

Supplementary materials: Chronic Low Dose Oral Exposure to Microcystin-LR Exacerbates Hepatic Injury in a Murine Model of Non-Alcoholic Fatty Liver Disease

Apurva Lad, Robin C. Su, Joshua D. Breidenbach, Paul M. Stemmer, Nicholas J. Carruthers, Nayeli K. Sanchez, Fatimah K. Khalaf MBChB, Shungang Zhang, Andrew L. Kleinhenz, Prabhatchandra Dube, Chrysan J. Mohammed, Judy A. Westrick, Erin L. Crawford, Dilrukshika Palagama, David Baliu-Rodriguez, Dragan Isailovic, Bruce Levison, Nikolai Modyanov, Amira F. Gohara, Deepak Malhotra, Steven T. Haller and David J. Kennedy

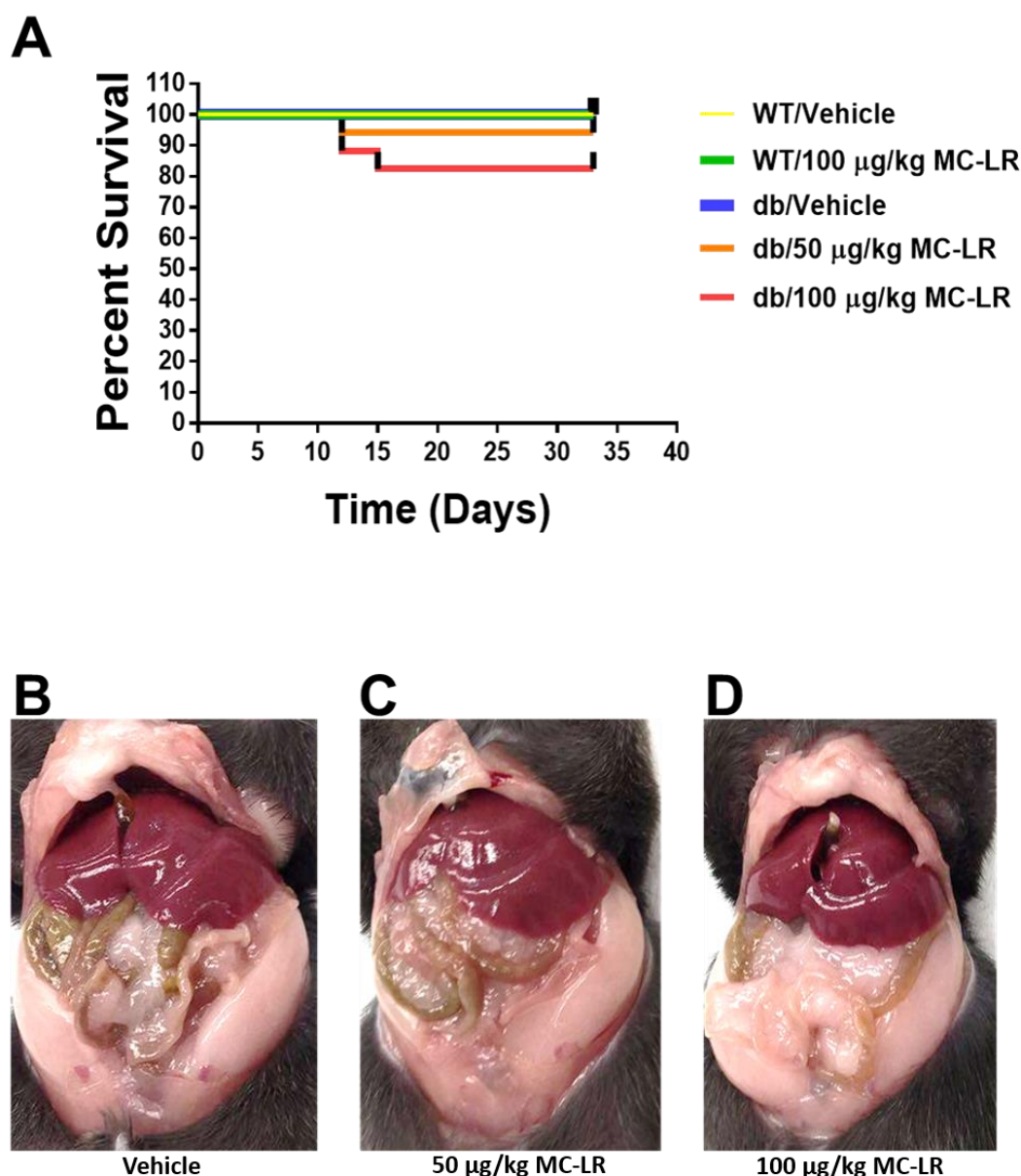


Figure S1. Effect of MC-LR on survival and gross liver morphology in both healthy (C57Bl/6J) and NAFLD (Lepr^{db}/J) mice. (A) Kaplan-Meier analysis of the survival period of the C57Bl/6J (WT) and LepR^{db}/J (db)

mice showed a non-significant (log-rank $p = 0.0702$) decrease in survival in mice receiving 50 $\mu\text{g/kg}$ ($n = 17$, 94% survival) and 100 $\mu\text{g/kg}$ MC-LR ($n = 17$, 82% survival) versus db/Vehicle ($n = 15$) (100% survival), no deaths were observed in the WT/Vehicle ($n = 5$) or WT/100 $\mu\text{g/kg}$ MC-LR exposure ($n = 5$) C57Bl/6J mice; Representative images showing the gross morphology of the livers of *Lepr^{db}/J* mice that were exposed to (B) Vehicle; (C) 50 $\mu\text{g/kg}$ MC-LR or (D) 100 $\mu\text{g/kg}$ MC-LR. In each case the animals died overnight and there was no observed acute trauma (e.g. tracheal rupture resulting in immediate death) or other signs of improper gavage technique such as visible signs of discomfort or bloating in the time preceding death. Full necropsies to determine cause of death were unable to be completed due to partial cannibalization by littermates, hence we are not able to fully exclude mortality attributable to the gavage procedure in these animals.

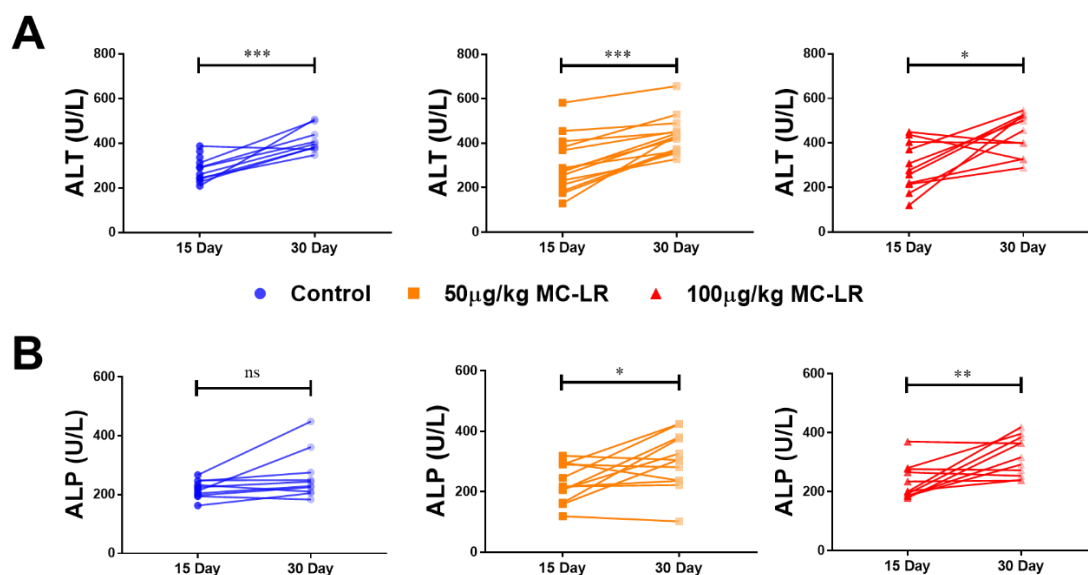


Figure S2. Effect of MC-LR exposure on liver injury enzymes in NAFLD (*Lepr^{db}/J*) mice. Circulating levels of (A) Alanine aminotransferase (ALT) were non-specifically elevated 30 days after study initiation across all exposure groups of *Lepr^{db}/J* mice compared with 15 days after study initiation (db/Vehicle ($n = 15$) ***, $p < 0.001$, db/50 $\mu\text{g/kg}$ MC-LR exposed ($n = 16$), ***, $p < 0.001$, db/100 $\mu\text{g/kg}$ MC-LR exposed ($n = 14$), *, $p < 0.05$), while (B) Alkaline Phosphatase (ALP) were significantly elevated only in the MC-LR exposed groups as assessed at 15- and 30-days after study initiation (50 $\mu\text{g/kg}$ MC-LR exposed *, $p < 0.05$, 100 $\mu\text{g/kg}$ MC-LR exposed **, $p < 0.01$) via paired t -tests. “ns” denotes not significant.

