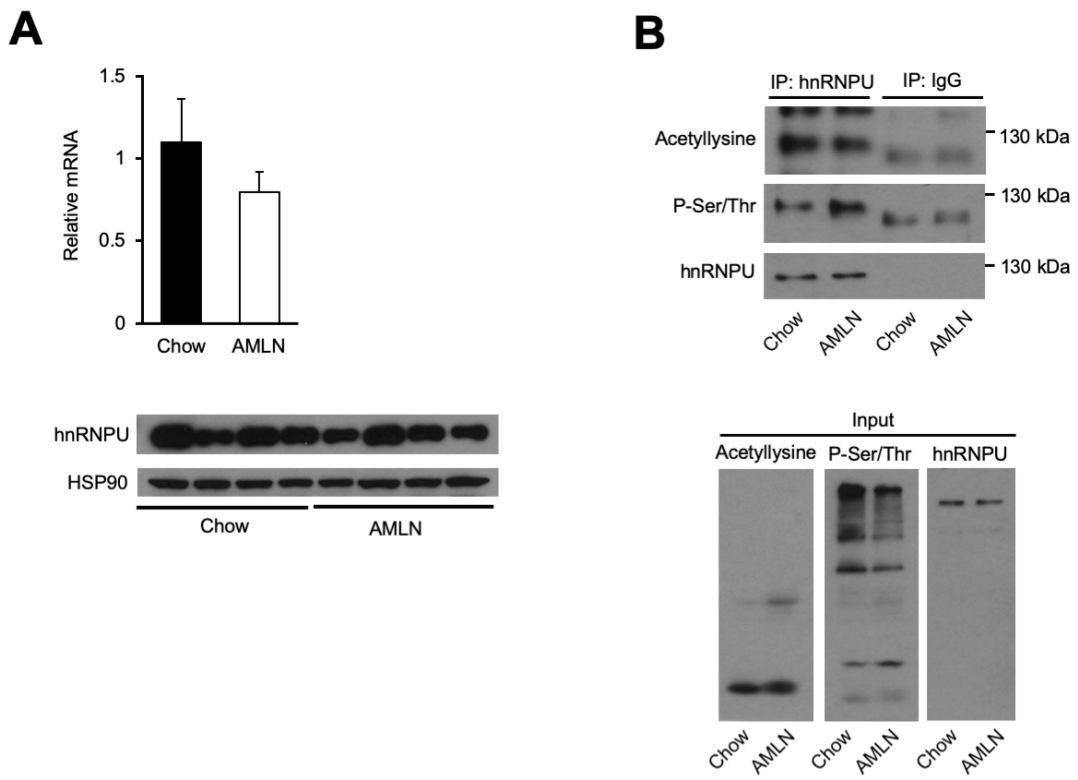

Figure S1. Regulation of hepatic hnRNPU expression in NASH.
(A) qPCR (top) and immunoblotting (bottom) analyses of liver hnRNPU expression in mice fed chow or AMLN NASH diet. Data represent mean ± SEM (Chow, n=3; AMLN, n=3); two-tailed unpaired Student's *t*-test.
(B) Immunoblots of liver nuclear extracts and hnRNPU immunocomplexes from mice fed chow or AMLN NASH diet.

