Figure S1

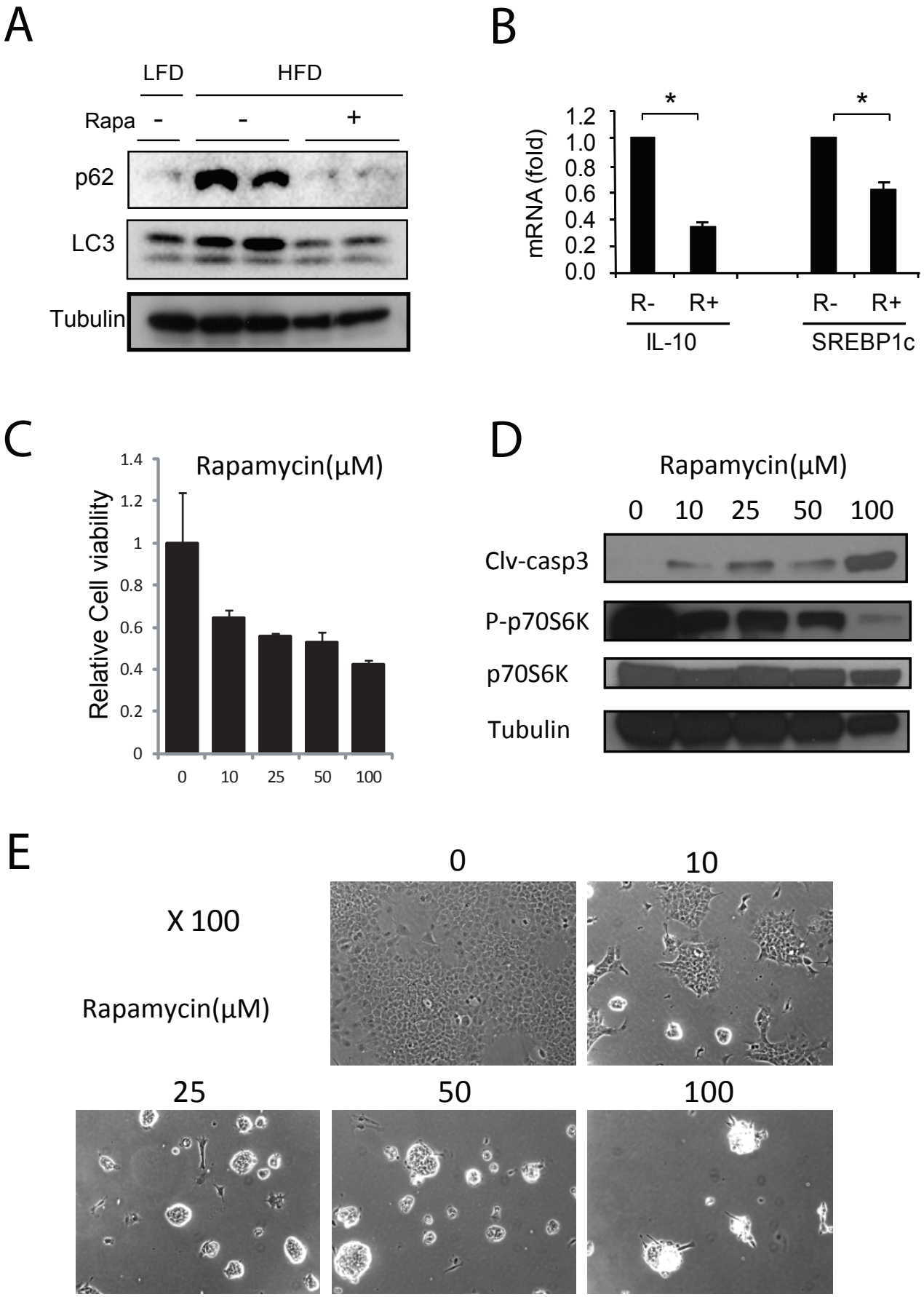

A
LFD
HFD
Rapa - - +
p62
LC3
Tubulin
B
mRNA (fold)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
*
R- R+ R- R+
IL-10
SREBP1c
C
Rapamycin(μM)
Relative Cell viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0 10 25 50 100
D
Rapamycin(μM)
0 10 25 50 100
Clv-casp3
P-p70S6K
p70S6K
Tubulin
E
X 100
Rapamycin(μM)
0
10
25
50
100

