1h4k, Hist1h4d, Hist1h4h, Hist4h4, Hist2h3c2, Hist1h3e, Hist1h1e, Hist1h2ak, Hist1h1a, Hist1h2af, Hist1h3b, Hist1h1d, H2afz, Hist1h4i, Hist1h4b, Hist2h2ac, Hist2h3b, Hist2h4, Hist1h4k, Hist1h4d, Hist1h4h, Hist4h4, Hist2h3c2, Hist1h3e, Hist1h1e, Hist1h3b, Hist1h4i, Hist1h4b, Hist2h3b, Hist2h4, Hist1h4k, Hist1h4d, Smarcc2, Hist1h4h, Hist4h4, Hist2h3c2, Hist1h3e, Smarcc1, Rbbp4, Hist1h1e, Hist1h2ak, Ncor1, Sfr1, Hist1h1a, Rcc1, Hist1h2af, Hist1h3b, Hist1h1d, H2afz, Morf4l1, Smarcc1, Ss18, Smarca2, Hist1h4i, Zeb2, Ruvbl1, Hist1h4b, Hist2h2ac,	0.000	19/88	3.900
GO:0000788	nuclear nucleosome	Hist2h3c2, Hist1h3e, Hist1h1e, Hist1h3b, Hist1h4i, Hist1h4b, Hist2h3b, Hist2h4, Hist1h4k, Hist1h4d, Smarcc2, Hist1h4h, Hist4h4, Hist2h3c2, Hist1h3e, Smarcc1, Rbbp4, Hist1h1e, Hist1h2ak, Ncor1, Sfr1, Hist1h1a, Rcc1, Hist1h2af, Hist1h3b, Hist1h1d, H2afz, Morf4l1, Smarcc1, Ss18, Smarca2, Hist1h4i, Zeb2, Ruvbl1, Hist1h4b, Hist2h2ac,	0.000	12/38	3.464
GO:0000790	nuclear chromatin	Hist1h2ak, Ncor1, Sfr1, Hist1h1a, Rcc1, Hist1h2af, Hist1h3b, Hist1h1d, H2afz, Morf4l1, Smarcc1, Ss18, Smarca2, Hist1h4i, Zeb2, Ruvbl1, Hist1h4b, Hist2h2ac,	0.000	31/402	4.131

			Hey2			
			Ybx1, Sf3b2, Ik, Sart1,			
			Cwc15, Zmat2, Snrnp70,			
			Prpf6, Rbm8a, Wac, Slu7,			
GO:00056	spliceosomal complex		Snw1, Aqr, Hnrnpc, Rbm17,	0.000	22/19	4.690
81			Hspa8, Prpf31, BC005624,		1	
			Lsm3, Snrpd1, Hnrnrm,			
			Mfap1a			
			Sf3b2, Ik, Sart1, Cwc15,			
GO:00056	U2-type spliceosomal		Zmat2, Prpf6, Rbm8a, Snw1,	0.000	13/86	3.606
84	complex		Aqr, Prpf31, Lsm3, Snrpd1,			
			Mfap1a			
			Ndufa12, Atp5h, Chchd10,			
			Slc25a3, Cox6b1, Pet100,			
			Atp5mpl, COX1, Ndufv3,			
			Ndufa5, Ndufa2, Cox5b,			
			Rdh13, Ndufb10, Atp5g1,			
GO:00057	mitochondrial inner		Atp5e, ND2, Mrps21, Cox5a,	0.000	36/44	1.667
43	membrane		Slc25a15, Ndufa8, Timm23,		7	
			Hspd1, Uqcrfs1, Slc8b1,			
			Ndufs6, Ndufa13, Pmpcb,			
			Cox11, Cyb5r3, Afg3l2, Polg,			
			Higd2a, Mgst1, Atp5l,			
			Ndufs8			
			Ndufa12, COX1, Ndufv3,			
GO:00057	mitochondrial respiratory		Ndufa5, Ndufa2, Ndufb10,	0.000	13/80	1.387
46	chain		ND2, Cox5a, Ndufa8,			
			Uqcrfs1, Ndufs6, Ndufa13,			
			Ndufs8			
			Ndufa12, Ndufv3, Ndufa5,			
GO:00057	mitochondrial respiratory		Ndufa2, Ndufb10, ND2,	0.000	10/51	1.897
47	chain complex I		Ndufa8, Ndufs6, Ndufa13,			
			Ndufs8			
			Mrpl32, Mrpl42, Mrpl38,			
			Pin4, Mrpl58, Mrps15,			
GO:0005	mitochondrial matrix		Mrpl40, Hspe1, Mrps21,	0.001	23/26	2.711
759			Mrps14, Mrps25, Mars2,		5	
			Nfs1, Pitrm1, Hspd1, Mrps22,			
			Mrps36, Pmpcb, Nsun4,			
			Mrps5, Polg, Lactb2, Mrpl39			
			Mrpl32, Mrpl42, Mrpl38,			
GO:0005	mitochondrial ribosome		Mrpl58, Mrps15, Mrpl40,	0.000	14/93	2.673
761			Mrps21, Mrps14, Mrps25,			
			Mrps22, Mrps36, Nsun4,			

