SUPPLEMENTAL INFORMATION

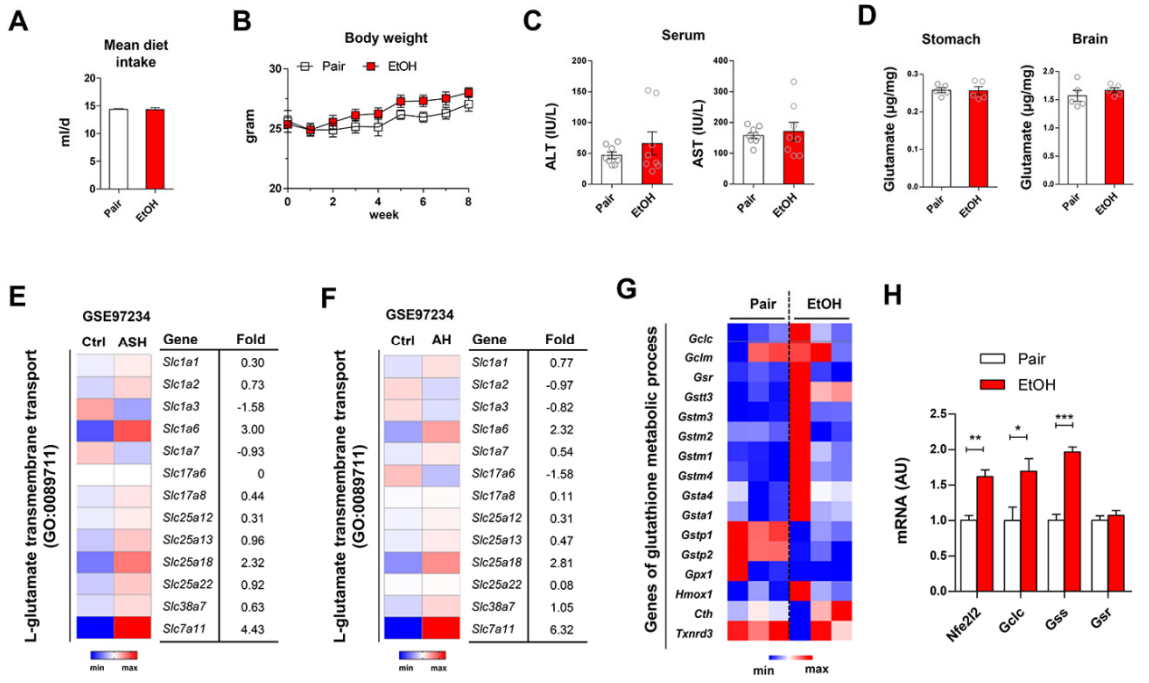

Figure S1. Related Figure 1. Induction of hepatic glutamate transporter xCT and glutathione synthetic gene expression by alcohol consumption.

(A) Mean diet intake of WT C57BL/6J mice fed with Pair or EtOH diet for 8 weeks (n = 8/group; 2 replicates).

(B) Body weight changes (n = 8/group).

(C) Serum levels of AST and ALT (n = 8/group).

(D) Glutamate concentrations in stomach and brain (n = 5/group) of WT mice fed with Pair or EtOH diet for 8 weeks.

(E and F) RNA sequencing data (GEO accession number: GSE97234) of mouse livers with control (n = 3), alcoholic steatohepatitis (ASH, n = 3) and alcoholic hepatitis (AH, n = 3). Heatmap representation of genes annotated by GO:0089711 (L-glutamate transmembrane transport) in control vs ASH (A) or AH (B).

(G) Heatmap showing differentially expressed genes related to glutathione metabolic processes in WT mice (n = 3/group).

(H) Relative mRNA expression of *Nfe2l2*, *Gclc*, *Gss*, and *Gsr* in isolated HEPs from WT mice (n = 4/group). Values represent the results from three experimental replicates.

Data are presented as mean ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

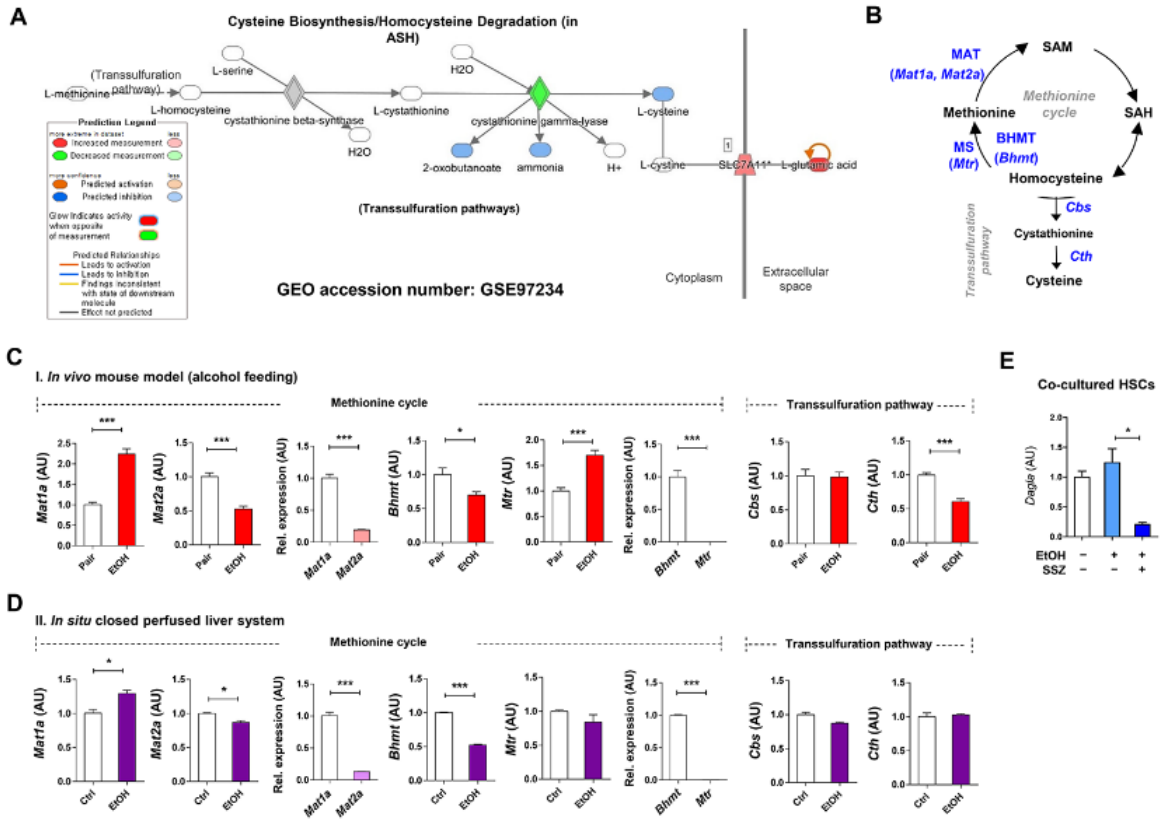

Figure S2. Related Figure 3. mRNA expression of methionine cycle and transsulfuration pathway-related genes in the liver of pair-fed and EtOH-fed mice.