Figure S2

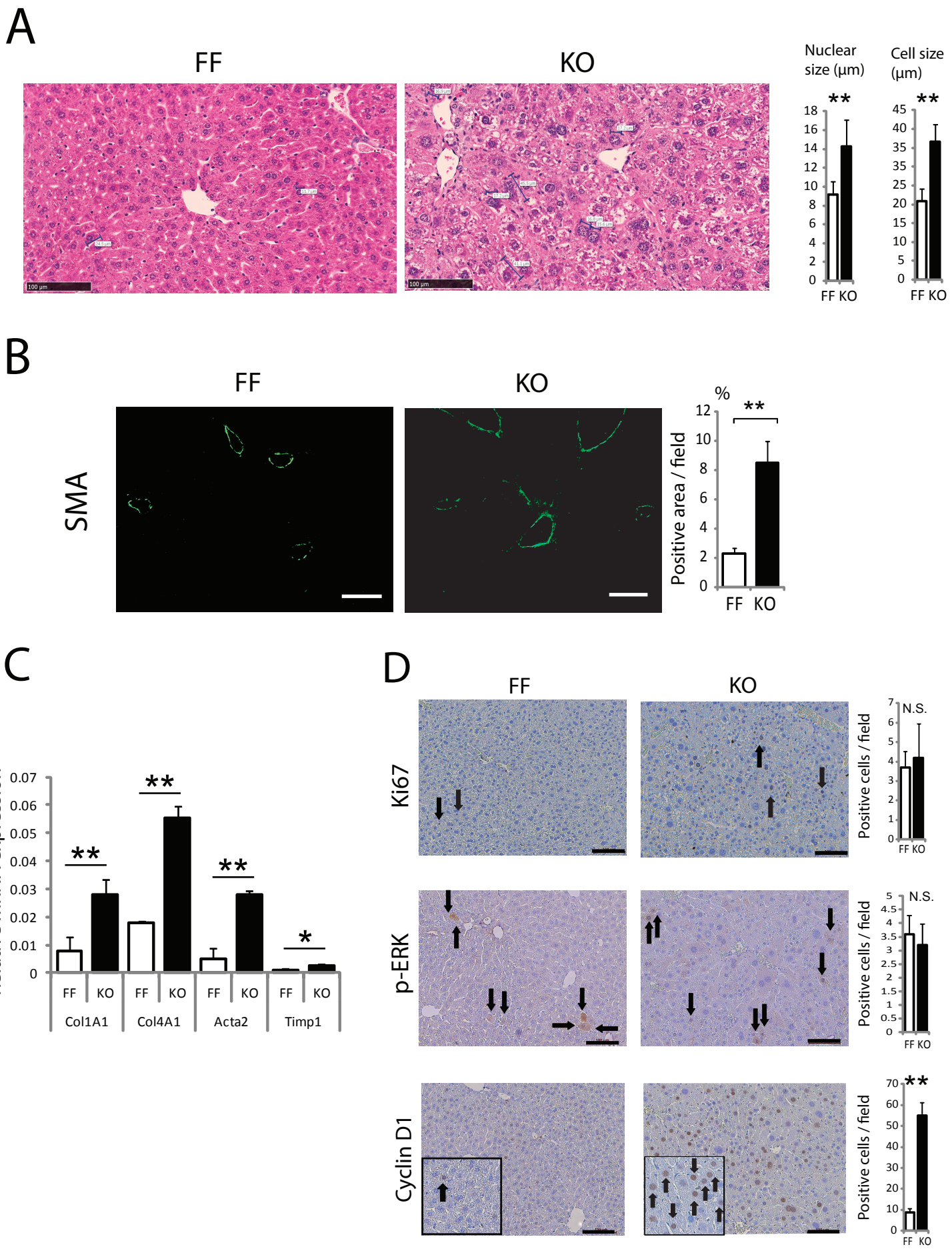