GO:0005762	mitochondrial large ribosomal subunit	Mrps5, Mrpl39 Mrpl32, Mrpl42, Mrpl38, Mrpl58, Mrpl40, Nsun4, Mrpl39	0.031	7/60	1.890
GO:0005763	mitochondrial small ribosomal subunit	Mrpl42, Mrps15, Mrps21, Mrps14, Mrps25, Mrps22, Mrps36, Mrps5	0.000	8/31	2.121
GO:0005840	ribosome	Rps7, Rps26, Rpl13, Rps19, Rps16, Rpl35, Fau, Mrpl32, Rps18, Rpl7a, Eif3h, Rpl37, Rps15a, Rps20, Rack1, Mrpl42, Apod, Rplp0, Mrpl38, Rpl14, Rpl17, Mrpl58, Mrps15, Mrpl40, Rps4x, Mrps21, Mrps14, Mrps25, Rpl9, Rpl2211, Mrps22, Mrps36, Gadd45gip1, Nsun4, Mrps5, Uba52, Rpl37rt, Rps24, Mrpl39	0.000	39/22 7	1.121
GO:0005844	polysome	Rps26, Rpl7a, Eif3h, Rpl17, Fus, Rps4x, Calr, Naa38	0.030	8/75	1.414
GO:0008023	transcription elongation factor complex	Paf1, Rtf1, Snw1, Elp1, Ctr9, Eaf1, Leo1	0.019	7/53	1.134
GO:0015629	actin cytoskeleton	Myl6, Tpm3, Ppp1r12a, Myzap, Tax1bp3, Myl12b, Ctnna1, Cnn3, Cfl2, Myh11, Arhgef2, Snx9, Hnrnpc, Tpm1, Gabarap, Cap1, Actr2, Crk, Abl2, Cfl1, Kansl2, Arpc2, Arpc1a, Lmod1, Calb2, Dctn5, Sptbn1, Epb4112, Filip1, Ndc1, Arpc1b, Afap1	0.004	32/49 2	2.121
GO:0015934	large ribosomal subunit	Rpl13, Rpl35, Mrpl32, Rpl7a, Rpl37, Mrpl42, Rplp0, Mrpl38, Rpl14, Rpl17, Mrpl58, Mrpl40, Rpl9, Rpl2211, Nsun4, Uba52, Mrpl39	0.000	17/12 2	1.213
GO:0016363	nuclear matrix	Nono, Csnk2b, Anp32a, Dgkq, Snw1, Chmp1a, Smc1a, Hnrnpm, Ruvb11	0.028	9/90	1.667
GO:00165	SWI/SNF complex	Smarcc2, Smarce1, Smarcc1,	0.003	5/17	2.236

14		Ss18, Smarca2			
GO:0016607	nuclear speck	Sf3b2, Glycer1, Ikbip1, Sart1, Cwc15, Snrnp70, Rbm10, Prpf6, Rbm8a, Pqbp1, Dgkq, Scnm1, Slu7, Snw1, Zc3h13, Morf4l1, Sgk1, Prpf31, Nampt, Hif3a, Foxo4 Ndufa12, Atp5h, Chchd10, Slc25a3, Cox6b1, Pet100, Atp5mpl, COX1, Ndufv3, Ndufa5, Ndufa2, Cox5b, Rdh13, Ndufb10, Atp5g1,	0.028	21/32 2	2.400
GO:0019866	organelle inner membrane	Atp5e, ND2, Mrps21, Cox5a, Slc25a15, Ndufa8, Timm23, Hspd1, Uqcrrf1, Slc8b1, Ndufs6, Ndufa13, Pmpcb, Cox11, Cyb5r3, Afg3l2, Polg, Higd2a, Mgst1, Atp5l, Ndufs8	0.000	36/49 0	1.667
GO:0022624	proteasome accessory complex	Psmc8, Psme3, Psmc3, Psme1, Psmc7 Rps7, Rps26, Rpl13, Rps19, Rps16, Rpl35, Fau, Rps18,	0.013	5/25	2.236
GO:0022626	cytosolic ribosome	Rpl7a, Rpl37, Rps15a, Rps20, Rack1, Apod, Rplp0, Rpl14, Rpl17, Rps4x, Rpl9, Rpl22l1, Uba52, Rps24	0.000	22/10 9	-1.279
GO:0022627	cytosolic small ribosomal subunit	Rps7, Rps26, Rps19, Rps16, Fau, Rps18, Rps15a, Rps20, Rack1, Rps4x, Uba52, Rps24	0.000	12/44	-1.155
GO:0030532	small nuclear ribonucleoprotein complex	Sf3b2, Sart1, Zmat2, Snrnp70, Nolc1, Prpf6, Slu7, Prpf31, Lsm3, Snrpd1	0.001	10/64	3.162
GO:0030964	NADH dehydrogenase complex	Ndufa12, Ndufv3, Ndufa5, Ndufa2, Ndufb10, ND2, Ndufa8, Ndufs6, Ndufa13, Ndufs8	0.000	10/51	1.897
GO:0031012	extracellular matrix	Efemp1, Igfbp7, S100a11, Dpt, Sparcl1, Col6a5, Pkm, Lrig2, Itgb4, Vcan, Htra1, Ccdc80, Hsp90aa1, Col14a1, Col12a1, Postn, Lamb3, Ecm1, Calr, Bgn, Lgals1, Optc, Gsto1, Cfdp1, Hnrnpm,	0.028	28/47 6	4.158