(A) Ingenuity pathway analysis prediction of cysteine biosynthesis/homocysteine degradation metabolic pathway and xCT interaction analysis using Ingenuity Molecule Activity Predictor in control vs ASH (GEO accession number: GSE97234).

(B) Schematic methionine cycle and transsulfuration pathway and their related genes.

(C and D) Representative mRNA expression of liver tissues in WT mice of Pair (n = 4) and EtOH (n = 6) groups (C) and perfused liver tissues (n = 3/group) with media containing 50 mM ethanol for 2 h (D) were assessed by qRT-PCR.

(E) Relative *Dagla* mRNA expression of co-cultured HSCs with HEPs were assessed after 50 mM ethanol treatment with or without pretreatment of 100 μM SSZ for 18 h (3 replicates).

Data are presented as mean ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

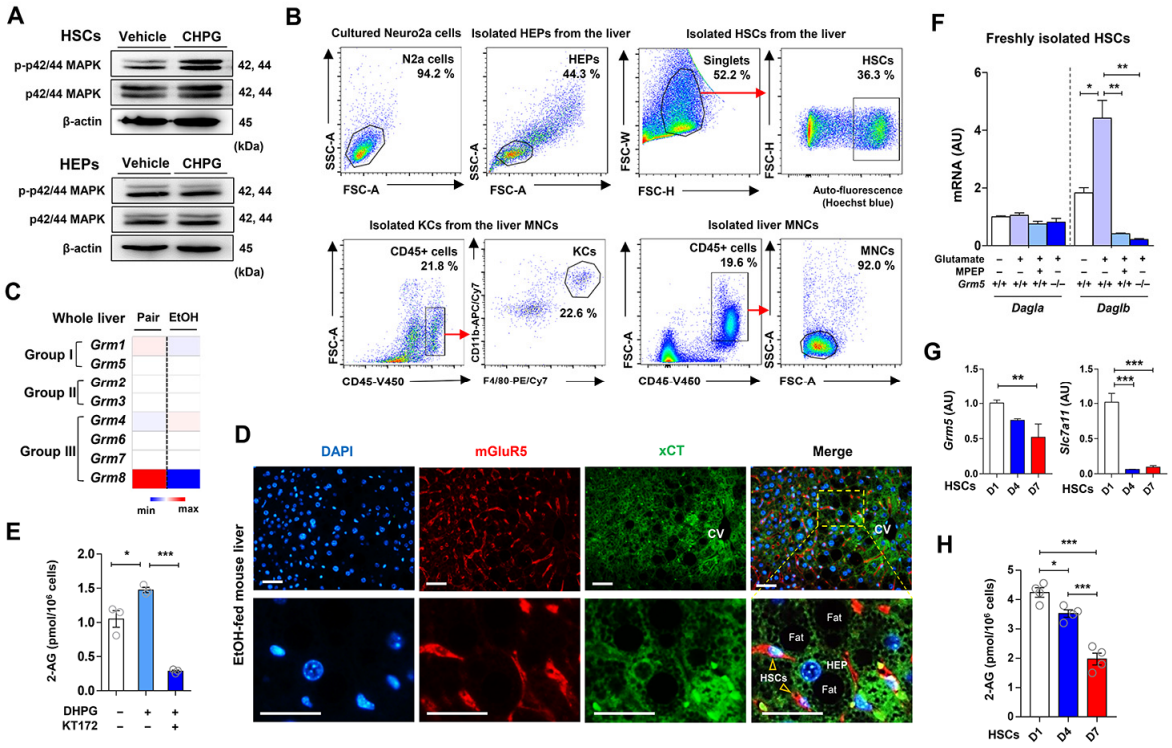

Figure S3. Related Figure 4. Expression of mGluRs in the liver and DAGLβ-dependent 2-AG production of HSCs.

(A) Representative western blotting analysis of MAPK in HSCs and HEPs by 10 μM CHPG for 30 min.

(B) Gating strategy of flow cytometry for Neuro-2a (N2a) cells, HEPs, HSCs, Kupffer cells and liver MNCs. HSCs were purified depending on auto-fluorescence. Among liver MNCs, Kupffer cells were further analyzed with antibodies of CD45, F4/80, and CD11b.

(C) RNA sequencing data of mGluRs in mouse livers of Pair and EtOH groups (n = 3/group).

(D) Representative immunofluorescent staining of mGluR5 and xCT in livers of EtOH-fed mice.

(E) 2-AG production of HSCs by 10 μM DHPG for 1 h with or without 15 min pretreatment of 2 μM KT172, DAGLβ specific inhibitor (n = 3/each, 2 replicates).

(F) Relative mRNA levels of *Dagla* and *Daglb* genes in primary HSCs isolated from WT and mGluR5$^{-/-}$ mice. HSCs were incubated with vehicle or 50 μM MSG for 30 min. 10 μM MPEP were treated 30 min prior to the treatment with MSG (3 replicates).

(G) Relative mRNA levels of *Grm5* and *Slc7a11* genes in cultured WT HSCs for 7 days (4 replicates).

(H) 2-arachidonoylglycerol (2-AG) levels in HSCs as in (G).

Data are presented as mean ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001. Scale bars, 25 μm.

