SUPPLEMENTAL METHODS

RNA Sequencing (RNA-Seq) and Bioinformatic Analysis

Total liver RNA of HuR^{hKO} mice fed with WDSW for 4 weeks was isolated using Chemagic Prepito®-D Nucleic Acid Extractor (PerkinElmer, USA) with a Prepito RNA kit (PerkinElmer, USA). The RNA-Seq was performed by Genewiz Company based on the Illumina Hiseq® X platform (Genewiz Co., USA), as previously described (1).

Sequencing reads were trimmed and filtered using bbduk to remove adapters and low-quality reads (2). Reads from mouse samples were mapped to Ensembl GRCm38 transcripts annotation (release 82), using RSEM (3). Gene expression data normalization and differential expression analysis were performed using the R package edgeR (4). Significantly up-or downregulated genes were determined as fold change ≥1.8 and p-value < 0.05. Hierarchical clustering was performed to show differential mRNA expression profiles among the samples (http://www.bioinformatics.com.cn). Volcano plot and heatmaps were created to visualize significantly dysregulated mRNAs using GraphPad Prism (version 8; GraphPad Software Inc., San Diego, CA). Gene Ontology (GO) analysis was performed to investigate three functionality domains: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) using DAVID v6.8 (https://david.ncifcrf.gov/). Pathway analysis was used to functionally analyze and map genes to Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (https://pathview.uncc.edu/)(1). QIAGEN IPA was used to explore the canonical pathways regulated by hepatic HuR.

Serum and Liver Biochemical Analysis

Serum levels of alkaline phosphatase (ALP), aspartate aminotransferase (AST) and

alanine aminotransferase (ALT), total triglyceride, total cholesterol, very-low-density lipoprotein (VLDL), and ALB (albumin) were determined using the Alfa Wassermann Vet ACE Axcel® System with commercially available assay kits from Alfa Wassermann diagnostic technologies (West Caldwell, NJ). Liver tissues were homogenized with a 10-fold 5% NP-40/ddH_2O solution. Total cholesterol and total triglyceride levels in the supernatant fluid of the liver homogenates were analyzed as described previously (1).

Histological and Immunohistochemical Staining

Liver tissues were processed for hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) staining for cytokeratin 19 (CK-19) and Ki67 at the Cancer Mouse Models Core at the VCU Massey Cancer Center (Richmond, VA, USA). Frozen liver tissue cut to 8 μm in thickness was preserved in 3.7% formaldehyde for 10 min and followed by Oil Red O staining described previously (1) . Picro Sirius Red Staining was performed using the Picro Sirius Red Stain Kit from Abcam (Boston, MA) with the paraffin-embedded tissue sections according to the manufacturer's instructions. All the stained slides were scanned using a Vectra Polaris Automated Quantitative Pathology Imaging System from Akoya Biosciences (Marlborough, MA) and the images were captured using Phenochart software (Akoya Biosciences) (1).

Bile acid (BA) analysis

The serum, liver tissues, intestinal contents, and cecal contents were processed for bile acid analysis, as described previously (1).

Quantitative RT-PCR

Total liver RNA was isolated using Chemagic Prepito®-D Nucleic Acid Extractor (PerkinElmer, USA) with Prepito RNA kit (PerkinElmer, USA). cDNA synthesis and Quantitative RT-PCR analysis of

relative mRNA expression levels of target genes were previously described (5). Primer sequences will be provided upon request.

Immunoblotting Analysis

Total and nuclear proteins were prepared and subjected to Western blot analysis as previously described (6). Immunoblot images were captured using the Bio-Rad Gel Doc XR+ imaging system (Hercules, CA, USA). The density of immunoblotted bands was analyzed using BioRad Image Lab computer software and normalized with histone H3 or β-Actin. The antibodies used in the study are listed in **Supplementary Table S1**.

Supplementary Figure Legends

Figure S1. Effect of hepatocyte-specific HuR deficiency on serum biochemical parameters. Age and gender-matched HuR^{hKO} and control mice were fed *ad libitum* a high-fat diet (HFD), with 42% kcal from fat and containing 0.1% cholesterol plus a high fructose-glucose solution (23.1 g/L d-fructose +18.9 g/L d-glucose) (Western diet and sugar water, WDSW) for 4 weeks. **a** Relative mRNA levels of HuR in the liver of HuR^{hKO} and control mice were determined by real-time RT-PCR and normalized with HPRT1. **b** Representative immunoblot images of HuR in the liver are shown and normalized with β-actin as an internal control. **c** Relative protein levels of HuR. **d** Representative images of immunofluorescence staining of HuR in the liver of HuR^{hKO} and control mice (scale bar, 100 μm for 10x magnification). **e** The ratio of liver/body weight. **f** Serum level of ALP. **g** Serum lipids analysis (total cholesterol, triglyceride, glucose). Data are expressed as the mean ± SEM. Statistical significance relative to control: *** $p < 0.001$, ** $p < 0.01$, n=10-12.

Figure S2. Gene Ontology (GO) and KEGG analysis for differentially expressed genes (DEGs). Total liver RNA of HuR^{hKO} and control mice fed with WDSW for 4 weeks was processed for transcriptome sequencing (RNA-Seq). Significantly up-or downregulated genes were determined as fold change ≥1.8 and *p*-value < 0.05. Top 10 enriched terms of the DEGs in GO-BP (biological process) **a**, GO-CC (cellular component) **b**, and GO-MF (molecular function) **c**, and KEGG pathways (Kyoto Encyclopedia of Genes and Genomes) **d**, respectively.

Figure S3. Heatmap of genes involved in inflammation and neutrophil activation. a

Heatmap of genes involved in inflammation and stress in the liver of HuR^{hKO} vs control group fed with WDSW for 4 weeks. **b** Heatmap of genes involved in neutrophil activation. A Z-score is calculated for the RNA-seq data to normalize tag counts. Red and blue colors indicate high and low gene expression, respectively.

Figure S4. Oxidative phosphorylation pathway of HuR^{hKO} vs Control. KEGG pathway analysis was performed on RNA-seq data to functionally analyze and map genes involved in the Oxidative phosphorylation pathway. Red and blue colors indicate upregulated and downregulated gene expression, respectively.

Figure S5. MAPK signaling pathway of HuR^{hKO} vs Control. KEGG pathway analysis was performed on RNA-seq data to functionally analyze and map genes involved in the MAPK signaling pathway. Red and green colors indicate upregulated and downregulated gene expression, respectively.

Figure S6. Hepatocyte-specific HuR deficiency enhances WDSW-induced dysregulation of bile acid homeostasis. a BA composition profile in the intestinal contents expressed by % of total BA. **b** Total BA, TCA, the ratio of total primary conjugated BA to total primary unconjugated BA, the ratio of total conjugated BA to total unconjugated BA in the intestinal contents.**c** BA composition profile in the cecal contents expressed by % of total BA. **d** αMCA, βMCA, CDCA, and ωMCA in the cecal contents. Data are expressed as the mean ± SEM. Statistical significance relative to control: * $p < 0.05$, n=10-12.

Figure S7. Hepatocyte-specific HuR deficiency enhances WDSW-induced dysregulation of fatty acid and lipid metabolism. HuR^{hKO} and control mice were fed *ad libitum* a WDSW for 12 weeks. **a** Representative immunoblot images of HuR in the liver of HuR^{hKO} and control mice were determined by Western blot and normalized with β-actin as an internal control. Relative protein levels of HuR are shown. **b** The mRNA expression levels of key genes involved in fatty acid synthesis and lipid metabolism, including Srebp2, Pparα, Elovl7, HMG-CoAR, Pgc1α, Lpl, Fgf21, Fads2, and Cyclin D1, were measured by real-time RT-PCR and normalized using HPRT1 as an internal control. Statistical significance relative to control: * $p < 0.05$, ** $p < 0.01$, n=10-12.

Figure S8. Hepatocyte-specific HuR deficiency enhances WDSW-induced inflammation and oxidative stress. HuR^{hKO} and control mice were fed *ad libitum* a WDSW for 12 weeks. Relative mRNA levels of genes involved in inflammation and stress were determined by real-time RT-PCR and normalized with HPRT1 as an internal control. **a** Macrophage markers: F4/80, Cd11b, Cd63 and Cd68; Chemokines: Ccl2, Ccr2; Innate immune responses inflammatory markers: Tnfα, Cd14 and Tlr4; Other inflammatory genes: Cerk, Caspase 1, and Cox-2. **b** Neutrophil activation: Nox2, Ncf1, Ncf2, Elastin, Ncf4, Cybα, IL2rg, and Selectin. Data are expressed as the mean ± SEM. Statistical significance relative to control: * $p < 0.05$, ** $p < 0.01$, n=10-12.

Figure S9. HuR was downregulated in the liver of NASH patients. a Relative mRNA levels of HuR in the liver of NASH patients and healthy control patients were determined by real-time

RT-PCR and normalized with HPRT1 as an internal control. Data are expressed as mean ± SEM. Statistical significance relative to control: *p<0.05, n=8-16. **b** Representative immunoblot images of HuR in the liver are shown and normalized with β-actin as an internal control. The relative protein level of HuR is shown. Statistical significance relative to control: *p<0.05, n=3. **c** Relative count of Cyp2c70 in the livers of HuR^{hKO} and control mice from the RNAseq analysis. Statistical significance relative to control: *p<0.05, n=4.