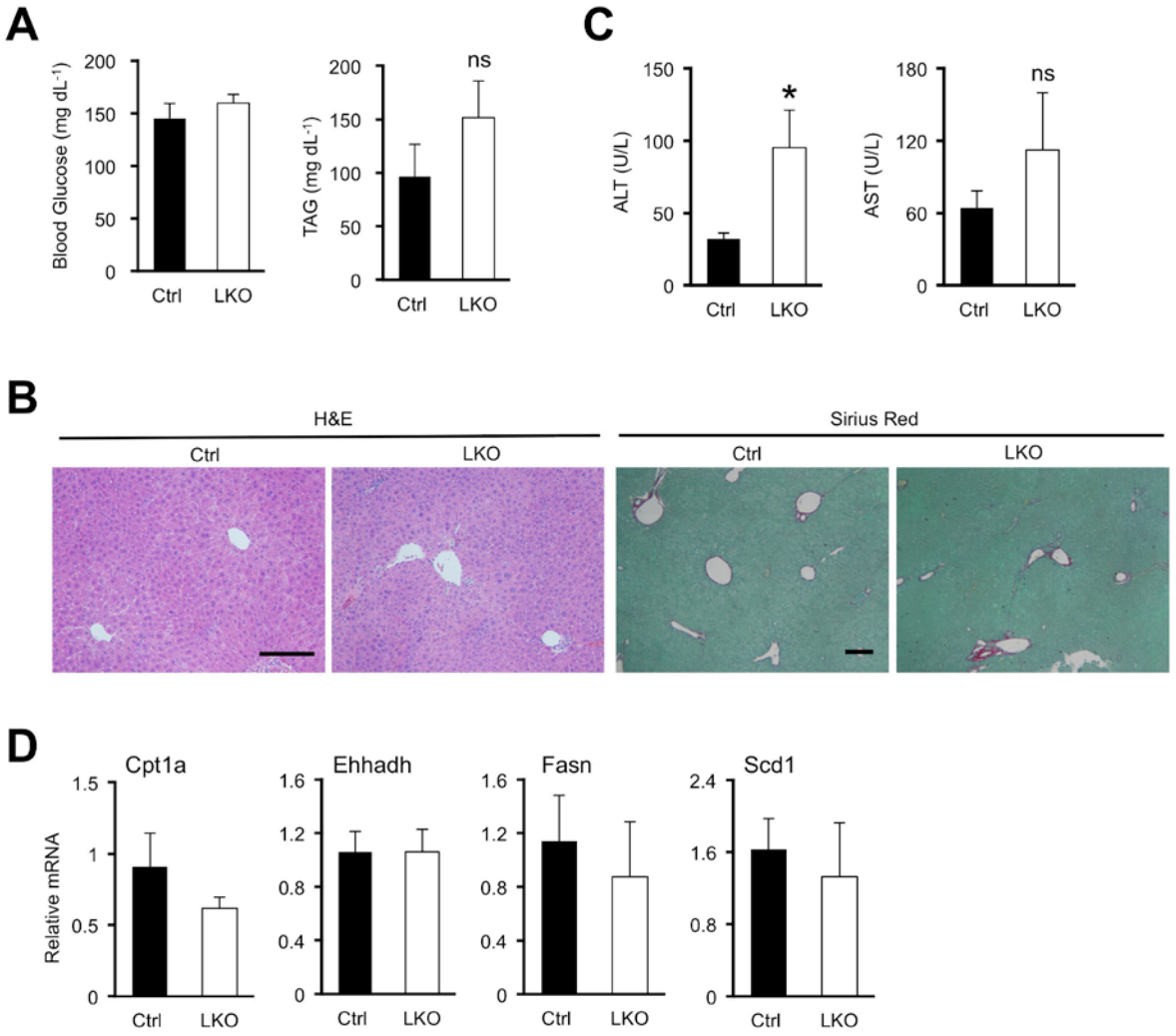

Figure S2. Effects of liver-specific hnRNPU inactivation on chow-fed mice.
(A) Blood glucose and plasma TAG concentrations in chow-fed Ctrl and hnRNPU LKO mice.
(B) H&E and Sirius red staining of liver sections.
(C) Plasma ALT and AST levels.
(D) qPCR analysis of hnRNPU Ctrl (n=5) or LKO (n=3) mice fed Chow diet. Data represent mean ± SEM (Chow, n=5; AMLN, n=3). *P<0.05; LKO vs. Ctrl, two-tailed unpaired Student's *t*-test.

