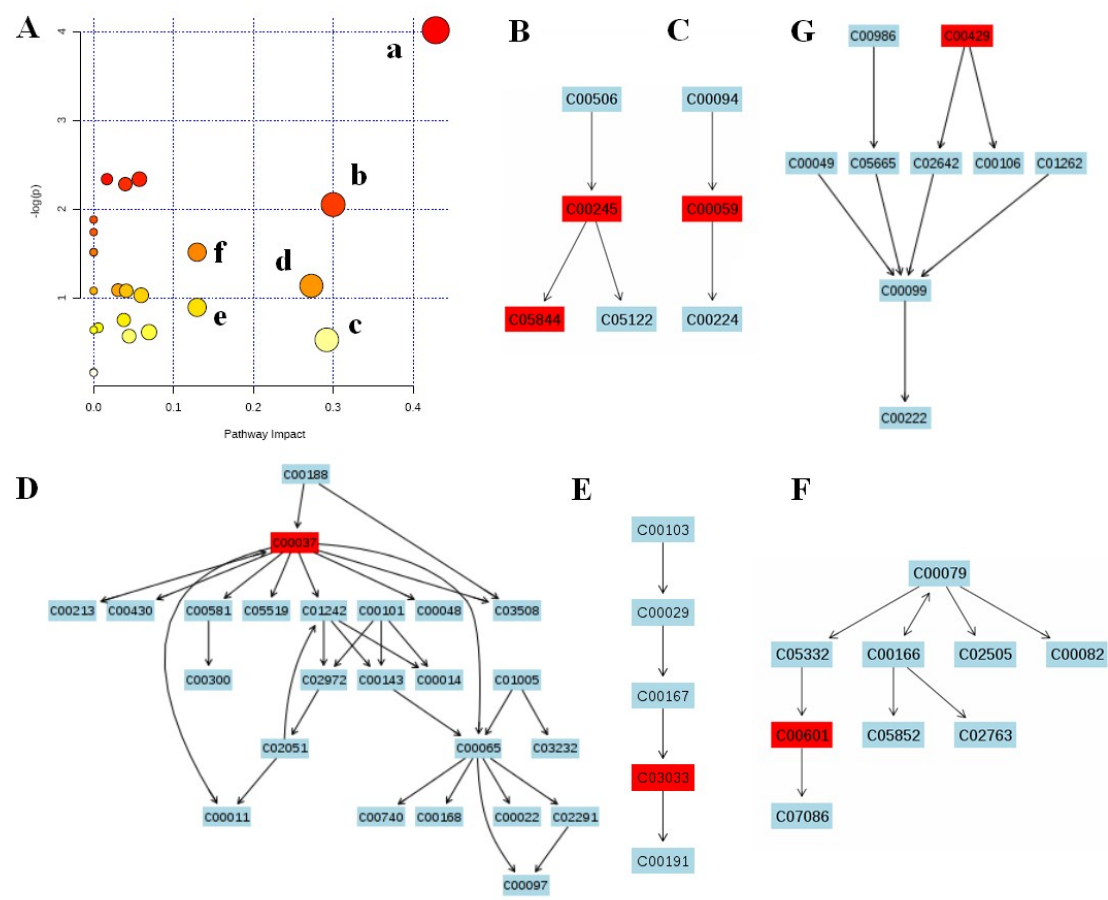
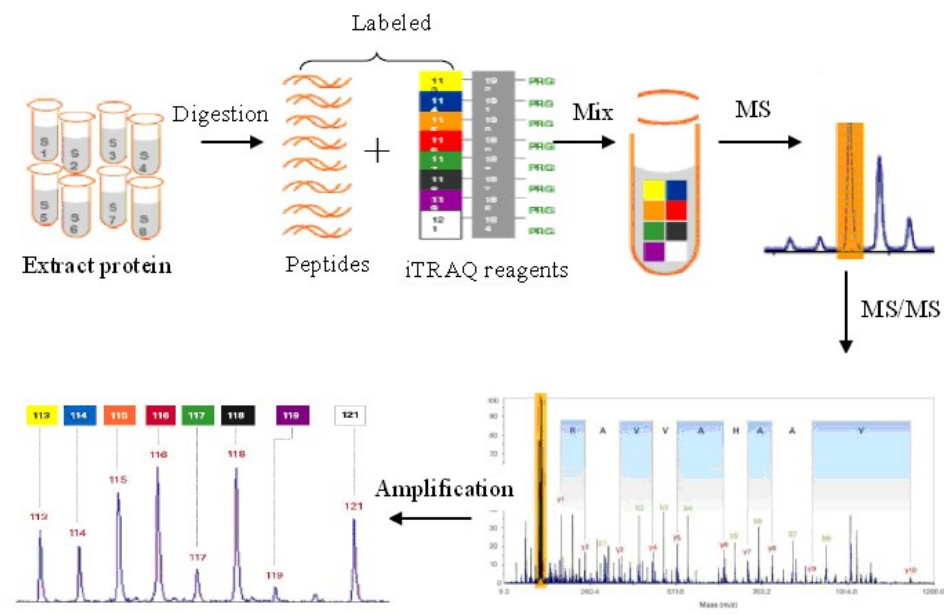