Supplementary Table 1. List of antibodies

Antibody	Species	Source	Catalog #	Application/ dilution
HuR	Mouse	Santa Cruz	Sc-5261	WB (1:500) or IF (1:50)
SphK2	Rabbit	Proteintech	17096-1-AP	WB (1:500)
S1PR2	Rabbit	Proteintech	21180-1-AP	WB (1:500)
CK19 (TROMA-III)	Rat	DSHB University of lowa	TROMA-III	IHC (1:50)
F4/80	Rabbit	Cell Signaling	70076S	IHC (1:200)
Histone H3	Rabbit	Cell Signaling	9715S	WB (1:1000)
Ki67	Rabbit	Cell Signaling	12202S	IHC (1:200)
β-actin (JLA20)	Mouse	DSHB University of lowa	JLA20	WB (1:500)
anti-Rabbit IgG (H+L)-HRP	Goat	Invitrogen	365-6120	WB (1:2500)
anti-Mouse IgG(H+L)-HRP	Goat	Bio-RAD	170-6516	WB (1:2500)
anti-Rat IgG Antibody (H+L)	Rabbit	Vector Laboratories	BA-4000	IHC (1:1000)

Supplementary Table S2: Bile acid profile in the serum of HuR^{hKO} mice (Mean±SD, nmol/L)		
Term	**Control**	**HuR^{hKO}**
Total BA	4,075.45±1,475.81	6,819.10±3,655.04*
Total primary BA	3,216.30±1,474.03	5,393.98±3,289.78*
Total primary conjugated BA	1,506.60±973.28	3,597.11±2,670.07*
Total primary unconjugated BA	1,709.69±1,107.79	1,796.87±1,410.80
Total secondary BA	859.15±345.78	1,425.12±556.35*
Total secondary conjugated BA	365.57±159.14	641.57±345.87*
Total secondary unconjugated BA	493.58±267.89	783.55±419.21*
Total conjugated BA	1,872.17±1,077.93	4,238.68±2,928.71*
Total unconjugated BA	2,203.28±1,149.17	2,580.42±1,776.82
Ratio of total primary BA to total BA	0.76±0.14	0.76±0.08
Ratio of total primary BA to total secondary BA	4.37±2.86	3.85±2.05
Ratio of total primary conjugated BA to total primary unconjugated BA	1.77±2.41	3.53±4.40
Ratio of total conjugated BA to total unconjugated BA	1.35±1.79	2.70±3.16
Ratio of total secondary BA to total BA	0.24±0.14	0.24±0.08
Ratio of total secondary conjugated BA to total secondary unconjugated BA	0.92±0.76	1.14±1.03
Statistical significance: *p< 0.05 vs Control, n=10-12.		

Supplementary Table S3: Bile acid in the serum of HuR^{hKO} mice (Mean±SD, nmol/L)		
Term	**Control**	**HuR^{hKO}**
TαMCA	408.07±525.57	656.01±447.78
TβMCA	827.34±611.16	1,442.89±851.35*
TCA	439.72±352.53	1,705.93±1,423.62*
TCDCA	39.46±28.26	90.47±77.53*
CA	389.71±324.82	518.93±577.56
CDCA	38.38±3.23	49.09±30.42
αMCA	267.86±95.28	285.26±177.52
βMCA	1,182.89±747.08	1,130.43±735.51
TωMCA	182.57±91.69	387.49±262.72*
TDCA	31.34±27.84	82.87±71.34
TUDCA	107.96±47.58	128.62±94.05
THDCA	20.27±11.66	57.86±45.28*
GLCA	50.34±16.24	45.72±12.89
ωMCA	257.46±143.96	370.46±236.93
DCA	225.18±133.56	399.67±210.35*
LCA	12.16±5.20	14.76±5.27
Statistical significance: *p< 0.05 vs Control, n=10-12. The contents of some bile acids were below their limit of quantitation, including GβMCA, GHCA, GUDCA, GHDCA, 7keto_DCA, GCA, MDCA,3Keto,7a,12a(OH)2, HCA, UDCA, HDCA, GCDCA, 7keto_LCA, isoDCA, 12keto_LCA, GDCA, TLCA, isoLCA, allo_isoLCA, 3KetoLCA.		

Supplementary Table S4: Bile acid in the liver of HuR^{hKO} mice (Mean±SD, ng/g)		
Term	**Control**	**HuR^{hKO}**
TαMCA	19.30±22.66	32.64±16.65
TβMCA	55.22±67.67	108.60±64.72
GβMCA	0.35±0.17	0.33±0.10
TCA	152.52±108.51	368.80±206.91*
TCDCA	11.12±4.55	12.88±3.54
GCA	0.26±0.17	0.75±0.93
αMCA	27.28±13.15	26.56±7.85
βMCA	223.26±131.20	223.62±64.83
CA	7.42±4.61	15.50±14.49
CDCA	0.10±0.07	0.68±0.82
TωMCA	15.06±17.74	44.24±46.10
TUDCA	8.33±7.25	9.00±4.81
THDCA	0.84±0.84	4.32±4.68
TDCA	13.34±9.91	26.60±8.36*
TLCA	0.32±0.11	0.38±0.04
GLCA	0.46±0.19	0.32±0.25
allo_isoLCA	0.62±0.04	0.52±0.23
7keto_DCA	3.00±3.45	1.64±0.79
ωMCA	21.70±9.70	30.54±18.28
UDCA	4.08±1.78	2.84±0.58
DCA	0.28±0.19	0.86±0.65*
LCA	0.26±0.15	0.18±0.08
MDCA	2.82±2.09	3.20±1.70
Statistical significance: *p< 0.05 vs Control, n=10-12. The contents of some bile acids were below their limit of quantitation, including GHCA, GUDCA, GHDCA, 3Keto,7a,12a(OH)2, HCA, HDCA, GCDCA, 7keto_LCA, isoDCA, 12keto_LCA, GDCA, isoLCA, 3KetoLCA.		

Supplementary Table S5: Bile acid profile in the liver of HuR^{hKO} mice (Mean±SD, ng/g)		
Term	**Control**	**HuR^{hKO}**
Total BA	566.20±361.61	914.78±391.04
Total primary BA	496.76±318.16	790.14±322.57
Total primary conjugated BA	238.70±199.56	523.78±287.92
Total primary unconjugated BA	258.06±146.92	266.36±69.09
Total secondary BA	69.44±44.70	124.64±75.83
Total secondary conjugated BA	40.30±36.24	87.02±58.28
Total secondary unconjugated BA	29.14±12.89	37.62±20.19
Total conjugated BA	279.00±235.63	610.80±343.99
Total unconjugated BA	287.20±158.66	303.98±78.30
Ratio of total primary BA to total BA	0.87±0.02	0.87±0.03
Ratio of total primary BA to total secondary BA	7.01±1.03	6.80±1.63
Ratio of total primary conjugated BA to total primary unconjugated BA	0.90±0.50	1.98±0.95*
Ratio of total conjugated BA to total unconjugated BA	0.94±0.53	2.00±0.87*
Ratio of total secondary BA to total BA	0.13±0.02	0.13±0.03
Ratio of total secondary conjugated BA to total secondary unconjugated BA	1.30±0.85	2.39±0.77*
Statistical significance: *p< 0.05 vs Control, n=10-12.		

Supplementary Table S6: Bile acid in the intestinal contents of HuR^{hKO} mice (Mean±SD, nmol/g)		
Term	**Control**	**HuR^{hKO}**
TαMCA	8,474.72±7,201.98	6,849.72±5,497.64
TβMCA	24,958.61±19,505.45	29,071.20±25,184.95
GβMCA	96.69±141.65	83.61±75.59
TCA	20,108.28±14,631.67	32,074.56±29,888.29
GCA	77.20±105.88	102.46±93.30
TCDCA	2,428.36±2,908.51	2,116.10±2,246.07
TUDCA	2,996.02±3,285.91	2,701.20±2,616.61
αMCA	852.81±1,089.32	1,143.49±1,870.00
βMCA	2,010.31±2,878.05	2,913.87±3,587.54
CA	3,813.73±5,153.83	6,811.49±7,827.47
CDCA	143.01±255.42	200.47±260.01
UDCA	114.84±216.54	127.77±170.82
TωMCA	4,476.46±3,676.82	4,898.66±4,078.76
THDCA	543.54±602.59	477.22±435.30
TDCA	1,844.17±1,862.37	2,233.56±2,282.91
7keto_DCA	104.19±156.50	133.56±155.80
TLCA	8.07±9.07	7.07±6.48
GLCA	4.38±5.82	2.42±2.97
ωMCA	224.88±336.96	365.61±526.36
HDCA	57.87±67.28	52.71±55.02
DCA	151.36±301.16	230.99±328.55
LCA	1.38±1.38	2.03±1.62
MDCA	49.66±77.87	79.84±36.52
CA-7-S	474.98±725.11	188.10±280.91
CDCA-3-S	0.72±0.47	0.76±0.58
The contents of some bile acids were below their limit of quantitation, including GHCA, GUDCA, GHDCA, 3Keto,7a,12a(OH)2, HCA, GCDCA, 7keto_LCA, isoDCA, 12keto_LCA, GDCA, isoLCA, allo_isoLCA, 3KetoLCA, DCA-3-S, LCA-3-S, UDCA-3-S.		