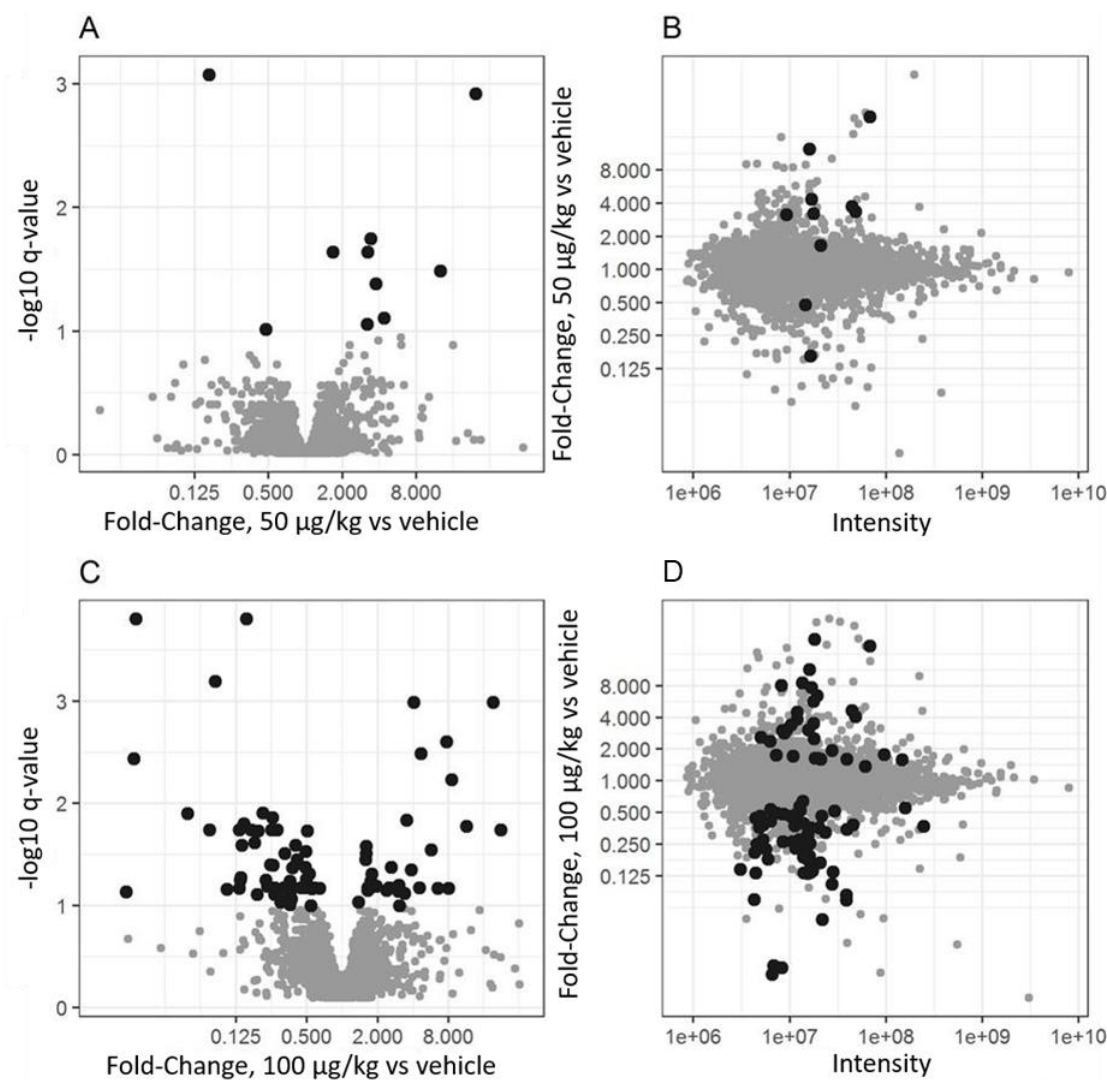


Figure S3. Phosphorylation sites affected by MC-LR exposure in NAFLD (Lepr^{db/J}) mice. Volcano plots (A and C) and minus-average plots (B and D). Values shown in parts A and B are comparisons of the 50 µg/kg microcystin exposed mice to vehicle controls and C and D are from the 100 µg/kg microcystin exposed vs vehicle controls. Sites that were affected by microcystin ($q < 0.1$) are highlighted in dark grey. 50 µg/kg MC-LR group ($n = 8$), 100 µg/kg MC-LR group ($n = 7$), Vehicle ($n = 8$), for all proteomics analyses.

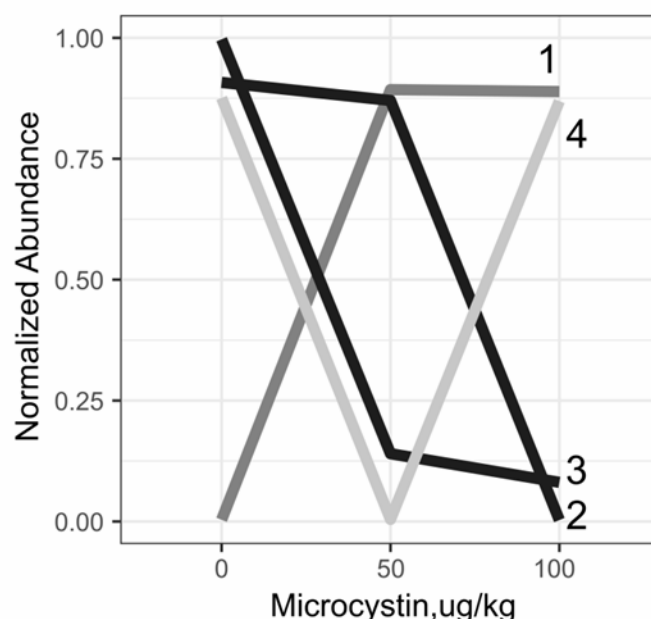


Figure S4: Fuzzy c-means clusters of phosphorylation site abundance versus microcystin dose in NAFLD (Lepr^{db/J}) mice. 6 clusters were generated. Only the 4 associated with Reactome pathways are shown, because the other two could not be interpreted biologically. Clusters that were dephosphorylated in microcystin exposed samples relative to unexposed are dark grey (clusters 2 and 3). Cluster 1 (medium grey) was hyperphosphorylated relative to unexposed samples. Cluster 4 (light grey) includes sites which were dephosphorylated at 50 µg/kg microcystin, but which were phosphorylated at 100 µg/kg microcystin. 50 µg/kg MC-LR group ($n = 8$), 100 µg/kg MC-LR group ($n = 7$), Vehicle ($n = 8$), for all proteomics analyses.

Table S1. Effect of MC-LR exposure on tissue weights in Lepr^{db/J} mice. The weights of the organs are measured in grams. One-way ANOVA was performed to determine the significance between the exposure groups.

Organ	db/Vehicle	db/50 µg/kg MCLR	db/100 µg/kg MCLR	
		Weight (grams) ± S.E.M.		ANOVA p -value
Heart	0.13 ± 0.02	0.148 ± 0.007	0.14 ± 0.004	0.74
Lung	0.11 ± 0.01	0.121 ± 0.005	0.121 ± 0.005	0.84
Liver	3.06 ± 0.22	3.242 ± 0.165	2.975 ± 0.148	0.58
Kidney	0.22 ± 0.04	0.202 ± 0.006	0.245 ± 0.026	0.47

Table S2. Effect of MC-LR exposure on tissue weights in C57Bl/6J mice. The weights of the organs are measured in grams. Unpaired t -test was performed to determine the significance between the exposure groups.