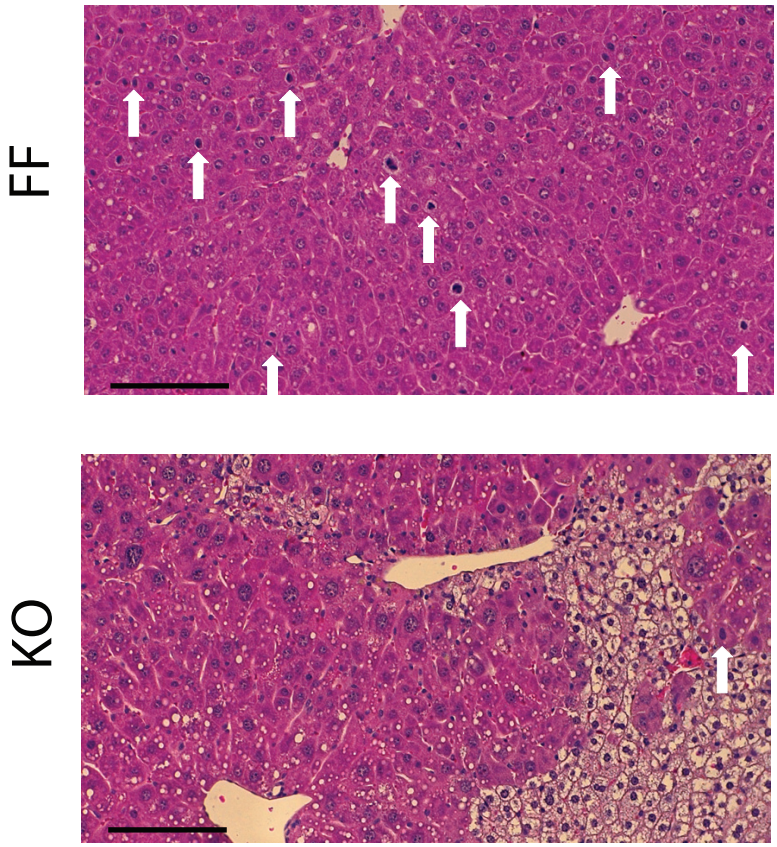