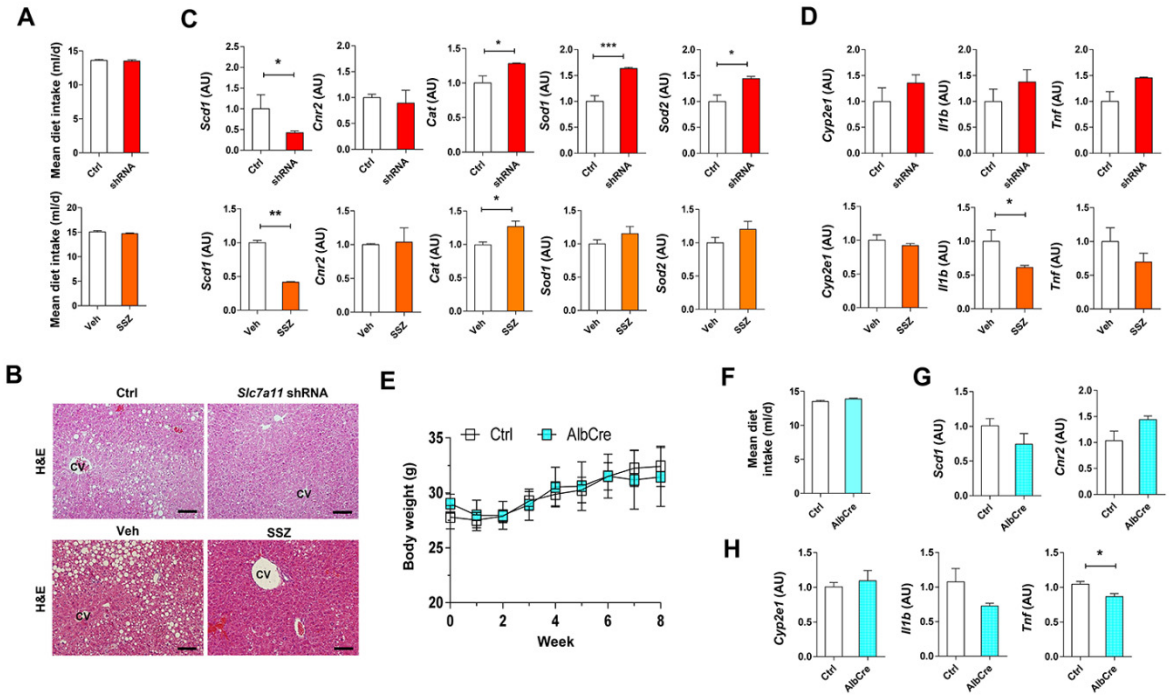

Figure S4. Related Figure 5. Inhibition of hepatic xCT by *Slc7a11* shRNA, sulfasalazine or genetic depletion attenuates alcoholic steatosis.

(A) Mean diet intake (ml/day) of shRNA- (n = 5/group; 2 replicates) or SSZ- (n = 4/group; 2 replicates) treated mice with their corresponding controls during entire experimental periods.

(B) Representative H&E stainings on the liver tissue sections of shRNA- or SSZ-treated mice with their corresponding controls.

(C) Hepatic mRNA expression of *Scd1, Cnr2, Cat, Sod1,* and *Sod2* in shRNA- or SSZ-treated mice with their corresponding controls.

(D) Hepatic mRNA expression of *Cyp2e1*, *Il1b* and *Tnf* in shRNA- or SSZ-treated mice and their corresponding controls.

(E) Body weight changes of WT control and hepatocyte-specific xCT KO (AlbCre) mice.

(F) Mean diet intake (ml/day) of WT and AlbCre mice (n = 4/group; 2 replicates) during entire experimental periods.

(G-H) Hepatic mRNA expression of *Scd1, Cnr2, Cyp2e1, Il1b,* and *Tnf* in WT and AlbCre mice (n = 4/group).

Data are presented as mean ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Scale bars, 50 μm.

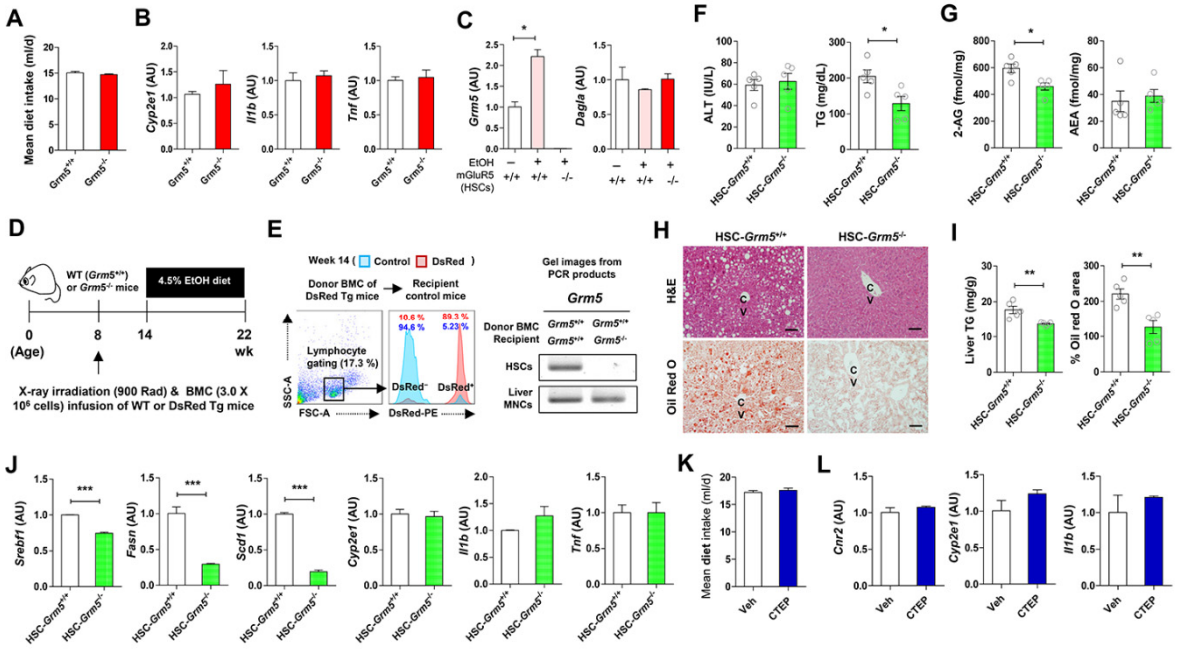

Figure S5. Related Figure 6. Effects of genetic or pharmacologic inhibition of mGluR5 in alcoholic steatosis.

(A-B) *Grm5*$^{-/-}$ and *Grm5*$^{+/+}$ mice were fed with ethanol diet for 8 weeks (n = 5/group; 3 replicates). Volume of mean diet intake (A), and representative hepatic expression of *Cnr2*, *Cyp2e1*, *Il1b* and *Tnf* mRNA levels (B) were measured.

(C) Representative *Grm5* and *Dagla* mRNA expression in co-cultured HSCs was assessed by qRT-PCR (3 replicates).

(D-J) Schematic for the experimental protocol. Chimeric mice were generated by bone marrow cell (BMC) transplantation isolated from *Grm5*$^{+/+}$ mice to *Grm5*$^{-/-}$ and *Grm5*$^{+/+}$ mice. 8 weeks old mice were irradiated with X-ray (900 Rad) and then infused with 3 × 10^6 BMCs of WT or DsRed Tg mice via tail vein injection. At week 6 after BMC transplantation, mice were fed with ethanol diet for additional 8 weeks (*n* = 5/group; 2 replicates).