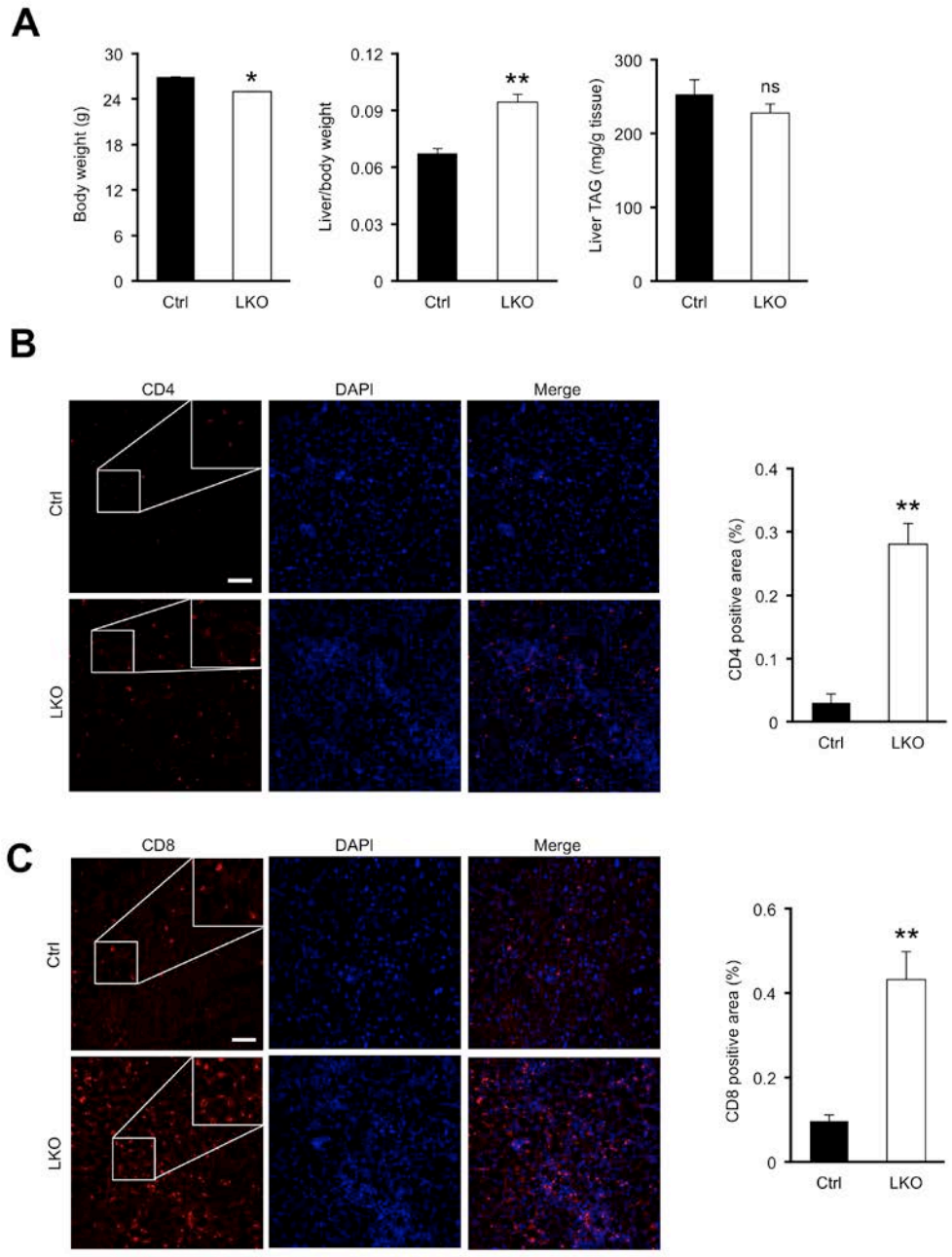

Figure S3. Hepatocyte-specific inactivation of hnRNPU exacerbates CDAHFD-induced NASH pathogenesis.

(A) Metabolic parameters of Ctrl and LKO mice fed CDAHFD for 3 weeks.

(B) CD4 immunofluorescence of liver sections. Scale bars: 100 μM.

(C) CD8 immunofluorescence of liver sections. Scale bars: 100 μM. Data in B-C represent mean $\pm$ SEM (Ctrl n=8; LKO n=6). *P<0.05, **P<0.01; LKO vs. Ctrl, two-tailed unpaired Student's *t*-test.