Supplementary Table S7: Bile acid profile in the intestinal contents of HuR^{hKO} mice (Mean±SD, nmol/g)		
Term	**Control**	**HuR^{hKO}**
Total BA	73,787.02±51,549.64	92,463.71±75,078.82
Total primary BA	65,973.61±45,959.30	83,881.55±68,550.98
Total primary conjugated BA	59,139.87±42,181.26	72,998.84±62,154.31
Total primary unconjugated BA	6,833.74±9,493.16	10,882.71±13,139.36
Total secondary BA	7,813.42±6,389.19	8,582.16±6,987.99
Total secondary conjugated BA	7,392.80±6,035.78	7,914.71±6,455.78
Total secondary unconjugated BA	420.62±734.63	667.44±888.35
Total conjugated BA	66,532.67±47,322.10	80,913.56±68,030.96
Total unconjugated BA	7,254.35±10,218.79	11,550.15±14,009.85
Ratio of total primary BA to total BA	0.91±0.03	0.90±0.03
Ratio of total primary BA to total secondary BA	10.82±4.34	10.22±4.28
Ratio of total primary conjugated BA to total primary unconjugated BA	25.57±36.88	18.82±21.89
Ratio of total conjugated BA to total unconjugated BA	26.39±37.65	19.39±22.24
Ratio of total secondary BA to total BA	0.09±0.03	0.10±0.03
Ratio of total secondary conjugated BA to total secondary unconjugated BA	40.58±43.91	35.87±46.18

Supplementary Table S8: Bile acid in the cecal contents of HuR^{hKO} mice (Mean±SD, nmol/g)		
Term	**Control**	**HuR^{hKO}**
TαMCA	235.35±265.83	86.85±65.37*
TβMCA	338.55±301.61	248.77±241.25
GβMCA	7.72±5.33	5.72±4.35
TCA	159.26±99.18	159.36±166.94
TCDCA	7.83±6.61	8.11±9.23
TUDCA	9.25±8.83	6.93±7.47
αMCA	3,856.89±3,212.25	1,407.31±766.38*
βMCA	15,760.91±13,689.94	6,930.74±2,477.66*
CA	1,595.15±1,192.52	929.06±650.83
CDCA	168.76±143.53	50.95±48.03*
UDCA	209.64±174.25	87.14±74.71*
TωMCA	141.56±159.39	78.89±72.37
THDCA	5.81±7.76	4.76±3.88
TDCA	70.43±87.13	30.10±37.19
7keto_DCA	515.87±508.53	283.41±223.33
TLCA	2.96±3.56	1.19±0.84
GLCA	1.31±0.92	1.96±1.17
7keto_LCA	108.34±110.89	29.81±19.75
12keto_LCA	281.29±270.63	473.49±407.40
isoLCA	8.13±9.50	4.49±4.04
3KetoLCA	5.46±3.52	11.36±12.46
ωMCA	5,248.64±3,945.43	2,670.08±1,051.10
HDCA	150.74±124.71	83.60±61.89
DCA	3,144.88±2,331.84	2,028.45±1,078.39
LCA	183.05±156.61	103.89±93.37
MDCA	119.05±92.52	52.31±29.87
CA-7-S	1,702.68±1,510.46	1,228.52±1,844.67
DCA-3-S	53.55±41.02	12.17±11.07*
LCA-3-S	4.25±4.63	0.83±0.69
Statistical significance: *p< 0.05 vs Control. The contents of some bile acids were below their limit of quantitation, including GHCA, GUDCA, GHDCA, 3Keto,7a,12a(OH)2, HCA, GCDCA, isoDCA, GDCA, GCA, allo_isoLCA, UDCA-3-S, CDCA-3-S.		

Supplementary Table S9: Bile acid profile in the cecal contents of HuR^{hKO} mice (Mean±SD, nmol/g)		
Term	**Control**	**HuR^{hKO}**
Total BA	33,995.42±24,186.92	16,967.15±5,432.34*
Total primary BA	22,309.90±18,265.57	9,896.78±3,654.79*
Total primary conjugated BA	756.39±650.54	514.59±440.95
Total primary unconjugated BA	21,553.51±17,730.08	9,382.19±3,553.50*
Total secondary BA	11,685.51±6,930.24	7,070.37±2,759.78*
Total secondary conjugated BA	1,106.59±1,071.94	900.43±451.95
Total secondary unconjugated BA	10,578.93±6,024.18	6,169.94±2,744.30*
Total conjugated BA	3,610.63±1,784.92	2,650.98±1,914.54
Total unconjugated BA	30,384.79±23,134.35	14,316.17±5,428.09*
Ratio of total primary BA to total BA	0.62±0.09	0.58±0.09
Ratio of total primary BA to total secondary BA	1.77±0.74	1.49±0.50
Ratio of total primary conjugated BA to total primary unconjugated BA	0.04±0.03	0.06±0.06
Ratio of total conjugated BA to total unconjugated BA	0.20±0.22	0.21±0.17
Ratio of total secondary BA to total BA	0.38±0.09	0.42±0.09
Ratio of total secondary conjugated BA to total secondary unconjugated BA	0.09±0.06	0.17±0.10*
Statistical significance: *p< 0.05 vs Control.		

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Figure S1

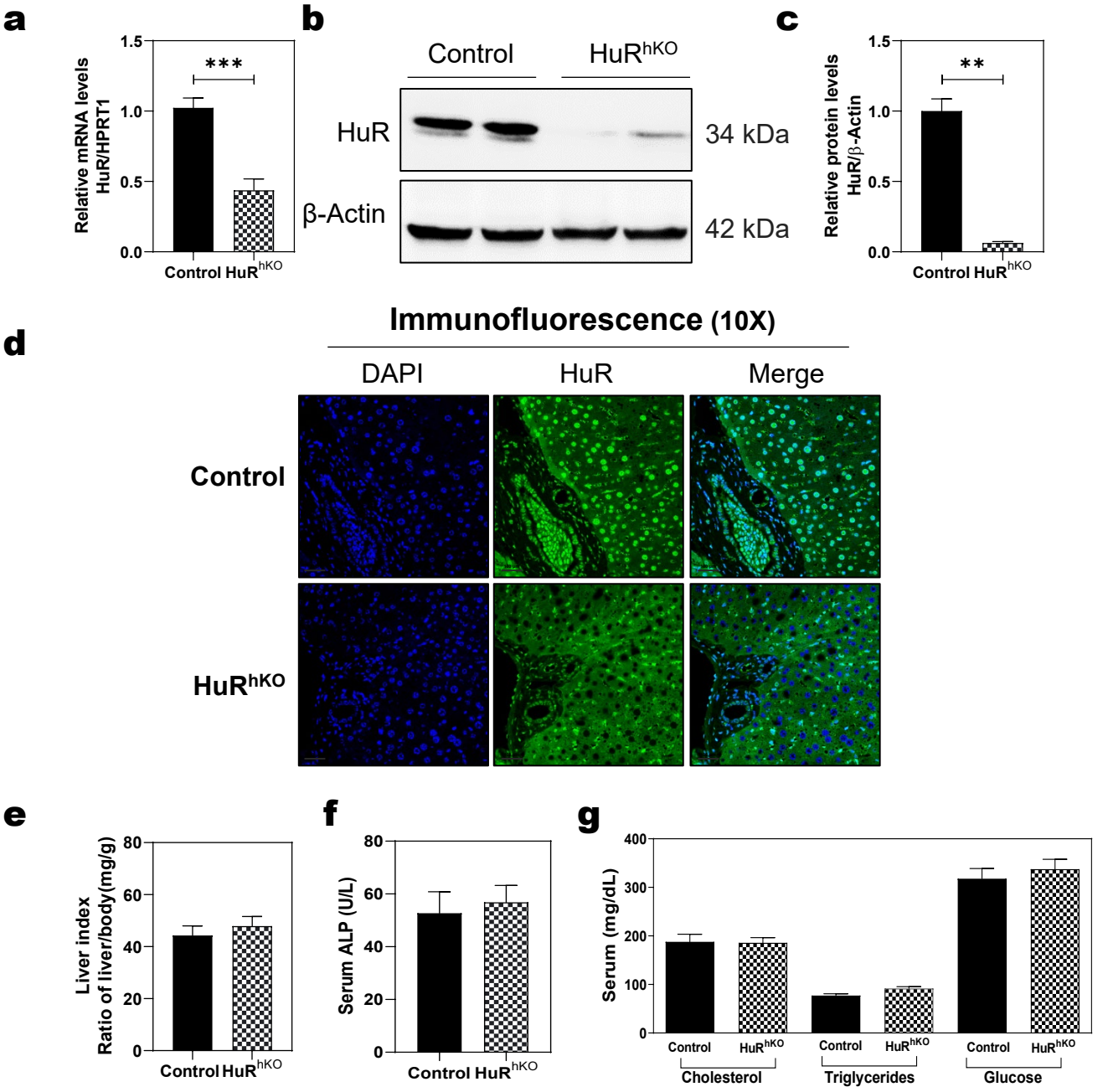

a
Relative mRNA levels HuR/HPRT1
1.5
1.0
0.5
0.0
***
Control HuRhKO
b
Control
HuRhKO
HuR
34 kDa
β-Actin
42 kDa
c
Relative protein levels HuR/β-Actin
1.5
1.0
0.5
0.0
**
Control HuRhKO
d
Immunofluorescence (10X)
DAPI
HuR
Merge
Control
HuRhKO
e
Liver index Ratio of liver/body(mg/g)
80
60
40
20
0
Control HuRhKO
f
Serum ALP (U/L)
80
60
40
20
0
Control HuRhKO
g
Serum (mg/dL)
400
300
200
100
0
Control
HuRhKO
Cholesterol
Control
HuRhKO
Triglycerides
Control
HuRhKO
Glucose