GO:00314 61	cullin-RING ubiquitin ligase complex	Cela2a, Mfap1a, Dag1 Fbx117, Anapc13, Gan, Dcaf10, Glmn, Anapc10, Fbx15, Fbx120, Kctd10, Cacybp, Cul4a, Ube2s, Skp1a, Vhl	0.012	14/16 0	-1.604
GO:00319 70	organelle envelope lumen	Chchd2, Chchd10, Prelid1, Cycs, Ndufa8, Timm23, Coa4, Cacybp, Fam3b Hist2h3b, Hist2h4, Glyr1, Hist1h4k, Hist1h4d, Hist1h4h, Hist4h4,	0.028	9/90	2.333
GO:00329 93	protein-DNA complex	Hist2h3c2, Hist1h3e, Hist1h1e, Hist1h2ak, Kdm5a, Hist1h1a, Hist1h2af, Hist1h3b, Hist1h1d, H2afz, Hist1h4i, Hist1h4b, Hist2h2ac	0.000	20/19 1	3.578
GO:00343 99	nuclear periphery	Nono, Csnk2b, Anp32a, Tnpo2, Dgkq, Snw1, Chmp1a, Smc1a, Hnrnpm, Ruvb1, Dag1 Atp5h, Calm3, Pitpna, Slc25a3, Gapdh, Stip1, Cycs,	0.025	11/12 1	1.508
GO:00432 09	myelin sheath	Pkm, Cox5b, Hsp90aa1, Cox5a, Hspd1, Hspa8, Uqcrfs1, Uba52, Gsto1, Rala, Gnb2, Prkci, Tuba1a Ndufa12, Atp5h, Chchd10, Slc25a3, Pet100, Atp5mpl, COX1, Bak1, Ndufv3, Ndufa5, Ndufa2, Ndufb10,	0.001	20/21 9	2.683
GO:00444 55	mitochondrial membrane part	Atp5g1, Atp5e, ND2, Cox5a, Ndufa8, Timm23, Hspd1, Uqcrfs1, Slc8b1, Ndufs6, Cisd1, Ndufa13, Cox11, Afg3l2, Atp5l, Ndufs8 Hist2h3b, Hist2h4, Glyr1, Hist1h4k, Hist1h4d, Hist1h4h, Hist4h4,	0.000	28/22 1	1.134
GO:00448 15	DNA packaging complex	Hist2h3c2, Hist1h3e, Hist1h1e, Hist1h2ak, Hist1h1a, Hist1h2af, Hist1h3b, Hist1h1d, H2afz, Hist1h4i, Hist1h4b, Hist2h2ac	0.000	19/96	3.900