**Fig. S1.** Typical total ion chromatograms (TIC) obtained from rat urine in the positive mode.

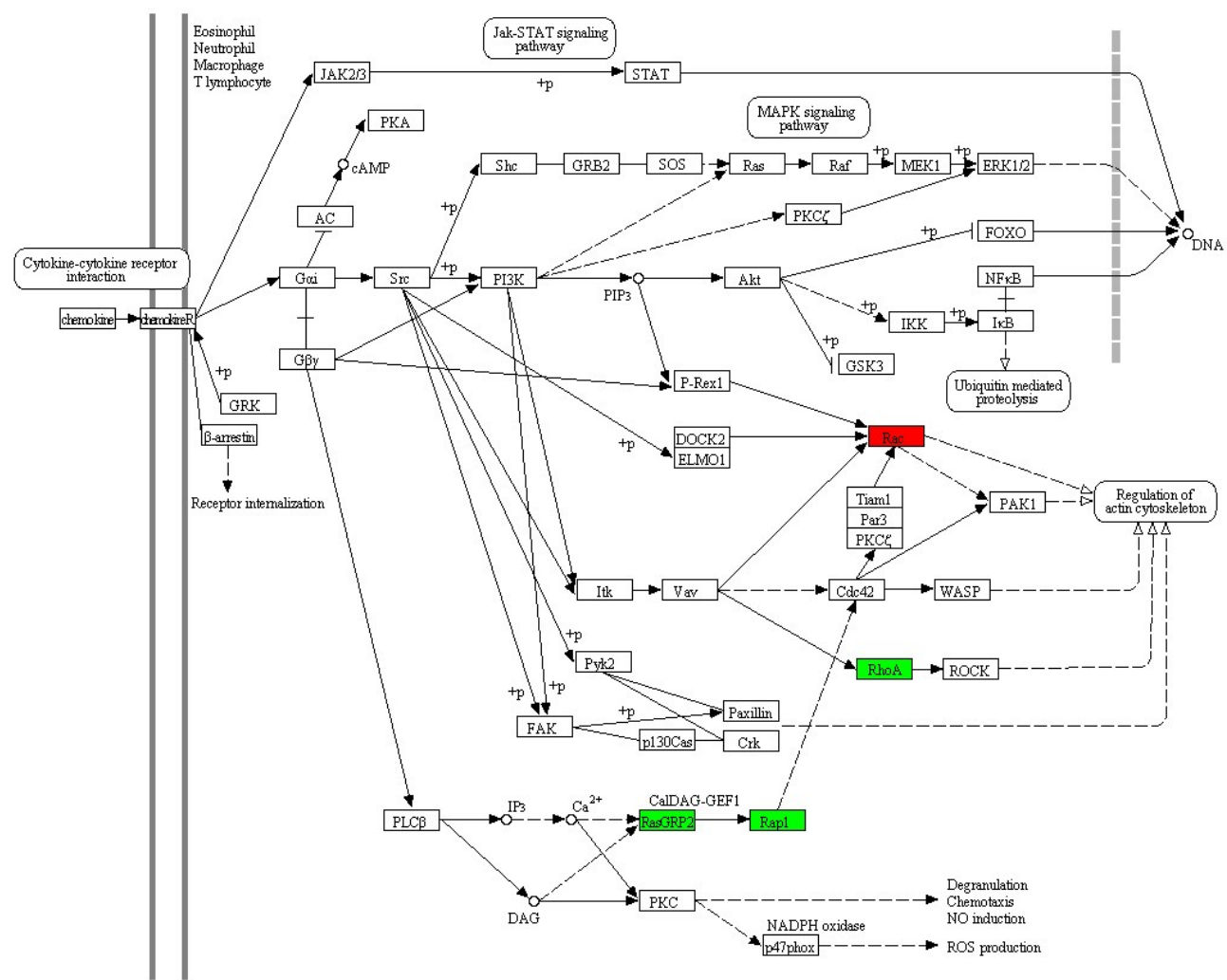
Control group (A), model group (B), JSP-treated group (C).