Figure S2

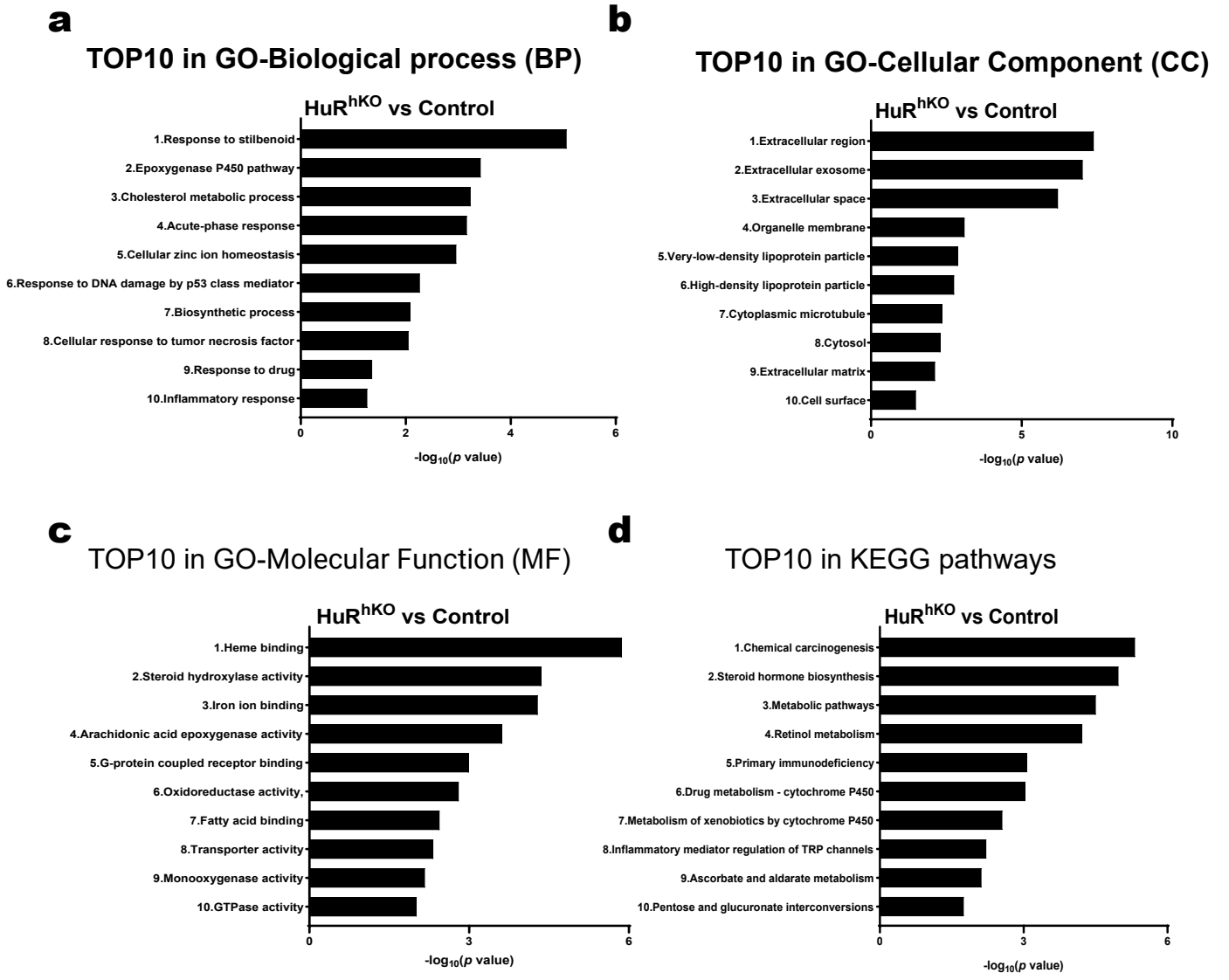

a
TOP10 in GO-Biological process (BP)
HuR^hKO vs Control
1.Response to stilbenoid
2.Epoxygenase P450 pathway
3.Cholesterol metabolic process
4.Acute-phase response
5.Cellular zinc ion homeostasis
6.Response to DNA damage by p53 class mediator
7.Biosynthetic process
8.Cellular response to tumor necrosis factor
9.Response to drug
10.Inflammatory response
0
2
4
6
-log10(p value)
b
TOP10 in GO-Cellular Component (CC)
HuR^hKO vs Control
1.Extracellular region
2.Extracellular exosome
3.Extracellular space
4.Organelle membrane
5.Very-low-density lipoprotein particle
6.High-density lipoprotein particle
7.Cytoplasmic microtubule
8.Cytosol
9.Extracellular matrix
10.Cell surface
0
5
10
-log10(p value)
c
TOP10 in GO-Molecular Function (MF)
HuR^hKO vs Control
1.Heme binding
2.Steroid hydroxylase activity
3.Iron ion binding
4.Arachidonic acid epoxygenase activity
5.G-protein coupled receptor binding
6.Oxidoreductase activity,
7.Fatty acid binding
8.Transporter activity
9.Monooxygenase activity
10.GTPase activity
0
3
6
-log10(p value)
d
TOP10 in KEGG pathways
HuR^hKO vs Control
1.Chemical carcinogenesis
2.Steroid hormone biosynthesis
3.Metabolic pathways
4.Retinol metabolism
5.Primary immunodeficiency
6.Drug metabolism - cytochrome P450
7.Metabolism of xenobiotics by cytochrome P450
8.Inflammatory mediator regulation of TRP channels
9.Ascorbate and aldarate metabolism
10.Pentose and glucuronate interconversions
0
3
6
-log10(p value)