Organ	WT/Vehicle	WT/100 µg/kg MCLR	
	Weight (grams) ± S.E.M.		Unpaired <i>t</i> -test <i>p</i> -value
Heart	0.16 ± 0.01	0.16 ± 0.01	0.91
Lung	0.26 ± 0.01	0.27 ± 0.04	0.87
Liver	1.88 ± 0.13	1.42 ± 0.16	0.07
Kidney	0.19 ± 0.01	0.18 ± 0.01	0.91

Table S3. Effect of MC-LR exposure on blood chemistry in Lepr^{db}/J mice.

Group	Albumin (g/dL)	Alkaline phosphatase (U/L)	Alanine amino-transferase (U/L)	Amylase (U/L)	BUN (mg/dL)	Non-fasted blood Glucose (mg/dL)	Total Protein (g/dL)	Globulin (g/dL)
Day 15								
Vehicle	4.5 ± 0.1	219 ± 8.4	287.6 ± 16.6	1294.2 ± 30.1	20.1 ± 0.9	426.4 ± 31	6 ± 0.1	1.5 ± 0.02
50 µg/kg MC-LR	4.3 ± 0.2	212.5 ± 21.7	302 ± 447.3	1251.4 ± 50.6	19.5 ± 0.7	400.2 ± 37.8	5.9 ± 0.2	1.5 ± 0.1
100 µg/kg MC-LR	4.3 ± 0.2	234.3 ± 17	293.8 ± 347.2	1212.2 ± 47.8	20 ± 0.9	450.8 ± 37.6	5.9 ± 0.2	1.5 ± 0.1
Day 30								
Vehicle	4.4 ± 0.2	263 ± 24.5	414.3 ± 17.7	1204.6 ± 59.4	20.9 ± 1.5	478.1 ± 44.0	6.1 ± 0.2	1.7 ± 0.1
50 µg/kg MC-LR	4.7 ± 0.2	301.8 ± 26	435.6 ± 304.8	1380.9 ± 68.7	20.4 ± 1.2	473.1 ± 32.8	6.5 ± 0.2	1.8 ± 0.1
100 µg/kg MC-LR	4.5 ± 0.1	322.4 ± 19.2	437.1 ± 296.7	1201.9 ± 75.5	23.4 ± 1.4	408.0 ± 40.0	5.4 ± 0.1	1.8 ± 0.1

Table S4. Effect of MC-LR exposure on blood chemistry in healthy C57Bl/6J (WT) mice.

Group	Albumin (g/dL)	Alkaline phosphatase (U/L)	Alanine amino-transferase (U/L)	Amylase (U/L)	BUN (mg/dL)	Non-fasted blood Glucose (mg/dL)	Total Protein (g/dL)	Globulin (g/dL)
Day 15								
Vehicle	3.7 ± 0.1	70.8 ± 4.7	67.6 ± 17.8	780 ± 21.8	24.6 ± 0.8	275.8 ± 8.04	4.8 ± 0.1	1.1 ± 0.1
100 µg/kg MC-LR	3.1 ± 0.1	72.6 ± 4.9	52.4 ± 21.2	721.6 ± 20.2	20.6 ± 1.2	253 ± 15.3	5 ± 0.2	1.9 ± 0.1
Day 30:								
Vehicle	3.2 ± 0.1	58.4 ± 8.0	59 ± 8.5	737.8 ± 47.6	24.4 ± 1.4	284.6 ± 13.8	4.8 ± 0.1	1.6 ± 0.1
100 µg/kg MC-LR	3.2 ± 0.1	58.2 ± 12.3	70.8 ± 17.5	730.0 ± 28.1	16.8 ± 0.9	204.6 ± 16.2	5.1 ± 0.2	1.9 ± 0.1

Table S5. Hematoxylin & Eosin (H&E), Periodic Acid-Schiff (PAS), and Composite Liver Injury Scores in Lepr^{db}/J (db) mice.

Exposure group	Mouse number	H&E Injury Score	PAS Injury Score	Composite Injury Score
db/Vehicle	1	2	1	1.5
	2	2	3	2.5
	3	2	2	2.0
	4	2	2	2.0
	5	2	2	2.0
	6	0	1	0.5
	7	2	3	2.5
	8	2	2	2.0
	9	2	3	2.5
	10	2	3	2.5
	11	2	3	2.5
	12	2	3	2.5
	13	2	2	2.0
db/50 µg/kg MC-LR exposed	1	4	4	4.0
	2	4	4	4.0
	3	4	4	4.0
	4	1	4	2.5
	5	2	1	1.5
	6	4	2	3.0
	7	4	4	4.0
	8	3	2	2.5
	9	3	2	2.5
	10	3	3	3.0
	11	2	3	2.5
	12	3	3	3.0
	13	3	4	3.5
	14	3	3	3.0
	15	(Dead)	(Dead)	(Dead)
db/100 µg/kg MC-LR exposed	16	3	3	3.0
	17	2	2	2.0
	1	2	3	2.5
	2	3	4	3.5
	3	2	4	3.0
	4	4	3	3.5
	5	2	3	2.5
	6	4	4	4.0
	7	(Dead)	(Dead)	(Dead)
	8	3	3	3.0
	9	2	2	2.0
	10	2	2	2.0
	11	(Dead)	(Dead)	(Dead)
	12	2	3	2.5
	13	(Dead)	(Dead)	(Dead)
	14	2	3	2.5
	15	3	2	2.5
	16	3	3	3.0
	17	3	3	3.0

Table S6. Genetic analysis of hepatotoxicity in liver tissues in NAFLD (Lepr^{db}/J) mice. Hepatotoxicity Array for gene expression of liver tissue homogenates from MC-LR exposed Lepr^{db}/J mice (db/100 µg/kg and db/50 µg/kg MC-LR exposure) relative to db/Vehicle exposed mice. qPCR arrays were run with liver cDNA from $n = 4$ pooled samples per array and $n = 3$ arrays per group. Student's t-test was used for comparison between MC-LR exposure group and vehicle control.

Gene	Description	50 µg/kg vs. Vehicle		100 µg/kg vs. Vehicle	
		Fold Regulation	<i>p</i> -value	Fold Regulation	<i>p</i> -value
Cholestasis					
<i>Abcc3</i>	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	174.2	0.091	123.3	0.214
<i>Abcb1a</i>	ATP-binding cassette, sub-family B (MDR/TAP), member 1A	26.6	0.132	15.8	0.365
<i>Abcb4</i>	ATP-binding cassette, sub-family B (MDR/TAP), member 4	95.1	0.123	46.1	0.258
<i>Abcc2</i>	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	14.3	0.562	11.1	0.778
<i>Atp8b1</i>	ATPase, class I, type 8B, member 1	5.9	0.250	5.9	0.163
<i>Pdyn</i>	Prodynorphin	−480.5	0.368	−161.4	0.370
<i>Rdx</i>	Radixin	9.2	0.084	5.0	0.384
<i>Slc51a</i>	Organic solute transporter alpha	3.9	0.171	2.9	0.072
Hepatotoxicity					
<i>Aldoa</i>	Aldolase A, fructose-bisphosphate	229.4	0.073	122.7	0.082
<i>Apex1</i>	Apurinic/apyrimidinic endonuclease 1	5.8	0.487	5.1	0.526
<i>Avpr1a</i>	Arginine vasopressin receptor 1A	5.5	0.322	7.4	0.090
<i>Bhmt</i>	Betaine-homocysteine methyltransferase	34.7	0.481	32.5	0.433
<i>Btg2</i>	B-cell translocation gene 2, anti-proliferative	3.4	0.509	3.1	0.511
<i>Car3</i>	Carbonic anhydrase 3	17.5	0.145	19.1	0.079
<i>Casp3</i>	Caspase 3	15.6	0.010	11.8	0.087
<i>Ccng1</i>	Cyclin G1	19.3	0.019	11.4	0.176
<i>Cryl1</i>	Crystallin, lambda 1	8.2	0.417	8.8	0.232
<i>Cxcl12</i>	Chemokine (C-X-C motif) ligand 12	170.3	0.008	150.0	0.085
<i>Cyp1a2</i>	Cytochrome P450, family 1, subfamily a, polypeptide 2	187.2	0.017	238.1	0.016
<i>Ddit4l</i>	DNA-damage-inducible transcript 4-like	19.7	0.115	46.3	0.364
<i>Ddx39</i>	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39	33.3	0.098	54.7	0.230
<i>Dnajb11</i>	DnaJ (Hsp40) homolog, subfamily B, member 11	4.1	0.409	9.0	0.340
<i>Dnajc3</i>	DnaJ (Hsp40) homolog, subfamily C, member 3	1.5	0.358	2.1	0.232
<i>Fads1</i>	Fatty acid desaturase 1	2.3	0.129	2.4	0.135