(E) After BMC transplantation, FACS and PCR analyses were performed on isolated liver MNCs and HSCs to confirm chimerism. Depending on *Grm5* depletion in HSCs, mice were designated as HSC-*Grm5*$^{+/+}$ or HSC-*Grm5*$^{-/-}$.

(F) Representative serum levels of ALT, and TG were assessed (*n* = 5/group; 2 replicates).

(G) Representative hepatic levels of 2-AG and AEA were measured (*n* = 5/group; 2 replicates).

(H) Representative H&E and Oil Red O stainings.

(I) Representative liver TG levels and percentage of Oil Red O-stained areas (*n* = 5/group; 2 replicates).

(J) Representative expression of *Srebf1*, *Fasn, Scd1, Cyp2e1*, *Il1b* and *Tnf* mRNA levels (*n* = 3/group; 2 replicates).

(K and L) CTEP (2 mg kg^{-1} body weight) was administered to WT mice per os every other day for the last four weeks of ethanol feeding (*n* = 7/group). Volume of mean diet intake (K), and representative hepatic expression of *Cnr2*, *Cyp2e1*, and *Il1b* mRNA levels (L) were measured (3 replicates).

Data are presented as mean ± SEM. **P* < 0.05, ***P* < 0.01, ****P* < 0.001. Scale bars, 50 μm.

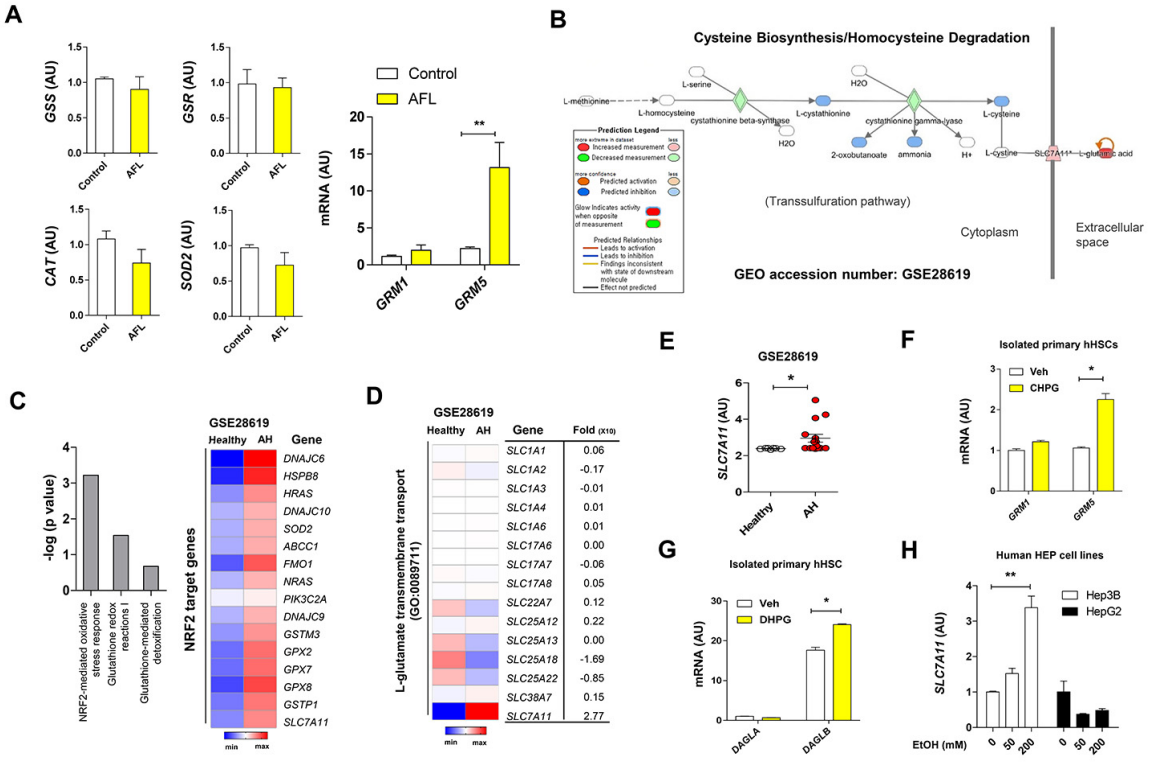

Figure S6. Related Figure 7. Increased hepatic mRNA expression of *GRM5*, *SLC7A11*, and *DAGLB* genes in patients with AFL.

(A) Relative mRNA levels of *GSS*, *GSR, CAT, SOD2, GRM1* and *GRM5* genes in controls (n = 4) and patients with AFL (n = 4).

(B) Ingenuity Pathway Analysis prediction of cysteine biosynthesis/homocysteine degradation metabolic pathway and xCT interaction analysis using Ingenuity Molecule Activity Predictor in patients with AH (GEO accession number: GSE28619).

(C-E) IPA of canonical pathways most enriched in sets of genes of the liver from patients with AH and heatmap representation of genes controlled by NRF2 (C), heatmap representation of genes annotated by GO:0089711 (L-glutamate transmembrane transport) (D), and relative *SLC7A11* mRNA expression (E) in healthy controls and patients with AH (GEO accession number: GSE28619).

(F) Relative mRNA levels of *GRM1* and *GRM5* genes in isolated primary hHSCs treated with 10 μM CHPG for 30 min (3 replicates).

(G) Relative mRNA levels of *DAGLA* and *DAGLB* genes in isolated primary hHSCs treated with vehicle or 10 μM DHPG for 30 min (3 replicates).

(H) Relative expression of *SLC7A11* mRNA in Hep3B cells and HepG2 cells after treatment with or without 50 mM ethanol for 24 h (3 replicates).

Data are presented as mean ± SEM. *$P < 0.05$, **$P < 0.01$.

Table S1. Related Figure 7. Clinical characteristics of patients with alcoholic liver disease.