Figure S3

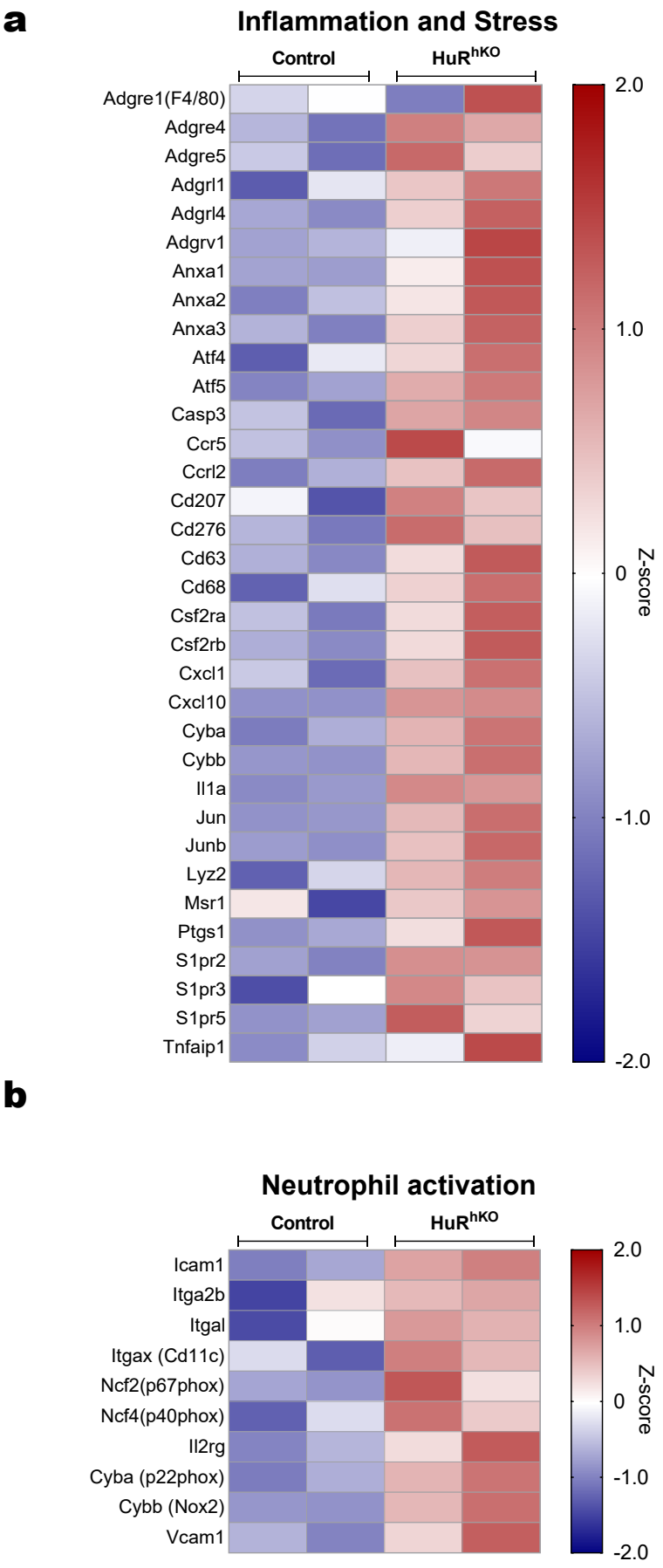

a
Inflammation and Stress
Control
HuR^hKO
Adgre1(F4/80)
Adgre4
Adgre5
Adgrl1
Adgrl4
Adgrv1
Anxa1
Anxa2
Anxa3
Atf4
Atf5
Casp3
Ccr5
Ccrl2
Cd207
Cd276
Cd63
Cd68
Csf2ra
Csf2rb
Cxcl1
Cxcl10
Cyba
Cybb
Il1a
Jun
Junb
Lyz2
Msr1
Ptgs1
S1pr2
S1pr3
S1pr5
Tnfaip1
2.0
1.0
0
-1.0
-2.0
Z-score
b
Neutrophil activation
Control
HuR^hKO
Icam1
Itga2b
Itgal
Itgax (Cd11c)
Ncf2(p67phox)
Ncf4(p40phox)
Il2rg
Cyba (p22phox)
Cybb (Nox2)
Vcam1
2.0
1.0
0
-1.0
-2.0
Z-score

Figure S4

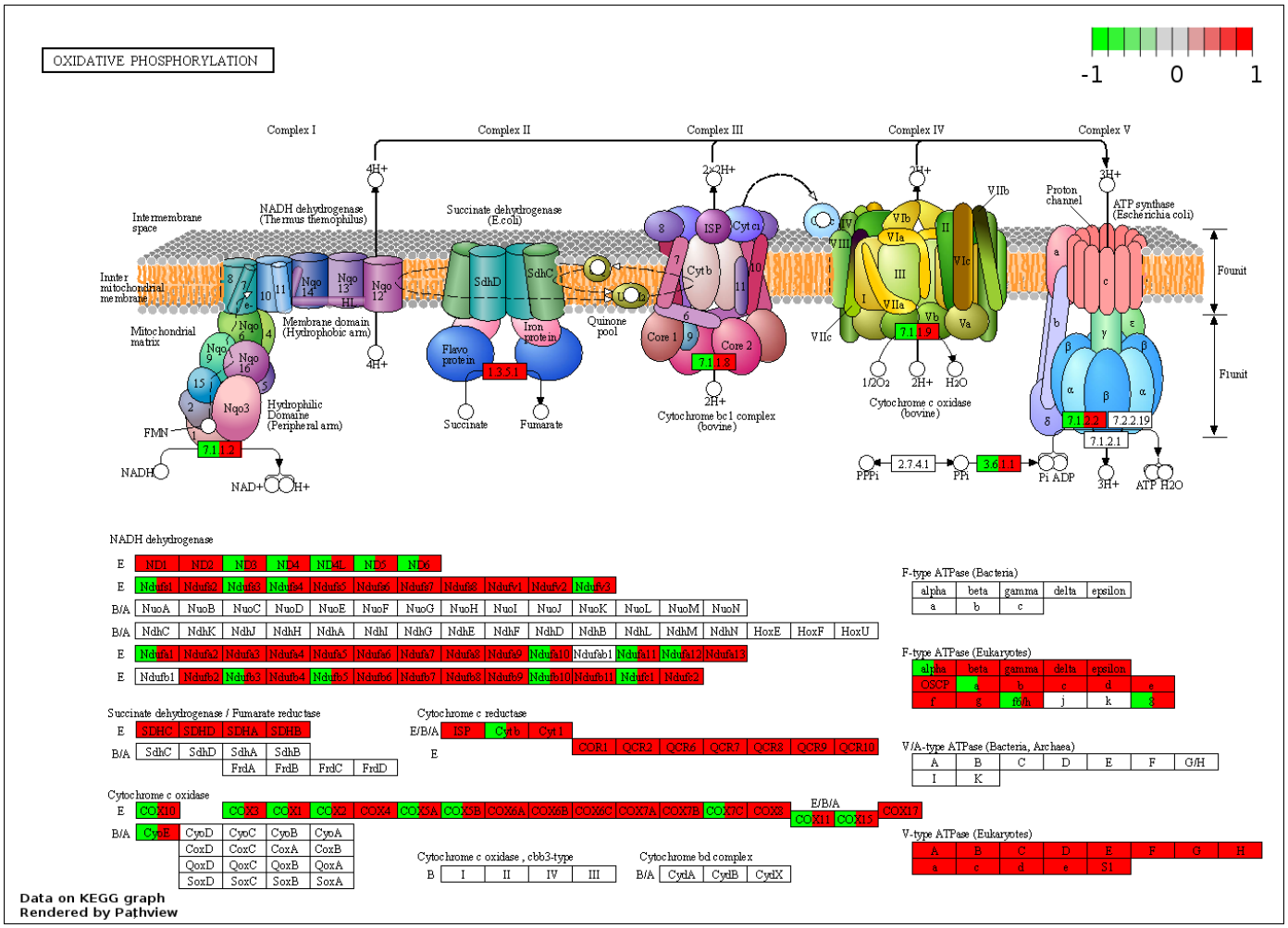

Oxidative Phosphorylation
OXIDATIVE PHOSPHORYLATION
-1
0
1
Complex I
Complex II
Complex III
Complex IV
Complex V
Intermembrane space
Inner mitochondrial membrane
Mitochondrial matrix
NADH dehydrogenase (Thermus thermophilus)
Membrane domain (Hydrophobic arm)
Hydrophilic Domain (Peripheral arm)
Succinate dehydrogenase (E.coli)
Flavo protein
Iron protein
Succinate
Fumarate
Quinone pool
Cytochrome bc1 complex (bovine)
Cytochrome c oxidase (bovine)
Proton channel
ATP synthase (Escherichia coli)
Founit
F1unit
NADH
NAD+
FMN
PPPi
PPi
Pi
ADP
ATP
H2O
NADH dehydrogenase
F-type ATPase (Bacteria)
F-type ATPase (Eukaryotes)
Succinate dehydrogenase / Fumarate reductase
Cytochrome c reductase
V/A-type ATPase (Bacteria, Archaea)
Cytochrome c oxidase
Cytochrome c oxidase , cbb3-type
Cytochrome bd complex
V-type ATPase (Eukaryotes)
Data on KEGG graph
Rendered by Pathview