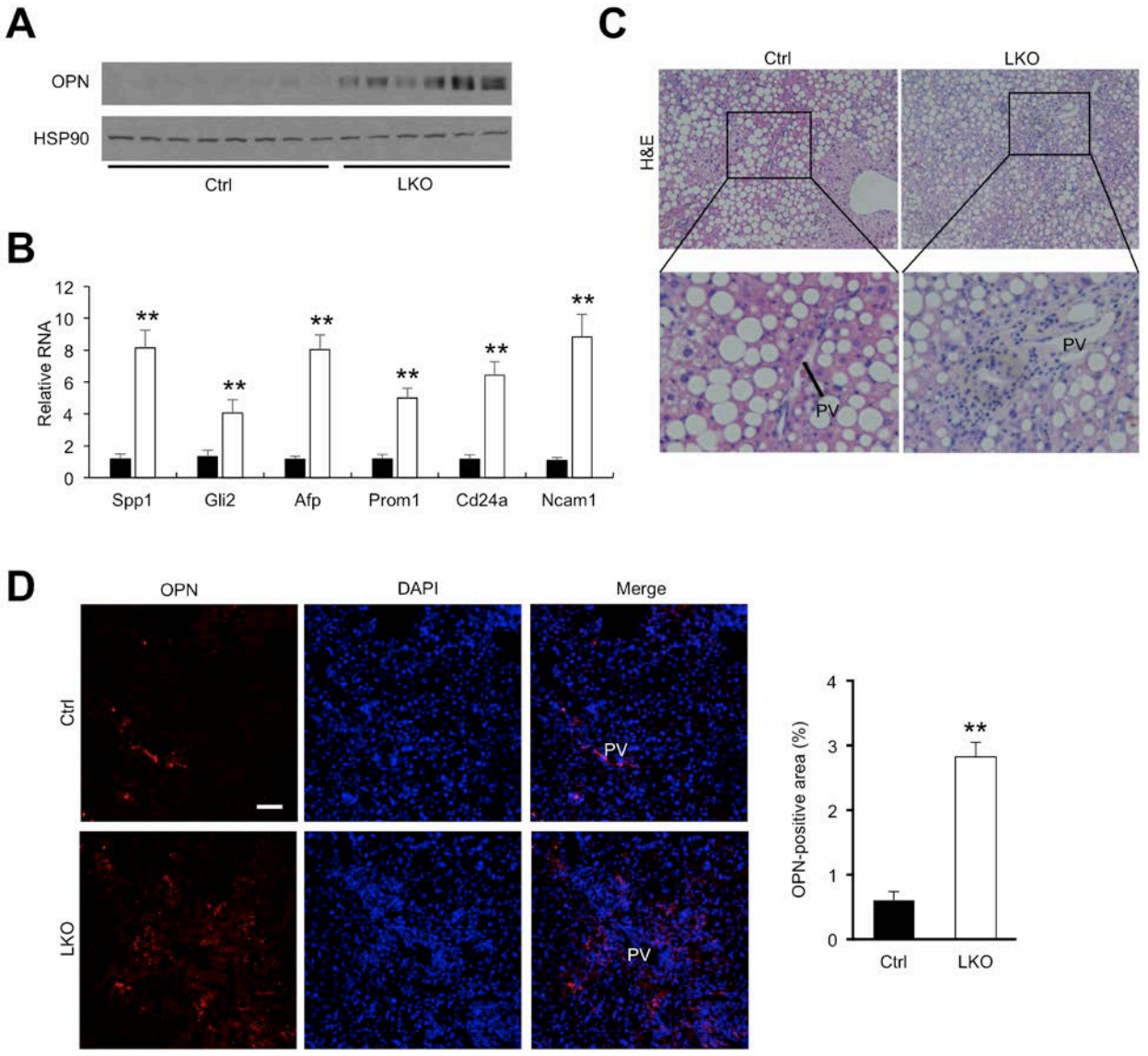

Figure S4. Hepatocyte-specific inactivation of hnRNPU promotes ductular reaction.

(A) Immunoblots of total liver lysates from mice fed CDAHFD for 3 weeks.

(B) qPCR analysis of hepatic gene expression.

(C) H&E staining of liver sections.

(D) OPN immunofluorescence of liver sections. Scale bars: 100 μM. Data in (B) and (D) represent mean $\pm$ SEM (Ctrl n=8; LKO n=6). **P<0.01, LKO vs. Ctrl, two-tailed unpaired Student's *t*-test.

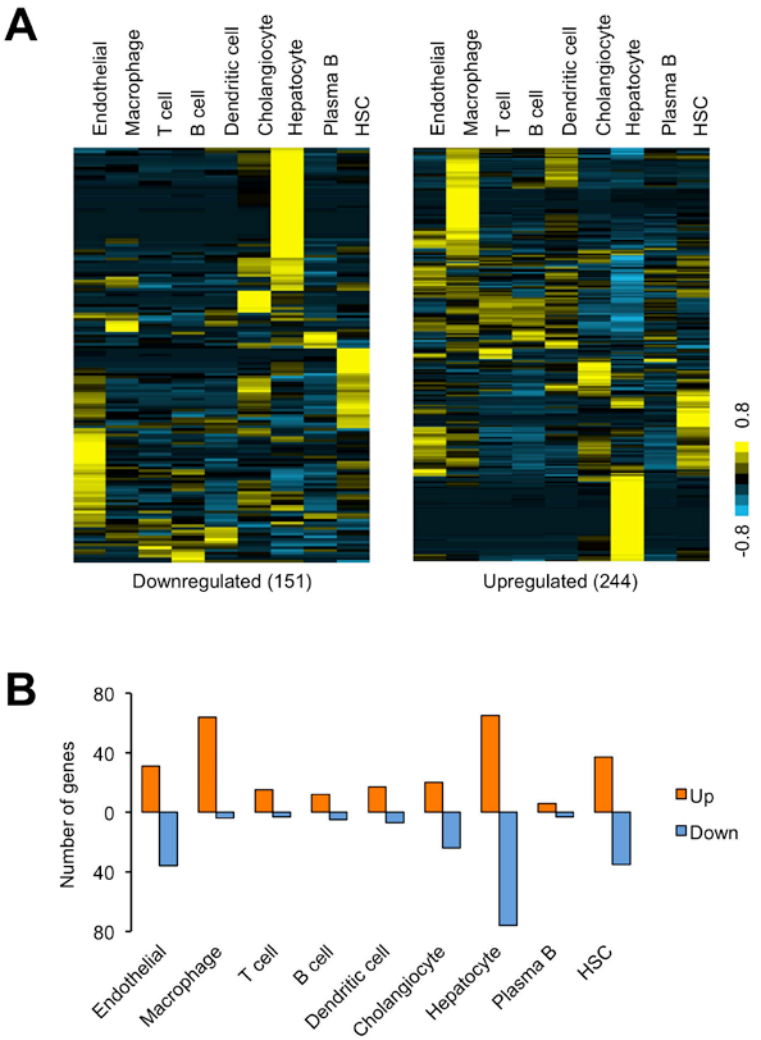

Figure S5. hnRNPU deficiency promotes transcriptional reprogramming in multiple liver cell types.
(A) Heat map of single cell RNA-seq data among different liver cell types for the clusters of genes upregulated or downregulated by hnRNPU inactivation.
(B) Distribution of hnRNPU-regulated genes among individual liver cell types.