Variables	Mean ± SEM or percentage					
	Healthy (n=4)	**AWLD (n=8)**	**AFL (n=6)**	**ASH (n=6)**	**ALC (n=6)**	**ASH on LC (n=7)**
Age (years)	35.0±1.1	60.7±4.3	64.7±4.2	49.7±6.8	56.5±5.0	59.2±4.2
Male (%)	100	100	100	83	100	86
Body weight (kg)	75.0±2.7	61.6±2.7	64.4±4.3	59.1±2.9	67.9±5.2	66.8±7.4
MDF	-	5.0±1.2	3.8±1.0	14.4±7.7	24.8±6.4	29.8±11.1
MELD score	-	6.1±0.6	5.3±0.9	12.5±2.5	12.7±2.3	16.1±2.4
ABIC score	-	7.3±0.4	7.6±0.4	6.6±0.7	7.3±0.3	7.8±0.6
Alcohol intake (g/d)	4.0±2.1	64.1±11.5	99.6±24.2	82.5±24.3	130.9±46.4	110.7±26.6
Creatinine (mg/dl)	1.00±0.06	0.83±0.05	0.85±0.07	0.89±0.19	0.81±0.06	0.69±0.06
AST (U/L)	23.3±0.6	21.7±1.8	23.7±5.2	96.7±29.1	55.3±12.3	108.2±17.3
ALT (U/L)	22.3±2.3	18.7±5.4	13.8±2.8	62.7±18.8	28.5±7.4	34.4±5.9
GGT (U/L)	21.3±1.8	56.7±20.8	55.2±14.5	376.2±93.2	85.0±31.5	264.4±106.8
Bilirubin (mg/dl)	0.80±0.06	0.73±0.09	0.68±0.17	5.43±3.71	2.63±1.28	4.62±1.18
Albumin (mg/dl)	4.58±0.03	4.00±0.13	3.90±0.22	3.53±0.25	3.37±0.33	3.08±0.23
Platelet count ($\times 10^3/\mu l$)	191.8±11.6	207.0±11.6	167.8±26.9	183.2±38.6	95.8±26.4	174.2±96.3
Leucocytes count ($\times 10^3/\mu l$)	5.83±0.66	5.44±0.41	6.47±0.81	6.67±0.82	5.59±1.07	8.69±3.53
ANC (mm^3)	3097.2±181.0	3163.1±401.0	4100.2±585.4	4122.0±668.6	3532.8±789.7	6428.0±3316.2
PT INR	-	1.10±0.02	1.07±0.03	1.22±0.09	1.51±0.12	1.57±0.24

Abbreviations: ABIC score, age-bilirubin-INR-creatinine score; AFL, alcoholic fatty liver; ALC, alcoholic liver cirrhosis; ALT, alanine aminotransferase; ANC, absolute neutrophil count; ASH, alcoholic steatohepatitis; AST, aspartate aminotransferase; AWLD, alcoholics without liver disease; GGT, gamma-glutamyl transferase; LC, liver cirrhosis; MDF, Maddrey's discriminant function; MELD, model for end-stage liver disease; PT INR, prothrombin time international normalized ratio

Table S2. Related Figure 7. Clinical characteristics of patients with fresh liver biopsy samples.

Patients		Ctrl#1	Ctrl#2	Ctrl#3	Ctrl#4	AFL#1	AFL#2	AFL#3	AFL#4
Clinical parameters	Age	32	70	71	56	74	71	59	34
	Sex	F	M	M	M	M	M	M	M
	Alcohol intake (gr/d)	0	7.0	0	0	37.7	141.3	78.5	56.5
	ALT (IU/L)	9	27	38	12	27	15	11	45
	PT INR	1.00	1.00	0.90	1.10	1.12	1.14	0.95	1.00
	Bilirubin (mg/dl)	0.9	1.6	0.8	2.3	0.5	0.7	0.5	1.0
	Albumin (mg/dl)	3.8	3.7	4.5	4.3	3.8	4.2	4.5	3.5
	Creatinine (mg/dl)	0.70	0.99	0.55	0.91	0.87	0.91	1.00	0.66
Pathology	Steatosis	No	No	Mild	No	Moderate	Moderate	Moderate	Moderate
	Lobular inflammation	No	No	No	Mild	No	Mild	No	No
	Hepatocyte ballooning	No	No	No	No	No	Mild	No	No
Remarks		WB, PCR	WB, PCR	WB, PCR	WB, PCR, Cell isolation	WB, PCR	WB, PCR	WB, PCR	WB, PCR

Abbreviations: AFL, alcoholic fatty liver; ALT, alanine aminotransferase; Ctrl, Control; PT INR, prothrombin time international normalized ratio. † Remarks. **Ctrl#1**: patient with liver resection for focal nodular hyperplasia; **Ctrl#2**: patient with liver resection for hepatocellular carcinoma in normal liver; **Ctrl#3**: patient with liver resection for hepatocellular carcinoma in mild steatotic liver; **Ctrl#4**: inactive carrier for hepatitis B with liver resection for hepatocellular carcinoma without any evidence of advanced fibrosis or cirrhosis

Table S3. Related to STAR Methods. Primer sequences for qPCR.

For qPCR in mouse samples:

Genes	Forward	Reverse
18S	ACA GGA TTG ACA GAT TGA TAG C	GCC AGA GTC TCG TTC GTT A
Actb	GTT ACC AAC TGG GAC GAC	CTC AAA CAT GAT CTG GGT CA
Aldh4a1	TGC AGC CGA ACT CAT CGA CTT	TGC CAG GTT GCC TCC AAT C
Bhmt	CTC AGA GCT GGA TCG AAC GTC	CCG TGC AAT GTC ACA AGC AG
Cat	GGA GGC GGG AAC CCA ATA G	GTG TGC CAT CTC GTC AGT GAA
Cbs	GGA AAA TTG GGA ACA CCC CTA T	CCA CCC GCA TTG AAG AAC TCA
Cnr1	ACA GGG CAG TAC CCC TTC TT	AGC CCC TGG TGG TAT TCT CT
Cnr2	ACG GTG GCT TGG AGT TCA AC	GCC GGG AGG ACA GGA TAA T
Cth	TTG GAT CGA AAC ACC CAC AAA	AGC CGA CTA TTG AGG TCA TCA
Cyp2e1	CCA CCC TCC TCC TCG TAT	CTT GAC AGC CTT GTA GCC
Dagla	TTC GCC GAG TTC ATT GAC AG	TCT CAG GCA CCA TCA TGC A
Daglb	AGC GAC GAC TTG GTG TTC C	GCG TGA GAT ACA ACG TCA GAC T
Fasn	TGG GTT CTA GCC AGC AGA GT	ACC ACC AGA GAC CGT TAT GC
Gclc	GGA CAA ACC CCA ACC ATC C	GTT GAA CTC AGA CAT CGT TCC T
Glud1	CCC AAC TTC TTC AAG ATG GTG G	AGA GGC TCA ACA CAT GGT TGC
Glul	TGA ACA AAG GCA TCA AGC AAA TG	CAG TCC AGG GTA CGG GTC TT
Gls1	CTA CAG GAT TGC GAA CAT CTG AT	ACA CCA TCT GAC GTT GTC TGA
Gls2	TCA GGC ATT CCG AAA GAA GTT T	CAG AAG GGG ATC TTC GTG TGG
Grm1	TGG AAC AGA GCA TTG AGT TCA TC	CAA TAG GCT TCT TAG TCC TGC C
Grm5	AGA AAC CCA TAG TGG GAG TCA T	ATG CTA GTT GCA GAG TAA GCA AT
Gsr	GCG TGA ATG TTG GAT GTG TAC C	GTT GCA TAG CCG TGG ATA ATT TC
Gss	GGG CCT GAA TCG CTC AGA TTA	CAG GAC ATT GAG AAC GTG TCG
Il1b	GCC CAT CCT CTG TGA CTC AT	AGG CCA CAG GTA TTT TGT CG
Mat1a	GTG CTG GAT GCT CAC CTC AAG	CCA CCC GCT GGT AAT CAA CC
Mat2a	CAA CAA GAC CCT GAT GCT AAA GT	AGG CAA CCA ACA CAT TAC AAG T
Mtr	TCC TCC TCG GCC TAT CTT TAT TT	GGT CCG AAT GAG ACA CGC T
Nfe2l2	CTT TAG TCA GCG ACA GAA GGA C	AGG CAT CTT GTT TGG GAA TGT G
Oat	TGC CAC CCA AAG ATC ATA GAT GC	TGT ACT CCT CGT ATT CAC CAA GG
Prodh	ATC CGG CAC AAC AAA GCC TT	GCT TCA TTG GCA TAG AAG TAG GT
Pycr2	TCC TGT ATC CGA ACC AGA GA	GGG TTT CTT GTA AGG AGT TT
Scd1	TTC TTG CGA TAC ACT CTG GTG C	CGG GAT TGA ATG TTC TTG TCG T
Slc7a11	GAT GGT CCT AAA TAG CAC GAG TG	GGG CAA CCC CAT TAG ACT TGT
Sod1	AAC CAG TTG TGT TGT CAG GAC	CCA CCA TGT TTC TTA GAG TGA GG
Sod2	CAG ACC TGC CTT ACG ACT ATG G	CTC GGT GGC GTT GAG ATT GTT
Srebf1	CTT AAC GTG GGC CTA GTC CGA AGC C	CCA GTT CGC ACA TCT CGG CCA
Tnf	AAG CCT GTA GCC CAC GTC GTA	AAG GTA CAA CCC ATC GGC TGG