<i>Fxc1</i>	Fractured callus expressed transcript 1	−1.1	0.989	−1.1	0.989
<i>Gadd45a</i>	Growth arrest and DNA-damage-inducible 45 alpha	5.1	0.054	9.0	0.366
<i>Gclc</i>	Glutamate-cysteine ligase, catalytic subunit	−2.1	0.386	−5.0	0.376
<i>Gusb</i>	Glucuronidase, beta	−1.3	0.390	−16.0	0.209
<i>Hsp90ab1</i>	Heat shock protein 90 alpha (cytosolic), class B member 1	−13.7	0.882	−17.4	0.835
<i>Krt18</i>	Keratin 18	27.3	0.094	6.4	0.356
<i>Krt8</i>	Keratin 8	18.8	0.258	14.8	0.423
<i>Mbl2</i>	Mannose-binding lectin (protein C) 2	18.9	0.574	19.2	0.568
<i>MGDC</i>	Mouse Genomic DNA Contamination	−12.5	0.374	−16.5	0.374
<i>Nqo1</i>	NAD(P)H dehydrogenase, quinone 1	9.3	0.136	4.0	0.387
<i>Pla2g12a</i>	Phospholipase A2, group XIA	1.0	0.737	−2.8	0.118
<i>Rb1</i>	Retinoblastoma 1	2.5	0.044	2.0	0.108
<i>Slc17a3</i>	Solute carrier family 17 (sodium phosphate), member 3	2.5	0.963	2.4	0.881
<i>Txnrd1</i>	Thioredoxin reductase 1	3.5	0.707	3.5	0.707
Necrosis:					
<i>Cd68</i>	CD68 antigen	5.0	0.460	6.4	0.193
<i>Cdc14b</i>	CDC14 cell division cycle 14 homolog B (<i>S. cerevisiae</i>)	−3.9	0.377	−3.2	0.379
<i>Cdkn1a</i>	Cyclin-dependent kinase inhibitor 1A (P21)	22.2	0.272	23.8	0.245
<i>Col4a1</i>	Collagen, type IV, alpha 1	33.2	0.025	36.1	0.229
<i>Ddx39</i>	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39	33.3	0.098	33.3	0.098
<i>Emc9</i>	Family with sequence similarity 158, member A	1.5	0.311	1.5	0.311
<i>Fam214a</i>	CDNA sequence BC031353	15.6	0.013	19.5	0.011
<i>Lgr5</i>	Leucine rich repeat containing G protein coupled receptor 5	3.2	0.188	3.2	0.138
<i>Mcm10</i>	Minichromosome maintenance deficient 10 (<i>S. cerevisiae</i>)	14.1	0.188	3.3	0.371
<i>Mlxipl</i>	MLX interacting protein-like	97.1	0.016	46.3	0.207
<i>Osmr</i>	Oncostatin M receptor	3.5	0.416	3.5	0.416
<i>Rhbg</i>	Rhesus blood group-associated B glycoprotein	2.0	0.274	2.2	0.317
<i>Serpine1</i>	Serine (or cysteine) peptidase inhibitor, clade E, member 1	−2.4	0.933	−2.9	0.069
<i>Skil</i>	SKI-like	−1.3	0.649	−73.9	0.374
<i>Tmem2</i>	Transmembrane protein 2	−2.2	0.372	−2.2	0.372
Nongenotoxic Hepatocarcinogenicity:					
<i>Aldoa</i>	Aldolase A, fructose-bisphosphate	229.4	0.073	122.7	0.082

<i>Apex1</i>	Apurinic/apyrimidinic endonuclease 1	5.8	0.487	5.1	0.526
<i>Btg2</i>	B-cell translocation gene 2, anti-proliferative	3.4	0.509	3.1	0.511
<i>Ccng1</i>	Cyclin G1	19.3	0.019	11.4	0.176
<i>Cdkn1a</i>	Cyclin-dependent kinase inhibitor 1A (P21)	22.2	0.272	23.8	0.245
<i>Ddx39</i>	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39	33.3	0.098	54.7	0.230
<i>Krt18</i>	Keratin 18	27.3	0.094	6.4	0.356
<i>Krt8</i>	Keratin 8	18.8	0.258	14.8	0.423
<i>Mrps18b</i>	Mitochondrial ribosomal protein S18B	12.0	0.433	10.4	0.499
<i>Txnrd1</i>	Thioredoxin reductase 1	3.5	0.707	3.5	0.707
Phosholipidosis:					
<i>Abcb1a</i>	ATP-binding cassette, sub-family B (MDR/TAP), member 1A	26.6	0.132	15.8	0.365
<i>Asah1</i>	N-acylsphingosine amidohydrolase 1	9.1	0.273	6.2	0.427
<i>Fxc1</i>	Fractured callus expressed transcript 1	−1.1	0.989	−1.1	0.989
<i>Hpn</i>	Hepsin	16.0	0.092	16.0	0.092
<i>Lss</i>	Lanosterol synthase	2.7	0.113	2.7	0.113
<i>Mrps18b</i>	Mitochondrial ribosomal protein S18B	12.0	0.433	10.4	0.499
<i>S100a8</i>	S100 calcium binding protein A8 (calgranulin A)	3.0	0.334	2.2	0.765
<i>Serpina3n</i>	Serine (or cysteine) peptidase inhibitor, clade A, member 3N	280.5	0.374	13.3	0.708
Steatosis:					
<i>Cd36</i>	CD36 antigen	32.0	0.115	15.4	0.307
<i>Fasn</i>	Fatty acid synthase	38.6	0.156	22.9	0.328
<i>Scd1</i>	Stearoyl-Coenzyme A desaturase 1	−7.0	0.862	−2.7	0.740

Table S7: Genetic analysis of oxidative stress response in liver tissues of NAFLD (Lepr^{db}/J) mice. Oxidative Stress Array for gene expression of liver tissue homogenates from MC-LR exposed Lepr^{db}/J mice (db/100 µg/kg and db/50 µg/kg MC-LR exposure) relative to db/Vehicle exposed mice. qPCR arrays were run with liver cDNA from $n = 4$ pooled samples per array and $n = 3$ arrays per group. Student's t-test was used for comparison between MC-LR exposure group and vehicle control.

Gene	Description	50 µg/kg vs. Vehicle		100 µg/kg vs. Vehicle	
		Fold Regulation	p-value	Fold Regulation	p-value
Antioxidants:					
Glutathione Peroxidases (GPx):					
Gpx2	Glutathione peroxidase 2	3.4	0.378	1.1	0.826
Gpx5	Glutathione peroxidase 5	4.7	0.044	6.0	0.133
Gpx6	Glutathione peroxidase 6	4.0	0.855	3.7	0.753
Peroxiredoxins (TPx):					
Ehd2	EH-domain containing 2	7.0	0.590	5.7	0.921
Prdx1	Peroxiredoxin 1	568.1	0.097	534.2	0.110
Prdx2	Peroxiredoxin 2	2876.3	< 0.001	3121.4	< 0.001
Prdx3	Peroxiredoxin 3	36.2	0.513	37.7	0.453
Prdx4	Peroxiredoxin 4	27.6	0.558	29.8	0.445
Prdx5	Peroxiredoxin 5	39.7	0.310	39.9	0.300
Prdx6	Peroxiredoxin 6	40.5	0.482	39.6	0.513
Other Peroxidases:					
Apc	Adenomatosis polyposis coli	14.0	0.528	13.6	0.574
Cat	Catalase	68.4	0.616	77.1	0.441
Epx	Eosinophil peroxidase	−2.9	0.373	−5.9	0.235
Mpo	Myeloperoxidase	2.3	0.343	1.2	0.765
Ptgs2	Prostaglandin-endoperoxide synthase 2	1.9	0.455	−8.3	0.149
Serpinb1b	Serine (or cysteine) peptidase inhibitor, clade B, member 1b	4.3	0.236	1.1	0.815
Tpo	Thyroid peroxidase	−7.4	0.307	−6.8	0.309
Other Antioxidants:					
Sod3	Superoxide dismutase 3, extracellular	2.1	0.435	2.5	0.267
Genes Involved in Reactive Oxygen Species (ROS) Metabolism:					
Superoxide Dismutases (SOD):					
Sod3	Superoxide dismutase 3, extracellular	2.1	0.435	2.5	0.267
Other Genes Involved in Superoxide Metabolism:					
Cyba	Cytochrome b-245, alpha polypeptide	15.5	0.276	15.0	0.311
Ncf1	Neutrophil cytosolic factor 1	32.1	0.228	43.1	0.103
Ncf2	Neutrophil cytosolic factor 2	105.4	0.217	119.8	0.152

