

Adaptation to acetaminophen exposure elicits major changes in expression and distribution of the hepatic proteome

Eakins R*¹, Walsh J*¹, Randle L*², Jenkins RE¹, Schuppe-Koistinen I³, Rowe C¹, Starkey Lewis P¹, Vasieva O⁴, Prats N⁵, Auli M⁵, Bayliss M¹, Webb S¹, Rees, JA¹, Kitteringham NR¹, Goldring CE^{#1}, Park BK¹.

¹MRC Centre for Drug Safety Science, University of Liverpool, Liverpool L69 3GE, UK

²Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK

³Almirall S. A. R&D Centre, Barcelona, Spain

⁴Institute of Integrative Biology, University of Liverpool, Liverpool, L69 7ZL, UK

⁵AstraZeneca R&D, Innovative Medicines, Personalised Healthcare & Biomarkers, Translational Science Centre, Science for Life Laboratory, Solna, Sweden

*These authors contributed equally

#Corresponding author

Supplementary Table 1A: *i*TRAQ-based proteomic comparison of liver proteins in vehicle control- and APAP-treated rats (24h timepoint). Proteins with expression that was different (raw P < 0.05) between control and APAP-treated rats at 24h are listed. Mean expression values relative to a common pool are given for n=4 animals. Proteins are ordered according to the ratio between the 24h and control groups (lowest to highest) such that proteins with expression that was most markedly reduced at 24h appear at the top of the list.

^aAverage number of peptides used for quantification across the four individual iTRAQ runs.

^bUncorrected raw P value.

Uniprot Accession	Name	Peptides ^a	Vehicle control		24h		24h/ctrl Ratio	P-value ^b
			Mean	SD	Mean	SD		
Proteins reduced at 24h								
P49890	Estrogen sulfotransferase, isoform 6	18	3.22	0.91	0.14	0.07	0.04	<0.001
P05369	Farnesyl pyrophosphate synthase	27	1.50	0.39	0.62	0.21	0.42	0.009
O35760	Isopentenyl-diphosphate Delta-isomerase 1	4	1.38	0.41	0.69	0.27	0.50	0.035
O88813	Long-chain-fatty-acid--CoA ligase 5	28	1.89	0.67	0.97	0.31	0.52	0.036
Q9ES38	Bile acyl-CoA synthetase	26	2.80	0.86	1.45	0.44	0.52	0.022
P52847	Sulfotransferase family cytosolic 1B member 1	16	1.97	0.42	1.06	0.43	0.54	0.025
P36510	UDP-glucuronosyltransferase 2A1	3	1.35	0.34	0.75	0.29	0.56	0.033
P63174	60S ribosomal protein L38	5	0.96	0.24	0.56	0.24	0.58	0.041
Q9WUS0	Adenylate kinase isoenzyme 4, mitochondrial	14	1.38	0.19	0.81	0.26	0.59	0.024
Q4V8F9	Hydroxysteroid dehydrogenase-like protein 2	9	0.95	0.24	0.56	0.16	0.59	0.041
P15083	Polymeric immunoglobulin receptor	16	1.20	0.24	0.73	0.10	0.61	0.007
Q6AXX6	Redox-regulatory protein PAMM	8	1.54	0.33	0.94	0.10	0.61	0.010
P16970	ATP-binding cassette sub-family D member 3	13	1.69	0.46	1.03	0.07	0.61	0.018
P02692	Fatty acid-binding protein, liver	69	1.94	0.49	1.18	0.12	0.61	0.017
P62271	40S ribosomal protein S18	13	1.05	0.27	0.66	0.20	0.63	0.043
P09527	Ras-related protein Rab-7a	11	0.96	0.11	0.61	0.09	0.63	0.003
P00173	Cytochrome b5	31	1.37	0.20	0.88	0.21	0.64	0.018
P27605	Hypoxanthine-guanine phosphoribosyltransferase	12	1.35	0.20	0.87	0.18	0.64	0.012
Q7TQM4	Sterol O-acyltransferase 2	5	1.32	0.32	0.87	0.15	0.66	0.034

P29411	GTP:AMP phosphotransferase, mitochondrial	7	1.41	0.24	0.94	0.28	0.66	0.049
P54921	Alpha-soluble NSF attachment protein	10	1.22	0.29	0.81	0.07	0.66	0.023
P10867	L-gulonolactone oxidase	18	2.00	0.36	1.35	0.29	0.67	0.030
P97612	Fatty-acid amide hydrolase 1	26	1.67	0.31	1.15	0.20	0.69	0.033
P57093	Phytanoyl-CoA dioxygenase, peroxisomal	10	1.36	0.22	0.95	0.21	0.70	0.040
Q5XIM9	T-complex protein 1 subunit beta	31	0.97	0.08	0.68	0.09	0.70	0.004
P11507	Sarcoplasmic/endoplasmic reticulum calcium ATPase 2	30	1.01	0.10	0.75	0.09	0.74	0.007
P50237	Sulfotransferase 1C1	27	1.95	0.15	1.44	0.30	0.74	0.029
Q9WUW9	Sulfotransferase 1C2A	5	1.20	0.17	0.89	0.09	0.74	0.015
P04646	60S ribosomal protein L35a	3	1.04	0.06	0.78	0.16	0.75	0.041
O88941	Mannosyl-oligosaccharide glucosidase	12	1.12	0.13	0.85	0.08	0.76	0.008
Q68FP2	Serum paraoxonase/lactonase 3	16	1.43	0.10	1.09	0.15	0.76	0.011
P29314	40S ribosomal protein S9	13	0.86	0.10	0.65	0.05	0.76	0.009
P06214	Delta-aminolevulinic acid dehydratase	35	1.50	0.26	1.15	0.08	0.76	0.027
P97562	Peroxisomal acyl-coenzyme A oxidase 2	38	1.45	0.15	1.13	0.15	0.78	0.029
Q03336	Regucalcin	45	1.98	0.18	1.54	0.25	0.78	0.030
P85108	Tubulin beta-2A chain	72	1.11	0.05	0.87	0.06	0.78	0.001
P18445	60S ribosomal protein L27a	9	0.86	0.08	0.68	0.08	0.79	0.023
Q5XI32	F-actin-capping protein subunit beta	11	1.03	0.11	0.82	0.12	0.80	0.045
P61107	Ras-related protein Rab-14	9	1.11	0.14	0.89	0.04	0.80	0.016
Q497B0	Omega-amidase NIT2	34	1.58	0.09	1.28	0.13	0.81	0.013
P41562	Isocitrate dehydrogenase [NADP] cytoplasmic	59	1.21	0.08	1.00	0.07	0.82	0.007
Q920J4	Thioredoxin-like protein 1	8	1.12	0.11	0.94	0.06	0.84	0.026
Q68FS4	Cytosol aminopeptidase	53	1.52	0.14	1.33	0.06	0.88	0.044
Proteins increased at 24h								
P08541	UDP-glucuronosyltransferase 2B2	37	0.46	0.87	2.34	0.85	5.05	0.020
P02091	Hemoglobin subunit beta-1	179	0.44	0.20	2.03	1.54	4.58	0.029
P38918	Aflatoxin B1 aldehyde reductase member 3	42	0.20	0.17	0.69	0.31	3.40	0.024
P13221	Aspartate aminotransferase, cytoplasmic	30	0.51	0.20	1.35	0.49	2.66	0.010
Q62651	Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial	17	0.62	0.20	1.59	0.44	2.55	0.005
O70199	UDP-glucose 6-dehydrogenase	38	0.32	0.10	0.77	0.16	2.42	0.003
P06866	Haptoglobin	21	0.33	0.15	0.77	0.28	2.35	0.033
O09171	Betaine--homocysteine S-methyltransferase 1	123	1.06	0.39	2.49	1.05	2.35	0.028

P09034	Argininosuccinate synthase	95	0.70	0.51	1.62	0.48	2.32	0.045
P08649	Complement C4	30	0.52	0.34	1.20	0.15	2.31	0.046
P23562	Band 3 anion transport protein	17	0.90	0.23	2.02	0.98	2.24	0.033
P27139	Carbonic anhydrase 2	18	0.68	0.32	1.52	0.49	2.23	0.032
P20059	Hemopexin	24	0.45	0.12	0.98	0.25	2.16	0.007
P13255	Glycine N-methyltransferase	37	0.86	0.37	1.83	0.71	2.14	0.044
Q68FT5	Betaine--homocysteine S-methyltransferase 2	82	0.99	0.45	2.08	0.57	2.10	0.028
P48508	Glutamate--cysteine ligase regulatory subunit	9	0.68	0.26	1.39	0.40	2.05	0.041
P05182	Cytochrome P450 2E1	29	0.89	0.14	1.74	0.48	1.96	0.006
Q6URK4	Heterogeneous nuclear ribonucleoprotein A3	20	0.56	0.07	0.99	0.29	1.76	0.027
Q63416	Inter-alpha-trypsin inhibitor heavy chain H3	10	0.81	0.25	1.31	0.25	1.62	0.036
P20817	Cytochrome P450 4A14	23	1.06	0.19	1.71	0.45	1.61	0.030
Q58FK9	Kynurenine--oxoglutarate transaminase 3	23	1.01	0.27	1.61	0.18	1.59	0.011
P13635	Ceruloplasmin	19	0.67	0.20	1.05	0.07	1.57	0.031
P25409	Alanine aminotransferase 1	19	0.85	0.09	1.13	0.14	1.32	0.018
Q63584	Transmembrane emp24 domain-containing protein 10	11	0.90	0.07	1.17	0.21	1.31	0.038
P38062	Methionine aminopeptidase 2	2	0.87	0.12	1.11	0.16	1.28	0.049
P21571	ATP synthase-coupling factor 6, mitochondrial	13	0.93	0.09	1.17	0.17	1.25	0.045
P85834	Elongation factor Tu, mitochondrial	26	1.01	0.12	1.23	0.13	1.22	0.045
P63086	Mitogen-activated protein kinase 1	5	0.83	0.08	1.00	0.11	1.21	0.041
Q9Z1W6	Protein LYRIC	7	1.17	0.14	1.38	0.06	1.18	0.037
P02770	Serum albumin	193	0.97	0.04	1.10	0.08	1.13	0.026

Supplementary Table 1B: *i*TRAQ-based proteomic comparison of liver proteins in vehicle control- and APAP-treated rats (48h timepoint). Proteins with expression that was different (raw P < 0.05) between control and APAP-treated rats at 48h are listed. Mean expression values relative to a common pool are given for n=4 animals. Proteins are ordered according to the ratio between the 48h and control groups (lowest to highest) such that proteins with expression that was most markedly reduced at 48h appear at the top of the list.

^aAverage number of peptides used for quantification across the four individual iTRAQ runs.

^bUncorrected raw P value.

Uniprot Accession	Name	Peptides ^a	Vehicle control		48h		48h/ctrl	P- value ^b
			Mean	SD	Mean	SD	Ratio	
Proteins reduced at 48h								
P49890	Estrogen sulfotransferase, isoform 6	18	3.22	0.91	0.27	0.17	0.08	0.001
P05183	Cytochrome P450 3A2	15	2.49	0.97	0.29	0.23	0.12	0.001
P08683	Cytochrome P450 2C11	51	2.53	0.52	0.38	0.23	0.15	0.001
P09606	Glutamine synthetase	17	2.73	0.78	0.47	0.30	0.17	0.011
P08010	Glutathione S-transferase Mu 2	70	1.42	0.86	0.31	0.15	0.22	0.022
Q9ES38	Bile acyl-CoA synthetase	26	2.80	0.86	0.62	0.24	0.22	0.001
P02761	Major urinary protein	22	2.27	0.42	0.52	0.23	0.23	<0.001
P10867	L-gulonolactone oxidase	18	2.00	0.36	0.48	0.09	0.24	<0.001
P16232	Corticosteroid 11-beta- dehydrogenase isozyme 1	21	2.55	0.83	0.62	0.31	0.24	0.006
P02692	Fatty acid-binding protein, liver	69	1.94	0.49	0.48	0.32	0.25	0.003
P52847	Sulfotransferase family cytosolic 1B member 1	16	1.97	0.42	0.51	0.15	0.26	<0.001
Q8VHE9	All-trans-retinol 13,14- reductase	10	1.54	0.84	0.40	0.20	0.26	0.009
P55051	Fatty acid-binding protein, brain	9	1.61	0.57	0.42	0.47	0.26	0.037
P24470	Cytochrome P450 2C23	25	1.53	0.32	0.41	0.23	0.26	0.004
P13107	Cytochrome P450 2B3	27	1.48	0.55	0.40	0.52	0.27	0.033
P18163	Long-chain-fatty-acid--CoA ligase 1	78	1.54	0.13	0.41	0.16	0.27	0.001
P50237	Sulfotransferase 1C1	27	1.95	0.15	0.53	0.20	0.27	<0.001
P36365	Dimethylaniline monooxygenase [N-oxide- forming] 1	13	2.34	0.94	0.64	0.17	0.27	0.002
Q03336	Regucalcin	45	1.98	0.18	0.55	0.06	0.28	<0.001
O88813	Long-chain-fatty-acid--CoA ligase 5	28	1.89	0.67	0.53	0.30	0.28	0.007
Q64638	UDP- glucuronosyltransferase 1-5	25	3.79	1.58	1.08	0.77	0.28	0.009
P30839	Fatty aldehyde dehydrogenase	36	1.74	0.55	0.50	0.08	0.29	0.001