GO:00452 71	respiratory chain complex I	Ndufa12, Ndufv3, Ndufa5, Ndufa2, Ndufb10, ND2, Ndufa8, Ndufs6, Ndufa13, Ndufs8	0.000	10/51	1.897
GO:00465 40	U4/U6 x U5 tri-snRNP complex	Sart1, Zmat2, Prpf6, Prpf31, Lsm3, Snrpd1 Efemp1, Igfbp7, S100a11, Dpt, Sparcl1, Col6a5, Pkm, Itgb4, Vcan, Htra1, Ccdc80,	0.008	6/33	2.449
GO:00620 23	collagen-containing extracellular matrix	Hsp90aa1, Col14a1, Col12a1, Postn, Lamb3, Ecm1, Calr, Bgn, Lgals1, Gsto1, Cfdp1, Hnrnpm, Cela2a, Dag1 Ndufa12, Cox6b1, COX1, Ndufv3, Ndufa5, Ndufa2, Ndufb10, ND2, Cox5a, Ndufa8, Uqcrfs1, Ndufs6, Ndufa13, Ndufs8	0.007	25/36 0	4.200
GO:00704 69	respiratory chain	Ndufb10, ND2, Cox5a, Ndufa8, Uqcrfs1, Ndufs6, Ndufa13, Ndufs8	0.000	14/92	1.604
GO:00710 05	U2-type precatalytic spliceosome	Sf3b2, Ik, Sart1, Zmat2, Prpf6, Prpf31, Lsm3, Snrpd1, Mfap1a	0.000	9/47	3.000
GO:00710 11	precatalytic spliceosome	Sf3b2, Ik, Sart1, Zmat2, Prpf6, Prpf31, Lsm3, Snrpd1, Mfap1a	0.000	9/48	3.000
GO:00710 13	catalytic step 2 spliceosome	Sf3b2, Sart1, Cwc15, Prpf6, Rbm8a, Slu7, Snw1, Aqr, Hnrnpc, Lsm3, Snrpd1, Hnrnpm	0.000	12/82	3.464
GO:00715 64	npBAF complex	Smarcc2, Smarce1, Smarcc1, Ss18, Smarca2	0.000	5/12	2.236
GO:00715 65	nBAF complex	Smarcc2, Smarce1, Smarcc1, Smarca2	0.013	4/15	2.000
GO:00975 25	spliceosomal snRNP complex	Sf3b2, Sart1, Zmat2, Snrnp70, Prpf6, Prpf31, Lsm3, Snrpd1	0.009	8/59	2.828
GO:00975 26	spliceosomal tri-snRNP complex	Sart1, Zmat2, Prpf6, Prpf31, Lsm3, Snrpd1	0.008	6/33	2.449
GO:00985 62	cytoplasmic side of membrane	Esyt2, Cdip1, Rhoa, Myzap, Gnas, Map2k2, Gnai3, Fgfr3, Snx9, Pkp4, Chmp4b, Cisd1, Cyth1, Gnb2	0.028	14/18 1	-1.069
GO:0098 798	mitochondrial protein complex	Ndufa12, Atp5h, Chchd10, Mrpl32, Atp5mpl, COX1, Ndufv3, Mrpl42, Ndufa5,	0.000	37/26 8	2.795

Table S7 Gene sets significantly enriched in mice under stress (FDR q-value < 0.05). (a) Gene sets that were upregulated in Control group, and (b) gene sets that were upregulated in Model group. SIZE is number of genes belonging the gene set. NES is normalized enrichment score

	NAME	SIZE	NES	FDR q-value
(a)				
	GNF2_MKI67	23	3.097	0.000
	GNF2_ESPL1	30	3.087	0.000
	GNF2_CCNB2	41	3.068	0.000
	KEGG_PPAR_SIGNALING_PATHWAY	53	3.025	0.000
	GO_TRIGLYCERIDE_CATABOLIC_PROCESS	24	2.830	0.000
	GNF2_SMC2L1	26	2.745	0.000
	CROONQUIST_NRAS_SIGNALING_DN	55	2.529	0.000
	REACTOME_EXTENSION_OF_TELOMERES	34	2.568	0.000
	GNF2_CCNA2	49	2.626	0.000
	GNF2_CENPE	31	2.674	0.000
	GNF2_CDC20	43	2.491	0.001
	KANG_DOXORUBICIN_RESISTANCE_UP	40	2.447	0.001
	GNF2_RRM2	31	2.459	0.001
	GNF2_CENPF	41	2.398	0.001
	GNF2_HMMR	38	2.401	0.001
	GO_NEUTRAL_LIPID_METABOLIC_PROCESS	79	2.383	0.002
	REACTOME_DNA_STRAND_ELONGATION	28	2.337	0.002
	REACTOME_TELOMERE_MAINTENANCE	34	2.285	0.003
	GO_CHEMOKINE_ACTIVITY	24	2.225	0.004
	GNF2_RFC3	30	2.240	0.004
(b)				
	REACTOME_EUKARYOTIC_TRANSLATION_ELONGATION	32	-2.609	0.000
	KEGG_RIBOSOME	30	-2.500	0.000
	GO_CYTOSOLIC_RIBOSOME	41	-2.445	0.000
	REACTOME_RESPONSE_OF_EIF2AK4_GCN2_TO_AMINO_ACID_DEFICIENCY	37	-2.433	0.000

BILANGES_SERUM_AND_RAPAMYCIN_SENSITIVE_GENES	35	-2.392	0.000
GO_CYTOSOLIC_SMALL_RIBOSOMAL_SUBUNIT	22	-2.340	0.000
GCM_TPT1	22	-2.316	0.000
REACTOME_NONSENSE_MEDIATED_DECAY_NMD	46	-2.227	0.000
REACTOME_SELENOAMINO_ACID_METABOLISM	47	-2.228	0.000
GO_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE	42	-2.212	0.000