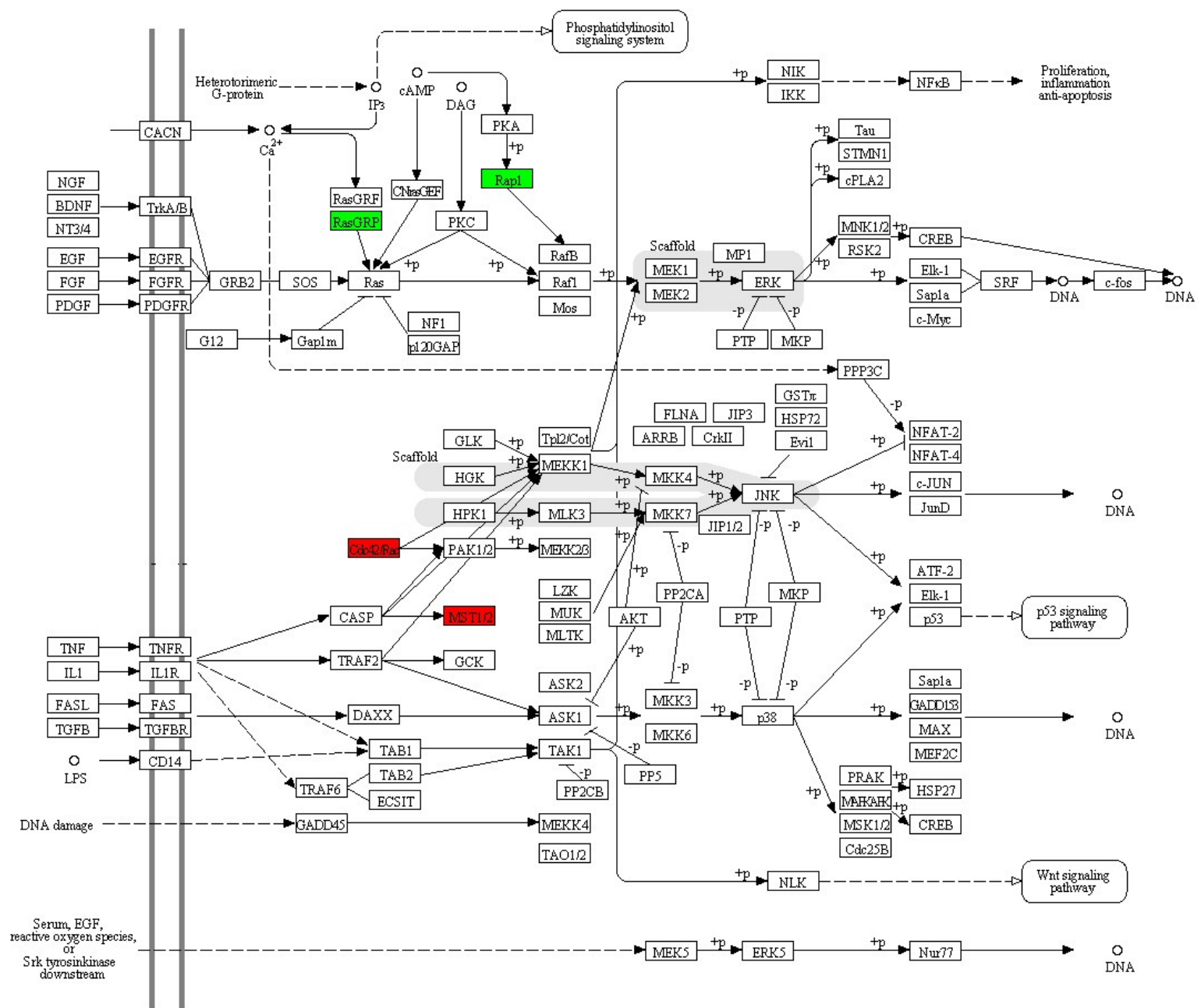
**Fig.S2** Summary of pathway analysis with MetPA (A). Taurine and hypotaurine metabolism (B), Sulfur metabolism (C), Glycine, serine and threonine metabolism (D), Pentose and glucuronate interconversions (E), Phenylalanine metabolism (F), beta-Alanine metabolism (G)