P17988	Sulfotransferase 1A1	30	1.99	0.34	0.58	0.09	0.29	<0.001
P05178	Cytochrome P450 2C6	20	1.67	0.62	0.50	0.24	0.30	0.009
P14141	Carbonic anhydrase 3	70	1.99	1.30	0.59	0.26	0.30	0.046
P09811	Glycogen phosphorylase, liver form	76	1.40	0.26	0.43	0.13	0.31	0.001
P00502	Glutathione S-transferase alpha-1	51	1.57	1.21	0.50	0.35	0.32	0.050
P12928	Pyruvate kinase isozymes R/L	61	1.64	0.53	0.55	0.19	0.34	0.003
Q64232	Very-long-chain enoyl-CoA reductase	35	1.76	0.41	0.60	0.22	0.34	0.003
O35077	Glycerol-3-phosphate dehydrogenase [NAD+], cytoplasmic	39	1.45	0.42	0.51	0.07	0.35	0.001
Q64611	Cysteine sulfinic acid decarboxylase	25	1.81	0.70	0.64	0.15	0.35	0.003
P05182	Cytochrome P450 2E1	29	0.89	0.14	0.32	0.17	0.36	0.013
P15865	Histone H1.4	19	1.04	0.35	0.38	0.12	0.36	0.008
P31210	3-oxo-5-beta-steroid 4-dehydrogenase	51	1.07	0.22	0.39	0.30	0.36	0.014
Q5U2Q3	Ester hydrolase C11orf54 homolog	12	2.00	0.36	0.74	0.38	0.37	0.006
Q497B0	Omega-amidase NIT2	34	1.58	0.09	0.59	0.13	0.37	<0.001
P04799	Cytochrome P450 1A2	7	1.32	0.36	0.49	0.48	0.37	0.024
Q6AYT9	Acyl-coenzyme A synthetase ACSM5, mitochondrial	14	1.53	0.30	0.57	0.17	0.37	0.001
Q07071	Glucokinase regulatory protein	27	1.71	0.64	0.65	0.23	0.38	0.015
P43278	Histone H1.0	4	1.51	0.31	0.58	0.19	0.38	0.003
P16638	ATP-citrate synthase	65	1.93	0.71	0.74	0.12	0.38	0.003
Q4KLPO	Probable 2-oxoglutarate dehydrogenase E1 component DHKTD1, mitochondrial	35	1.59	0.56	0.61	0.22	0.39	0.006
P15149	Cytochrome P450 2A2	35	1.28	0.09	0.50	0.07	0.39	<0.001
P97612	Fatty-acid amide hydrolase 1	26	1.67	0.31	0.65	0.19	0.39	0.002
P18757	Cystathionine gamma-lyase	37	1.40	0.63	0.55	0.21	0.39	0.021
P19112	Fructose-1,6-bisphosphatase 1	72	1.71	0.38	0.67	0.16	0.39	0.002
Q5PPL3	Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating	20	1.74	0.46	0.69	0.25	0.40	0.008
P05545	Serine protease inhibitor A3K	34	1.50	0.50	0.60	0.28	0.40	0.016
P00884	Fructose-bisphosphate aldolase B	129	1.31	0.33	0.52	0.16	0.40	0.005
Q64550	UDP-glucuronosyltransferase 1-1	29	1.54	0.70	0.62	0.21	0.40	0.016
P29147	D-beta-hydroxybutyrate dehydrogenase, mitochondrial	42	1.40	0.23	0.56	0.18	0.40	0.002
P33274	Cytochrome P450 4F1	14	1.35	0.35	0.55	0.28	0.41	0.029
P27867	Sorbitol dehydrogenase	26	1.21	0.44	0.50	0.10	0.41	0.011

Q02253	Methylmalonate-semialdehyde dehydrogenase [acylating], mitochondrial	124	1.22	0.24	0.51	0.06	0.42	<0.001
Q9Z339	Glutathione S-transferase omega-1	10	1.42	0.40	0.59	0.32	0.42	0.025
P55159	Serum paraoxonase/arylesterase 1	17	1.68	0.55	0.71	0.06	0.42	0.003
P17764	Acetyl-CoA acetyltransferase, mitochondrial	60	1.28	0.07	0.54	0.26	0.42	0.014
Q63357	Myosin-IId	93	1.01	0.12	0.43	0.22	0.42	0.014
Q4KLZ6	Bifunctional ATP-dependent dihydroxyacetone kinase/FAD-AMP lyase (cyclizing)	64	1.70	0.39	0.72	0.23	0.43	0.005
Q6AYT0	Quinone oxidoreductase	9	1.37	0.36	0.59	0.21	0.43	0.017
Q07523	Hydroxyacid oxidase 2	8	1.99	0.34	0.87	0.24	0.44	0.002
P16303	Carboxylesterase 3	33	1.85	0.85	0.81	0.19	0.44	0.030
P22791	Hydroxymethylglutaryl-CoA synthase, mitochondrial	106	1.46	0.40	0.65	0.26	0.44	0.010
Q62730	Estradiol 17-beta-dehydrogenase 2	17	1.72	0.47	0.76	0.36	0.44	0.034
P13803	Electron transfer flavoprotein subunit alpha, mitochondrial	50	1.29	0.23	0.59	0.25	0.46	0.011
Q63150	Dihydropyrimidinase	29	1.41	0.17	0.64	0.32	0.46	0.020
P24329	Thiosulfate sulfurtransferase	41	1.33	0.20	0.61	0.08	0.46	<0.001
P46953	3-hydroxyanthranilate 3,4-dioxygenase	25	1.42	0.40	0.66	0.06	0.47	0.003
Q6DGG1	Alpha/beta hydrolase domain-containing protein 14B	12	1.36	0.25	0.64	0.14	0.47	0.002
P57113	Maleylacetoacetate isomerase	36	1.58	0.34	0.74	0.14	0.47	0.002
P97532	3-mercaptopyruvate sulfurtransferase	23	1.27	0.28	0.61	0.09	0.48	0.001
Q5FVQ4	Malectin	8	1.39	0.58	0.67	0.31	0.48	0.043
P52759	Ribonuclease UK114	51	1.29	0.41	0.62	0.23	0.48	0.035
P02696	Retinol-binding protein 1	13	1.29	0.23	0.62	0.15	0.48	0.003
P22734	Catechol O-methyltransferase	46	1.49	0.39	0.72	0.22	0.48	0.009
P08011	Microsomal glutathione S-transferase 1	25	1.57	0.62	0.76	0.34	0.48	0.044
A0J PQ8	Alkylglycerol monooxygenase	6	1.64	0.20	0.80	0.12	0.49	<0.001
Q498D5	Regulator of microtubule dynamics protein 2	8	1.34	0.14	0.65	0.21	0.49	0.003
P30713	Glutathione S-transferase theta-2	19	1.34	0.31	0.65	0.10	0.49	0.002
Q9QZX8	Solute carrier organic anion transporter family member 1B2	3	1.36	0.40	0.67	0.19	0.49	0.009

Q7TP52	Carboxymethylenebutenolidase homolog	16	1.79	0.45	0.88	0.32	0.49	0.018
P27605	Hypoxanthine-guanine phosphoribosyltransferase	12	1.35	0.20	0.66	0.12	0.49	0.001
P25093	Fumarylacetoacetase	48	1.45	0.12	0.71	0.12	0.49	<0.001
Q02974	Ketohexokinase	25	1.56	0.28	0.77	0.07	0.50	<0.001
Q5BK17	Iodotyrosine dehalogenase 1	4	1.75	0.28	0.87	0.22	0.50	0.004
P57093	Phytanoyl-CoA dioxygenase, peroxisomal	10	1.36	0.22	0.68	0.18	0.50	0.004
Q66HG4	Aldose 1-epimerase	5	1.37	0.18	0.70	0.27	0.51	0.008
P46720	Solute carrier organic anion transporter family member 1A1	4	1.41	0.30	0.72	0.10	0.51	0.003
Q63060	Glycerol kinase	20	1.68	0.28	0.87	0.19	0.51	0.002
Q68FP2	Serum paraoxonase/lactonase 3	16	1.43	0.10	0.74	0.11	0.51	<0.001
P10760	Adenosylhomocysteinase	54	1.29	0.20	0.67	0.25	0.51	0.011
P23680	Serum amyloid P-component	4	1.61	0.24	0.83	0.08	0.52	<0.001
P23457	3-alpha-hydroxysteroid dehydrogenase	48	1.51	0.36	0.78	0.33	0.52	0.048
P10860	Glutamate dehydrogenase 1, mitochondrial	118	1.63	0.34	0.84	0.15	0.52	0.005
Q64581	Cytochrome P450 3A18	8	1.50	0.57	0.78	0.17	0.52	0.019
P06214	Delta-aminolevulinic acid dehydratase	35	1.50	0.26	0.78	0.14	0.52	0.002
B0BNE5	S-formylglutathione hydrolase	23	1.32	0.33	0.69	0.25	0.52	0.020
Q562C4	Methyltransferase-like protein 7B	8	1.63	0.70	0.85	0.17	0.52	0.028
P08461	Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial	11	1.13	0.26	0.59	0.06	0.52	0.005
P41562	Isocitrate dehydrogenase [NADP] cytoplasmic	59	1.21	0.08	0.63	0.15	0.52	0.002
Q63270	Cytoplasmic aconitate hydratase	36	1.21	0.20	0.64	0.21	0.52	0.010
P70712	Kynureninase	19	1.41	0.32	0.74	0.13	0.52	0.005
Q510M2	Nicotinate-nucleotide pyrophosphorylase [carboxylating]	11	1.28	0.42	0.67	0.27	0.53	0.041
P62959	Histidine triad nucleotide-binding protein 1	8	1.59	0.36	0.84	0.20	0.53	0.008
Q9WUS0	Adenylate kinase isoenzyme 4, mitochondrial	14	1.38	0.19	0.73	0.38	0.53	0.026
O89000	Dihydropyrimidine dehydrogenase [NADP+]	12	1.36	0.32	0.72	0.32	0.53	0.030
P00173	Cytochrome b5	31	1.37	0.20	0.73	0.30	0.53	0.020
P10868	Guanidinoacetate N-methyltransferase	16	1.58	0.51	0.85	0.15	0.53	0.018
Q6P6R2	Dihydrolipoyl dehydrogenase, mitochondrial	25	1.16	0.23	0.62	0.23	0.54	0.023

P11915	Non-specific lipid-transfer protein	31	1.23	0.23	0.66	0.31	0.54	0.049
Q03248	Beta-ureidopropionase	30	1.21	0.25	0.66	0.11	0.54	0.005
P11884	Aldehyde dehydrogenase, mitochondrial	98	1.17	0.24	0.64	0.16	0.55	0.011
P04762	Catalase	160	1.35	0.36	0.74	0.27	0.55	0.038
P0C2X9	Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial	43	1.30	0.10	0.71	0.09	0.55	<0.001
P11348	Dihydropteridine reductase	27	1.29	0.44	0.71	0.15	0.55	0.039
Q9WVK7	Hydroxyacyl-coenzyme A dehydrogenase, mitochondrial	54	1.22	0.31	0.68	0.18	0.55	0.026
P10634	Cytochrome P450 2D26	57	1.53	0.31	0.85	0.25	0.56	0.022
P12938	Cytochrome P450 2D3	46	1.52	0.33	0.85	0.17	0.56	0.010
P38652	Phosphoglucomutase-1	58	1.05	0.17	0.59	0.13	0.56	0.007
P51869	Cytochrome P450 4F4	14	1.42	0.51	0.80	0.05	0.56	0.038
P19643	Amine oxidase [flavin-containing] B	29	1.30	0.32	0.74	0.03	0.56	0.003
Q5FVQ8	NLR family member X1	9	1.14	0.25	0.65	0.26	0.57	0.046
P84817	Mitochondrial fission 1 protein	2	1.28	0.25	0.74	0.09	0.58	0.004
P07953	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 1	13	1.47	0.11	0.85	0.09	0.58	<0.001
P97524	Very long-chain acyl-CoA synthetase	34	1.53	0.35	0.89	0.25	0.58	0.021
P07896	Peroxisomal bifunctional enzyme	45	1.24	0.32	0.72	0.22	0.58	0.038
Q5XIC0	Enoyl-CoA delta isomerase 2, mitochondrial	14	1.20	0.24	0.71	0.24	0.59	0.046
Q5HZY2	GTP-binding protein SAR1b	13	1.22	0.23	0.72	0.11	0.59	0.004
Q0VGK3	Glycerate kinase	16	1.22	0.15	0.72	0.29	0.59	0.043
P38718	Mitochondrial pyruvate carrier 2/Brain protein 44	3	1.35	0.43	0.79	0.18	0.59	0.041
P16617	Phosphoglycerate kinase 1	54	1.09	0.24	0.65	0.19	0.59	0.031
P00481	Ornithine carbamoyltransferase, mitochondrial	57	1.30	0.19	0.77	0.12	0.59	0.003
P81155	Voltage-dependent anion-selective channel protein 2	10	1.09	0.22	0.65	0.24	0.59	0.039
Q68FS4	Cytosol aminopeptidase	53	1.52	0.14	0.90	0.19	0.59	0.003
P48500	Triosephosphate isomerase	33	1.17	0.32	0.69	0.22	0.59	0.040
Q68FU3	Electron transfer flavoprotein subunit beta	29	1.17	0.22	0.70	0.20	0.60	0.025
P00507	Aspartate aminotransferase, mitochondrial	73	1.07	0.15	0.64	0.19	0.60	0.016
Q6UPE1	Electron transfer flavoprotein-ubiquinone oxidoreductase, mitochondrial	36	1.12	0.12	0.67	0.07	0.60	0.001
P51635	Alcohol dehydrogenase [NADP+]	24	1.25	0.27	0.75	0.15	0.60	0.014