Figure S5

MAPK Signaling Pathway

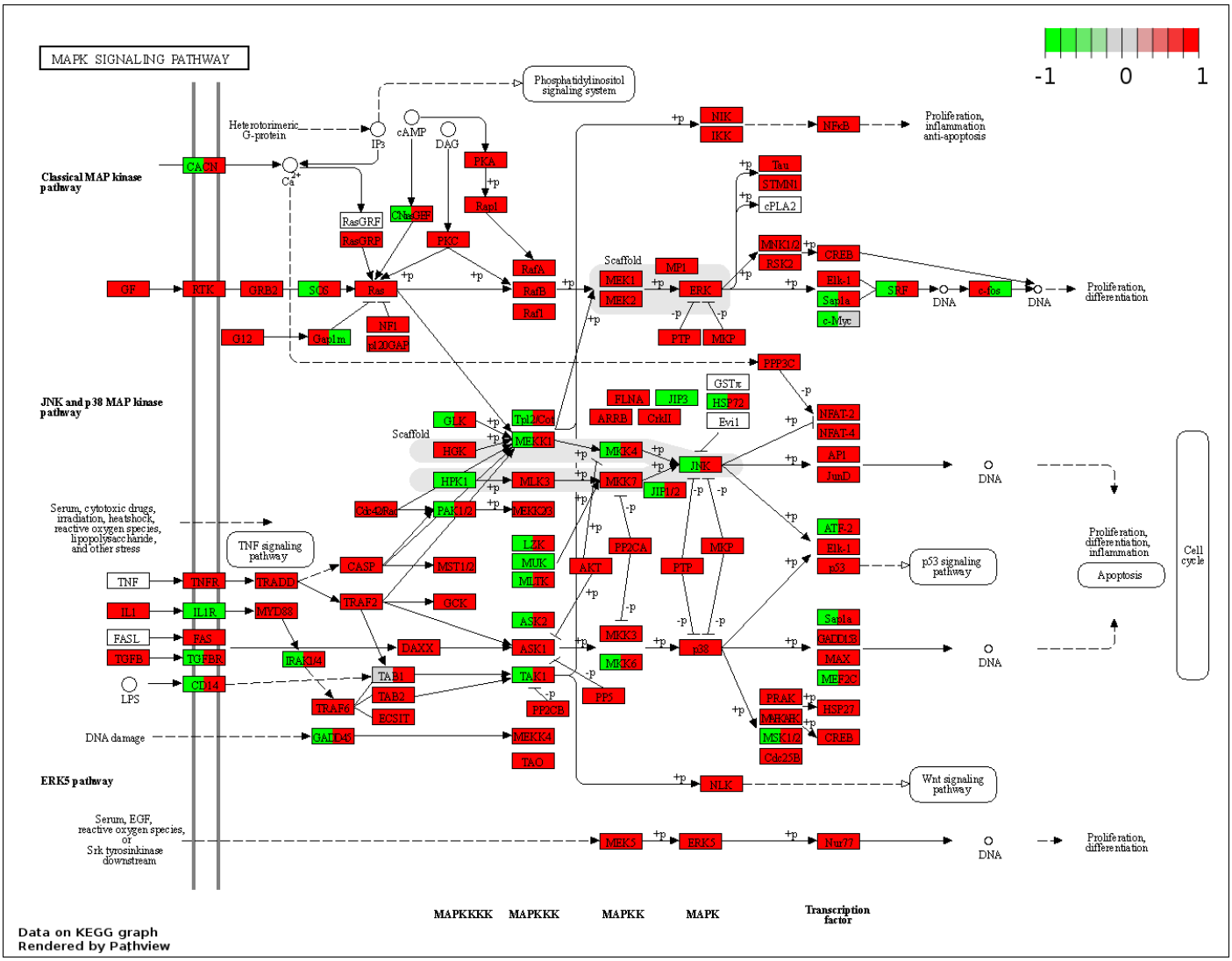
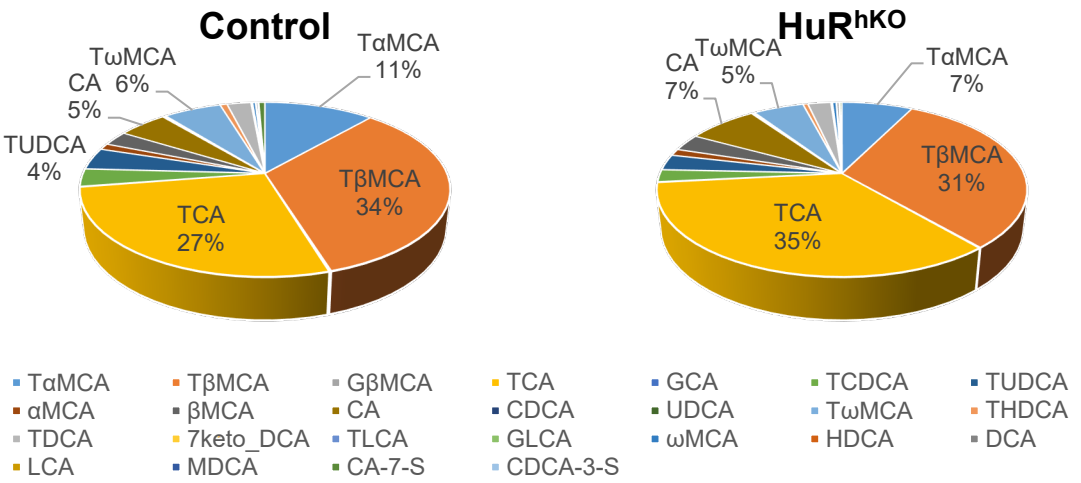
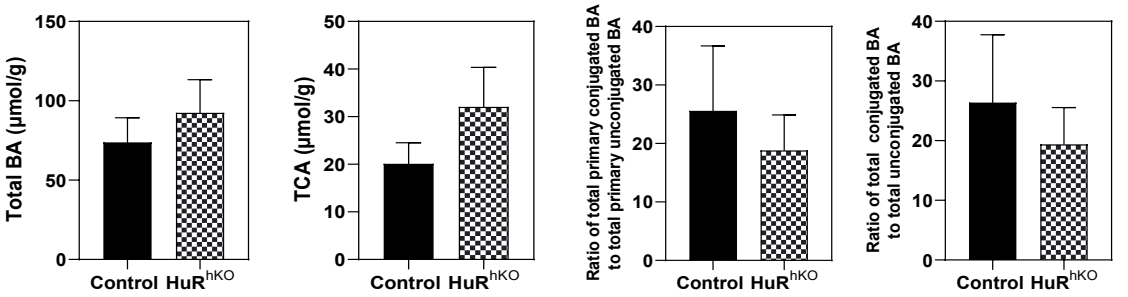


Figure S6

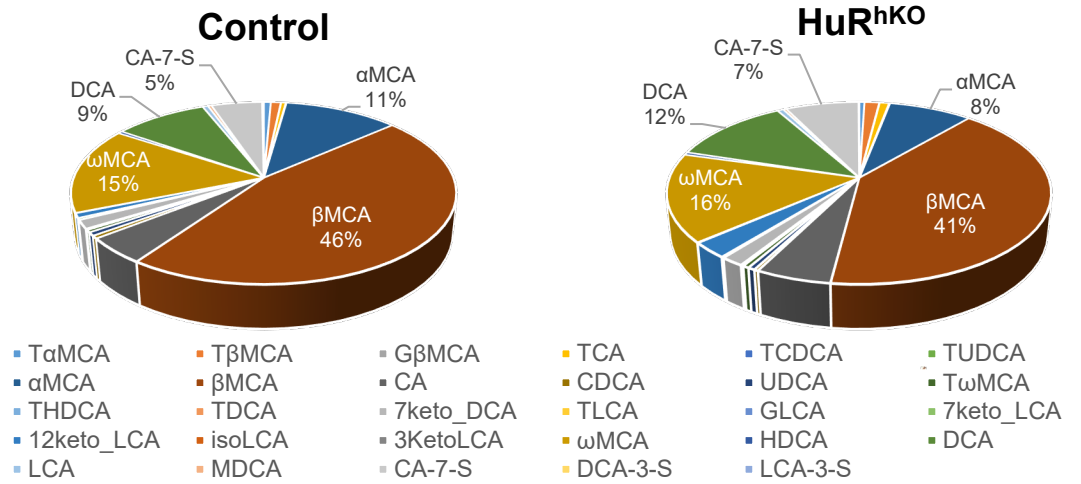
a Bile acid composition in intestinal contents