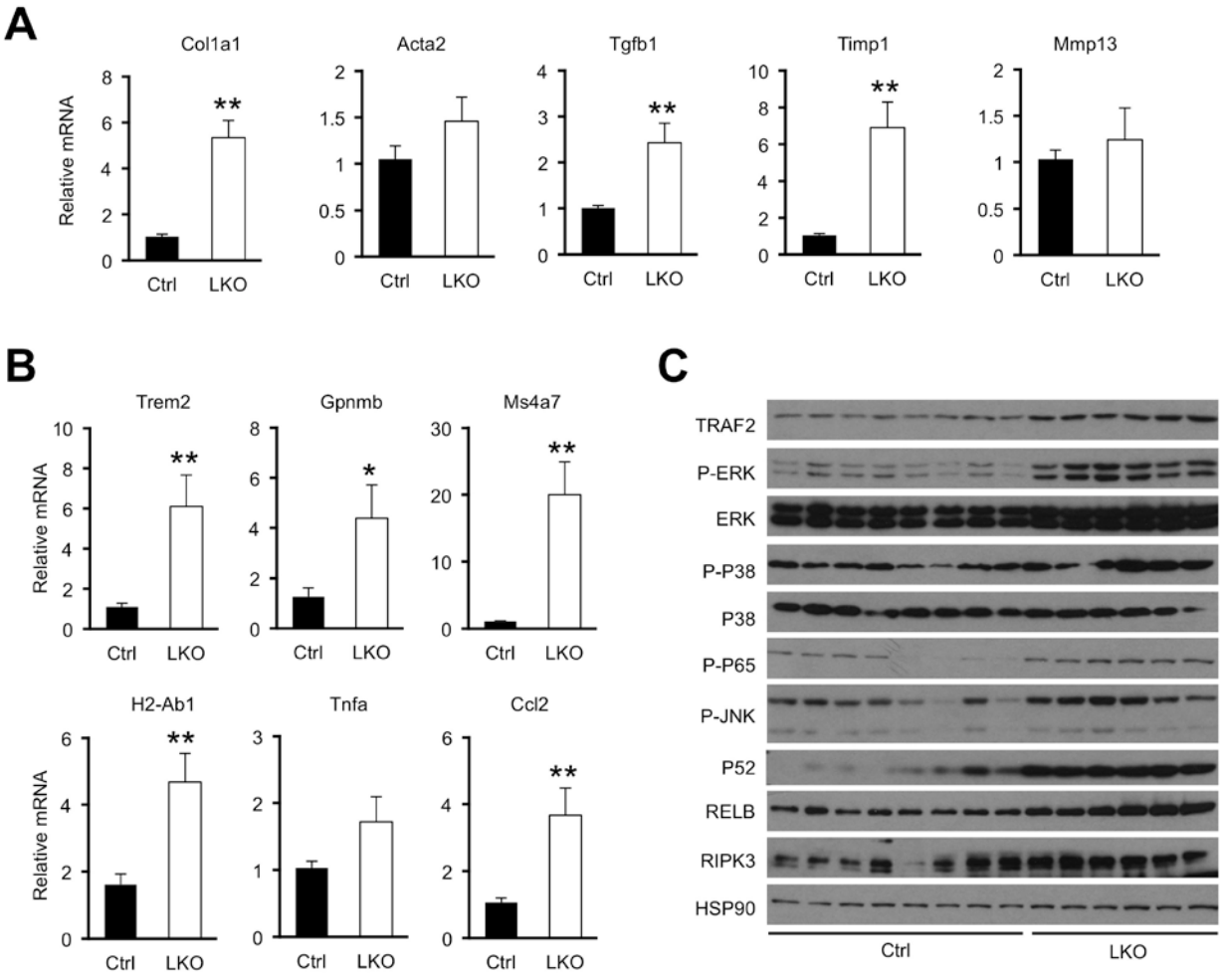

Figure S6. Effects of hnRNPU deficiency on liver gene expression and signaling.
(A-B) qPCR analysis of hepatic gene expression in mice fed CDAHFD for 3 weeks (Ctrl n=8; LKO n=6). Data represent mean ± SEM. *P<0.05, **P<0.01; Ctrl vs. LKO, two-tailed unpaired Student's *t*-test.
(C) Immunoblots of total liver lysates from CDAHFD-fed mice.