P27364	3 beta-hydroxysteroid dehydrogenase type 5	19	1.41	0.31	0.85	0.06	0.60	0.004
Q6P6V0	Glucose-6-phosphate isomerase	32	1.23	0.31	0.74	0.15	0.60	0.025
Q9QZH8	Arylacetamide deacetylase	6	1.64	0.55	0.99	0.15	0.60	0.034
Q6AXX6	Redox-regulatory protein PAMM	8	1.54	0.33	0.93	0.25	0.60	0.026
P56574	Isocitrate dehydrogenase [NADP], mitochondrial	27	1.10	0.24	0.67	0.18	0.61	0.037
P49432	Pyruvate dehydrogenase E1 component subunit beta, mitochondrial	16	1.20	0.30	0.73	0.20	0.61	0.034
Q6I7R3	Isochorismatase domain-containing protein 1	10	1.44	0.23	0.87	0.12	0.61	0.005
P08503	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	26	1.49	0.32	0.91	0.22	0.61	0.017
P30904	Macrophage migration inhibitory factor	22	1.31	0.21	0.80	0.19	0.61	0.018
P41034	Alpha-tocopherol transfer protein	16	1.28	0.15	0.78	0.03	0.61	<0.001
Q562C9	1,2-dihydroxy-3-keto-5-methylthiopentene dioxygenase	8	1.34	0.34	0.82	0.16	0.61	0.025
P31044	Phosphatidylethanolamine-binding protein 1	22	1.26	0.27	0.78	0.15	0.62	0.018
P07153	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1	56	1.08	0.27	0.67	0.21	0.62	0.049
P05369	Farnesyl pyrophosphate synthase	27	1.50	0.39	0.93	0.14	0.62	0.024
P35738	2-oxoisovalerate dehydrogenase subunit beta, mitochondrial	13	1.23	0.12	0.76	0.23	0.62	0.016
Q5M875	17-beta-hydroxysteroid dehydrogenase 13	22	1.09	0.17	0.68	0.10	0.62	0.005
P50137	Transketolase	80	1.15	0.20	0.72	0.16	0.62	0.016
P11951	Cytochrome c oxidase subunit 6C-2	4	1.03	0.20	0.64	0.26	0.63	0.050
Q920P0	L-xylulose reductase	12	1.44	0.45	0.91	0.05	0.63	0.028
P20070	NADH-cytochrome b5 reductase 3	26	1.62	0.42	1.02	0.32	0.63	0.043
P51650	Succinate-semialdehyde dehydrogenase, mitochondrial	10	1.21	0.32	0.76	0.06	0.63	0.019
Q63276	Bile acid-CoA:amino acid N-acyltransferase	57	1.25	0.27	0.79	0.20	0.63	0.026
Q5PQT3	Glycine N-acyltransferase	22	1.05	0.24	0.67	0.06	0.64	0.016
Q9QYU4	Thiomorpholine-carboxylate dehydrogenase	9	1.31	0.25	0.84	0.17	0.64	0.017
P25235	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2	46	1.18	0.28	0.76	0.15	0.64	0.028

P85971	6-phosphogluconolactonase	12	1.56	0.23	1.02	0.10	0.65	0.003
P97562	Peroxisomal acyl-coenzyme A oxidase 2	38	1.45	0.15	0.94	0.22	0.65	0.021
P29266	3-hydroxyisobutyrate dehydrogenase, mitochondrial	23	1.21	0.17	0.79	0.15	0.65	0.010
Q1HCL7	NAD kinase domain- containing protein 1	17	1.25	0.18	0.82	0.05	0.66	0.002
Q923K9	APOBEC1 complementation factor	10	1.09	0.26	0.72	0.16	0.66	0.040
P18297	Sepiapterin reductase	11	1.36	0.27	0.90	0.17	0.66	0.017
P32089	Tricarboxylate transport protein, mitochondrial	11	1.11	0.09	0.74	0.17	0.67	0.015
Q6P7R8	Estradiol 17-beta- dehydrogenase 12	6	1.15	0.20	0.77	0.10	0.67	0.013
P07633	Propionyl-CoA carboxylase beta chain, mitochondrial	23	1.21	0.18	0.81	0.17	0.67	0.017
P85973	Purine nucleoside phosphorylase	41	1.12	0.20	0.75	0.12	0.67	0.016
P15999	ATP synthase subunit alpha, mitochondrial	122	1.05	0.08	0.71	0.16	0.68	0.012
O88767	Protein DJ-1	16	1.21	0.20	0.82	0.16	0.68	0.025
P14942	Glutathione S-transferase alpha-4	12	0.99	0.12	0.67	0.12	0.68	0.008
Q9JM53	Apoptosis-inducing factor 1, mitochondrial	27	1.24	0.13	0.85	0.20	0.69	0.026
P07872	Peroxisomal acyl-coenzyme A oxidase 1	42	1.33	0.25	0.92	0.17	0.70	0.046
Q923M1	Mitochondrial peptide methionine sulfoxide reductase	3	1.19	0.24	0.84	0.12	0.70	0.024
Q6AYQ8	Acylpyruvase FAHD1, mitochondrial	10	1.15	0.22	0.81	0.11	0.71	0.039
Q6P7Q4	Lactoylglutathione lyase	8	1.19	0.21	0.85	0.16	0.71	0.046
Q5XIH7	Prohibitin-2	29	1.66	0.28	1.21	0.24	0.73	0.046
P52873	Pyruvate carboxylase, mitochondrial	134	1.16	0.13	0.86	0.14	0.74	0.018
Q5M7T9	Threonine synthase-like 2	6	1.26	0.23	0.94	0.11	0.74	0.037
P12336	Solute carrier family 2, facilitated glucose transporter member 2	5	1.16	0.21	0.86	0.09	0.74	0.038
P46462	Transitional endoplasmic reticulum ATPase	71	1.14	0.18	0.85	0.11	0.75	0.034
Q64380	Sarcosine dehydrogenase, mitochondrial	41	1.28	0.19	0.96	0.15	0.75	0.047
Q8CG45	Aflatoxin B1 aldehyde reductase member 2	22	1.11	0.05	0.84	0.07	0.75	0.001
P97700	Mitochondrial 2- oxoglutarate/malate carrier protein	7	1.15	0.19	0.87	0.05	0.75	0.016
Q68FT1	Ubiquinone biosynthesis protein COQ9, mitochondrial	9	1.01	0.06	0.77	0.08	0.76	0.004
Q7TMA5	Apolipoprotein B-100	29	1.09	0.21	0.83	0.08	0.76	0.047
P97519	Hydroxymethylglutaryl-CoA lyase, mitochondrial	14	0.99	0.09	0.77	0.14	0.78	0.036

Q641Y0	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit	16	1.18	0.12	0.92	0.13	0.78	0.032
P80067	Dipeptidyl peptidase 1	12	1.09	0.19	0.86	0.04	0.79	0.039
Q9JLA3	UDP-glucose:glycoprotein glucosyltransferase 1	28	0.97	0.06	0.78	0.06	0.80	0.003
P26453	Basigin	7	1.15	0.14	0.96	0.00	0.84	0.028
Q05096	Myosin-Ib	94	1.03	0.04	0.87	0.08	0.84	0.013
P84903	Stromal interaction molecule 1	5	1.03	0.03	0.91	0.09	0.88	0.047
Proteins increased at 48h								
P42930	Heat shock protein beta-1	10	0.12	0.11	2.87	1.41	23.49	<0.001
Q07439	Heat shock 70 kDa protein 1A/1B	56	0.21	0.20	2.77	1.50	13.39	0.002
P38918	Aflatoxin B1 aldehyde reductase member 3	42	0.20	0.17	1.55	0.68	7.60	0.003
P01048	T-kininogen 1	15	0.25	0.21	1.83	0.91	7.21	0.010
P02764	Alpha-1-acid glycoprotein	6	0.31	0.37	1.83	0.22	5.87	0.017
P06866	Haptoglobin	21	0.33	0.15	1.74	0.81	5.26	0.003
P82995	Heat shock protein HSP 90-alpha	74	0.47	0.29	2.00	0.82	4.25	0.006
P05370	Glucose-6-phosphate 1-dehydrogenase	15	0.38	0.22	1.63	0.36	4.24	0.004
O70199	UDP-glucose 6-dehydrogenase	38	0.32	0.10	1.28	0.34	4.04	0.001
Q66HA8	Heat shock protein 105 kDa	23	0.47	0.24	1.72	0.21	3.64	0.004
P02680	Fibrinogen gamma chain	17	0.54	0.24	1.86	0.65	3.43	0.008
P20059	Hemopexin	24	0.45	0.12	1.53	0.73	3.37	0.005
P06762	Heme oxygenase 1	5	0.57	0.28	1.82	0.76	3.21	0.027
P06399	Fibrinogen alpha chain	39	0.50	0.29	1.58	0.31	3.18	0.019
P09006	Serine protease inhibitor A3N	19	0.61	0.19	1.82	0.67	3.00	0.003
P04961	Proliferating cell nuclear antigen	4	0.41	0.07	1.21	0.37	2.97	0.001
O89049	Thioredoxin reductase 1, cytoplasmic	17	0.42	0.29	1.19	0.36	2.87	0.031
P13383	Nucleolin	21	0.47	0.15	1.33	0.13	2.87	<0.001
P11980	Pyruvate kinase isozymes M1/M2	19	0.44	0.09	1.23	0.38	2.81	0.002
P17475	Alpha-1-antiproteinase	39	0.47	0.18	1.31	0.57	2.77	0.012
P62982	Ubiquitin-40S ribosomal protein S27a	23	0.50	0.30	1.38	0.33	2.73	0.018
P05982	NAD(P)H dehydrogenase [quinone] 1	8	0.50	0.12	1.37	0.37	2.73	0.002
P07150	Annexin A1	12	0.55	0.23	1.47	0.49	2.70	0.015
P05371	Clusterin	6	0.56	0.31	1.52	0.52	2.70	0.041
P04906	Glutathione S-transferase P	12	0.26	0.22	0.70	0.41	2.69	0.045
O35821	Myb-binding protein 1A	15	0.53	0.17	1.40	0.25	2.63	0.002
P14480	Fibrinogen beta chain	25	0.52	0.24	1.36	0.55	2.63	0.026

Q3B8Q1	Nucleolar RNA helicase 2	7	0.48	0.20	1.26	0.26	2.62	0.005
P13084	Nucleophosmin	14	0.51	0.21	1.29	0.17	2.53	0.011
P63018	Heat shock cognate 71 kDa protein	106	0.60	0.12	1.51	0.35	2.50	0.001
P06761	78 kDa glucose-regulated protein	112	0.69	0.25	1.70	0.50	2.47	0.008
P52631	Signal transducer and activator of transcription 3	10	0.64	0.30	1.57	0.46	2.45	0.011
P08430	UDP-glucuronosyltransferase 1-6	40	0.58	0.23	1.37	0.48	2.34	0.017
D4A4T9	Cysteine and histidine-rich domain-containing protein 1	3	0.86	0.23	2.00	1.03	2.32	0.046
Q62812	Myosin-9	161	0.57	0.26	1.31	0.35	2.30	0.018
P63029	Translationally-controlled tumor protein	9	0.69	0.20	1.52	0.27	2.20	0.004
P05765	40S ribosomal protein S21	10	0.55	0.32	1.21	0.25	2.20	0.032
P62961	Nuclease-sensitive element-binding protein 1	22	0.71	0.33	1.55	0.19	2.17	0.025
P05197	Elongation factor 2	70	0.71	0.15	1.55	0.27	2.17	0.001
O35814	Stress-induced-phosphoprotein 1	24	0.72	0.16	1.54	0.71	2.15	0.031
P34058	Heat shock protein HSP 90-beta	80	0.77	0.18	1.65	0.41	2.14	0.005
B0BNA5	Coactosin-like protein	3	0.60	0.19	1.27	0.44	2.11	0.022
Q63525	Nuclear migration protein nudC	9	0.51	0.16	1.05	0.42	2.05	0.035
P31000	Vimentin	32	0.51	0.15	1.03	0.26	2.04	0.012
Q62651	Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial	17	0.62	0.20	1.26	0.50	2.03	0.026
O35763	Moesin	19	0.58	0.12	1.18	0.14	2.03	0.001
Q6AYC2	Immunity-related GTPase family M protein	3	0.71	0.25	1.43	0.29	2.02	0.017
P50503	Hsc70-interacting protein	14	0.69	0.32	1.39	0.50	2.02	0.047
P13221	Aspartate aminotransferase, cytoplasmic	30	0.51	0.20	1.01	0.37	1.99	0.043
Q9JJ19	Na(+)/H(+) exchange regulatory cofactor NHE-RF1	13	0.70	0.17	1.37	0.43	1.95	0.021
Q6URK4	Heterogeneous nuclear ribonucleoprotein A3	20	0.56	0.07	1.08	0.26	1.91	0.004
Q1JU68	Eukaryotic translation initiation factor 3 subunit A	23	0.66	0.17	1.26	0.26	1.91	0.007
Q07936	Annexin A2	15	0.61	0.20	1.13	0.38	1.87	0.036
P26772	10 kDa heat shock protein, mitochondrial	13	0.72	0.29	1.34	0.12	1.87	0.016
Q9Z2G8	Nucleosome assembly protein 1-like 1	5	0.72	0.14	1.35	0.24	1.87	0.005
Q5M9G3	Caprin-1	4	0.88	0.24	1.65	0.58	1.87	0.035
P45592	Cofilin-1	14	0.65	0.06	1.21	0.16	1.86	<0.001
P70619	Glutathione reductase (Fragment)	8	0.68	0.17	1.25	0.29	1.85	0.014
O35987	NSFL1 cofactor p47	14	0.71	0.37	1.29	0.21	1.82	0.036
Q5BJY9	Keratin, type I cytoskeletal 18	82	0.77	0.29	1.35	0.23	1.76	0.040