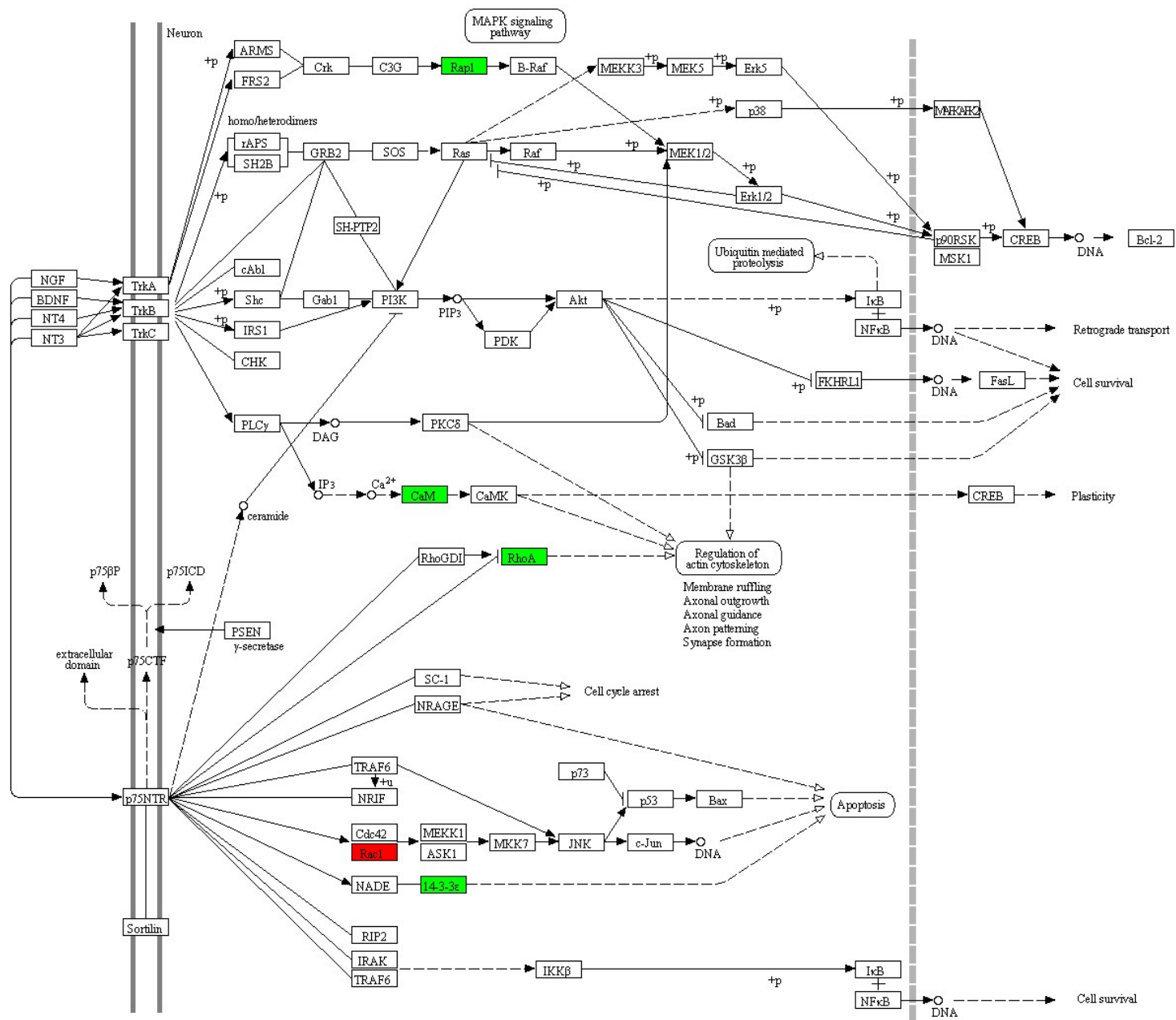
**Fig. S3** The iTRAQ quantitative proteomic analyses.



**Fig.S4** iTRAQ-proteomics analysis for Pathway map of the chemokine signaling pathway (KEGG) with marked entries. Decreased (green nodes), increased (red nodes).



**Fig.S5** Regulation of MAPK signaling pathway. The map was generated using the reference map by KEGG (<http://www.genome.jp/kegg/>). Decreased (green nodes), increased (red nodes).



**Fig. S6** Regulation of neurotrophin signaling pathway.

The map was generated using the reference map by KEGG (<http://www.genome.jp/kegg/>). Decreased (green nodes), increased (red nodes).

**Table S1.** Identification and change trend of marker metabolites related with KYDS based on urine metabolic profiling.