For qPCR in human samples:

Genes	Forward	Reverse
ACTB	AGC GAG CAT CCC CCA AAG TT	GGG CAC GAA GGC TCA TCA TT
ALDH4A1	CCA TCT CGC CCT TTA ACT TCA C	ACT GGG CTT CCA TAG GAC CA
CAT	GTT ACT CAG GTG CGG GCA TTC TAT	GAA GTT CTT GAC CGC TTT CTT CTG
CBS	GGG GCT GAG ATT GTG AGG AC	CGG TAC TGG TCT AGG ATG TGA
CNR1	TTA CAA CAA GTC TCT CTC GTC CT	GGC TGC CGA TGA AGT GGT A
CTH	CAT GAG TTG GTG AAG CGT CAG	AGC TCT CGG CCA GAG TAA ATA
DAGLA	CCT CAC TGC CAA GAA TGT CA	CAG GTT GTA GGT CCG CAG GTT A
DAGLB	AGT CTG TTG TGG TCG CTG TG	AAT CCC GTC GTT GAT GAG TC
FASN	TGC TCC CAG CTG CAG GC	GCC CGG TAG CTC TGG GTG TA
GCLC	GGA GAC CAG AGT ATG GGA GTT	CCG GCG TTT TCG CAT GTT G
GRM1	CCA GCG ATC TTT TTG GAG GTG	TGG TGA TGG ACT GAG AAG AGG
GRM5	ATG CCG GGT GAC ATC ATT ATT G	TGA ATG CCA TAC TGT TCA CGG
GSR	ATC CCC GGT GCC AGC TTA GG	AGC AAT GTA ACC TGC ACC AAC AA
GSS	ACT CAC TGG ATG TGG GTG AAG AAG	TCC TCC CCA TAT AGG TTG TTA CCT C
SLC7A11	GGT CCA TTA CCA GCT TTT GTA CG	AAT GTA GCG TCC AAA TGC CAG
SOD2	CTC CCC GAC CTG CCC TAC GAC TAC	AAA CCA AGC CAA CCC CAA CCT GAG
SREBF1	CGG AAC CAT CTT GGC AAC AGT	CGC TTC TCA ATG GCG TTG T

Table S4. Related to STAR Methods. Summary of the statistics for the main figures with statistical significance

Figures	Sample (size)	Statistical method	Statistical values
Figure 1A	Pair, n=8; EtOH, n=8	Unpaired t-test, two-sided	Serum: df=14, t=4, P<0.01
	Pair, n=8; EtOH, n=8		Liver: df=14, t=4.15, P<0.01
Figure 1B	Pair, n=8; EtOH, n=8	Linear regression	Liver TG: r^2=0.62, P<0.001
	Pair, n=8; EtOH, n=8		*Fasn* mRNA: r^2=0.80, P<0.001
Figure 1G	3 biologic replicates	One-way ANOVA with multiple comparisons	Column A vs. B, q=10.22, adjusted P<0.001
			Column A vs. C, q=28.76, adjusted P<0.001
Figure 1H	Pair, n=8; EtOH, n=8	Unpaired t-test, two-sided	df=14, t=6.254, P<0.001
Figure 2A	Pair, n=8; EtOH, n=8	Unpaired t-test, two-sided	*Glud1*: df=14, t=7.62, P<0.001
			Oat: df=14, t=6.34, P<.0.001
			Aldh4a1: df=14, t=6.37, P<0.001
			Glul: df=14, t=6.11, P<0.001
Figure 2B	Pair, n=4; EtOH, n=4	Unpaired t-test, two-sided	*Glul*: df=4, t=3.32, P=0.029
			Oat: df=4, t=3.36, P=0.028
			Aldh4a1: df=4, t=8.52, P<0.01
			Glud1: df=4, t=5.75, P<0.01
Figure 2D	Pair, n=8; EtOH, n=8	Unpaired t-test, two-sided	df=14, t=2.37, P=0.033
Figure 2F	3 biologic replicates	One-way ANOVA with multiple comparisons	*Glud1*: 0 vs. 50: q=3.92, adjusted P=0.0272
			Aldh4a1:
			0 vs. 10: q=4.87, adjusted P=0.010
			0 vs. 20: q=4.87, adjusted P=0.010
			0 vs. 50, q=6.17, adjusted P=0.003
			0 vs. 100, q=5.38, adjusted P=0.006
			0 vs. 200, q=9.90, adjusted P<0.001
Figure 3B	Pair, n=4; EtOH, n=6	Unpaired t-test, two-sided	methionine: df=8, t=3.71, P<0.01
			homocysteine: df=8, t=2.86, P=0.021
			cysteine: df=8, t=5.51, P<0.001
			GSH: df=8, t =1.91, P=0.046
			homocysteine (serum): df=8, t=2.04, P=0.038
Figure 3D	Ctrl, n=3; EtOH, n=3	Unpaired t-test, two-sided	methionine: df=4, t=3.77, P=0.020
			SAH: df=4, t=3.77, P=0.020
			homocysteine: df=4, t=2.97, P=0.041
			cystathionine: df=4, t=6.13, P<0.01
			cysteine: df=4, t=3.63, P=0.022
			GSH: df=4, t=5.98, P<0.01
			ALT: df=4, t=10, P<0.001
			glutamate: df=4, t=47.03, P<0.001
Figure 3F	3 biologic replicates	One-way ANOVA with multiple comparisons	glutamate:
			Column B vs. A, q=16.42, adjusted P<0.01
			Column B vs. C, q=38.72, adjusted P<0.001
			cystine:
			Column B vs. A, q=3.46, adjusted P<0.05
			Column B vs. C, q=4.23, adjusted P<0.01
Figure 3G	3 biologic replicates	One-way ANOVA with multiple comparisons	Column B vs. A, q=7.17, adjusted P<0.001
			Column B vs. C, q=13.69, adjusted P<0.001
Figure 3H	3 biologic replicates	One-way ANOVA with multiple comparisons	*Cnr1*:
			Column B vs. A, q=5.01, adjusted P<0.01
			Srebf1:
			Column B vs. A, q=6.22, adjusted P<0.01
			Column B vs. C, q=5.68, adjusted P<0.01
			Fasn:
			Column B vs. A, q=6.00, adjusted P<0.01
			Column B vs. C, q=11.12, adjusted P<0.001