P69897	Tubulin beta-5 chain Hypoxia up-regulated	75	0.53	0.17	0.92	0.20	1.75	0.027
Q63617	protein 1	55	0.66	0.13	1.16	0.17	1.74	0.005
O88600	Heat shock 70 kDa protein 4 Nucleolar and coiled-body	28	0.73	0.13	1.26	0.11	1.72	0.001
P41777	phosphoprotein 1	4	0.65	0.19	1.11	0.13	1.71	0.023
P13635	Ceruloplasmin	19	0.67	0.20	1.14	0.22	1.70	0.028
P11442	Clathrin heavy chain 1	103	0.77	0.10	1.28	0.15	1.67	0.001
P30009	Myristoylated alanine-rich C- kinase substrate	12	0.50	0.17	0.84	0.10	1.67	0.032
Q8K1Q0	Glycylpeptide N- tetradecanoyltransferase 1	5	0.87	0.15	1.45	0.34	1.66	0.016
P62425	60S ribosomal protein L7a Stress-70 protein,	13	0.70	0.20	1.16	0.15	1.65	0.012
P48721	mitochondrial	67	0.75	0.14	1.23	0.25	1.64	0.015
P63102	14-3-3 protein zeta/delta	26	0.63	0.11	1.03	0.17	1.63	0.006
Q68FR6	Elongation factor 1-gamma	21	0.73	0.08	1.19	0.20	1.63	0.002
P20673	Argininosuccinate lyase	42	0.69	0.14	1.13	0.27	1.62	0.035
P04276	Vitamin D-binding protein 60 kDa heat shock protein,	15	0.78	0.14	1.24	0.33	1.60	0.031
P63039	mitochondrial Polyadenylate-binding	161	0.87	0.30	1.39	0.34	1.60	0.049
Q9EPH8	protein 1	24	0.82	0.14	1.30	0.36	1.59	0.038
P08082	Clathrin light chain B	3	0.67	0.13	1.07	0.10	1.59	0.005
P11232	Thioredoxin	7	0.69	0.12	1.10	0.30	1.58	0.032
P19945	60S acidic ribosomal protein P0	24	0.68	0.12	1.08	0.14	1.58	0.007
P62634	Cellular nucleic acid-binding protein	5	0.71	0.18	1.11	0.08	1.56	0.012
P28064	Proteasome subunit beta type-8	6	0.76	0.16	1.18	0.22	1.56	0.019
P02401	60S acidic ribosomal protein P2	31	0.71	0.09	1.11	0.16	1.56	0.004
B5DFC8	Eukaryotic translation initiation factor 3 subunit C	14	0.85	0.12	1.31	0.10	1.55	0.002
Q5RKI1	Eukaryotic initiation factor 4A-II	22	0.84	0.12	1.31	0.11	1.55	0.002
P81795	Eukaryotic translation initiation factor 2 subunit 3	11	0.77	0.09	1.19	0.31	1.54	0.021
O08629	Transcription intermediary factor 1-beta	8	0.82	0.21	1.24	0.22	1.51	0.036
Q62667	Major vault protein	19	0.77	0.08	1.13	0.16	1.47	0.007
P38656	Lupus La protein homolog GMP synthase [glutamine-	7	0.83	0.16	1.21	0.16	1.47	0.017
Q4V7C6	hydrolyzing] Proteasome inhibitor PI31	7	0.78	0.19	1.15	0.13	1.47	0.025
Q5XIU5	subunit	2	0.85	0.20	1.25	0.18	1.46	0.027
P62250	40S ribosomal protein S16	13	0.83	0.17	1.22	0.18	1.46	0.022
Q08163	Adenylyl cyclase-associated protein 1	9	0.85	0.23	1.23	0.20	1.45	0.044
P04256	Heterogeneous nuclear ribonucleoprotein A1	18	0.86	0.02	1.24	0.26	1.45	0.012

A0JPM9	Eukaryotic translation initiation factor 3 subunit J	5	0.80	0.22	1.16	0.16	1.45	0.047
Q6AXS5	Plasminogen activator inhibitor 1 RNA-binding protein	12	0.72	0.16	1.05	0.19	1.45	0.036
Q6P799	Seryl-tRNA synthetase, cytoplasmic	14	0.84	0.15	1.21	0.26	1.45	0.045
Q07205	Eukaryotic translation initiation factor 5	10	0.80	0.11	1.13	0.18	1.40	0.023
P62815	V-type proton ATPase subunit B, brain isoform	14	0.82	0.20	1.14	0.15	1.39	0.042
Q9EQS0	Transaldolase	15	0.73	0.09	0.99	0.13	1.37	0.012
P63086	Mitogen-activated protein kinase 1	5	0.83	0.08	1.12	0.14	1.36	0.009
P38650	Cytoplasmic dynein 1 heavy chain 1	51	0.76	0.07	1.03	0.14	1.36	0.011
Q63347	26S protease regulatory subunit 7	15	0.88	0.06	1.19	0.18	1.35	0.013
P62859	40S ribosomal protein S28	7	0.79	0.14	1.07	0.16	1.35	0.036
Q6P502	T-complex protein 1 subunit gamma	34	0.92	0.14	1.24	0.09	1.34	0.013
Q63945	Protein SET	9	0.77	0.15	1.03	0.15	1.34	0.049
Q4FZY0	EF-hand domain-containing protein D2	4	0.84	0.13	1.08	0.15	1.30	0.043
Q6P7P5	Basic leucine zipper and W2 domain-containing protein 1	7	0.79	0.14	1.03	0.09	1.30	0.041
P68511	14-3-3 protein eta	15	0.85	0.10	1.09	0.12	1.29	0.020
P12001	60S ribosomal protein L18	9	0.83	0.13	1.07	0.09	1.29	0.025
P38659	Protein disulfide-isomerase A4	45	0.86	0.14	1.09	0.09	1.27	0.039
Q505J9	ATPase family AAA domain-containing protein 1	2	0.93	0.08	1.14	0.16	1.24	0.044
P29314	40S ribosomal protein S9	13	0.86	0.10	1.06	0.08	1.24	0.022
P18395	Cold shock domain-containing protein E1	3	0.82	0.11	1.01	0.01	1.22	0.026
Q9ER24	Ataxin-10	4	0.91	0.08	1.10	0.05	1.21	0.009
Q6RUV5	Ras-related C3 botulinum toxin substrate 1	4	0.88	0.11	1.04	0.03	1.18	0.042
Q6AXS3	Protein DEK	4	0.93	0.12	1.09	0.05	1.18	0.043

Supplementary Table 1C: *i*TRAQ-based proteomic comparison of liver proteins in vehicle control- and APAP-treated rats (72h timepoint). Proteins with expression that was different (raw P < 0.05) between control and APAP-treated rats at 72h are listed. Mean expression values relative to a common pool are given for n=4 animals. Proteins are ordered according to the ratio between the 72h and control groups (lowest to highest) such that proteins with expression that was most markedly reduced at 72h appear at the top of the list.

^aAverage number of peptides used for quantification across the four individual iTRAQ runs.

^bUncorrected raw P value.

Uniprot Accession	Name	Peptides ^a	Vehicle control		72h		72h/ctrl	P-value ^b
			Mean	SD	Mean	SD	Ratio	
Proteins reduced at 72h								
P09606	Glutamine synthetase	17	2.73	0.78	0.06	0.03	0.02	<0.001
P08683	Cytochrome P450 2C11	51	2.53	0.52	0.16	0.09	0.06	<0.001
P49890	Estrogen sulfotransferase, isoform 6	18	3.22	0.91	0.22	0.15	0.07	<0.001
P14141	Carbonic anhydrase 3	70	1.99	1.30	0.18	0.20	0.09	0.007
P36365	Dimethylaniline monooxygenase [N-oxide- forming] 1	13	2.34	0.94	0.22	0.15	0.10	0.002
P02761	Major urinary protein	22	2.27	0.42	0.30	0.30	0.13	0.006
Q9ES38	Bile acyl-CoA synthetase	26	2.80	0.86	0.39	0.39	0.14	0.007
P17988	Sulfotransferase 1A1	30	1.99	0.34	0.28	0.16	0.14	0.001
P00502	Glutathione S-transferase alpha-1	51	1.57	1.21	0.28	0.27	0.18	0.015
Q03336	Regucalcin	45	1.98	0.18	0.36	0.38	0.18	0.011
P05183	Cytochrome P450 3A2	15	2.49	0.97	0.46	0.24	0.18	0.009
P16303	Carboxylesterase 3	33	1.85	0.85	0.36	0.33	0.20	0.012
Q64565	Alanine--glyoxylate aminotransferase 2, mitochondrial	28	1.26	0.46	0.25	0.14	0.20	0.002
P04182	Ornithine aminotransferase, mitochondrial	8	1.44	0.74	0.29	0.13	0.20	0.007
P50237	Sulfotransferase 1C1	27	1.95	0.15	0.39	0.17	0.20	<0.001
Q64611	Cysteine sulfinic acid decarboxylase	25	1.81	0.70	0.41	0.61	0.23	0.025
Q07523	Hydroxyacid oxidase 2	8	1.99	0.34	0.47	0.07	0.24	<0.001
P12928	Pyruvate kinase isozymes R/L	61	1.64	0.53	0.40	0.17	0.24	0.002
P14173	Aromatic-L-amino-acid decarboxylase	13	1.74	0.94	0.42	0.39	0.24	0.019
P10867	L-gulonolactone oxidase	18	2.00	0.36	0.49	0.28	0.24	0.002
P10860	Glutamate dehydrogenase 1, mitochondrial	118	1.63	0.34	0.40	0.35	0.25	0.019
Q64638	UDP- glucuronosyltransferase 1-5	25	3.79	1.58	0.97	0.93	0.26	0.022
P50169	Retinol dehydrogenase 3	30	1.54	0.61	0.40	0.27	0.26	0.008

P09811	Glycogen phosphorylase, liver form	76	1.40	0.26	0.38	0.15	0.27	0.002
P25093	Fumarylacetoacetase	48	1.45	0.12	0.41	0.29	0.29	0.012
Q5U2Q3	Ester hydrolase C11orf54 homolog	12	2.00	0.36	0.58	0.29	0.29	0.011
P02692	Fatty acid-binding protein, liver	69	1.94	0.49	0.57	0.18	0.29	0.002
Q4KLP0	Probable 2-oxoglutarate dehydrogenase E1 component DHKTD1, mitochondrial	35	1.59	0.56	0.48	0.26	0.30	0.015
P55051	Fatty acid-binding protein, brain	9	1.61	0.57	0.49	0.40	0.30	0.024
Q4KLZ6	Bifunctional ATP-dependent dihydroxyacetone kinase/FAD-AMP lyase (cyclizing)	64	1.70	0.39	0.52	0.25	0.31	0.013
Q497B0	Omega-amidase NIT2	34	1.58	0.09	0.49	0.24	0.31	0.003
P23680	Serum amyloid P-component	4	1.61	0.24	0.50	0.34	0.31	0.014
P55159	Serum paraoxonase/arylesterase 1	17	1.68	0.55	0.53	0.36	0.32	0.025
P07872	Peroxisomal acyl-coenzyme A oxidase 1	42	1.33	0.25	0.43	0.28	0.32	0.017
P23457	3-alpha-hydroxysteroid dehydrogenase	48	1.51	0.36	0.49	0.41	0.32	0.035
P30839	Fatty aldehyde dehydrogenase	36	1.74	0.55	0.56	0.37	0.32	0.018
Q9QYU4	Thiomorpholine-carboxylate dehydrogenase	9	1.31	0.25	0.44	0.24	0.33	0.010
P16638	ATP-citrate synthase	65	1.93	0.71	0.65	0.21	0.34	0.006
P20070	NADH-cytochrome b5 reductase 3	26	1.62	0.42	0.57	0.21	0.35	0.005
Q920P0	L-xylulose reductase	12	1.44	0.45	0.51	0.18	0.35	0.004
Q07071	Glucokinase regulatory protein	27	1.71	0.64	0.60	0.35	0.35	0.029
P29147	D-beta-hydroxybutyrate dehydrogenase, mitochondrial	42	1.40	0.23	0.50	0.47	0.36	0.047
Q8CHM7	2-hydroxyacyl-CoA lyase 1	28	1.66	0.35	0.61	0.40	0.36	0.021
P11497	Acetyl-CoA carboxylase 1	44	1.46	0.57	0.53	0.18	0.37	0.010
P57113	Maleylacetoacetate isomerase	36	1.58	0.34	0.58	0.42	0.37	0.033
B0BNE5	S-formylglutathione hydrolase	23	1.32	0.33	0.49	0.16	0.37	0.003
Q6DGG1	Alpha/beta hydrolase domain-containing protein 14B	12	1.36	0.25	0.51	0.29	0.37	0.042
P12785	Fatty acid synthase	155	1.79	1.03	0.67	0.11	0.38	0.030
P12938	Cytochrome P450 2D3	46	1.52	0.33	0.57	0.11	0.38	0.001
Q9R063	Peroxioredoxin-5, mitochondrial	21	1.83	0.94	0.70	0.23	0.38	0.032
A0JQP8	Alkylglycerol monooxygenase	6	1.64	0.20	0.63	0.19	0.38	0.001
P70712	Kynureninase	19	1.41	0.32	0.54	0.19	0.38	0.007