b Bile acids in intestinal contents



c Bile acid composition in cecal contents



d Bile acids in cecal contents

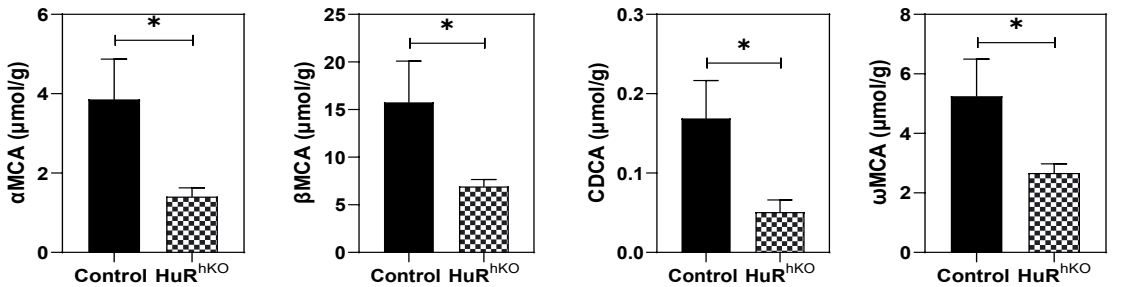


Figure S7

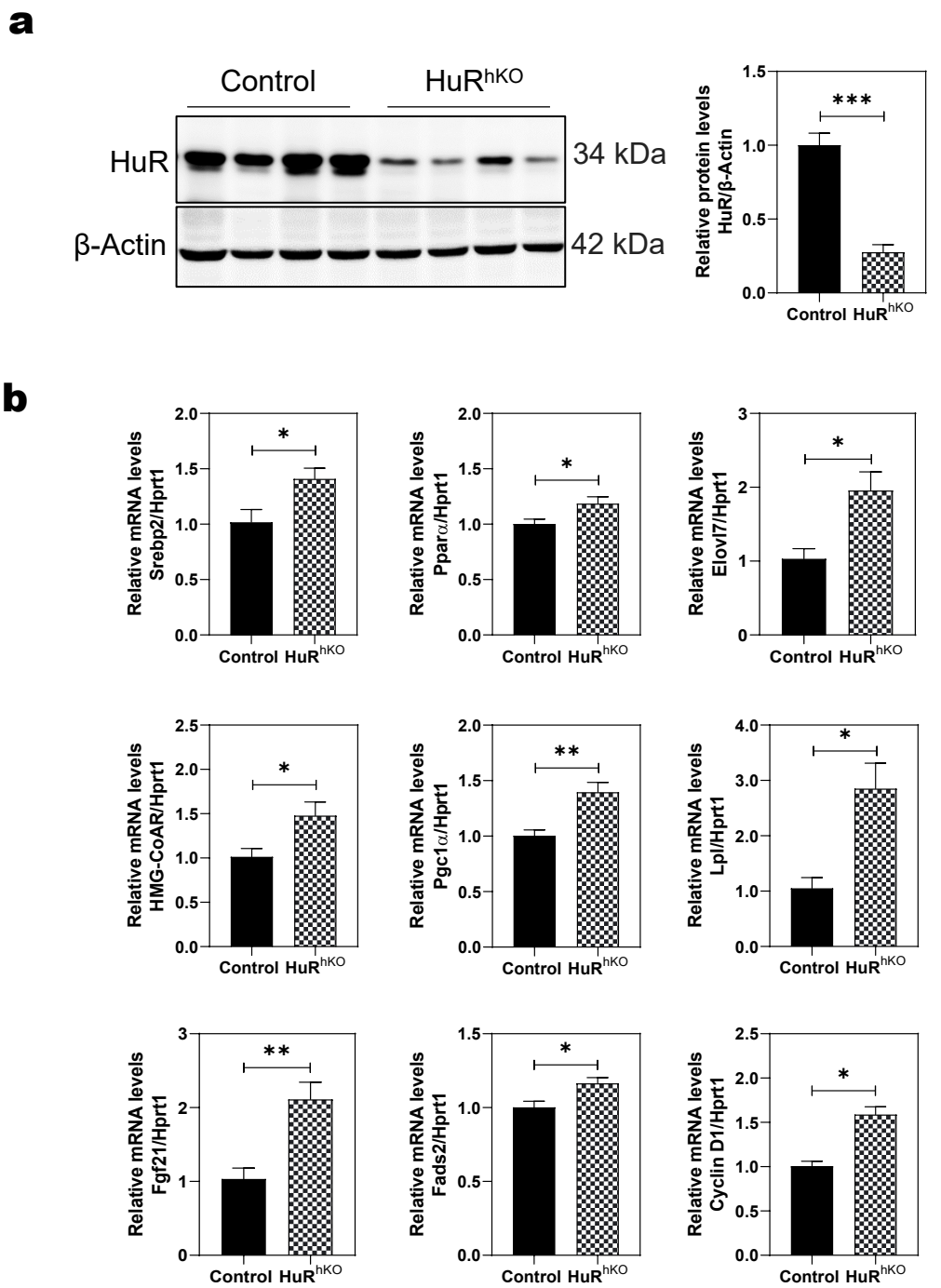

a
Control
HuR^hKO
HuR
β-Actin
34 kDa
42 kDa
Relative protein levels HuR/β-Actin
***
Control HuR^hKO
b
Relative mRNA levels Srebp2/Hprt1
Relative mRNA levels Pparα/Hprt1
Relative mRNA levels Elovl7/Hprt1
Relative mRNA levels HMG-CoAR/Hprt1
Relative mRNA levels Pgc1α/Hprt1
Relative mRNA levels Lpl/Hprt1
Relative mRNA levels Fgf21/Hprt1
Relative mRNA levels Fads2/Hprt1
Relative mRNA levels Cyclin D1/Hprt1
Control HuR^hKO

Figure S8

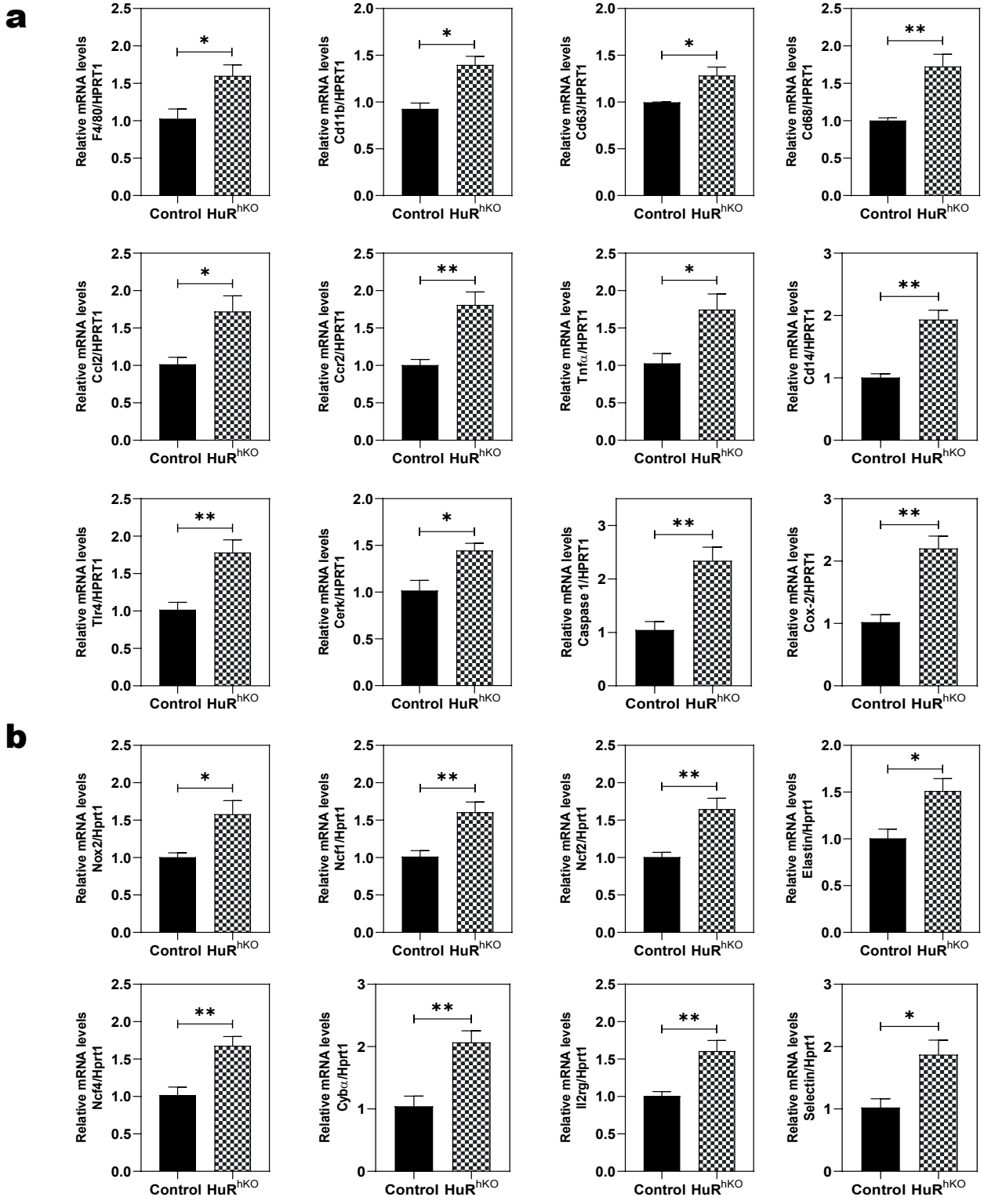
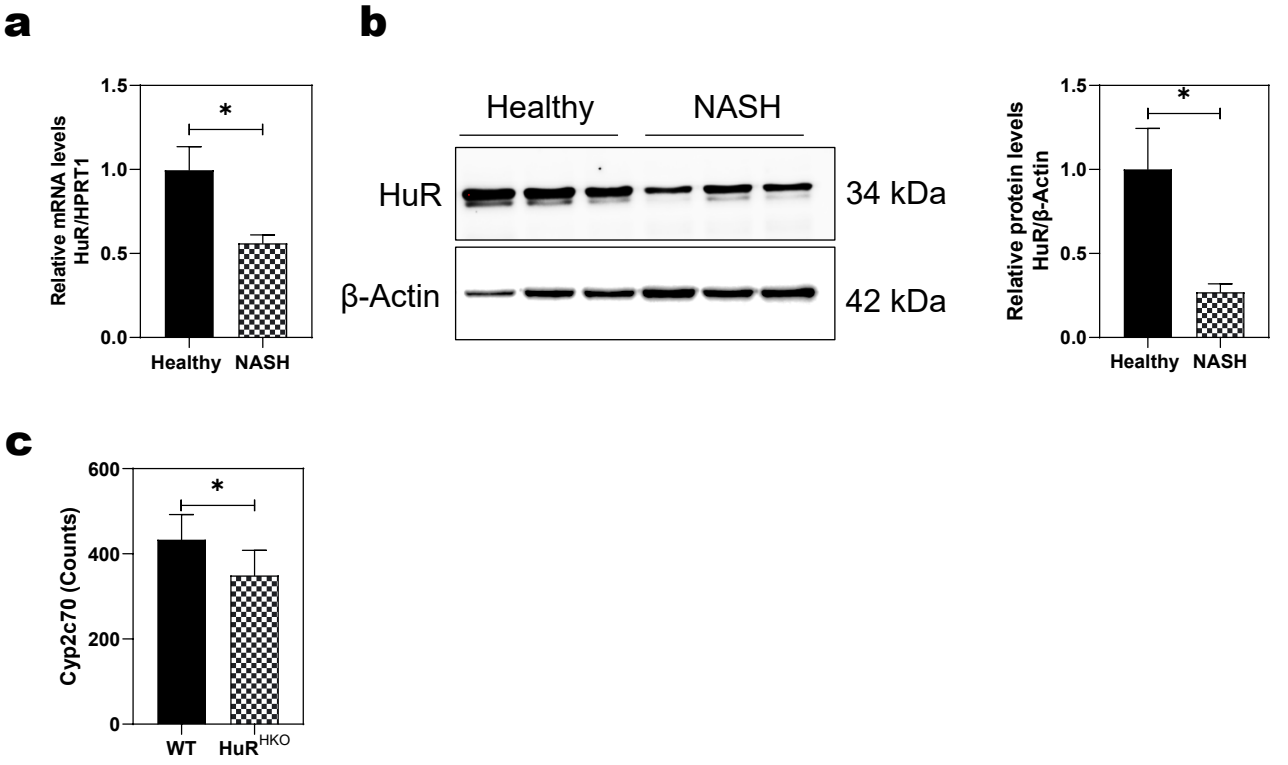