Figure 4C	n = 4 for each group	One-way ANOVA with multiple comparisons	Column B vs. A, q=11.54, adjusted P<0.001
			Column B vs. C, q=10.19, adjusted P<0.001
			Column B vs. D, q=11.63, adjusted P<0.001
Figure 4E	3 biologic replicates	Unpaired t-test, two-sided	df=4, t=10.56, P<0.001
Figure 4F	2 biologic replicates	Unpaired t-test, two-sided	df=2, t=5.42, P=0.032
Figure 4G	3 biologic replicates	Unpaired t-test, two-sided	df=6, t=4.53, P<0.01
Figure 4H	Veh, n=5; CHPG, n=5	Unpaired t-test, two-sided	df=8, t=5.55, P<0.001
Figure 4I	4 biologic replicates	Unpaired t-test, two-sided	*Dagla* (15min): df=4, t=3.95, P=0.02
			Daglb (15min): df=4, t=21.58, P<0.001
			Daglb (30min): df=4, t=7.19, P<0.01
Figure 4J	3 biologic replicates	One-way ANOVA with multiple comparisons	Column B vs. A, q=4.39, adjusted P<0.01
			Column B vs. C, q=3.03, adjusted P<0.05
			Column B vs. D, q=3.54, adjusted P<0.05
Figure 4K	2 biologic replicates	One-way ANOVA with multiple comparisons	*Srebf1* (3hr):
			Column B vs. A, q=4.84, adjusted P<0.01
			Column B vs. C, q=7.59, adjusted P<0.001
			Srebf1 (6hr):
			Column B vs. C, q=12.50, adjusted P<0.001
			Fasn (3hr):
			Column B vs. C, q=4.85, adjusted P<0.01
			Fasn (6hr):
			Column B vs. A, q=3.01, adjusted P<0.05
			Column B vs. C, q=5.04, adjusted P<0.01
Figure 5A	2 biologic replicates	Unpaired t-test, two-sided	df = 2, t=10.66, P<0.01
Figure 5D	Ctrl, n=5; shRNA, n=5	Unpaired t-test, two-sided	df=8, t=3.04, P=0.016
	Veh, n=4; SSZ, n=4	Unpaired t-test, two-sided	df = 6, t=5.78, P<0.01
Figure 5E	Ctrl, n=5; shRNA, n=5	Unpaired t-test, two-sided	df=8, t=8.84, P<0.001
	Veh, n=4; SSZ, n=4	Unpaired t-test, two-sided	df=6, t=3.18, P=0.019
Figure 5G	Ctrl, n=4; shRNA, n=4	Unpaired t-test, two-sided	*Cnr1*: df=6, t=2.91, P=0.027
			Srebf1: df=6, t=3.23, P=0.018
			Fasn: df=6, t=2.88, P=0.028
	Veh, n=3; SSZ, n=3	Unpaired t-test, two-sided	*Cnr1*: df=4, t=4.06, P=0.015
			Srebf1: df=4, t=6.22, P<0.01
			Fasn: df=4, t=6.47, P<0.01
Figure 5K	Ctrl, n=3; AlbCre, n=3	Unpaired t-test, two-sided	*Cnr1*: df=6, t=5.80, P<0.01
			Srebf1: df=6, t=3.26, P=0.017
			Fasn: df=6, t=4.17, P<0.01
			Cat: df=6, t=2.82, P=0.030
			Sod1: df=6, t=3.34, P=0.016
Figure 6C	$Grm5^{+/+}$, n=5; $Grm5^{-/-}$, n=5	Unpaired t-test, two-sided	df=8, t=2.63, P=0.030
Figure 6D	$Grm5^{+/+}$, n=5; $Grm5^{-/-}$, n=5	Unpaired t-test, two-sided	df=8, t=4.05, P<0.01
Figure 6G	3 biologic replicates	One-way ANOVA with multiple comparisons	*Daglb* (HSCs):
			Column B vs. A, q=5.23, adjusted P<0.01
			Column B vs. C, q=6.13, adjusted P<0.01
			Srebf1 (HEPs):
			Column B vs. A, q=4.04, adjusted P<0.05
			Column B vs. C, q=4.82, adjusted P<0.01
			Fasn (HEPs):
			Column B vs. A, q=17.02, adjusted P<0.001
			Column B vs. C, q=11.66, adjusted P<0.001
Figure 6K	Veh, n=3; CTEP, n=3	Unpaired t-test, two-sided	*Cnr1*: df=4, t=7.81, P<0.01
			Srebf1: df=4, t=2.86, P=0.046
			Fasn: df=4, t=3.05, P=0.038
			Scd1: df=4, t=7.18, P<0.01
Figure 7A	Healthy, n=4; AWLD, n=8;	One-way ANOVA with multiple comparisons	Column A vs. C, q=2.72, adjusted P<0.05
			Column A vs. D, q=4.08, adjusted P<0.01
Figure 7B	Alcohol patients, n=33	Linear regression	r^2=0.21, P=0.01