P70473	Alpha-methylacyl-CoA racemase	18	1.07	0.04	0.41	0.30	0.39	0.028
Q68FU3	Electron transfer flavoprotein subunit beta	29	1.17	0.22	0.46	0.24	0.39	0.010
P19112	Fructose-1,6-bisphosphatase 1	72	1.71	0.38	0.67	0.38	0.39	0.018
Q66HG4	Aldose 1-epimerase	5	1.37	0.18	0.54	0.12	0.39	<0.001
P24329	Thiosulfate sulfurtransferase	41	1.33	0.20	0.52	0.41	0.39	0.042
Q02253	Methylmalonate-semialdehyde dehydrogenase [acylating], mitochondrial	124	1.22	0.24	0.48	0.39	0.39	0.044
P00884	Fructose-bisphosphate aldolase B	129	1.31	0.33	0.52	0.39	0.40	0.047
P29411	GTP:AMP phosphotransferase, mitochondrial	7	1.41	0.24	0.56	0.11	0.40	0.001
O35077	Glycerol-3-phosphate dehydrogenase [NAD+], cytoplasmic	39	1.45	0.42	0.58	0.32	0.40	0.026
P97612	Fatty-acid amide hydrolase 1	26	1.67	0.31	0.67	0.50	0.40	0.037
P52873	Pyruvate carboxylase, mitochondrial	134	1.16	0.13	0.47	0.35	0.40	0.042
P22791	Hydroxymethylglutaryl-CoA synthase, mitochondrial	106	1.46	0.40	0.60	0.42	0.41	0.050
P05544	Serine protease inhibitor A3L	30	1.22	0.12	0.50	0.43	0.41	0.042
Q02974	Ketohexokinase	25	1.56	0.28	0.64	0.31	0.41	0.010
P18163	Long-chain-fatty-acid--CoA ligase 1	78	1.54	0.13	0.65	0.48	0.42	0.044
P22734	Catechol O-methyltransferase	46	1.49	0.39	0.63	0.37	0.42	0.034
Q62730	Estradiol 17-beta-dehydrogenase 2	17	1.72	0.47	0.74	0.42	0.43	0.029
P06214	Delta-aminolevulinic acid dehydratase	35	1.50	0.26	0.65	0.13	0.43	0.001
Q68FP2	Serum paraoxonase/lactonase 3	16	1.43	0.10	0.62	0.19	0.43	0.003
P08503	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	26	1.49	0.32	0.65	0.32	0.44	0.015
P05545	Serine protease inhibitor A3K	34	1.50	0.50	0.66	0.38	0.44	0.035
P13803	Electron transfer flavoprotein subunit alpha, mitochondrial	50	1.29	0.23	0.57	0.37	0.44	0.045
P30713	Glutathione S-transferase theta-2	19	1.34	0.31	0.60	0.26	0.45	0.020
P46720	Solute carrier organic anion transporter family member 1A1	4	1.41	0.30	0.63	0.23	0.45	0.008
P46953	3-hydroxyanthranilate 3,4-dioxygenase	25	1.42	0.40	0.64	0.26	0.45	0.030
P08009	Glutathione S-transferase Yb-3	53	1.10	0.29	0.50	0.26	0.45	0.030

Q64232	Very-long-chain enoyl-CoA reductase	35	1.76	0.41	0.80	0.41	0.45	0.045
O88813	Long-chain-fatty-acid--CoA ligase 5	28	1.89	0.67	0.87	0.36	0.46	0.029
P10760	Adenosylhomocysteinase	54	1.29	0.20	0.61	0.24	0.47	0.010
P41034	Alpha-tocopherol transfer protein	16	1.28	0.15	0.61	0.19	0.47	0.004
Q68G31	Phenazine biosynthesis-like domain-containing protein	16	1.23	0.55	0.59	0.13	0.48	0.023
P07953	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 1	13	1.47	0.11	0.71	0.17	0.48	0.001
Q6AYT0	Quinone oxidoreductase	9	1.37	0.36	0.67	0.24	0.49	0.023
Q561R9	Beta-lactamase-like protein 2	11	1.20	0.24	0.59	0.18	0.49	0.008
P57093	Phytanoyl-CoA dioxygenase, peroxisomal	10	1.36	0.22	0.67	0.18	0.50	0.004
Q9Z339	Glutathione S-transferase omega-1	10	1.42	0.40	0.70	0.22	0.50	0.026
P62959	Histidine triad nucleotide-binding protein 1	8	1.59	0.36	0.80	0.30	0.50	0.031
P11348	Dihydropteridine reductase	27	1.29	0.44	0.65	0.25	0.51	0.044
Q99MS0	SEC14-like protein 2	16	1.32	0.14	0.67	0.11	0.51	0.001
Q63060	Glycerol kinase	20	1.68	0.28	0.86	0.16	0.51	0.002
P85971	6-phosphogluconolactonase	12	1.56	0.23	0.80	0.10	0.51	<0.001
Q63448	Peroxisomal acyl-coenzyme A oxidase 3	27	1.27	0.23	0.65	0.26	0.51	0.027
Q68FS4	Cytosol aminopeptidase	53	1.52	0.14	0.78	0.30	0.51	0.031
P16970	ATP-binding cassette sub-family D member 3	13	1.69	0.46	0.87	0.35	0.52	0.032
P45380	Sulfate anion transporter 1	3	1.09	0.35	0.57	0.21	0.52	0.029
Q9Z0V5	Peroxiredoxin-4	16	1.03	0.11	0.55	0.19	0.53	0.016
P52847	Sulfotransferase family cytosolic 1B member 1	16	1.97	0.42	1.04	0.26	0.53	0.007
Q66H45	Tetratricopeptide repeat protein 36	5	1.20	0.34	0.65	0.13	0.54	0.014
P43278	Histone H1.0	4	1.51	0.31	0.82	0.26	0.54	0.021
Q8CG45	Aflatoxin B1 aldehyde reductase member 2	22	1.11	0.05	0.60	0.27	0.54	0.042
Q6AXX6	Redox-regulatory protein PAMM	8	1.54	0.33	0.84	0.13	0.55	0.005
P30904	Macrophage migration inhibitory factor	22	1.31	0.21	0.73	0.30	0.55	0.032
P10868	Guanidinoacetate N-methyltransferase	16	1.58	0.51	0.88	0.23	0.56	0.030
P29117	Peptidyl-prolyl cis-trans isomerase F, mitochondrial	8	1.25	0.26	0.70	0.29	0.56	0.044
Q03626	Murinoglobulin-1	65	1.26	0.20	0.70	0.22	0.56	0.014
P51650	Succinate-semialdehyde dehydrogenase, mitochondrial	10	1.21	0.32	0.68	0.05	0.56	0.007
P14604	Enoyl-CoA hydratase, mitochondrial	35	1.08	0.04	0.62	0.23	0.57	0.030

Q6AYT9	Acyl-coenzyme A synthetase ACSM5, mitochondrial	14	1.53	0.30	0.88	0.16	0.58	0.007
P31044	Phosphatidylethanolamine-binding protein 1	22	1.26	0.27	0.74	0.22	0.58	0.034
Q8VID1	Dehydrogenase/reductase SDR family member 4	6	1.10	0.23	0.65	0.15	0.59	0.011
O89000	Dihydropyrimidine dehydrogenase [NADP+]	12	1.36	0.32	0.80	0.21	0.59	0.037
Q63150	Dihydropyrimidinase	29	1.41	0.17	0.83	0.22	0.59	0.008
P97852	Peroxisomal multifunctional enzyme type 2	47	1.20	0.09	0.71	0.30	0.59	0.040
P29266	3-hydroxyisobutyrate dehydrogenase, mitochondrial	23	1.21	0.17	0.71	0.12	0.59	0.003
Q5BK17	Iodotyrosine dehalogenase 1	4	1.75	0.28	1.04	0.24	0.59	0.013
P35738	2-oxoisovalerate dehydrogenase subunit beta, mitochondrial	13	1.23	0.12	0.73	0.24	0.60	0.020
Q6I7R3	Isochorismatase domain-containing protein 1	10	1.44	0.23	0.86	0.15	0.60	0.007
P27364	3 beta-hydroxysteroid dehydrogenase type 5	19	1.41	0.31	0.84	0.29	0.60	0.037
Q7TP48	Adipocyte plasma membrane-associated protein	10	1.55	0.48	0.94	0.13	0.61	0.035
O35952	Hydroxyacylglutathione hydrolase, mitochondrial	14	1.36	0.35	0.83	0.06	0.61	0.009
Q64380	Sarcosine dehydrogenase, mitochondrial	41	1.28	0.19	0.81	0.24	0.63	0.037
Q6AYQ8	Acylpyruvase FAHD1, mitochondrial	10	1.15	0.22	0.74	0.15	0.64	0.023
P46462	Transitional endoplasmic reticulum ATPase	71	1.14	0.18	0.73	0.23	0.64	0.041
P07633	Propionyl-CoA carboxylase beta chain, mitochondrial	23	1.21	0.18	0.79	0.21	0.65	0.037
Q9ES21	Phosphatidylinositide phosphatase SAC1	9	1.33	0.25	0.90	0.16	0.67	0.030
Q923M1	Mitochondrial peptide methionine sulfoxide reductase	3	1.19	0.24	0.81	0.15	0.68	0.027
Q505J8	Phenylalanine--tRNA ligase alpha subunit	31	0.99	0.10	0.67	0.12	0.68	0.007
B0BNG0	Tetratricopeptide repeat protein 35	11	1.31	0.30	0.89	0.14	0.68	0.028
P70552	GTP cyclohydrolase 1 feedback regulatory protein	5	1.09	0.21	0.75	0.09	0.69	0.020
P16617	Phosphoglycerate kinase 1	54	1.09	0.24	0.76	0.17	0.69	0.046
O88767	Protein DJ-1	16	1.21	0.20	0.84	0.12	0.69	0.021
P27605	Hypoxanthine-guanine phosphoribosyltransferase	12	1.35	0.20	0.96	0.15	0.72	0.025
Q64591	2,4-dienoyl-CoA reductase, mitochondrial	23	1.02	0.10	0.75	0.14	0.73	0.023
O35331	Pyridoxal kinase	13	1.22	0.21	0.91	0.13	0.75	0.045
P35433	Amidophosphoribosyltransferase	2	1.25	0.17	0.94	0.06	0.75	0.008

Q9R1Z0	Voltage-dependent anion-selective channel protein 3	8	1.17	0.16	0.90	0.11	0.77	0.027
P17625	Glycogen [starch] synthase, liver	5	1.10	0.11	0.85	0.16	0.77	0.048
B2RYT9	Translational activator of cytochrome c oxidase 1	3	1.10	0.10	0.88	0.13	0.80	0.042
Q641Y0	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit	16	1.18	0.12	0.97	0.07	0.82	0.021
Q6AY78	Solute carrier family 22 member 18	4	1.00	0.11	0.83	0.05	0.82	0.025
Q4G064	2-methoxy-6-polyprenyl-1,4-benzoquinol methylase, mitochondrial	6	1.07	0.10	0.89	0.07	0.83	0.027
Q8VI04	Isoaspartyl peptidase/L-asparaginase	7	0.99	0.07	0.83	0.04	0.84	0.006
Q9Z1N4	3'(2'),5'-bisphosphate nucleotidase 1	4	0.94	0.07	0.83	0.05	0.88	0.044

Proteins increased at 72h

P01048	T-kininogen 1	15	0.25	0.21	1.91	0.92	7.52	0.009
P02764	Alpha-1-acid glycoprotein	6	0.31	0.37	1.91	0.33	6.13	0.017
P42930	Heat shock protein beta-1	10	0.12	0.11	0.67	0.33	5.46	0.006
P11980	Pyruvate kinase isozymes M1/M2	19	0.44	0.09	2.32	1.65	5.28	0.004
P31000	Vimentin	32	0.51	0.15	2.40	1.34	4.74	0.004
P04961	Proliferating cell nuclear antigen	4	0.41	0.07	1.88	1.39	4.62	0.005
P06866	Haptoglobin	21	0.33	0.15	1.51	0.53	4.57	0.002
P38918	Aflatoxin B1 aldehyde reductase member 3	42	0.20	0.17	0.87	0.66	4.29	0.042
Q07439	Heat shock 70 kDa protein 1A/1B	56	0.21	0.20	0.81	0.35	3.93	0.020
P30009	Myristoylated alanine-rich C-kinase substrate	12	0.50	0.17	1.90	1.07	3.76	0.031
P69897	Tubulin beta-5 chain	75	0.53	0.17	1.83	0.76	3.48	0.004
P11762	Galectin-1	4	0.73	0.12	2.38	0.75	3.29	0.001
P20059	Hemopexin	24	0.45	0.12	1.47	0.25	3.26	<0.001
P04906	Glutathione S-transferase P	12	0.26	0.22	0.84	0.56	3.21	0.034
P05370	Glucose-6-phosphate 1-dehydrogenase	15	0.38	0.22	1.16	0.21	3.01	0.011
P07150	Annexin A1	12	0.55	0.23	1.62	0.67	2.96	0.015
Q62812	Myosin-9	161	0.57	0.26	1.69	0.72	2.96	0.017
Q5XFX0	Transgelin-2	13	0.55	0.23	1.61	0.49	2.95	0.010
Q3B8Q1	Nucleolar RNA helicase 2	7	0.48	0.20	1.40	0.38	2.90	0.004
P07335	Creatine kinase B-type	11	0.64	0.11	1.83	0.58	2.86	0.001
P13383	Nucleolin	21	0.47	0.15	1.30	0.42	2.80	0.004
P17475	Alpha-1-antiproteinase	39	0.47	0.18	1.30	0.36	2.74	0.005
P06302	Prothymosin alpha	6	0.70	0.47	1.88	0.95	2.70	0.038
B0BNA5	Coactosin-like protein	3	0.60	0.19	1.63	0.51	2.70	0.007
Q07936	Annexin A2	15	0.61	0.20	1.62	0.92	2.68	0.032