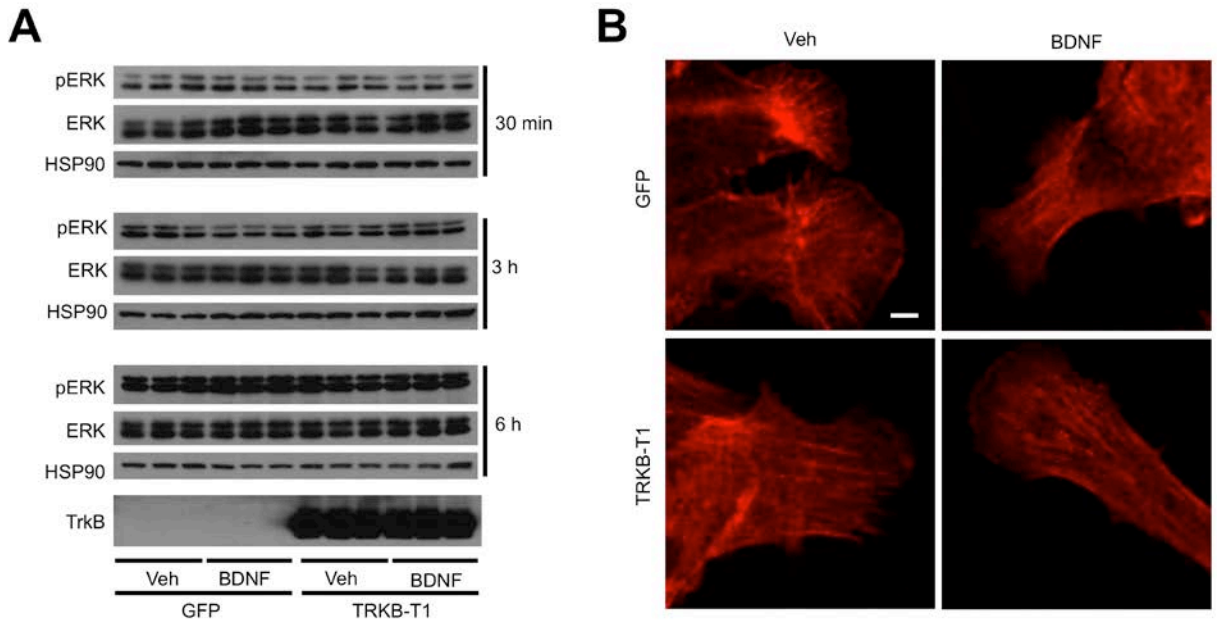

Figure S7. Effects of BDNF on primary hepatocytes.
(A) Immunoblots of total cell lysates from primary hepatocytes transduced with GFP or TrkB-T1 adenovirus followed by treatment with vehicle (Veh) or BDNF (100 ng/mL) for 30 minutes, 3 or 6 hrs.
(B) Phalloidin staining on transduced hepatocytes treated with Veh or BDNF for 30 minutes.

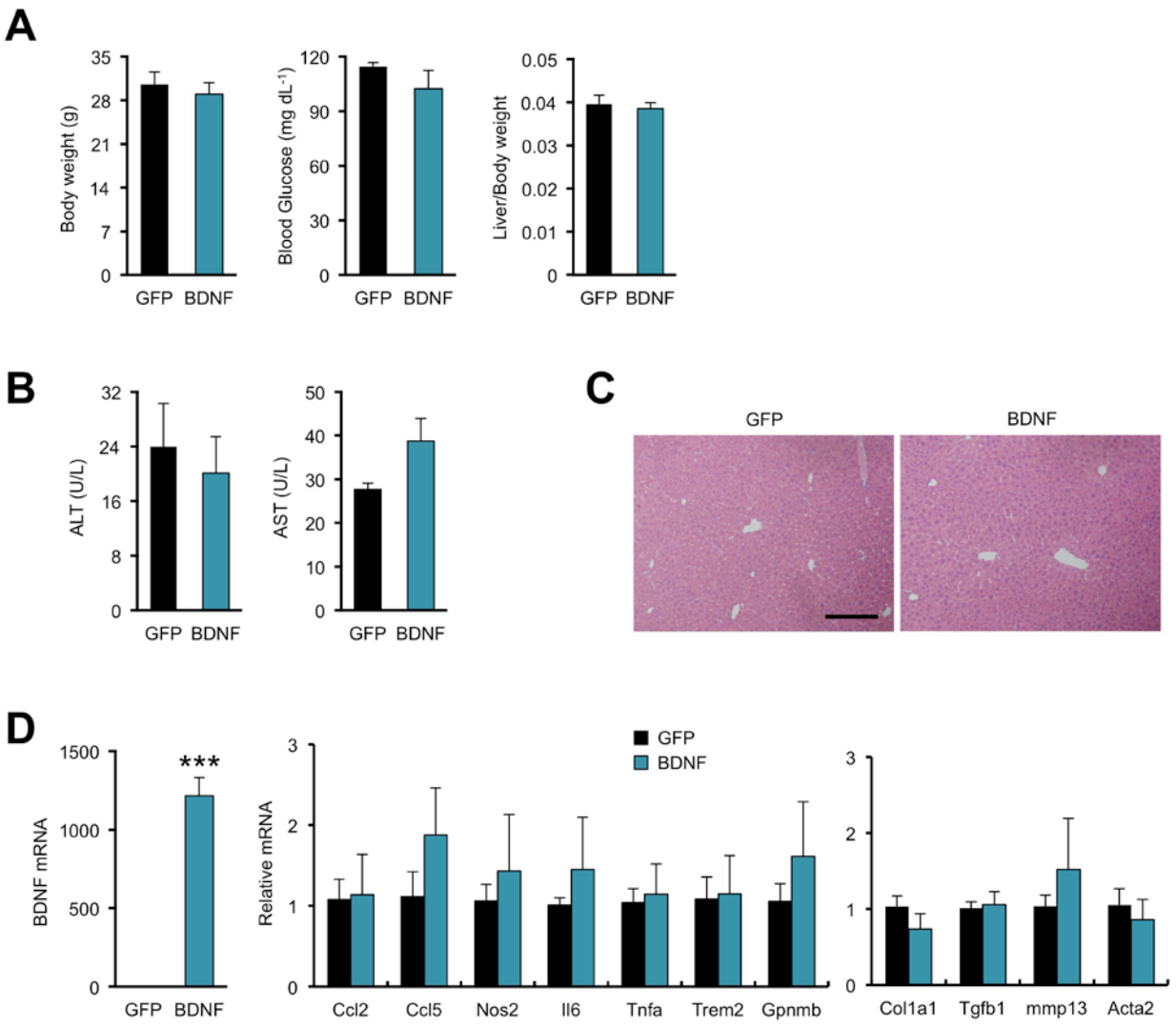

Figure S8. Effects of hepatic BDNF overexpression in chow-fed mice.
(A) Metabolic parameters in chow-fed mice transduced with AAV-GFP or AAV-BDNF.
(B) Plasma ALT and AST levels.
(C) H&E staining of liver sections from transduced mice.
(D) qPCR analysis of hepatic gene expression. Data in (A), (B) and (D) represent mean ± SEM (GFP n=4; BDNF n=4). **P<0.01, BDNF vs. GFP, two-tailed unpaired Student's *t*-test.