<i>Nox4</i>	NADPH oxidase 4	45.5	0.157	44.5	0.188
<i>Noxa1</i>	NADPH oxidase activator 1	32.5	0.327	34.0	0.293
<i>Noxo1</i>	NADPH oxidase organizer 1	14.2	0.580	32.1	0.093
<i>Recql4</i>	RecQ protein-like 4	4.8	0.355	1.5	0.629
<i>Ucp2</i>	Uncoupling protein 2 (mitochondrial, proton carrier)	−4.6	0.375	−4.7	0.375
Oxidative Stress Responsive Genes:					
<i>Cat</i>	Catalase	68.4	0.616	77.1	0.441
<i>Epx</i>	Eosinophil peroxidase	−2.9	0.373	−5.9	0.235
<i>Gclc</i>	Glutamate-cysteine ligase, catalytic subunit	54.4	0.164	40.4	0.416
<i>Gpx2</i>	Glutathione peroxidase 2	3.4	0.378	1.1	0.826
<i>Gpx5</i>	Glutathione peroxidase 5	4.7	0.044	6.0	0.133
<i>Gpx6</i>	Glutathione peroxidase 6	4.0	0.855	3.7	0.753
<i>Hspa1a</i>	Heat shock protein 1A	2.7	0.180	−1.2	0.499
<i>Krt1</i>	Keratin 1	13.3	0.218	1.0	0.898
<i>Mpo</i>	Myeloperoxidase	2.3	0.343	1.2	0.765
<i>Nqo1</i>	NAD(P)H dehydrogenase, quinone 1	236.7	0.071	197.8	0.125
<i>Park7</i>	Parkinson disease (autosomal recessive, early onset) 7	−1.2	0.598	28.4	0.965
<i>Prdx1</i>	Peroxiredoxin 1	568.1	0.097	534.2	0.110
<i>Prdx2</i>	Peroxiredoxin 2	2876.3	<0.001	3121.4	<0.001
<i>Prdx6</i>	Peroxiredoxin 6	40.5	0.482	39.6	0.513
<i>Prnp</i>	Prion protein	14.3	0.323	16.5	0.200
<i>Psmb5</i>	Proteasome (prosome, macropain) subunit, beta type 5	40.6	0.424	40.4	0.434
<i>Tpo</i>	Thyroid peroxidase	−7.4	0.307	−6.8	0.309
<i>Txn1</i>	Thioredoxin 1	3.7	0.296	4.1	0.199
<i>Ucp3</i>	Uncoupling protein 3 (mitochondrial, proton carrier)	6.6	0.375	9.7	0.342
Oxygen Transporters:					
<i>Mb</i>	Myoglobin	98.4	0.374	1.0	0.898
<i>Ngb</i>	Neuroglobin	11.4	0.074	10.6	0.030
Other Reactive Oxygen Species (ROS) Metabolism Genes:					
<i>Il19</i>	Interleukin 19	−16.4	0.141	−6.9	0.206

Table S8. Identification of the clusters of pathways affected by 50 µg/kg MC-LR versus control in NAFLD (Lepr^{db/J}) mice using Reactome database. Reactome pathways in liver were identified as affected by 50 µg/kg MC-LR versus control (False Discovery Rate, FDR < 0.2) and enriched in a c-means cluster (Fisher's exact test $p < 0.02$).

Pathway	Mean t-statistic	Sites	FDR
Cluster 1			
Processing of capped intron containing pre-mRNA	0.239	243	0.13031
Metabolism of RNA	0.191	403	0.13031
Pre-mRNA splicing	0.275	223	0.11026
mRNA splicing	0.275	223	0.11026
Sphingolipid metabolism	0.746	41	0.05012
Regulation of Actin dynamics for phagocytic cup formation	0.705	24	0.16038
Cluster 2			
ER to Golgi anterograde transport	0.539	83	0.020048
Asparagine N-linked glycosylation	0.442	98	0.064154
Transport to the Golgi and subsequent modification	0.520	84	0.026731
Cluster 5			
ER to Golgi anterograde transport	0.539	83	0.020048
Asparagine N-linked glycosylation	0.442	98	0.064154
Transport to the Golgi and subsequent modification	0.520	84	0.026731
Copii-mediated vesicle transport	1.149	36	0.020048

Table S9. GO Biological Process enrichment analysis in NAFLD (Lepr^{db/J}) mice.

Name	Test Statistic 50 µg/kg	FDR up, 50 µg/kg	FDR down, 50 µg/kg	Test Statistic, 100 µg/kg	FDR up, 100 µg/kg	FDR down, 100 µg/kg
Coronary vasculature development	-1.0323	1	0.039853	-0.75538	0.9996	0.35437
Embryonic limb morphogenesis	-0.9234	1	0.03282	-0.24075	0.9996	0.60095
Embryonic appendage morphogenesis	-0.9234	1	0.03282	-0.24075	0.9996	0.60095
Regulation of stem cell proliferation	-0.83803	1	0.03282	-0.36321	0.9996	0.48615
Regulation of glial cell differentiation	-0.83542	1	0.050215	-0.80835	0.9996	0.32969
Embryonic skeletal system development	-0.83197	1	0.050215	-0.57295	0.9996	0.4033
Appendage morphogenesis	-0.81328	1	0.03282	-0.1334	0.9996	0.71406
Limb morphogenesis	-0.81328	1	0.03282	-0.1334	0.9996	0.71406
Secondary metabolic process	-0.79835	1	0.090477	-0.74858	0.9996	0.35437
Regulation of reproductive process	-0.7809	1	0.060867	-0.33621	0.9996	0.54364
Kidney epithelium development	-0.75495	1	0.046495	-0.88391	0.9996	0.31733
Lung alveolus development	-0.73629	1	0.050215	-0.80052	0.9996	0.32969
Regulation of T cell proliferation	-0.72964	1	0.039853	-0.72412	0.9996	0.32969
Limb development	-0.70986	1	0.039056	-0.31014	0.9996	0.53082
Appendage development	-0.70986	1	0.039056	-0.31014	0.9996	0.53082
Regulation of mononuclear cell proliferation	-0.68949	1	0.03282	-0.72014	0.9996	0.31733
Regulation of leukocyte proliferation	-0.68949	1	0.03282	-0.72014	0.9996	0.31733
Regulation of lymphocyte proliferation	-0.68949	1	0.03282	-0.72014	0.9996	0.31733
Positive regulation of neuron apoptotic process	-0.68007	1	0.050215	-0.93462	0.9996	0.2897
Regulation of cellular response to oxidative stress	-0.67735	1	0.047824	-0.38762	0.9996	0.47396
Aerobic respiration	-0.67186	1	0.067418	-0.21038	0.9996	0.634
Tricarboxylic acid metabolic process	-0.66531	1	0.075278	-0.64745	0.9996	0.33792
Regulation of sister chromatid segregation	-0.65905	1	0.047824	-0.34456	0.9996	0.49524
Regulation of oxidative stress-induced cell death	-0.65798	1	0.078197	-0.45709	0.9996	0.45018
T cell differentiation in thymus	-0.65302	1	0.079111	-0.43452	0.9996	0.45298
Antibiotic metabolic process	-0.63816	1	0.03282	-0.61795	0.9996	0.32969
Cellular aldehyde metabolic process	-0.63584	1	0.074243	-0.46195	0.9996	0.42795
Cellular respiration	-0.63557	1	0.050215	-0.36331	0.9996	0.47936