No.	Rt (min)	m/z determined	m/z calculated	Error (ppm)	Ion form	Molecular Formula	Metabolite Name	VIP Value	Trend
1	6.52	255.0651	255.0651	0	[M+H] <sup>+</sup>	C <sub>7</sub> H <sub>14</sub> N <sub>2</sub> O <sub>6</sub> S	5-L-Glutamyl-aurine	8.62363	↑
2	4.06	121.0657	121.0653	3.3	[M+H] <sup>+</sup>	C <sub>8</sub> H <sub>8</sub> O	Phenylacetaldehyde	4.48357	↑
3	5.04	162.0551	162.0555	-2.5	[M+H] <sup>+</sup>	C <sub>9</sub> H <sub>7</sub> NO <sub>2</sub>	4,6-Dihydroxyquinoline	5.86728	↑
4	3.46	206.0449	206.0453	-1.9	[M+H] <sup>+</sup>	C <sub>10</sub> H <sub>7</sub> NO <sub>4</sub>	Xanthurenic acid	7.24889	↓
5	4.06	180.1017	180.1025	-4.4	[M+H] <sup>+</sup>	C <sub>10</sub> H <sub>13</sub> NO <sub>2</sub>	(R)-Salsolinol	2.83317	↑
6	1.44	190.1194	190.1192	1.1	[M+H] <sup>+</sup>	C <sub>7</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>	L-Homocitrulline	3.47929	↑
7	0.73	129.0660	129.0664	-3.1	[M+H] <sup>+</sup>	C <sub>5</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub>	Hydrouracil	3.29001	↓
8	5.75	349.2378	349.2379	-0.3	[M+H] <sup>+</sup>	C <sub>21</sub> H <sub>32</sub> O <sub>4</sub>	11β,21-Dihydroxy-5β-pregnane-3,20-dione	2.8392	↑
9	4.21	126.0224	126.0225	-0.8	[M+H] <sup>+</sup>	C <sub>2</sub> H <sub>7</sub> NO <sub>3</sub> S	Taurine	4.40552	↑
10	0.87	229.1194	229.1188	2.6	[M+H] <sup>+</sup>	C <sub>10</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub>	Prolylhydroxyproline	6.2257	↓
11	1.19	124.0397	124.0399	-1.6	[M+H] <sup>+</sup>	C <sub>6</sub> H <sub>5</sub> NO <sub>2</sub>	Niacin (Nicotinic acid)	3.89617	↓
12	0.87	176.1030	176.1035	-2.8	[M+H] <sup>+</sup>	C <sub>6</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub>	Citrulline	4.05663	↓
13	3.68	190.0502	190.0504	-1.1	[M+H] <sup>+</sup>	C <sub>10</sub> H <sub>7</sub> NO <sub>3</sub>	Kynurenic acid	6.27684	↓
14	0.92	127.0505	127.0508	-2.4	[M+H] <sup>+</sup>	C <sub>5</sub> H <sub>6</sub> N <sub>2</sub> O <sub>2</sub>	Thymine	7.86767	↑
15	0.92	259.0929	259.0930	-0.4	[M+H] <sup>+</sup>	C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O <sub>6</sub>	ribosylimidazoleacetic acid	5.34566	↑
16	1.26	112.0516	112.0511	4.5	[M+H] <sup>+</sup>	C <sub>4</sub> H <sub>5</sub> N <sub>3</sub> O	Cytosine	2.89274	↓
17	1.27	138.0923	138.0919	2.9	[M+H] <sup>+</sup>	C <sub>8</sub> H <sub>11</sub> NO	Tyramine	3.08608	↑
18	5.15	215.0327	215.0321	2.8	[M+H] <sup>+</sup>	C <sub>5</sub> H <sub>11</sub> O <sub>7</sub> P	Deoxyribose 1-phosphate	3.55279	↓
19	2.51	174.1244	174.1243	0.6	[M+H] <sup>+</sup>	C <sub>7</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	apo-[3-methylcrotonoyl-CoA:carbon-dioxide ligase (ADP-forming)]	3.56549	↑
20	1.15	204.1229	204.1236	-3.4	[M+H] <sup>+</sup>	C <sub>9</sub> H <sub>17</sub> NO <sub>4</sub>	Acetylcarnitine	3.25817	↓