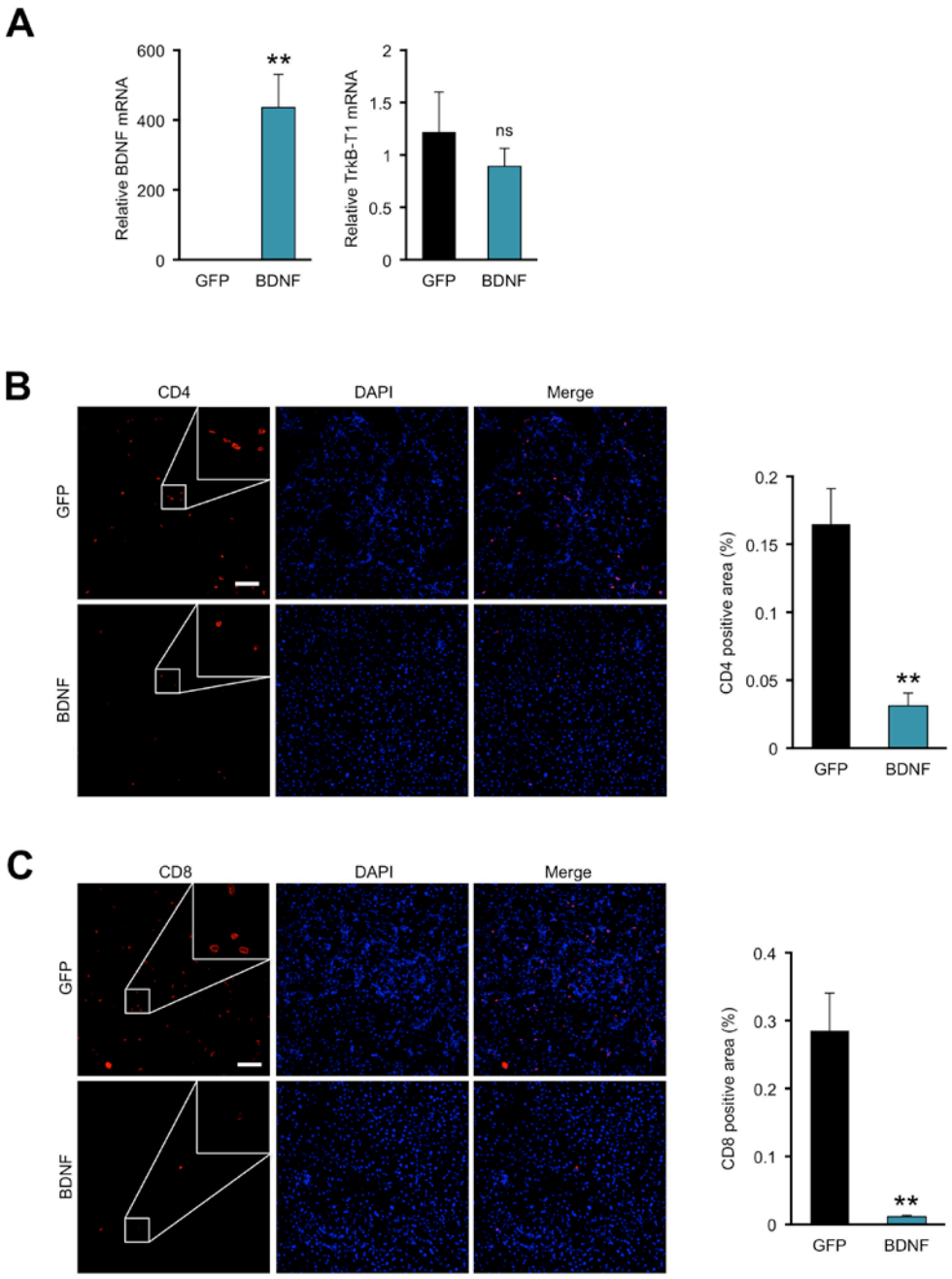

Figure S9. Hepatic overexpression of BDNF protects NASH pathogenesis.
(A) qPCR analysis of BDNF and TrkB-T1 expression in AMLN diet-fed mice transduced with AAV-GFP or AAV-BDNF vector (GFP n=7; BDNF n=6). **P<0.01; BDNF vs. GFP, two-tailed unpaired Student's *t*-test.
(B) CD4 immunofluorescence of liver sections. Scale bars: 100 μM.
(C) CD8 immunofluorescence of liver sections. Scale bars: 100 μM. Data in B-C represent mean $\pm$ SEM. **P<0.01; BDNF vs. GFP, two-tailed unpaired Student's *t*-test.