Regeneration	−0.63153	1	0.097937	−0.34434	0.9996	0.52374
Regulation of response to oxidative stress	−0.62609	1	0.050215	−0.29387	0.9996	0.54364
Regulation of mitotic nuclear division	−0.60244	1	0.03282	−0.47837	0.9996	0.35519
Positive regulation of WNT signaling pathway	−0.59662	1	0.097937	−0.28342	0.9996	0.56835
Regulation of centrosome cycle	−0.5964	1	0.097937	−0.59589	0.9996	0.36526
Positive regulation of neuron death	−0.59283	1	0.039056	−0.66786	0.9996	0.32114
Regulation of striated muscle tissue development	−0.5898	1	0.050215	−0.54419	0.9996	0.35437
Regulation of muscle tissue development	−0.5898	1	0.050215	−0.54419	0.9996	0.35437
Regulation of muscle organ development	−0.5898	1	0.050215	−0.54419	0.9996	0.35437
Regulation of nuclear division	−0.5872	1	0.036707	−0.42514	0.9996	0.38427
Cell maturation	−0.58646	1	0.099436	−0.52822	0.9996	0.38824
Defense response to bacterium	−0.58604	1	0.097937	−1.1837	0.9996	0.2441
Regulation of chromosome segregation	−0.58367	1	0.041846	−0.36938	0.9996	0.4541
Lung morphogenesis	−0.57429	1	0.09821	−0.78393	0.9996	0.32969
Kidney development	−0.56637	1	0.03282	−0.51822	0.9996	0.32969
Regulation of lipid catabolic process	−0.56276	1	0.050215	−0.77661	0.9996	0.31733
Positive regulation of muscle tissue development	−0.54693	1	0.097937	−0.56794	0.9996	0.35654
Positive regulation of muscle organ development	−0.54693	1	0.097937	−0.56794	0.9996	0.35654
Positive regulation of striated muscle tissue development	−0.54693	1	0.097937	−0.56794	0.9996	0.35654
Response to interferon-gamma	−0.51951	1	0.056828	−0.26497	0.9996	0.56008
Regulation of DNA binding	−0.51891	1	0.099436	−0.34696	0.9996	0.49524
Renal system development	−0.50585	1	0.03282	−0.49304	0.9996	0.32969
Drug catabolic process	−0.50027	1	0.067418	−0.2297	0.9996	0.59712
Protein-DNA complex assembly	−0.49815	1	0.078197	−0.47807	0.9996	0.37118
Negative regulation of DNA-binding transcription factor activity	−0.49449	1	0.0547	−0.80439	0.9996	0.24798
Urogenital system development	−0.49283	1	0.041846	−0.48143	0.9996	0.32969
Memory	−0.49241	1	0.097937	−0.4507	0.9996	0.39629
Dicarboxylic acid metabolic process	−0.4887	1	0.080861	−0.10898	0.9996	0.73234
Positive regulation of mitotic cell cycle	−0.48853	1	0.046495	−0.32172	0.9996	0.4541
Cellular response to interferon-gamma	−0.488	1	0.097937	−0.29948	0.9996	0.53749
Monosaccharide metabolic process	−0.47864	1	0.039056	−0.40071	0.9996	0.37118
Response to hydrogen peroxide	−0.47562	1	0.063625	−0.41561	0.9996	0.39616
Regulation of organ growth	−0.4692	1	0.081699	−0.24578	0.9996	0.56323
Positive regulation of cell cycle process	−0.46384	1	0.03282	−0.34756	0.9996	0.38824

Energy derivation by oxidation of organic compounds	−0.46023	1	0.03282	−0.44166	0.9996	0.32969
Hindbrain development	−0.45555	1	0.078197	−0.47906	0.9996	0.35437
Response to light stimulus	−0.44092	1	0.039056	−0.32478	0.9996	0.43147
Learning	−0.4314	1	0.082513	−0.50844	0.9996	0.33792
Defense response to another organism	−0.43079	1	0.036707	−0.5297	0.9996	0.31733
Regulation of epithelial cell differentiation	−0.42359	1	0.074243	−0.085002	0.9996	0.77042
Regulation of epithelial cell proliferation	−0.41428	1	0.03282	−0.53129	0.9996	0.2897
Cognition	−0.4137	1	0.046495	−0.43928	0.9996	0.33792
Blood vessel morphogenesis	−0.4099	1	0.050215	−0.40647	0.9996	0.35437
Morphogenesis of a branching structure	−0.3965	1	0.09821	−0.3946	0.9996	0.39616
Positive regulation of developmental growth	−0.39581	1	0.056331	−0.36499	0.9996	0.38824
Embryonic organ morphogenesis	−0.39286	1	0.049009	−0.21415	0.9996	0.56404
Response to reactive oxygen species	−0.38934	1	0.085241	−0.36628	0.9996	0.41163
Hexose metabolic process	−0.38425	1	0.091131	−0.38871	0.9996	0.38824
Generation of precursor metabolites and energy	−0.37515	1	0.03282	−0.40782	0.9996	0.32969
Alpha-amino acid metabolic process	−0.37459	1	0.050215	0.14898	0.9996	0.97806
Regulation of DNA-binding transcription factor activity	−0.36756	1	0.039056	−0.58771	0.9996	0.2441
Response to wounding	−0.3666	1	0.049009	−0.34247	0.9996	0.38427
Regulation of developmental growth	−0.36623	1	0.039853	−0.32618	0.9996	0.38427
Innate immune response	−0.3635	1	0.03282	−0.35999	0.9996	0.33792
Cellular amino acid metabolic process	−0.35803	1	0.063625	0.11727	0.9996	0.97096
Heart morphogenesis	−0.35388	1	0.097937	−0.38264	0.9996	0.36832
Learning or memory	−0.35308	1	0.09821	−0.47487	0.9996	0.33477
Protein autophosphorylation	−0.34599	1	0.056828	−0.52372	0.9996	0.31733
Regulation of microtubule cytoskeleton organization	−0.34505	1	0.050215	−0.28394	0.9996	0.44346
Wound healing	−0.34439	1	0.089806	−0.35837	0.9996	0.388
Ribose phosphate biosynthetic process	−0.32493	1	0.097937	−0.40958	0.9996	0.33792
Activation of protein kinase activity	−0.32491	1	0.097821	−0.58535	0.9996	0.31733
Lung development	−0.32251	1	0.097937	−0.4715	0.9996	0.32969
Respiratory tube development	−0.32251	1	0.097937	−0.4715	0.9996	0.32969
Stress-activated protein kinase signaling cascade	−0.31809	1	0.097937	−0.3516	0.9996	0.39629
Immune effector process	−0.30741	1	0.067338	−0.44791	0.9996	0.32969
Regulation of microtubule-based process	−0.30347	1	0.079999	−0.24658	0.9996	0.48779
Cell junction assembly	−0.30113	1	0.099436	−0.29692	0.9996	0.44346

Epithelial tube morphogenesis	−0.29883	1	0.097937	−0.31585	0.9996	0.39616
Multicellular organismal homeostasis	−0.27123	1	0.091767	−0.2067	0.9996	0.54364
Positive regulation of growth	−0.26326	1	0.097937	−0.24782	0.9996	0.47936
Embryonic organ development	−0.25395	1	0.097937	−0.14627	0.9996	0.64959
Sulfur compound metabolic process	−0.25007	1	0.09821	−0.21717	0.9996	0.53134
Membrane docking	1.7117	0.13949	1	1.1412	0.34872	0.9997

Table S10. REACTOME enrichment analysis in NAFLD (Lepr^{db/J}) mice.