P10960	Sulfated glycoprotein 1	14	0.60	0.11	1.62	0.42	2.68	0.001
P45592	Cofilin-1	14	0.65	0.06	1.73	0.41	2.65	<0.001
O35763	Moesin	19	0.58	0.12	1.51	0.45	2.61	0.002
P18437	Non-histone chromosomal protein HMG-17	3	0.51	0.22	1.31	0.52	2.58	0.022
O35821	Myb-binding protein 1A	15	0.53	0.17	1.36	0.37	2.56	0.005
O70199	UDP-glucose 6-dehydrogenase	38	0.32	0.10	0.80	0.29	2.53	0.011
P14480	Fibrinogen beta chain	25	0.52	0.24	1.24	0.41	2.40	0.033
Q9Z2G8	Nucleosome assembly protein 1-like 1	5	0.72	0.14	1.72	0.25	2.39	0.001
P16391	RT1 class I histocompatibility antigen, AA alpha chain	6	0.60	0.37	1.43	0.26	2.38	0.024
P13084	Nucleophosmin	14	0.51	0.21	1.22	0.39	2.38	0.026
P13221	Aspartate aminotransferase, cytoplasmic	30	0.51	0.20	1.12	0.28	2.22	0.013
Q6URK4	Heterogeneous nuclear ribonucleoprotein A3	20	0.56	0.07	1.20	0.05	2.14	<0.001
P63102	14-3-3 protein zeta/delta	26	0.63	0.11	1.34	0.35	2.13	0.004
P52555	Endoplasmic reticulum resident protein 29	12	0.95	0.19	1.99	0.93	2.09	0.023
Q62667	Major vault protein	19	0.77	0.08	1.59	0.61	2.06	0.010
P13635	Ceruloplasmin	19	0.67	0.20	1.36	0.23	2.03	0.008
P82995	Heat shock protein HSP 90-alpha	74	0.47	0.29	0.95	0.23	2.02	0.044
P05197	Elongation factor 2	70	0.71	0.15	1.42	0.46	2.00	0.012
O35814	Stress-induced-phosphoprotein 1	24	0.72	0.16	1.44	0.63	2.00	0.025
P68255	14-3-3 protein theta	20	0.87	0.30	1.74	0.69	2.00	0.040
Q63525	Nuclear migration protein nudC	9	0.51	0.16	1.02	0.36	1.99	0.028
P24268	Cathepsin D	12	0.86	0.30	1.71	0.28	1.97	0.006
P34064	Proteasome subunit alpha type-5	15	0.63	0.31	1.22	0.30	1.93	0.042
P50503	Hsc70-interacting protein	14	0.69	0.32	1.30	0.28	1.89	0.042
Q66HD0	Endoplasmin	95	0.71	0.27	1.32	0.34	1.86	0.036
P29457	Serpin H1	11	0.81	0.17	1.51	0.45	1.86	0.019
Q68FR6	Elongation factor 1-gamma	21	0.73	0.08	1.33	0.22	1.83	0.001
P63018	Heat shock cognate 71 kDa protein	106	0.60	0.12	1.10	0.21	1.82	0.006
O54753	17-beta-hydroxysteroid dehydrogenase type 6	12	0.85	0.33	1.53	0.31	1.80	0.024
Q63617	Hypoxia up-regulated protein 1	55	0.66	0.13	1.19	0.10	1.80	0.002
P04639	Apolipoprotein A-I	20	0.82	0.28	1.46	0.27	1.77	0.035
P19945	60S acidic ribosomal protein P0	24	0.68	0.12	1.18	0.36	1.73	0.026
Q5BJY9	Keratin, type I cytoskeletal 18	82	0.77	0.29	1.30	0.16	1.70	0.043
Q5M9G3	Caprin-1	4	0.88	0.24	1.46	0.40	1.65	0.035
Q1JU68	Eukaryotic translation initiation factor 3 subunit A	23	0.66	0.17	1.07	0.24	1.64	0.026

P38656	Lupus La protein homolog	7	0.83	0.16	1.32	0.25	1.60	0.018
P62634	Cellular nucleic acid-binding protein	5	0.71	0.18	1.14	0.24	1.60	0.024
P62425	60S ribosomal protein L7a	13	0.70	0.20	1.11	0.13	1.58	0.015
P62828	GTP-binding nuclear protein Ran	8	0.80	0.17	1.26	0.28	1.57	0.022
P81795	Eukaryotic translation initiation factor 2 subunit 3	11	0.77	0.09	1.21	0.12	1.57	0.001
Q62651	Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial	17	0.62	0.20	0.97	0.15	1.56	0.035
P62250	40S ribosomal protein S16	13	0.83	0.17	1.29	0.18	1.56	0.011
P11442	Clathrin heavy chain 1	103	0.77	0.10	1.20	0.25	1.56	0.011
P38650	Cytoplasmic dynein 1 heavy chain 1	51	0.76	0.07	1.18	0.32	1.56	0.018
O08557	N(G),N(G)-dimethylarginine dimethylaminohydrolase 1	11	0.68	0.19	1.04	0.20	1.54	0.033
P12346	Serotransferrin	78	0.76	0.13	1.16	0.31	1.54	0.049
P04644	40S ribosomal protein S17	17	0.80	0.26	1.23	0.19	1.54	0.041
Q08163	Adenylyl cyclase-associated protein 1	9	0.85	0.23	1.31	0.35	1.54	0.049
O08629	Transcription intermediary factor 1-beta	8	0.82	0.21	1.27	0.11	1.54	0.016
Q9JJ22	Endoplasmic reticulum aminopeptidase 1	8	0.93	0.14	1.39	0.37	1.49	0.038
Q9R0J8	Legumain	3	0.94	0.13	1.39	0.19	1.48	0.008
P69736	Endothelial differentiation-related factor 1	2	0.81	0.20	1.20	0.18	1.48	0.040
Q9JI85	Nucleobindin-2	17	1.02	0.17	1.50	0.32	1.47	0.029
P62853	40S ribosomal protein S25	9	0.76	0.12	1.12	0.19	1.47	0.014
Q63797	Proteasome activator complex subunit 1	26	0.81	0.15	1.19	0.10	1.47	0.009
Q9R1T1	Barrier-to-autointegration factor	3	0.90	0.25	1.32	0.13	1.47	0.026
Q4AEF8	Coatomer subunit gamma-1	18	0.85	0.23	1.24	0.09	1.46	0.026
P62752	60S ribosomal protein L23a	8	0.78	0.12	1.14	0.17	1.46	0.014
P23514	Coatomer subunit beta	30	0.88	0.12	1.27	0.30	1.45	0.040
P51583	Multifunctional protein ADE2	8	1.12	0.06	1.60	0.34	1.43	0.034
Q63945	Protein SET	9	0.77	0.15	1.10	0.08	1.43	0.012
Q8K1Q0	Glycopeptide N-tetradecanoyltransferase 1	5	0.87	0.15	1.24	0.19	1.42	0.023
B5DFC8	Eukaryotic translation initiation factor 3 subunit C	14	0.85	0.12	1.20	0.19	1.42	0.018
Q5RJR8	Leucine-rich repeat-containing protein 59	21	0.80	0.14	1.14	0.14	1.42	0.021
P43244	Matrin-3	12	0.91	0.07	1.28	0.09	1.41	0.001
P25113	Phosphoglycerate mutase 1	20	0.92	0.10	1.30	0.25	1.41	0.024
P41123	60S ribosomal protein L13	16	0.76	0.10	1.06	0.13	1.40	0.011
Q3T1J1	Eukaryotic translation initiation factor 5A-1	13	0.84	0.08	1.16	0.22	1.39	0.021
P68511	14-3-3 protein eta	15	0.85	0.10	1.18	0.25	1.39	0.036

P21531	60S ribosomal protein L3	23	0.80	0.13	1.11	0.20	1.39	0.037
Q63584	Transmembrane emp24 domain-containing protein 10	11	0.90	0.07	1.23	0.26	1.37	0.030
P63086	Mitogen-activated protein kinase 1	5	0.83	0.08	1.12	0.12	1.36	0.006
Q64126	EH domain-containing protein 1	20	0.87	0.03	1.17	0.06	1.35	<0.001
P02401	60S acidic ribosomal protein P2	31	0.71	0.09	0.95	0.06	1.34	0.008
Q66H80	Coatomer subunit delta	13	0.91	0.15	1.22	0.16	1.34	0.030
P28023	Dynactin subunit 1	6	0.85	0.11	1.12	0.14	1.31	0.020
Q6RUV5	Ras-related C3 botulinum toxin substrate 1	4	0.88	0.11	1.14	0.14	1.30	0.025
Q62871	Cytoplasmic dynein 1 intermediate chain 2	6	0.89	0.15	1.14	0.13	1.28	0.048
Q5M7W5	Microtubule-associated protein 4	8	0.89	0.09	1.14	0.13	1.27	0.020
P85125	Polymerase I and transcript release factor	5	0.85	0.03	1.07	0.05	1.26	<0.001
P85972	Vinculin	35	0.85	0.10	1.07	0.15	1.26	0.047
Q8CFN2	Cell division control protein 42 homolog	8	0.93	0.10	1.14	0.08	1.23	0.014
P29314	40S ribosomal protein S9	13	0.86	0.10	1.03	0.09	1.20	0.048
Q5U211	Sorting nexin-3	5	0.93	0.08	1.07	0.08	1.16	0.040
Q62991	Sec1 family domain-containing protein 1	8	0.98	0.05	1.14	0.04	1.16	0.002
O35142	Coatomer subunit beta'	9	0.93	0.05	1.04	0.04	1.11	0.020

Supplementary Table 1D: *i*TRAQ-based proteomic comparison of liver proteins in vehicle control- and APAP-treated rats (96h timepoint). Proteins with expression that was different (raw P < 0.05) between control and APAP-treated rats at 96h are listed. Mean expression values relative to a common pool are given for n=3 animals. Proteins are ordered according to the ratio between the 96h and control groups (lowest to highest) such that proteins with expression that was most markedly reduced at 96h appear at the top of the list.

^aAverage number of peptides used for quantification across the four individual iTRAQ runs.

^bUncorrected raw P value.

Uniprot Accession	Name	Peptides ^a	Vehicle control		96h		96h/ctrl	P- value ^b
			Mean	SD	Mean	SD	Ratio	
Proteins reduced at 96h								
P08683	Cytochrome P450 2C11	51	2.53	0.52	0.09	0.04	0.03	<0.001
P49890	Estrogen sulfotransferase, isoform 6	18	3.22	0.91	0.11	0.08	0.03	<0.001
P09606	Glutamine synthetase	17	2.73	0.78	0.10	0.03	0.03	<0.001
P14141	Carbonic anhydrase 3	70	1.99	1.30	0.10	0.08	0.05	0.004
Q07523	Hydroxyacid oxidase 2	8	1.99	0.34	0.12	0.08	0.06	<0.001
P36365	Dimethylaniline monooxygenase [N-oxide- forming] 1	13	2.34	0.94	0.24	0.05	0.10	<0.001
P02761	Major urinary protein	22	2.27	0.42	0.25	0.08	0.11	<0.001
P10867	L-gulonolactone oxidase	18	2.00	0.36	0.31	0.12	0.15	<0.001
P50237	Sulfotransferase 1C1	27	1.95	0.15	0.31	0.12	0.16	<0.001
P17988	Sulfotransferase 1A1	30	1.99	0.34	0.34	0.15	0.17	0.001
Q9ES38	Bile acyl-CoA synthetase	26	2.80	0.86	0.53	0.32	0.19	0.005
P05183	Cytochrome P450 3A2	15	2.49	0.97	0.48	0.42	0.19	0.028
P12785	Fatty acid synthase	155	1.79	1.03	0.36	0.07	0.20	0.009
P04182	Ornithine aminotransferase, mitochondrial	8	1.44	0.74	0.29	0.18	0.20	0.014
Q62730	Estradiol 17-beta- dehydrogenase 2	17	1.72	0.47	0.35	0.11	0.20	0.001
Q02769	Squalene synthase	8	1.70	0.55	0.36	0.14	0.21	0.005
P11497	Acetyl-CoA carboxylase 1	44	1.46	0.57	0.33	0.07	0.22	0.003
P16638	ATP-citrate synthase	65	1.93	0.71	0.45	0.01	0.23	0.001
Q03336	Regucalcin	45	1.98	0.18	0.49	0.08	0.25	<0.001
P05369	Farnesyl pyrophosphate synthase	27	1.50	0.39	0.39	0.35	0.26	0.025
P22734	Catechol O- methyltransferase	46	1.49	0.39	0.39	0.13	0.26	0.002
P52847	Sulfotransferase family cytosolic 1B member 1	16	1.97	0.42	0.53	0.15	0.27	0.001
P17425	Hydroxymethylglutaryl-CoA synthase, cytoplasmic	9	1.30	0.44	0.36	0.26	0.28	0.045
P19225	Cytochrome P450 2C70	19	1.56	0.65	0.45	0.35	0.29	0.041
P12928	Pyruvate kinase isozymes R/L	61	1.64	0.53	0.49	0.25	0.30	0.009
Q63060	Glycerol kinase	20	1.68	0.28	0.53	0.10	0.31	<0.001

Q9EQ76	Dimethylaniline monooxygenase [N-oxide-forming] 3	21	1.24	0.60	0.40	0.28	0.32	0.031
Q68FT5	Betaine--homocysteine S-methyltransferase 2	82	0.99	0.45	0.32	0.17	0.32	0.026
Q5PPL3	Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating	20	1.74	0.46	0.56	0.28	0.32	0.008
P07953	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 1	13	1.47	0.11	0.49	0.34	0.33	0.018
O35760	Isopentenyl-diphosphate Delta-isomerase 1	4	1.38	0.41	0.47	0.11	0.34	0.006
P02692	Fatty acid-binding protein, liver	69	1.94	0.49	0.67	0.20	0.34	0.004
P16303	Carboxylesterase 3	33	1.85	0.85	0.64	0.38	0.35	0.050
P18757	Cystathionine gamma-lyase	37	1.40	0.63	0.48	0.19	0.35	0.026
Q63276	Bile acid-CoA:amino acid N-acyltransferase	57	1.25	0.27	0.45	0.15	0.36	0.004
P30839	Fatty aldehyde dehydrogenase	36	1.74	0.55	0.64	0.15	0.37	0.011
Q64611	Cysteine sulfinic acid decarboxylase	25	1.81	0.70	0.67	0.19	0.37	0.012
Q5FVR2	Thymidine phosphorylase	11	1.80	0.99	0.69	0.08	0.38	0.033
P11030	Acyl-CoA-binding protein	20	1.87	1.03	0.72	0.23	0.38	0.036
P20070	NADH-cytochrome b5 reductase 3	26	1.62	0.42	0.62	0.09	0.38	0.002
P06214	Delta-aminolevulinic acid dehydratase	35	1.50	0.26	0.58	0.07	0.39	<0.001
Q5I0J9	Putative L-aspartate dehydrogenase	17	1.35	0.44	0.53	0.12	0.39	0.017
P18163	Long-chain-fatty-acid--CoA ligase 1	78	1.54	0.13	0.61	0.06	0.40	<0.001
Q8CHM7	2-hydroxyacyl-CoA lyase 1	28	1.66	0.35	0.67	0.01	0.40	0.001
P08290	Asialoglycoprotein receptor 2	4	1.04	0.35	0.42	0.21	0.40	0.035
P57093	Phytanoyl-CoA dioxygenase, peroxisomal	10	1.36	0.22	0.55	0.23	0.41	0.012
P23680	Serum amyloid P-component	4	1.61	0.24	0.68	0.05	0.43	<0.001
Q5BK17	Iodotyrosine dehalogenase 1	4	1.75	0.28	0.75	0.42	0.43	0.017
Q64654	Lanosterol 14-alpha demethylase	9	1.45	0.43	0.63	0.09	0.43	0.008
Q68FS4	Cytosol aminopeptidase	53	1.52	0.14	0.66	0.12	0.43	<0.001
Q07071	Glucokinase regulatory protein	27	1.71	0.64	0.74	0.35	0.43	0.037
P08009	Glutathione S-transferase Yb-3	53	1.10	0.29	0.48	0.18	0.44	0.020
P55051	Fatty acid-binding protein, brain	9	1.61	0.57	0.71	0.31	0.44	0.041
P85973	Purine nucleoside phosphorylase	41	1.12	0.20	0.49	0.17	0.44	0.009
P14669	Annexin A3	17	1.09	0.27	0.49	0.12	0.45	0.007
P25409	Alanine aminotransferase 1	19	0.85	0.09	0.38	0.08	0.45	0.001