A
FF
KO
Nuclear size (μm)
Cell size (μm)
**
**
FF KO
FF KO
B
FF
KO
SMA
%
**
Positive area / field
FF KO
C
Relative mRNA expression
**
**
**
*
FF KO FF KO FF KO FF KO
Col1A1
Col4A1
Acta2
Timp1
D
FF
KO
Ki67
p-ERK
Cyclin D1
Positive cells / field
N.S.
N.S.
**
FF KO

Figure S3

A



B

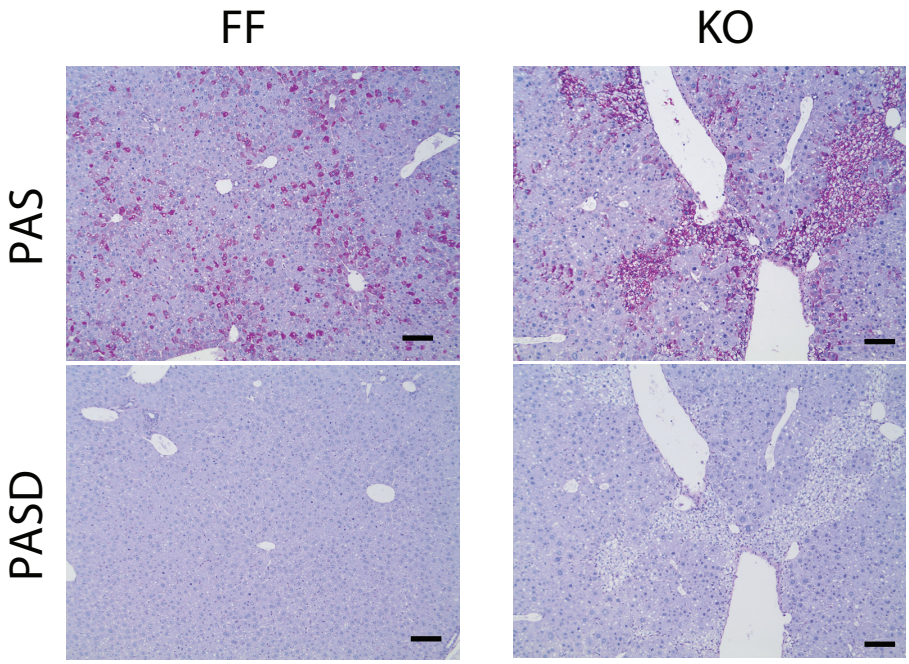


Figure S4

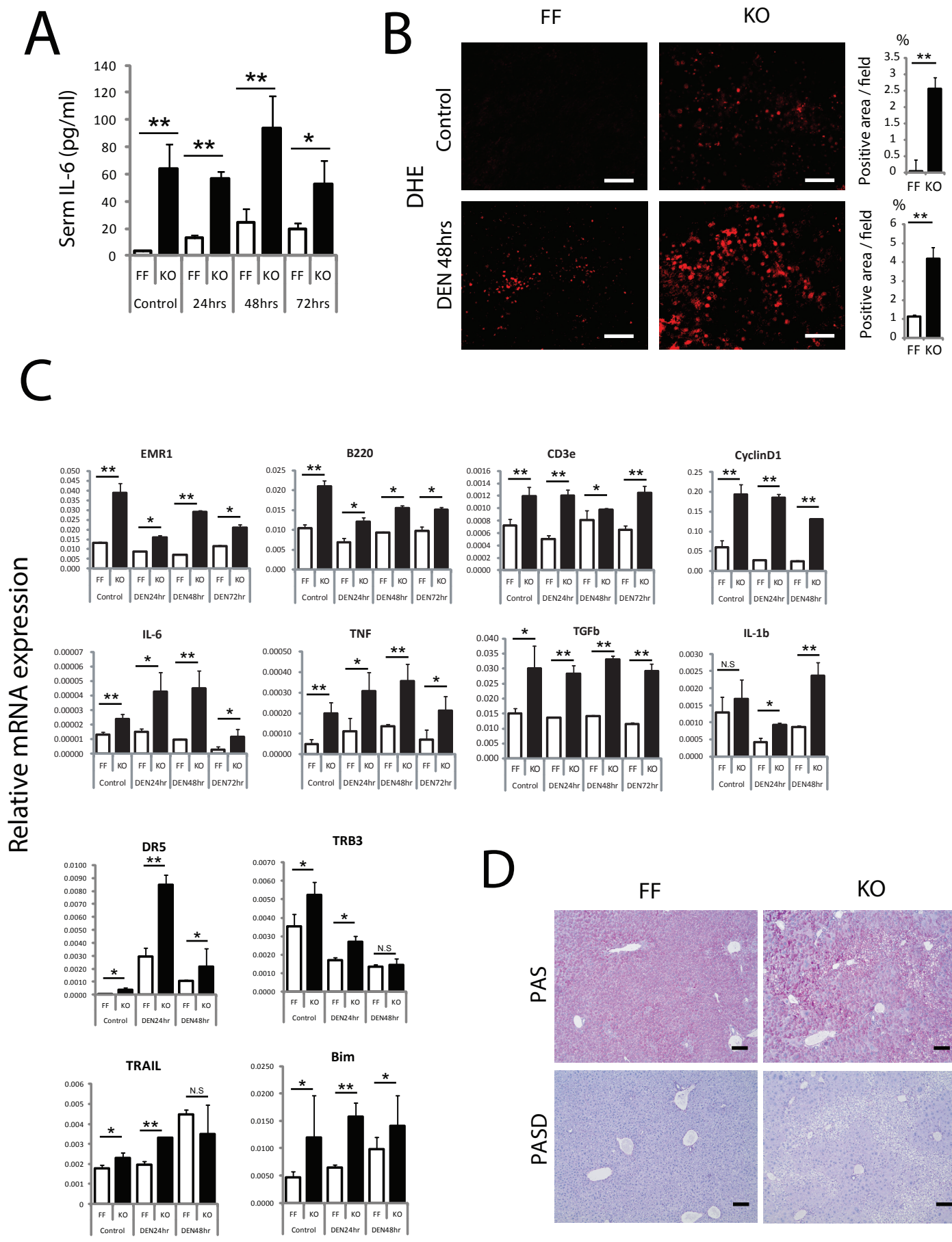
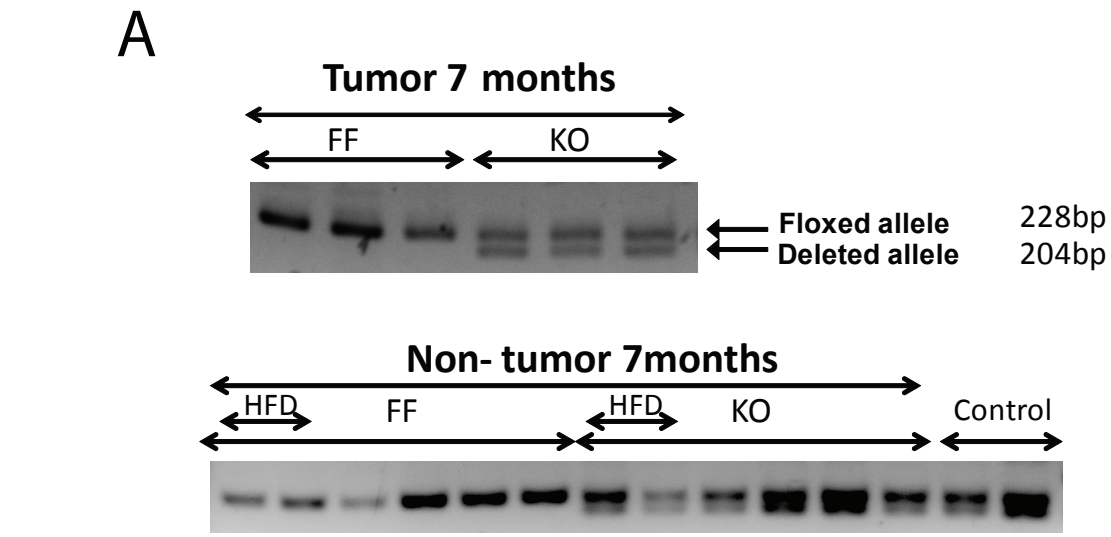
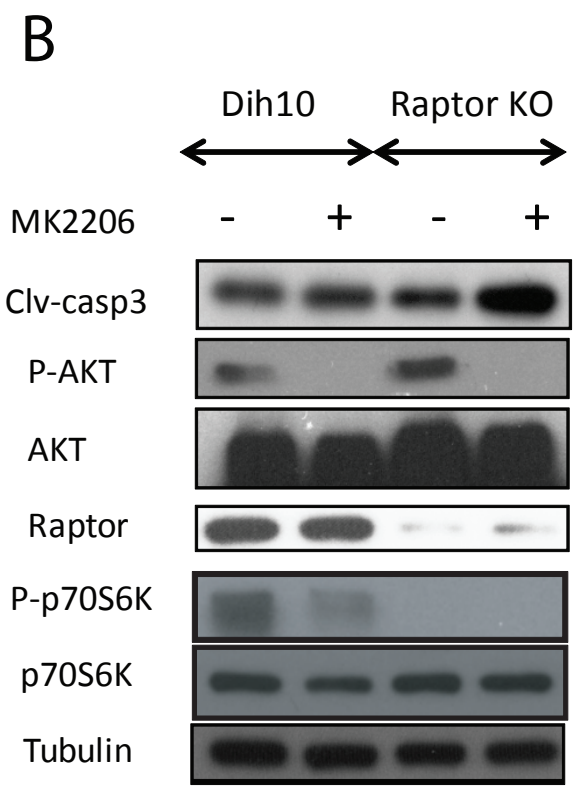