21	2.93	197.0309	197.0311	-1.0	[M+H] <sup>+</sup>	C <sub>6</sub> H <sub>4</sub> N <sub>4</sub> O <sub>4</sub>	Xanthine-8-carboxylate	2.87283	↑
22	5.12	302.1394	302.1392	0.7	[M+H] <sup>+</sup>	C <sub>17</sub> H <sub>19</sub> NO <sub>4</sub>	noroxycodone	2.75347	↓
23	4.6	315.0594	315.0593	0.3	[M+H] <sup>+</sup>	C <sub>8</sub> H <sub>15</sub> N <sub>2</sub> O <sub>9</sub> P	5'-Phosphoribosyl-N-formylglycinamide (FGAR)	2.50632	↓
24	4.99	130.0653	130.0657	-3.1	[M+H] <sup>+</sup>	C <sub>9</sub> H <sub>7</sub> N	Quinoline	7.92895	↑
25	1.27	314.1236	314.1240	-1.3	[M+H] <sup>+</sup>	C <sub>14</sub> H <sub>19</sub> NO <sub>7</sub>	Tyramine glucuronide	5.50204	↑
26	5.04	270.0382	270.0379	1.1	[M+H] <sup>+</sup>	C <sub>7</sub> H <sub>12</sub> NO <sub>8</sub> P	N-Acetyl-L-glutamate 5-phosphate	5.33969	↓
27	6.4	170.0590	170.0582	4.7	[M+H] <sup>+</sup>	C <sub>4</sub> H <sub>12</sub> NO <sub>4</sub> P	Phosphorylcholine	6.66665	↑
28	1.78	139.0505	139.0508	-2.2	[M+H] <sup>+</sup>	C <sub>6</sub> H <sub>6</sub> N <sub>2</sub> O <sub>2</sub>	Nicotinamide N-oxide	4.60596	↓
29	0.77	143.0825	143.0821	2.8	[M+H] <sup>+</sup>	C <sub>6</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	Ectoine	4.60012	↓
30	2.3	271.1397	241.1406	-3.3	[M+H] <sup>+</sup>	C <sub>11</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub>	2-[3-Carboxy-3-(methylammonio)propyl]-L-histidine	4.22563	↑
31	1.03	141.0660	141.0664	-2.8	[M+H] <sup>+</sup>	C <sub>6</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub>	1,4-Methylimidazoleacetic acid	3.15977	↓
32	0.94	194.0923	194.0930	-3.6	[M+H] <sup>+</sup>	C <sub>9</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	4-(Nitrosoamino)-1-(3-pyridinyl)-1-butanone	2.95164	↓
33	1.04	190.0168	190.0174	-3.2	[M+H] <sup>+</sup>	C <sub>6</sub> H <sub>7</sub> NO <sub>4</sub> S	Lanthionine ketimine	3.8959	↑
34	0.73	138.0551	138.0555	-2.9	[M+H] <sup>+</sup>	C <sub>7</sub> H <sub>7</sub> NO <sub>2</sub>	Anthranilic acid	2.99686	↑
35	2.58	145.0502	145.0501	0.7	[M+H] <sup>+</sup>	C <sub>6</sub> H <sub>8</sub> O <sub>4</sub>	3-hexenedioic acid	2.82142	↓
36	5.14	399.1465	399.1451	3.5	[M+H] <sup>+</sup>	C <sub>15</sub> H <sub>22</sub> N <sub>6</sub> O <sub>5</sub> S	S-Adenosylmethionine	2.70582	↓
37	2.93	345.0771	345.0786	-4.3	[M+H] <sup>+</sup>	C <sub>12</sub> H <sub>17</sub> N <sub>4</sub> O <sub>4</sub> PS	Thiamine monophosphate	2.68747	↓
38	1.08	86.0603	86.0606	-3.5	[M+H] <sup>+</sup>	C <sub>4</sub> H <sub>7</sub> NO	2-Pyrrolidinone	2.60115	↓
39	3.44	178.0531	178.0538	-3.9	[M+H] <sup>+</sup>	C <sub>6</sub> H <sub>11</sub> NO <sub>3</sub> S	N-Formylmethionine	2.55577	↓