P27364	3 beta-hydroxysteroid dehydrogenase type 5	19	1.41	0.31	0.64	0.13	0.45	0.004
P10860	Glutamate dehydrogenase 1, mitochondrial	118	1.63	0.34	0.74	0.34	0.45	0.037
P97562	Peroxisomal acyl-coenzyme A oxidase 2	38	1.45	0.15	0.66	0.34	0.46	0.038
O88813	Long-chain-fatty-acid--CoA ligase 5	28	1.89	0.67	0.87	0.04	0.46	0.015
P24329	Thiosulfate sulfurtransferase	41	1.33	0.20	0.62	0.19	0.47	0.006
O89000	Dihydropyrimidine dehydrogenase [NADP+]	12	1.36	0.32	0.64	0.12	0.47	0.011
Q920P0	L-xylulose reductase	12	1.44	0.45	0.69	0.10	0.48	0.013
A0JPQ8	Alkylglycerol monooxygenase	6	1.64	0.20	0.78	0.08	0.48	<0.001
P00884	Fructose-bisphosphate aldolase B	129	1.31	0.33	0.64	0.10	0.49	0.006
P13107	Cytochrome P450 2B3	27	1.48	0.55	0.72	0.11	0.49	0.036
Q6AXX6	Redox-regulatory protein PAMM	8	1.54	0.33	0.75	0.24	0.49	0.015
Q4KLZ6	Bifunctional ATP-dependent dihydroxyacetone kinase/FAD-AMP lyase (cyclizing)	64	1.70	0.39	0.83	0.18	0.49	0.009
Q66H45	Tetratricopeptide repeat protein 36	5	1.20	0.34	0.59	0.21	0.49	0.036
P12938	Cytochrome P450 2D3	46	1.52	0.33	0.75	0.12	0.50	0.006
P10868	Guanidinoacetate N-methyltransferase	16	1.58	0.51	0.79	0.18	0.50	0.028
Q5I0M2	Nicotinate-nucleotide pyrophosphorylase [carboxylating]	11	1.28	0.42	0.64	0.13	0.50	0.035
Q5U2Q3	Ester hydrolase C11orf54 homolog	12	2.00	0.36	1.01	0.30	0.51	0.015
Q63150	Dihydropyrimidinase	29	1.41	0.17	0.72	0.33	0.51	0.021
Q9Z339	Glutathione S-transferase omega-1	10	1.42	0.40	0.72	0.28	0.51	0.048
Q63448	Peroxisomal acyl-coenzyme A oxidase 3	27	1.27	0.23	0.65	0.09	0.51	0.003
Q9WUS0	Adenylate kinase isoenzyme 4, mitochondrial	14	1.38	0.19	0.71	0.15	0.52	0.004
Q9WU49	Calcium-regulated heat stable protein 1	7	1.17	0.20	0.61	0.17	0.52	0.009
P70712	Kynureninase	19	1.41	0.32	0.74	0.08	0.52	0.008
P57113	Maleylacetoacetate isomerase	36	1.58	0.34	0.83	0.37	0.53	0.035
Q7TP48	Adipocyte plasma membrane-associated protein	10	1.55	0.48	0.83	0.07	0.53	0.026
P97612	Fatty-acid amide hydrolase 1	26	1.67	0.31	0.90	0.31	0.54	0.029
P00173	Cytochrome b5	31	1.37	0.20	0.76	0.14	0.55	0.005
Q6P7R8	Estradiol 17-beta-dehydrogenase 12	6	1.15	0.20	0.64	0.14	0.56	0.014
P55159	Serum paraoxonase/arylesterase 1	17	1.68	0.55	0.94	0.06	0.56	0.037

Q64232	Very-long-chain enoyl-CoA reductase	35	1.76	0.41	0.99	0.22	0.56	0.017
Q02974	Ketohexokinase	25	1.56	0.28	0.89	0.20	0.57	0.015
Q497B0	Omega-amidase NIT2	34	1.58	0.09	0.90	0.26	0.57	0.008
Q9QZH8	Arylacetamide deacetylase	6	1.64	0.55	0.93	0.07	0.57	0.038
Q9QZX8	Solute carrier organic anion transporter family member 1B2	3	1.36	0.40	0.78	0.05	0.57	0.021
P04937	Fibronectin	27	0.74	0.22	0.43	0.01	0.58	0.041
Q6AXM8	Serum paraoxonase/arylesterase 2	8	1.10	0.24	0.65	0.19	0.59	0.046
P52873	Pyruvate carboxylase, mitochondrial	134	1.16	0.13	0.68	0.14	0.59	0.005
B0BNG0	Tetratricopeptide repeat protein 35	11	1.31	0.30	0.77	0.15	0.59	0.022
P29147	D-beta-hydroxybutyrate dehydrogenase, mitochondrial	42	1.40	0.23	0.83	0.28	0.59	0.033
O35331	Pyridoxal kinase	13	1.22	0.21	0.73	0.20	0.60	0.032
P41034	Alpha-tocopherol transfer protein	16	1.28	0.15	0.77	0.15	0.60	0.008
P25093	Fumarylacetoacetase	48	1.45	0.12	0.88	0.24	0.61	0.015
Q498D5	Regulator of microtubule dynamics protein 2	8	1.34	0.14	0.83	0.34	0.62	0.044
Q9QYU4	Thiomorpholine-carboxylate dehydrogenase	9	1.31	0.25	0.81	0.25	0.62	0.039
Q06647	ATP synthase subunit O, mitochondrial	35	1.09	0.27	0.67	0.08	0.62	0.043
P0C2X9	Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial	43	1.30	0.10	0.81	0.23	0.62	0.016
P09456	cAMP-dependent protein kinase type I-alpha regulatory subunit	7	1.22	0.20	0.76	0.14	0.62	0.018
Q6DGG1	Alpha/beta hydrolase domain-containing protein 14B	12	1.36	0.25	0.85	0.20	0.63	0.031
P08503	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	26	1.49	0.32	0.94	0.13	0.63	0.024
P70473	Alpha-methylacyl-CoA racemase	18	1.07	0.04	0.68	0.19	0.64	0.024
Q5M876	Aspartoacylase-2	5	1.35	0.26	0.88	0.04	0.65	0.013
Q68FP2	Serum paraoxonase/lactonase 3	16	1.43	0.10	0.95	0.13	0.66	0.003
Q99MS0	SEC14-like protein 2	16	1.32	0.14	0.88	0.19	0.67	0.020
Q66HG4	Aldose 1-epimerase	5	1.37	0.18	0.93	0.13	0.68	0.015
Q6I7R3	Isochorismatase domain-containing protein 1	10	1.44	0.23	0.97	0.06	0.68	0.017
Q63524	Transmembrane emp24 domain-containing protein 2	8	1.29	0.21	0.89	0.09	0.69	0.018
P41562	Isocitrate dehydrogenase [NADP] cytoplasmic	59	1.21	0.08	0.88	0.15	0.72	0.014

P17764	Acetyl-CoA acetyltransferase, mitochondrial	60	1.28	0.07	0.93	0.15	0.72	0.009
Q9Z1W6	Protein LYRIC	7	1.17	0.14	0.87	0.05	0.75	0.011
P27605	Hypoxanthine-guanine phosphoribosyltransferase	12	1.35	0.20	1.01	0.06	0.75	0.035
Q64057	Alpha-aminoadipic semialdehyde dehydrogenase	55	1.17	0.20	0.89	0.07	0.76	0.050
P60892	Ribose-phosphate pyrophosphokinase 1	6	1.08	0.15	0.84	0.04	0.78	0.035
P85108	Tubulin beta-2A chain	72	1.11	0.05	0.88	0.12	0.79	0.021
O88941	Mannosyl-oligosaccharide glucosidase	12	1.13	0.13	0.89	0.10	0.79	0.044
P11507	Sarcoplasmic/endoplasmic reticulum calcium ATPase 2	30	1.01	0.10	0.81	0.07	0.80	0.028
Q7TQ16	Cytochrome b-c1 complex subunit 8	4	0.99	0.06	0.80	0.06	0.81	0.010
P35738	2-oxoisovalerate dehydrogenase subunit beta, mitochondrial	13	1.23	0.12	1.03	0.05	0.84	0.039
B2RYT9	Translational activator of cytochrome c oxidase 1	3	1.10	0.10	0.93	0.05	0.84	0.043
Q62920	PDZ and LIM domain protein 5	5	1.00	0.03	0.93	0.03	0.93	0.019
Proteins increased at 96h								
P04906	Glutathione S-transferase P	12	0.26	0.22	3.37	1.12	12.94	0.002
P38918	Aflatoxin B1 aldehyde reductase member 3	42	0.20	0.17	2.42	0.14	11.89	0.002
P05982	NAD(P)H dehydrogenase [quinone] 1	8	0.50	0.12	3.08	2.86	6.14	0.044
O70199	UDP-glucose 6-dehydrogenase	38	0.32	0.10	1.82	0.75	5.76	0.001
P07687	Epoxide hydrolase 1	54	0.40	0.19	2.11	0.48	5.32	0.004
P04903	Glutathione S-transferase alpha-2	51	0.54	0.23	2.46	0.87	4.58	0.005
O89049	Thioredoxin reductase 1, cytoplasmic	17	0.42	0.29	1.57	0.29	3.78	0.026
P08430	UDP-glucuronosyltransferase 1-6	40	0.58	0.23	2.06	0.36	3.52	0.003
Q9Z0U5	Aldehyde oxidase	52	0.68	0.20	2.21	0.58	3.23	0.002
P05370	Glucose-6-phosphate 1-dehydrogenase	15	0.38	0.22	1.20	0.33	3.13	0.028
P13383	Nucleolin	21	0.47	0.15	1.43	0.11	3.07	0.001
Q62651	Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial	17	0.62	0.20	1.76	0.44	2.83	0.005
P48508	Glutamate--cysteine ligase regulatory subunit	9	0.68	0.26	1.74	0.31	2.57	0.021
P23965	Enoyl-CoA delta isomerase 1, mitochondrial	18	0.59	0.37	1.46	0.30	2.50	0.046
P18437	Non-histone chromosomal protein HMG-17	3	0.51	0.22	1.26	0.52	2.49	0.037

Q9Z2Y0	Glycine N-acyltransferase-like protein Keg1	6	0.79	0.21	1.94	0.24	2.45	0.003
O35547	Long-chain-fatty-acid--CoA ligase 4	9	0.78	0.11	1.88	0.58	2.40	0.003
P51647	Retinal dehydrogenase 1	29	0.85	0.45	2.00	0.05	2.35	0.040
Q99PS8	Histidine-rich glycoprotein	9	1.03	0.33	2.41	0.76	2.34	0.027
P13084	Nucleophosmin	14	0.51	0.21	1.17	0.03	2.29	0.036
P17475	Alpha-1-antitrypsin	39	0.47	0.18	1.08	0.28	2.28	0.022
P13221	Aspartate aminotransferase, cytoplasmic	30	0.51	0.20	1.15	0.05	2.26	0.016
Q3B8Q1	Nucleolar RNA helicase 2	7	0.48	0.20	1.06	0.16	2.21	0.021
Q64633	UDP-glucuronosyltransferase 1-7	23	0.72	0.20	1.58	0.26	2.20	0.009
Q9EQS0	Transaldolase	15	0.73	0.09	1.58	0.60	2.18	0.011
O35821	Myb-binding protein 1A	15	0.53	0.17	1.16	0.11	2.17	0.010
P19468	Glutamate--cysteine ligase catalytic subunit	22	0.87	0.17	1.74	0.13	2.01	0.002
P06761	78 kDa glucose-regulated protein	112	0.69	0.25	1.37	0.23	1.99	0.029
Q6P6S9	Ectonucleoside triphosphate diphosphohydrolase 5	12	0.79	0.26	1.55	0.40	1.96	0.026
P70619	Glutathione reductase (Fragment)	8	0.68	0.17	1.31	0.32	1.94	0.019
Q6P747	Heterochromatin protein 1-binding protein 3	4	0.91	0.19	1.75	0.51	1.93	0.019
P18886	Carnitine O-palmitoyltransferase 2, mitochondrial	21	0.84	0.19	1.59	0.48	1.89	0.037
P63102	14-3-3 protein zeta/delta	26	0.63	0.11	1.17	0.07	1.85	0.002
Q5M827	Pirin	3	0.78	0.33	1.45	0.20	1.85	0.048
P48721	Stress-70 protein, mitochondrial	67	0.75	0.14	1.39	0.32	1.84	0.013
P31210	3-oxo-5-beta-steroid 4-dehydrogenase	51	1.07	0.22	1.95	0.18	1.83	0.007
P41777	Nucleolar and coiled-body phosphoprotein 1	4	0.65	0.19	1.18	0.21	1.82	0.044
Q6URK4	Heterogeneous nuclear ribonucleoprotein A3	20	0.56	0.07	1.02	0.25	1.82	0.009
P63039	60 kDa heat shock protein, mitochondrial	161	0.87	0.30	1.58	0.22	1.82	0.027
P97584	Prostaglandin reductase 1	16	0.88	0.10	1.58	0.42	1.80	0.015
Q68FR9	Elongation factor 1-delta	19	0.75	0.20	1.35	0.43	1.79	0.040
P11442	Clathrin heavy chain 1	103	0.77	0.10	1.36	0.53	1.78	0.037
P61980	Heterogeneous nuclear ribonucleoprotein K	27	0.78	0.26	1.38	0.31	1.77	0.038
P04785	Protein disulfide-isomerase	89	0.89	0.30	1.57	0.32	1.76	0.046
P70580	Membrane-associated progesterone receptor component 1	18	0.87	0.20	1.51	0.25	1.74	0.015
Q9Z2G8	Nucleosome assembly protein 1-like 1	5	0.72	0.14	1.25	0.15	1.73	0.011
P24368	Peptidyl-prolyl cis-trans isomerase B	14	0.74	0.20	1.27	0.30	1.72	0.045