Gene	Primers	
	Forward	Reverse
mRplp0	GAAACTGCTGCCTCACATCCG	GCTGGCACAGTGACCTCACACG
m t-TRKB	*CCGTGGTGGTGATTGCATCT*	*CAGAGTTCAGCTCACAGGGC*
m FL-TRKB	*CCCAGGGAAGAGTCCTTCAG*	*GATGTTCTTCCGGGTGTGTG*
m Total TRKB	CATTTTGCGCCAACTATCACG	TGGCCCCATTGTAGAACCACT
hRplp0	AGGCGTCCTCGTGGAAGTGA	GCGGATCTGCTGCATCTGCT
hTRKB	CGTGGAAGAAACGCTAATGGA	GTACGTGCGGATCGTGTTCAT
mIfit1	CTGAGATGTCACTTCACATGGAA	GTGCATCCCCAATGGGTTCT
mIfit3	TCAGGCTTACGTTGACAAGGT	CACACTTTAGGCGTGTCCATC
mIfi27l2a	CTTCCTATGCTCTGCTGCTACC	AGCCAGAGCTCCTCCTATGG
mIfih1	TCCTGGATGTTCTGCGCCAA	GACGAGTTAGCCAAGTCTGTGTT
mC1qc	ATGGTCGTTGGACCCAGTTG	GGTAGGGCCAGAAGAAACAG
mCd5l	ACGGAAGCTGCAACAAGAAT	ACTCAAAAGGCAAGACCGAA
mGpnmb	GAGCACAACCAATTACGTGGCT	GGTGATATTGGAACCCACCAGA
mTrem2	CAGCACCTCCAGGAATCAAGA	AGGATCTGAAGTTGGTGCCC
mTgfb1	ACCATGCCAACTTCTGTCTGGGAC	ACAACTGCTCCACCTTGGGCTTG
mTimp1	CACCCACAGACGGCCTTCT	TCTGGTGTCCCCACGAACTT
mCol1a1	AAGAGGCGAGAGAGGTTTCC	AGAACCATCAGCACCTTTGG
mMmp13	TGCTTCCTGATGATGACGTTCAAGG	TGGGATGCTTAGGGTTGGGGTC
mActa2	CTGACAGAGGCACCACTGAA	CATCTCCAGAGTCCAGCACA
mMs4a7	TGAGTTCTCCCAGGAGCAGA	CCAGGGATGCTGTCCTCAC
mTnfa	AGCCCCAGTCTGTATCCTT	CTCCCTTTGCAGAACTCAGG
mCcl2	AGGTCCCTGTCATGCTTCTG	TCTGGACCCATTCCTTCTTG
mH2-Ab1	AGCCCCATCACTGTGGAGT	GATGCCGCTCAACATCTTGC
mIl1b	TGGCAACTGTTCCTGAACTCAA	AGCAGCCCTTCATCTTTTGG
mNos2	GAGGCCCAGGAGGAGAGAGATCCG	TCCATGCAGACAACCTTGGTGTTG

Antibodies	Source	Identifier
Cleaved caspase 3	Cell Signaling Technology	#9661
Phospho-ERK	Cell Signaling Technology	#4370
Total ERK	Cell Signaling Technology	#4695
Phospho-P65	Cell Signaling Technology	#3033
Total P65	Cell Signaling Technology	#8242
P52	Cell Signaling Technology	#4882
Phospho-JNK1/2 (T183/Y185)	Cell Signaling Technology	#4668
Total JNK1/2	Cell Signaling Technology	#9252
Phospho-IKKa/b	Cell Signaling Technology	#2697
Phospho-MLKL (S358)	Cell Signaling Technology	#91689
TRAF2	Cell Signaling Technology	#4712
NIK	Cell Signaling Technology	#4994
RelB	Cell Signaling Technology	#4922
IKBa	Cell Signaling Technology	#4812
c-FLIP	Cell Signaling Technology	#56343
Phospho-P38 (T180/Y182)	Cell Signaling Technology	#9215
Total P38	Cell Signaling Technology	#9212
Lamin A/C	Cell Signaling Technology	#2032
pEGFR	Cell Signaling Technology	#3777
PARP	Cell Signaling Technology	#9542
RIPK3	Novus	#NBP1-77299
β-actin	Sigma-Aldrich	A4700
Tubulin	Sigma-Aldrich	T6199
hnRNPU	Santa Cruz	Sc-32315
HSP90	Santa Cruz	Sc-7947
Osteopontin	R&D	AF808
Mouse TrkB	R&D	AF1494
Human TrkB	Cell Signaling Technology	#4603
Acetyllyine	Upstate	05-515
P-Ser/Thr	BD Transduction Laboratories	612546
BDNF	Abcam	#ab108319
DCN	R&D	AF1060
F4/80	Bio-Rad	MCA497G
CD4	Thermo Fisher	14-0042-82
CD8a	Thermo Fisher	14-0808-82