Figure 7C	Control, n=4; AFL, n=4	Unpaired t-test, two-sided	*CBS*: df=6, t=3.09, P=0.022
			CTH: df=6, t=3.75, P<0.01
			GCLC: df=6, t=3.35, P=0.015
			SLC7A11: df=6, t=3.52, P=0.013
			GRM5: df=6, t=3.74, P<0.01
			CNR1: df=6, t=3.09, P=0.021
			SREBF1: df=6, t=4.58, P<0.01
			FASN: df=6, t=3.90, P<0.01
Figure 7D	Control, n=4; AFL, n=4	Linear regression	*CNR1*: r^2=0.99, P<0.001
			SREBF1: r^2=0.42, P=0.08
			FASN: r^2=0.69, P=0.01
Figure 7E	Control, n=4; AFL, n=4	Unpaired t-test, two-sided	xCT: df=6, t=2.60, P=0.041
			DAGLβ; df=6, t=2.54, P=0.044
Figure 7G	3 biologic replicates	Unpaired t-test, two-sided	df=4, t=17.16, P<0.001
Figure 7H	Veh, n=3; CHPG, n=3	Unpaired t-test, two-sided	*GRM5*: df=4, t=8.33, P<0.01
			DAGLB: df=4, t=7.12, P<0.01

Table S5. Related to STAR Methods. Summary of the statistics for the supplementary figures with statistical significance

Figures	Sample (size)	Statistical method	Statistical values
Figure S1H	Pair, n=4; EtOH, n=4	Unpaired t-test, two-sided	*Nfe2l2*: df=6, t=5.26, P<0.01
			Gclc: df=6, t=3.36, P=0.015
			Gss: df=6, t=11.26, P<0.001
Figure S2C	Pair, n=4; EtOH, n=6	Unpaired t-test, two-sided	*Mat1a*: df=8, t=7.36, P<0.001
			Mat2a: df=8, t=7.13, P<0.001
			Mat1a vs *Mat2a*: df=6, t=13.93, P<0.001
			Bhmt: df=8, t=3.06, P=0.016
			Mtr: df=10, t=4.72, P<0.001
			Bhmt vs *Mtr*: df=6, t=10.21, P<0.001
			Cth: df=8, t=6.45, P<0.001
Figure S2D	Ctrl, n=3; EtOH, n=3	Unpaired t-test, two-sided	*Mat1a*: df=4, t=3.39, P=0.018
			Mat2a: df=4, t=3.55, P=0.024
			Mat1a vs *Mat2a*: df=2, t=43.25, P<0.001
			Bhmt: df=4, t=30.4, P<0.001
			Bhmt vs *Mtr*: df=2, t=99.8, P<0.001
Figure S2E	3 biologic replicates	One-way ANOVA with multiple comparisons	Column B vs. C: q=6.91, adjusted P=0.033
Figure S3E	3 biologic replicates	One-way ANOVA with multiple comparisons	Column B vs. A: q=4.04, adjusted P=0.014
			Column B vs. C: q=11.32, adjusted P<0.001
Figure S3F	3 biologic replicates	One-way ANOVA with multiple comparisons	*Daglb*:
			Column B vs. A: q=5.66, adjusted P=0.011
			Column B vs. C: q=8.76, adjusted P<0.01
			Column B vs. D: q=9.18, adjusted P<0.01
Figure S3G	4 biologic replicates	One-way ANOVA with multiple comparisons	*Grm5*: q=7.06, adjusted P<0.01
			Slc7a11:
			Column A vs. B: q=13.07, adjusted P<0.001
			Column A vs. C: q=12.61, adjusted P<0.001
Figure S3H	4 biologic replicates	One-way ANOVA with multiple comparisons	Column A vs. B: q=4.33, adjusted P=0.033
			Column A vs. C: q=13.69, adjusted P<0.001
			Column B vs. C: q=9.36, adjusted P<0.001
Figure S4C	Ctrl, n=4; shRNA, n=4	Unpaired t-test, two-sided	*Scd1*: df=7, t=2.68, P=0.032
			Cat: df=6, t=2.76, P=0.033
			Sod1: df=7, t=6.10, P<0.001
			Sod2: df=6, t=3.26, P=0.017
	Veh, n=4; SSZ, n=4	Unpaired t-test, two-sided	*Scd1*: df=4, t=5.48, P<0.01
			Cat: df=4, t=2.88, P=0.045
Figure S4D	Veh, n=4; SSZ, n=4	Unpaired t-test, two-sided	*Il1b*: df=4, t=2.50, P=0.047
Figure S4H	Ctrl, n=3; AlbCre, n=3	Unpaired t-test, two-sided	*Tnf*: df=6, t=3.05, P=0.022
Figure S5C	3 biologic replicates	Unpaired t-test, two-sided	*Grm5:* Column A vs. B: df=2, t=5.88, P=0.028
Figure S5F	HSC-*Grm5*$^{+/+}$, n=5;	Unpaired t-test, two-sided	Serum TG: df=8, t=2.82, P=0.022
	HSC-*Grm5*$^{-/-}$, n=5		
	(2 biologic replicates)		
Figure S5G	HSC-*Grm5*$^{+/+}$, n=5;	Unpaired t-test, two-sided	Liver 2-AG: df=8, t=3.23, P=0.012
	HSC-*Grm5*$^{-/-}$, n=5;		
	(2 biologic replicates)		
Figure S5I	HSC-*Grm5*$^{+/+}$, n=5;	Unpaired t-test, two-sided	Liver TG: df=8, t=4.01, P<0.01
	HSC-*Grm5*$^{-/-}$, n=5;		Oil red O: df=8, t=4.13, P<0.01
	(2 biologic replicates)		
Figure S5J	HSC-*Grm5*$^{+/+}$, n=3;	Unpaired t-test, two-sided	*Srebf1*: df=4, t=11.83, P<0.001
	HSC-*Grm5*$^{-/-}$, n=3;		*Fasn*: df=4, t=12.25, P<0.001
	(2 biologic replicates)		*Scd1*: df=4, t=20.92, P<0.001
Figure S6A	Control, n=4; AFL, n=4	Unpaired t-test, two-sided	*GRM5*: df=14, t=3.21, P<0.01
Figure S6E	Healthy, n=7; AH, n=15	Unpaired t-test, one-sided	*SLC7A11*: df=20, t=1.80, P=0.043
Figure S6F	3 biologic replicates	Unpaired t-test, two-sided	*GRM5*: df=2, t=8.35, P=0.014
Figure S6G	3 biologic replicates	Unpaired t-test, two-sided	*DAGLB*: df=2, t=8.56, P=0.013
Figure S6H	3 biologic replicates	One-way ANOVA with multiple comparisons	Hep3B : Column A vs. C: q=8.13, adjusted P<0.01