40	4.23	181.0868	181.0865	1.7	[M+H] <sup>+</sup>	C <sub>10</sub> H <sub>12</sub> O <sub>3</sub>	3-Methoxybenzenepropanoic acid	2.51977	↓
41	2.94	144.0655	144.0661	-4.2	[M-H] <sup>-</sup>	C <sub>6</sub> H <sub>11</sub> NO <sub>3</sub>	Allysine	4.88062	↓
42	3.91	228.0879	228.0872	3.1	[M-HCOO] <sup>-</sup>	C <sub>9</sub> H <sub>13</sub> NO <sub>3</sub>	Epinephrine	2.70176	↓
43	1.12	187.0715	187.0719	-2.1	[M-H] <sup>-</sup>	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	Nα-Acetyl-L-glutamine	5.30931	↓
44	3.09	225.0865	225.0875	-4.4	[M-HCOO] <sup>-</sup>	C <sub>9</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	5-Hydroxykynurenamine	2.55661	↓
45	3.59	280.0821	280.0821	0	[M-H] <sup>-</sup>	C <sub>13</sub> H <sub>15</sub> NO <sub>6</sub>	4-Hydroxyphenylacetylglutamine	3.92032	↑
46	5.64	248.0934	248.0923	4.4	[M-HCOO] <sup>-</sup>	C <sub>12</sub> H <sub>13</sub> NO <sub>2</sub>	3-Indolebutyric acid	3.4496	↑
47	7.41	365.2314	365.2328	-3.8	[M-H] <sup>-</sup>	C <sub>21</sub> H <sub>34</sub> O <sub>5</sub>	5α-Tetrahydrocortisol	3.28775	↑
48	1.39	96.9596	96.9596	0	[M-H] <sup>-</sup>	H <sub>2</sub> O <sub>4</sub> S	Sulfuric acid	5.79567	↑
49	3.74	144.0451	144.0449	1.4	[M-H] <sup>-</sup>	C <sub>9</sub> H <sub>7</sub> NO	3-methyleneoxindole	4.23378	↓
50	2.78	264.0518	264.0508	3.8	[M-HCOO] <sup>-</sup>	C <sub>11</sub> H <sub>9</sub> NO <sub>4</sub>	5-Hydroxyindolepyruvate	4.42036	↑
51	2.95	74.0243	74.0242	1.4	[M-H] <sup>-</sup>	C <sub>2</sub> H <sub>5</sub> NO <sub>2</sub>	Glycine	3.5757	↓
52	6.75	239.0920	239.0919	0.4	[M-H] <sup>-</sup>	C <sub>12</sub> H <sub>16</sub> O <sub>5</sub>	3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid	3.02591	↑
53	3.87	242.0435	242.0430	2.1	[M-HCOO] <sup>-</sup>	C <sub>5</sub> H <sub>12</sub> NO <sub>5</sub> P	2-Amino-5-phosphopentanoic acid	6.01274	↑
54	4.94	159.1015	159.1021	-3.8	[M-H] <sup>-</sup>	C <sub>8</sub> H <sub>16</sub> O <sub>3</sub>	7-Hydroxyoctanoic acid	2.91417	↓
55	2.83	142.0504	142.0504	0	[M-H] <sup>-</sup>	C <sub>6</sub> H <sub>9</sub> NO <sub>3</sub>	Vinylacetylglutamine	2.81308	↓
56	5.47	236.0934	236.0923	4.7	[M-HCOO] <sup>-</sup>	C <sub>11</sub> H <sub>13</sub> NO <sub>2</sub>	5-Methoxytryptophol	3.42729	↑
57	6.6	187.1326	187.1334	-4.3	[M-H] <sup>-</sup>	C <sub>10</sub> H <sub>20</sub> O <sub>3</sub>	3-Hydroxycapric acid	4.66398	↓
58	5.1	147.0403	147.0406	-2.0	[M-HCOO] <sup>-</sup>	C <sub>3</sub> H <sub>6</sub> N <sub>2</sub> O <sub>2</sub>	N-Formiminoglycine	2.53224	↑
59	1.59	238.0351	238.0352	-0.4	[M-HCOO] <sup>-</sup>	C <sub>9</sub> H <sub>7</sub> NO <sub>4</sub>	L-Dopachrome	2.8595	↑
60	3.86	338.0817	338.0876	-1.5	[M-H] <sup>-</sup>	C <sub>15</sub> H <sub>17</sub> NO <sub>8</sub>	6-Hydroxy-5-methoxyindole glucuronide	3.62112	↓