Name	Test Statistic, 50 µg/kg	FDR up, 50 µg/kg	FDR down, 50 µg/kg	Test Statistic, 100 µg/kg	FDR up, 100 µg/kg	FDR down, 100 µg/kg
Transport of mature mRNA derived from an intron less transcript	0.0058767	0.80688	0.95806	-1.2463	0.9998	0.034343
Transport of mature mRNAs derived from intron less transcripts	0.0058767	0.80688	0.95806	-1.2463	0.9998	0.034343
Amplification of signal from unattached kinetochores via a MAD2 inhibitory signal	-0.1484	0.89593	0.95806	-1.1858	0.9998	0.034343
Amplification of signal from the kinetochores	-0.1484	0.89593	0.95806	-1.1858	0.9998	0.034343
Mitotic spindle checkpoint	-0.1484	0.89593	0.95806	-1.1858	0.9998	0.034343
tRNA processing in the nucleus	0.26557	0.66085	0.95806	-1.151	0.9998	0.049062
Resolution of sister chromatid cohesion	-0.052978	0.85276	0.95806	-1.1431	0.9998	0.034343
Interactions of REV with host cellular proteins	-0.10241	0.85567	0.95806	-1.1382	0.9998	0.052566
Toll-like receptor TLR6:TLR2 cascade	-0.12584	0.89593	0.95806	-1.0464	0.9998	0.034343
Myd88:Mal cascade initiated on plasma membrane	-0.12584	0.89593	0.95806	-1.0464	0.9998	0.034343
Toll like receptor 2 (TLR2) cascade	-0.12584	0.89593	0.95806	-1.0464	0.9998	0.034343
Toll like receptor TLR1:TLR2 cascade	-0.12584	0.89593	0.95806	-1.0464	0.9998	0.034343
Rho GTPases activate formins	-0.14974	0.90799	0.95806	-1.0337	0.9998	0.038961
SNRNP assembly	0.014016	0.80688	0.95806	-1.0256	0.9998	0.052566
Non-coding RNA metabolism	0.014016	0.80688	0.95806	-1.0256	0.9998	0.052566
tRNA processing	0.15539	0.73985	0.95806	-0.99186	0.9998	0.056728
Sumoylation of chromatin organization proteins	0.049597	0.79947	0.95806	-0.98923	0.9998	0.079112
NS1 mediated effects on host pathways	0.035866	0.80688	0.95806	-0.98845	0.9998	0.079112
Interactions of VPR with host cellular proteins	-0.081569	0.85567	0.95806	-0.9872	0.9998	0.064672
Host interactions with influenza factors	-0.04111	0.83047	0.95806	-0.93593	0.9998	0.079875
Myd88 cascade initiated on plasma membrane	-0.082142	0.85567	0.95806	-0.86987	0.9998	0.064672
Toll like receptor 7,8 (TLR7, 8) cascade	-0.082142	0.85567	0.95806	-0.86987	0.9998	0.064672
Toll like receptor 9 (TLR9) cascade	-0.082142	0.85567	0.95806	-0.86987	0.9998	0.064672
Toll like receptor 10 (TLR10) cascade	-0.082142	0.85567	0.95806	-0.86987	0.9998	0.064672
Toll like receptor 5 (TLR5) cascade	-0.082142	0.85567	0.95806	-0.86987	0.9998	0.064672
Myd88 dependent cascade initiated on endosome	-0.082142	0.85567	0.95806	-0.86987	0.9998	0.064672
Traf6 mediated induction of NFκB and MAPKinases upon TLR7, 8 or 9 activation	-0.082142	0.85567	0.95806	-0.86987	0.9998	0.064672
Toll like receptor 4 (TLR4) cascade	-0.17957	0.94834	0.95806	-0.86876	0.9998	0.034343

Sumoylation of DNA damage response and repair proteins	−0.019179	0.8163	0.95806	−0.85362	0.9998	0.079112
Glycolysis	−0.20596	0.95309	0.95806	−0.83329	0.9998	0.034343
Neurotransmitter receptors and postsynaptic signal transmission	0.0099267	0.80688	0.95806	−0.82623	0.9998	0.079112
L1CAM interactions	−0.19482	0.95416	0.95806	−0.82517	0.9998	0.034343
Mitotic prometaphase	−0.097994	0.89593	0.95806	−0.82129	0.9998	0.034343
Toll-like receptors cascades	−0.17753	0.94834	0.95806	−0.82067	0.9998	0.056728
MAPKinase activation	−0.034018	0.83047	0.95806	−0.77462	0.9998	0.094619
Interleukin-17 signaling	−0.034018	0.83047	0.95806	−0.77462	0.9998	0.094619
Glucose metabolism	−0.30347	0.98499	0.95806	−0.77425	0.9998	0.038961
Gene silencing by RNA	0.25973	0.65381	0.95806	−0.77197	0.9998	0.094619
G alpha (q) signaling events	−0.011793	0.8163	0.95806	−0.75782	0.9998	0.079112
Transmission across chemical synapses	0.022646	0.80688	0.95806	−0.73544	0.9998	0.094619
Separation of sister chromatids	0.096406	0.77449	0.95806	−0.73402	0.9998	0.060346
Carbohydrate metabolism	−0.3009	0.9976	0.73593	−0.72332	0.9998	0.034343
Interleukin-1 family signaling	−0.16524	0.94834	0.95806	−0.71753	0.9998	0.079112
Toll like receptor 3 (TLR3) cascade	−0.068011	0.85567	0.95806	−0.71637	0.9998	0.094619
Trif(ticam1)-mediated tlr4 signaling	−0.061923	0.85567	0.95806	−0.70443	0.9998	0.089482
Myd88-independent tlr4 cascade	−0.061923	0.85567	0.95806	−0.70443	0.9998	0.089482
Cellular senescence	−0.20013	0.95309	0.95806	−0.66012	0.9998	0.079112
Host interactions of HIV factors	0.036324	0.80155	0.95806	−0.60512	0.9998	0.096406
Neuronal system	−0.040978	0.85567	0.95806	−0.56144	0.9998	0.082354
M phase	0.12954	0.66085	0.95806	−0.52435	0.9998	0.056728
Asparagine n-linked glycosylation	0.4424	0.036796	1	−0.29577	0.9998	0.42546
Transport to the Golgi and subsequent modification	0.52014	0.044156	1	−0.18367	0.9998	0.79725
ER to Golgi anterograde transport	0.53861	0.036796	1	−0.18155	0.9998	0.80716
Copii-mediated vesicle transport	1.1485	0.018398	1	0.23287	0.9998	0.95442
Sphingolipid metabolism	0.74576	0.018398	1	0.55462	0.80952	0.9979

Table S11. Phosphorylation sites that were affected by microcystin exposure at 50 or 100 µg/kg in NAFLD (Lepr^{db/J}) mice.

UniProt Accession	Protein Description	Phospho-site position	Phospho-site Amino Acid	Localization Class	<i>t</i> -statistic, 50 µg/kg vs control	<i>q</i> -value 50 µg/kg vs control	<i>t</i> -statistic, 100 µg/kg vs control	<i>q</i> -value 100 µg/kg vs control
P0C7T6	Ataxin-1-like	328	T	ClassI	−9.167754324	0.000815569	−9.753024961	0.000150532
Q8BTI8	Serine/arginine repetitive matrix protein 2	928	S	ClassI	5.586003855	0.02596753	6.500707487	0.001607155
Q8CIT0	Corticoliberin	73	S	ClassI	6.038618108	0.027730577	5.649087123	0.016548359
P26149	3 beta-hydroxysteroid dehydrogenase/Delta 5->4-isomerase type 2;3-beta-hydroxy-Delta (5)-steroid dehydrogenase; Steroid Delta-isomerase	53	S	ClassI	5.515083534	0.027730577	4.511294451	0.035022941
Q9Z0U1	Tight junction protein ZO-2	145	S	ClassI	7.017959912	0.037975325	6.58785868	0.019903452
Q8BTI8	Serine/arginine repetitive matrix protein 2	926	S	ClassI	4.895673186	0.046850529	5.858124769	0.004386913
Q8BSE0	Regulator of microtubule dynamics protein 2	53	T	ClassII	5.009656453	0.087089651	6.89945043	0.003607616
P57748	Matrix metalloproteinase-20	64	S	ClassI	4.892490726	0.096329393	4.093640888	0.076462084
Q9CQX2	Cytochrome b5 type B	37	T	ClassI	9.036986063	0.153355051	6.763922306	0.082338031
Q8CIT0	Corticoliberin	86	T	ClassI	4.383353013	0.157871237	3.969038721	0.081052099
Q6P4S6	Serine/threonine-protein kinase SIK3	493	S	ClassI	−3.931888098	0.204431476	−4.674863414	0.024351089
Q8C4X2	Casein kinase I isoform gamma-3	271	T	ClassI	−5.166797928	0.217599691	−5.489980669	0.066911022