O35814	Stress-induced-phosphoprotein 1	24	0.72	0.16	1.23	0.31	1.71	0.029
P05182	Cytochrome P450 2E1	29	0.89	0.14	1.51	0.26	1.70	0.009
P04961	Proliferating cell nuclear antigen	4	0.41	0.07	0.69	0.16	1.70	0.021
P24268	Cathepsin D	12	0.86	0.30	1.47	0.32	1.70	0.046
P10960	Sulfated glycoprotein 1	14	0.60	0.11	1.02	0.19	1.68	0.013
Q6AXS5	Plasminogen activator inhibitor 1 RNA-binding protein	12	0.72	0.16	1.21	0.29	1.66	0.039
P62752	60S ribosomal protein L23a	8	0.78	0.12	1.26	0.07	1.62	0.004
P11232	Thioredoxin	7	0.69	0.12	1.11	0.05	1.60	0.009
P17178	Sterol 26-hydroxylase, mitochondrial	13	1.01	0.13	1.61	0.27	1.60	0.008
P19945	60S acidic ribosomal protein P0	24	0.68	0.12	1.08	0.16	1.59	0.017
Q9ER34	Aconitate hydratase, mitochondrial	46	0.78	0.23	1.23	0.08	1.58	0.029
Q1JU68	Eukaryotic translation initiation factor 3 subunit A	23	0.66	0.17	0.98	0.08	1.50	0.041
Q641Y8	ATP-dependent RNA helicase DDX1	12	0.73	0.13	1.09	0.15	1.50	0.025
P08082	Clathrin light chain B	3	0.67	0.13	1.01	0.09	1.50	0.022
P38656	Lupus La protein homolog	7	0.83	0.16	1.23	0.21	1.49	0.039
P62919	60S ribosomal protein L8	11	0.79	0.17	1.18	0.19	1.49	0.040
Q63797	Proteasome activator complex subunit 1	26	0.81	0.15	1.19	0.17	1.48	0.031
P62161	Calmodulin	20	0.78	0.14	1.15	0.13	1.48	0.024
O88600	Heat shock 70 kDa protein 4	28	0.73	0.13	1.07	0.05	1.47	0.011
O35244	Peroxiredoxin-6	32	0.87	0.20	1.27	0.11	1.46	0.045
P07151	Beta-2-microglobulin	3	0.81	0.10	1.17	0.17	1.45	0.012
Q68FR6	Elongation factor 1-gamma	21	0.73	0.08	1.05	0.24	1.44	0.044
P48679	Prelamin-A/C	35	0.78	0.07	1.12	0.25	1.43	0.043
Q9EPH8	Polyadenylate-binding protein 1	24	0.82	0.14	1.15	0.05	1.40	0.022
Q5M875	17-beta-hydroxysteroid dehydrogenase 13	22	1.09	0.17	1.51	0.14	1.39	0.024
Q05096	Myosin-Ib	94	1.03	0.04	1.42	0.01	1.38	<0.001
P14942	Glutathione S-transferase alpha-4	12	0.99	0.12	1.37	0.23	1.38	0.035
P04256	Heterogeneous nuclear ribonucleoprotein A1	18	0.86	0.02	1.15	0.20	1.34	0.019
P25113	Phosphoglycerate mutase 1	20	0.92	0.10	1.23	0.23	1.33	0.048
P02401	60S acidic ribosomal protein P2	31	0.71	0.09	0.93	0.11	1.31	0.042
B5DFC8	Eukaryotic translation initiation factor 3 subunit C	14	0.85	0.12	1.12	0.08	1.31	0.032
Q9Z0V6	Thioredoxin-dependent peroxide reductase, mitochondrial	10	0.87	0.13	1.13	0.10	1.30	0.045
P62853	40S ribosomal protein S25	9	0.76	0.12	0.97	0.05	1.27	0.045
Q3T1J1	Eukaryotic translation initiation factor 5A-1	13	0.84	0.08	1.03	0.04	1.23	0.016

Q924S5	Lon protease homolog, mitochondrial	27	1.01	0.10	1.23	0.10	1.22	0.033
Q9ER24	Ataxin-10	4	0.91	0.08	1.10	0.05	1.21	0.022
Q4G061	Eukaryotic translation initiation factor 3 subunit B	15	0.85	0.09	1.03	0.06	1.21	0.040
P61314	60S ribosomal protein L15	7	0.91	0.11	1.10	0.03	1.21	0.041
Q63584	Transmembrane emp24 domain-containing protein 10	11	0.90	0.07	1.08	0.03	1.20	0.014

Supplementary Table 2: Principle Component Analysis PC1 vs PC4 identifies a group of proteins which are highly expressed in rat livers after four daily doses of APAP (96 h group) and are therefore candidate proteins for further exploration of adaptation

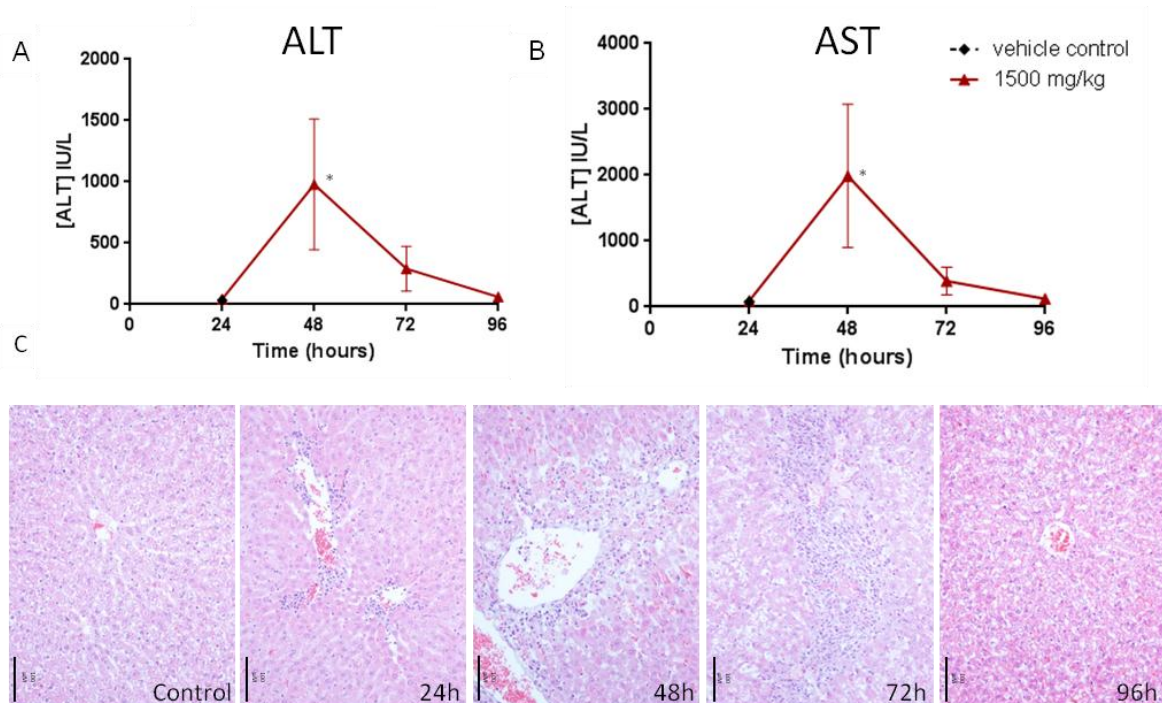
Accession	Name
P04906	Glutathione S-transferase P
P05982	NAD(P)H dehydrogenase [quinone] 1
P38918	Aflatoxin B1 aldehyde reductase member 3
P04903	Glutathione S-transferase alpha-2
P07687	Epoxide hydrolase 1
Q9Z0U5	Aldehyde oxidase
P05179	Cytochrome P450 2C7
P06757	Alcohol dehydrogenase 1
Q99PS8	Histidine-rich glycoprotein
P50137	Transketolase
P08430	UDP-glucuronosyltransferase 1-6
O70199	UDP-glucose 6-dehydrogenase
O35547	Long-chain-fatty-acid--CoA ligase 4
P48508	Glutamate--cysteine ligase regulatory subunit
P31210	3-oxo-5-beta-steroid 4-dehydrogenase
P04905	Glutathione S-transferase Mu 1
P05182	Cytochrome P450 2E1
P05545	Serine protease inhibitor A3K
P51647	Retinal dehydrogenase 1
Q9Z2Y0	Glycine N-acyltransferase-like protein Keg1

Superpathway of Cholesterol Biosynthesis	ACAT1 CYP51A1 FDFT1 FDPS HMGCS1 HMGCS2 IDI1 NSDHL
PXR/RXR Activation	ALDH1A1 ALDH3A2 CYP1A2 CYP2C9 CYP3A4 GSTA1 GSTM1 GSTM2 HMGCS2 PRKAR1A SLCO1B3 UGT1A1
Aldosterone Signaling in Epithelial Cells	AHCY HSP90AA1 HSP90AB1 HSP90B1 HSPA1A/HSPA1B HSPA5 HSPA8 HSPA9 HSPB1 HSPD1 HSPE1 HSPH1 MAPK1
Glutathione-mediated Detoxification	GSTA1 Gsta4 GSTA5 GSTM1 GSTM2 GSTO1 GSTP1 GSTT2/GSTT2B MGST1
Acetone Degradation I (to Methylglyoxal)	CYP1A2 CYP2C18 CYP2C9 CYP2D6 CYP2E1 CYP3A4 CYP4F8 CYP51A1
Bupropion Degradation	CYP1A2 CYP2C18 CYP2C9 CYP2D6 CYP2E1 CYP3A4 CYP4F8 CYP51A1
Aryl Hydrocarbon Receptor Signaling	ALDH1A1 ALDH3A2 ALDH4A1 ALDH5A1 CTSD CYP1A2 GSTA1 GSTA5 GSTM1 GSTM2 GSTO1 GSTP1 GSTT2/GSTT2B HSP90AA1 HSP90AB1 HSP90B1 HSPB1 MAPK1 MGST1 NQO1
Mitochondrial L-carnitine Shuttle Pathway	ACSL1 ACSL4 ACSL5 CPT2 SLC27A2 SLC27A5
Thyroid Hormone Metabolism II (Via Conjugation and/or Degradation)	Sult1a1 SULT1B1 SULT1C3 UGT1A1 UGT1A4 UGT1A6 Ugt1a7c Ugt2b
Fatty Acid Activation	ACSL1 ACSL4 ACSL5 SLC27A2 SLC27A5
Bile Acid Biosynthesis, Neutral Pathway	AKR1D1 AMACR BAAT CYP27A1 CYP3A4 SCP2 SLC27A5
Nicotine Degradation III	ALB AOX1 C4A/C4B CYP1A2 CYP2C18 CYP2C9 CYP2D6 CYP2E1 CYP3A4 CYP4F8 CYP51A1 HPX ITIH3 UGT1A1 UGT1A4 UGT1A6 Ugt1a7c Ugt2b

Supplementary Table 4: Transporters significantly changed in abundance over experimental timecourse compared to control data

Time (h)	Acc.no.	ID	fold change
48	P12336	GLUT-2	-0.43
48	P46720	OATP-1	-0.97
48	Q9QZX8	OATP-4	-1.03
72	P46720	OATP-1	-1.16
72	P45380	SAT-1	-0.93
72	P16970	PMP70	-0.96
96	POC546	SLC25A42	-0.47

Supplementary Figure 1:



Supplementary Figure 1 Legend: Single dosed control study. Rats received a single 1500 mg/kg dose of APAP (p.o.) at 0h, with sacrifice at 24 h, 48 h, 72 h and 96 h post dose. Biomarkers of liver injury were significantly elevated at 48 h alone. Statistical analyses were performed using a one-way ANOVA with Tukey post-hoc test. * indicates $P < 0.05$. Dose key: 1500 mg/kg, red triangles; 24h vehicle control, black diamond. A: ALT was measured in rat 24 h (43.7 IU/L, SEM 3.3), 48 h (979.6 IU/L, SEM 533.5, $P = 0.0458$), 72 h (290.2 IU/L, SEM 184.3) and 96 h (61.6 IU/L, SEM 14.7). 24 h vehicle control values are also shown (34.2 IU/L, SEM 1.5). B: AST was measured in rat 24 h (91.5 IU/L, SEM 15.9), 48 h (1988.3 IU/L, SEM 1085.6, $P = 0.0378$), 72 h (392.0 IU/L, SEM 211.8) and 96 h (120.8 IU/L, SEM 22.9). 24 h vehicle control values are also shown (74.8 IU/L, SEM 3.3). C: Formalin-fixed, paraffin embedded rat liver slices were stained with haematoxylin and eosin, showing progression of injury ($n = 4$, representative images shown). Scale bar represents 100 μm.