Note: '↑' and '↓' represent the compounds which were up- and down-regulated in the KYDS group compared with the control group.

**Table S2.** Result from ingenuity pathway analysis with MetPA

Name	Total	Expected	Hits	Raw p	Impact
Taurine and hypotaurine metabolism	8	0.21683	2	0.018075	0.42857
Tryptophan metabolism	41	1.1113	3	0.096574	0.01663
Pyrimidine metabolism	41	1.1113	3	0.096574	0.0573
Tyrosine metabolism	42	1.1384	3	0.10212	0.03971
Sulfur metabolism	5	0.13552	1	0.12854	0.3
Cyanoamino acid metabolism	6	0.16262	1	0.15225	0
Thiamine metabolism	7	0.18973	1	0.17533	0
Methane metabolism	9	0.24394	1	0.21966	0
Nitrogen metabolism	9	0.24394	1	0.21966	0
Phenylalanine metabolism	9	0.24394	1	0.21966	0.12963
Pentose and glucuronate interconversions	14	0.37946	1	0.32058	0.27273
Arginine and proline metabolism	44	1.1926	2	0.33659	0.03042
Histidine metabolism	15	0.40656	1	0.33918	0
Pantothenate and CoA biosynthesis	15	0.40656	1	0.33918	0.04082
Primary bile acid biosynthesis	46	1.2468	2	0.35674	0.05952
beta-Alanine metabolism	19	0.51498	1	0.40875	0.12963
Starch and sucrose metabolism	23	0.6234	1	0.47117	0.03778
Glutathione metabolism	26	0.70471	1	0.51372	0.00573
Porphyrin and chlorophyll metabolism	27	0.73181	1	0.52715	0
Cysteine and methionine metabolism	28	0.75892	1	0.54022	0.0694
Glycerophospholipid metabolism	30	0.81312	1	0.56531	0.04444
Glycine, serine and threonine metabolism	32	0.86733	1	0.58906	0.29197
Aminoacyl-tRNA biosynthesis	67	1.816	1	0.84839	0
Purine metabolism	68	1.8431	1	0.8527	0

**Table S3.** Differentially expressed proteins identified by iTRAQ.

No	Accession	Description	Score	Coverage	# Proteins	# Unique Peptides	# Peptides	# PSMs	# AAs	MW [kDa]	calc. pI	Fold change
1	Q62636	Ras-related protein Rap-1b	241.51	33.15%	1	1	5	26	184	20.8	5.78	0.6
		Serine/threonine-protein phosphatase 2A										
2	Q4QQT4	65 kDa regulatory subunit A beta isoform	36.39	3.00%	1	1	1	1	601	66	5.10	0.637
3	P06759	Apolipoprotein C-III	163.44	49.50%	1	4	4	47	101	11.1	4.77	0.657
4	P45592	Cofilin-1	230.39	46.99%	1	7	8	30	166	18.5	8.09	0.72
5	P61589	Transforming protein RhoA	23.57	5.18%	1	1	1	2	193	21.8	6.10	0.725
6	P63102	14-3-3 protein zeta/delta	502.95	61.22%	1	9	12	78	245	27.8	4.79	0.739
7	P85972	Vinculin	695.09	24.02%	1	20	20	35	1066	116.5	6.09	0.76
8	P04638	Apolipoprotein A-II	306.11	64.71%	1	6	6	89	102	11.4	6.65	0.776
9	P35213	14-3-3 protein beta/alpha	387.67	61.79%	2	8	13	37	246	28	4.88	0.804
10	P0C643	RAS guanyl-releasing protein 2	54.43	6.58%	1	3	3	4	608	69.2	7.68	0.814
11	Q9Z1P2	Alpha-actinin-1	1115.24	6.64%	1	21	33	99	892	102.9	5.38	0.824



12	P62161	Calmodulin	174.92	33.56%	2	5	5	24	149	16.8	4.22	0.825
13	Q6RUV5	Ras-related C3 botulinum toxin substrate 1	47.2	9.90%	1	2	2	4	192	21.4	8.50	1.227
14	P20761	Ig gamma-2B chain C region	220.41	25.53%	1	5	5	53	333	36.5	7.64	1.24
15	P20762	Ig gamma-2C chain C region	166.7	27.66%	1	6	6	22	329	36.5	8.22	1.306
16	O54748	Serine/threonine-protein kinase 3	22.21	2.24%	1	1	1	1	491	56.1	5.15	1.481
17	Q9QUH3	Apolipoprotein A-V	218.26	17.98%	1	5	5	11	367	41.4	6.48	1.707

**Table S4.** List of the pathway associated with differentially expressed proteins in the experiments.

No	Pathway	Proteins
1	Wnt signaling pathway	Q4QQT4, P61589, Q6RUV5
2	Adherens junction	P61589, P85972, Q9Z1P2, Q6RUV5
3	Neurotrophin signaling pathway	Q62636, P61589, P63102, P35213, P62161, Q6RUV5
4	B cell receptor signaling pathway	Q6RUV5, P20761, P20762
5	Chemokine signaling pathway	Q62636, P61589, P0C643, Q6RUV5
6	PPAR signaling pathway	P06759, P04638, Q9QUH3
7	Fc gamma R-mediated phagocytosis	P45592, Q6RUV5, P20761, P20762
8	MAPK signaling pathway	Q62636, P0C643, Q6RUV5, O54748