a
Relative mRNA levels F4/80/HPRT1
Relative mRNA levels Cd11b/HPRT1
Relative mRNA levels Cd63/HPRT1
Relative mRNA levels Cd68/HPRT1
Relative mRNA levels Ccl2/HPRT1
Relative mRNA levels Ccr2/HPRT1
Relative mRNA levels Tnfα/HPRT1
Relative mRNA levels Cd14/HPRT1
Relative mRNA levels Tlr4/HPRT1
Relative mRNA levels Cerk/HPRT1
Relative mRNA levels Caspase 1/HPRT1
Relative mRNA levels Cox-2/HPRT1
b
Relative mRNA levels Nox2/Hprt1
Relative mRNA levels Ncf1/Hprt1
Relative mRNA levels Ncf2/Hprt1
Relative mRNA levels Elastin/Hprt1
Relative mRNA levels Ncf4/Hprt1
Relative mRNA levels Cybα/Hprt1
Relative mRNA levels Il2rg/Hprt1
Relative mRNA levels Selectin/Hprt1
Control
HuR hKO

Figure S9


a
b
Relative mRNA levels
HuR/HPRT1
1.5
1.0
0.5
0.0
*
Healthy
NASH
Healthy
NASH
HuR
34 kDa
β-Actin
42 kDa
Relative protein levels
HuR/β-Actin
1.5
1.0
0.5
0.0
*
Healthy
NASH
c
Cyp2c70 (Counts)
600
400
200
0
*
WT
HuR^HKO

Raw images

Fig. 5a

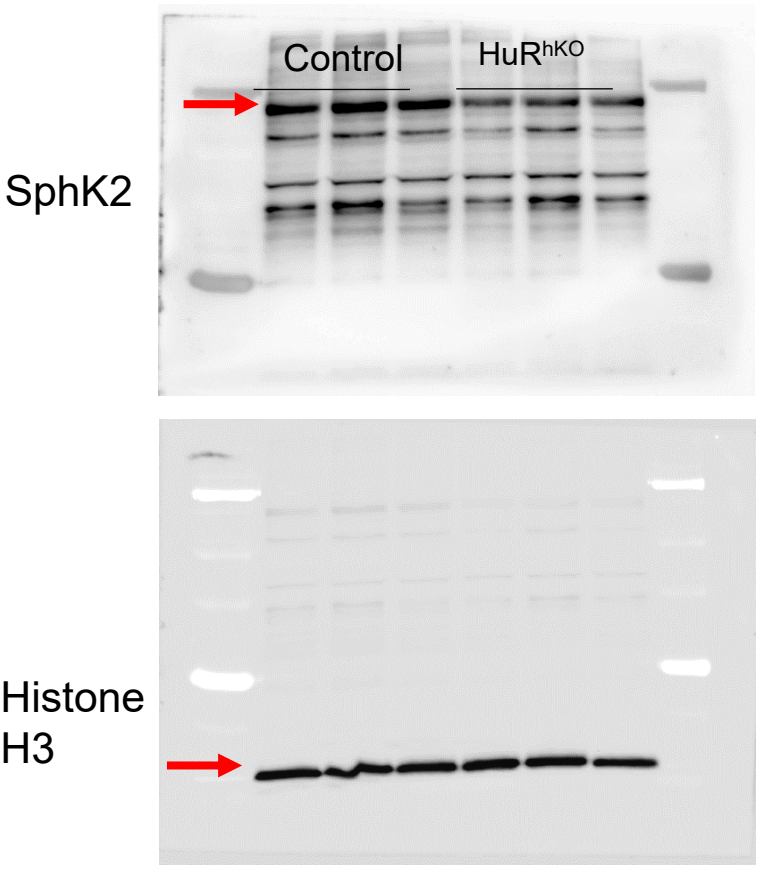


Fig. 5b

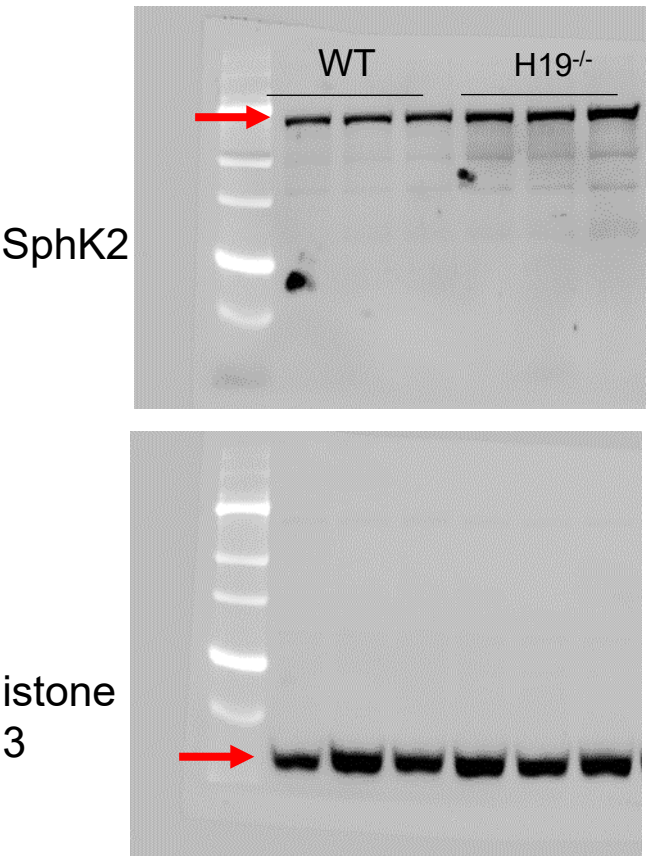


Fig. 5d

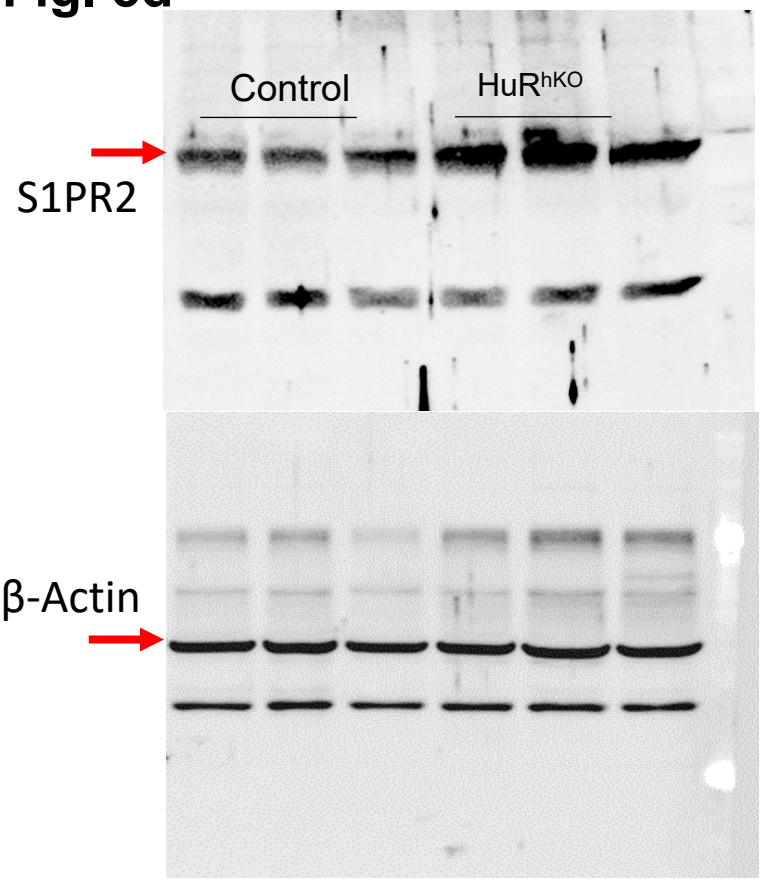


Fig. 8b