P35831	Tyrosine-protein phosphatase non-receptor type 12	550	S	ClassI	-3.55036785 3	0.32096707 5	-4.388593 243	0.0402522 48
P70441	Na(+)/H(+) exchange regulatory cofactor NHE-RF1	286	S	ClassII	4.287775135	0.35643436 4	9.6754525 47	0.0072806 85
Q9ERU9	E3 SUMO-protein ligase RanBP2	2729	S	ClassI	-3.55283551 1	0.35643436 4	-4.630854 899	0.0411500 62
Q5XG73	Acyl-CoA-binding domain-containing protein 5	418	S	ClassI	-3.27973947 2	0.35643436 4	-4.068487 104	0.0537279 85
P11983	T-complex protein 1 subunit alpha	544	S	ClassI	3.356286632	0.35643436 4	3.7585227 94	0.0810520 99
Q8CC35	Synaptopodin	672	S	ClassI	-3.09283606 3	0.39539108 7	-3.752820 137	0.0810520 99
Q8VHR5	Transcriptional repressor p66-beta	135	S	ClassII	3.234946516	0.39539108 7	3.8370083 09	0.0870387 17
Q8BYC6	Serine/threonine-protein kinase TAO3	324	S	ClassI	-3.08419321 5	0.40201859 5	-4.053466 047	0.0688952 59
Q8BTI8	Serine/arginine repetitive matrix protein 2	1832	S	ClassI	3.001399373	0.41252526 8	4.3455981 47	0.0411500 62
Q61081	Hsp90 co-chaperone Cdc37; Hsp90 co-chaperone Cdc37, N-terminally processed	13	S	ClassI	-2.82595893 4	0.46782556 5	-4.189869 127	0.0516332 5
Q8BTI8	Serine/arginine repetitive matrix protein 2	2535	S	ClassI	2.714245165	0.47821981 5	4.1939152 54	0.0464188 72
Q8BTI8	Serine/arginine repetitive matrix protein 2	1225	S	ClassII	2.69441292	0.50260590 5	3.6860226 47	0.0870387 17
P51660	Peroxisomal multifunctional enzyme type 2;(3R)-hydroxyacyl-CoA dehydrogenase;Enoyl-CoA hydratase 2	3	S	ClassI	2.774174943	0.50456285 8	4.4755929 05	0.0531960 91
P28867	Protein kinase C delta type; Protein kinase C delta type regulatory subunit; Protein kinase C delta type catalytic subunit	645	S	ClassII	-3.22793682 5	0.50456285 8	-5.326986 379	0.0810520 99

P18653	Ribosomal protein S6 kinase alpha-1	348	T	ClassII	-2.73992625 5	0.50590789 2	-4.632721 838	0.0515848 01
Q569Z6	Thyroid hormone receptor- associated protein 3	935	S	ClassI	-2.37785076 2	0.56971591 8	-3.837330 674	0.0810520 99
Q9QVP9	Protein-tyrosine kinase 2-beta	375	S	ClassI	-2.30491341 9	0.56971591 8	-3.721142 254	0.0810520 99
P24788	Cyclin-dependent kinase 11B	584	T	ClassI	-2.2959331	0.57932611 7	-3.723226 161	0.0810520 99
P98078	Disabled homolog 2	393	S	ClassII	2.46929904	0.60045070 5	-6.693720 307	0.0237185 06
Q9CZ44	NSFL1 cofactor p47	114	S	ClassI	-2.17228507	0.61030072 4	-3.638290 832	0.0837675 41
P24788	Cyclin-dependent kinase 11B	65	S	ClassI	-2.18456571	0.63247709 2	-4.413191 431	0.0464188 72
Q99L88	Beta-1-syntrophin	388	S	ClassI	-2.11730995 7	0.69009483 6	-5.006010 323	0.0349256 86
Q64735	Complement component receptor 1-like protein	454	S	ClassI	-1.92089503 6	0.72176907 9	-5.045062 234	0.0158141 82
Q5SZT7	NF-kappa-B-activating protein	141	S	ClassI	1.867301398	0.72423062 8	3.8103394 56	0.0810520 99
Q501J7	Phosphatase and actin regulator 4	264	S	ClassI	-1.73513327 9	0.76390831 9	-3.973485 431	0.0779384 74
Q3UQN2	F-BAR domain only protein 2	532	S	ClassI	-1.65311968 5	0.78657167 1	-6.120754 634	0.0219753 41
Q8K2L8	Trafficking protein particle complex subunit 12	343	S	ClassII	-1.45025654 8	0.79954299 5	-6.821162 211	0.0147738 48
A2ADY9	Protein DDI1 homolog 2	120	S	ClassII	-1.42473786 5	0.82453226 2	-6.668229 839	0.0340209 57
Q80U49	Centrosomal protein of 170 kDa protein B	881	S	ClassII	-1.34029148 4	0.82712687 2	-5.201899 116	0.0243510 89
Q62433	Protein NDRG1	330	S	ClassII	-1.29942601 6	0.86916035 1	-8.280938 473	0.0908769 72
O35623	BET1 homolog	50	S	ClassI	-1.03155168	0.90087827 8	-4.023962 258	0.0618286 4

Q8K0H1	Multidrug and toxin extrusion protein 1	18	S	ClassI	0.953298026	0.90434831 1	3.9038572 49	0.0699729 7
P26231	Catenin alpha-1	641	S	ClassI	0.857570987	0.91703734 4	4.0169168 43	0.0618286 4
Q5Y5T1	Probable palmitoyltransferase ZDHHC20	343	S	ClassII	-0.86634076	0.91733917 8	-11.89306 365	0.0001505 32
P18653	Ribosomal protein S6 kinase alpha-1	373	T	ClassII	0.831109336	0.92122497 4	-5.714702 657	0.0176594 11
O70472	Transmembrane protein 131	1153	S	ClassI	0.767365419	0.93096483 1	-4.865986 751	0.0249944 05
Q69ZA1	Cyclin-dependent kinase 13	318	S	ClassI	0.755169748	0.93180753 1	-3.652618 723	0.0823380 31
Q922J3	CAP-Gly domain-containing linker protein 1	199	S	ClassI	-0.67840811 6	0.93735344 5	-4.125208 303	0.0531960 91
Q9QZW0	Phospholipid-transporting ATPase 11C	1107	S	ClassI	-0.67441010 1	0.93786087 5	-3.760551 833	0.0810520 99
P70460	Vasodilator-stimulated phosphoprotein	235	S	ClassI	0.600316075	0.94483493 9	3.7878386 6	0.0787175 59
Q6ZQH8	Nucleoporin NUP188 homolog	1718	S	ClassII	0.574299295	0.94886216 6	-6.732854 378	0.0237185 06
Q61469	Lipid phosphate phosphohydrolase 1	273	S	ClassII	0.561059382	0.94886216 6	-3.819070 613	0.0787175 59
P48024	Eukaryotic translation initiation factor 1	17	S	ClassII	-0.51399380 6	0.95702985 4	-5.069176 293	0.0697381 48
P20152	Vimentin	419	S	ClassI	-0.41288558 5	0.96527466	-3.853956 429	0.0810520 99
Q58A65	C-Jun-amino-terminal kinase-interacting protein 4	203	S	ClassI	-0.42748799 4	0.96527466	-3.994386 768	0.0810520 99
Q4VA53	Sister chromatid cohesion protein PDS5 homolog B	1359	T	ClassII	0.4563077	0.96527466	-6.803008 444	0.0823380 31
Q8QZR5	Alanine aminotransferase 1	366	T	ClassII	-0.42690397 1	0.96527466	-4.715653 121	0.0939089 17
P97360	Transcription factor ETV6	22	S	ClassI	- 0.334452941	0.96759020 6	-3.920559 433	0.0810520 99

Q80XU3	Nuclear ubiquitous casein and cyclin-dependent kinase substrate 1	79	S	ClassI	0.188935232	0.97609729 7	−4.147958 263	0.0699729 7
Q63ZW7	InaD-like protein	455	S	ClassII	−0.11666925 9	0.97779601 7	−9.607922 028	0.0147738 48
Q9Z0R4	Intersectin-1	315	S	ClassII	0.089161269	0.97867671 1	−15.20728 177	0.0046930 39
Q9ERU9	E3 SUMO-protein ligase RanBP2	2087	S	ClassII	−0.07440205 6	0.97867671 1	−6.541475 964	0.0697381 48
Q80T79	CUB and sushi domain-containing protein 3	1314	S	ClassII	0.002195801	0.98210798 2	−8.325525 003	0.0349256 86