A
Serm IL-6 (pg/ml)
FF KO FF KO FF KO FF KO
Control 24hrs 48hrs 72hrs
B
FF
KO
DHE
Control
DEN 48hrs
Positive area / field
%
FF KO
C
Relative mRNA expression
EMR1
B220
CD3e
CyclinD1
IL-6
TNF
TGFb
IL-1b
DR5
TRB3
TRAIL
Bim
Control
DEN24hr
DEN48hr
DEN72hr
N.S
D
FF
KO
PAS
PASD

Figure S5


A
Tumor 7 months
FF
KO
Floxed allele
Deleted allele
228bp
204bp
Non- tumor 7months
HFD
FF
HFD
KO
Control


B
Dih10
Raptor KO
MK2206
- + - +
Clv-casp3
P-AKT
AKT
Raptor
P-p70S6K
p70S6K
Tubulin

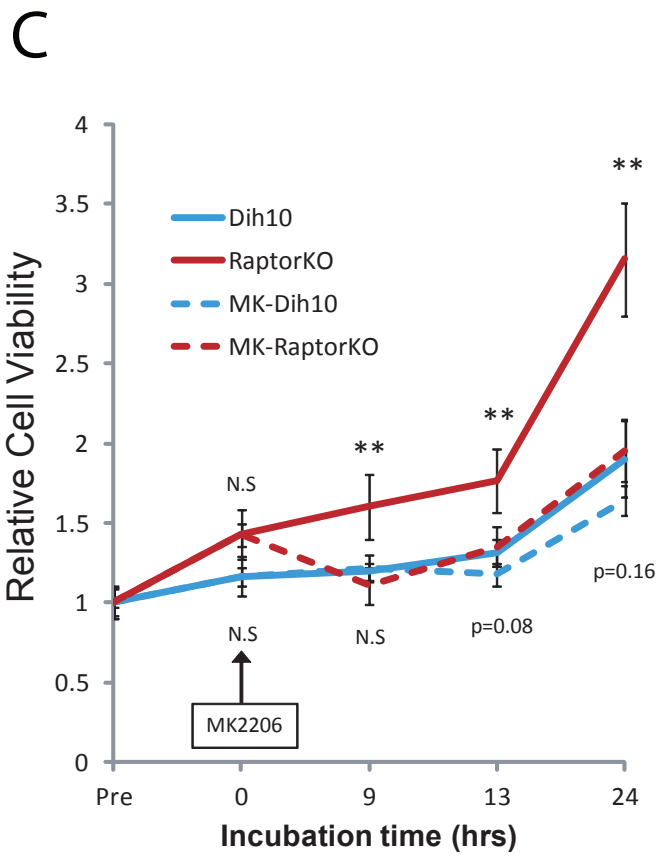
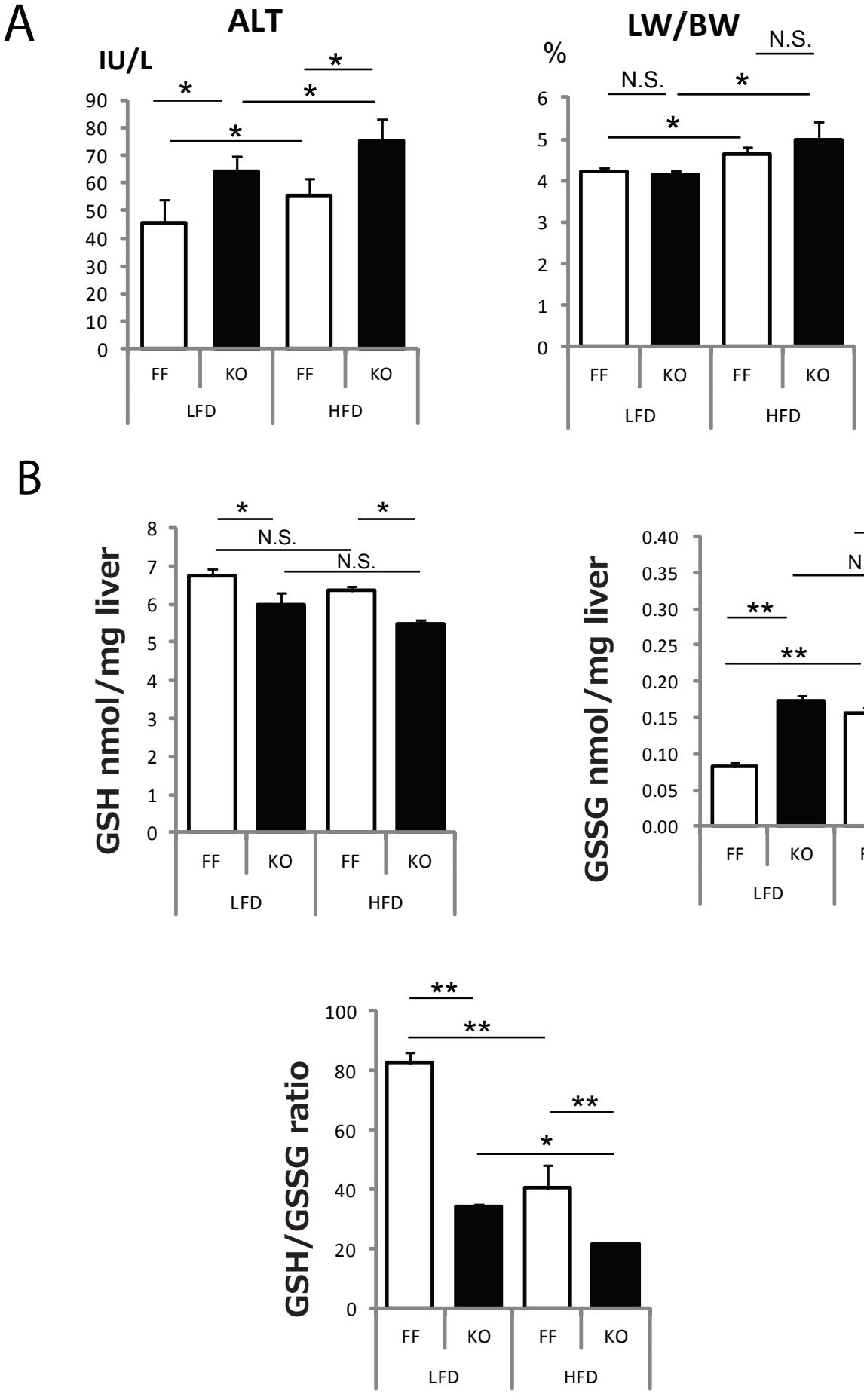

C
Relative Cell Viability
Dih10
RaptorKO
MK-Dih10
MK-RaptorKO
N.S
**
**
**
N.S
N.S
p=0.08
p=0.16
MK2206
Pre
0
9
13
24
Incubation time (hrs)

Figure S6


A
ALT
IU/L
90
80
70
60
50
40
30
20
10
0
*
*
*
*
FF
KO
FF
KO
LFD
HFD
LW/BW
%
6
5
4
3
2
1
0
N.S.
N.S.
*
*
FF
KO
FF
KO
LFD
HFD
B
GSH nmol/mg liver
8
7
6
5
4
3
2
1
0
*
N.S.
N.S.
*
FF
KO
FF
KO
LFD
HFD
GSSG nmol/mg liver
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
**
N.S.
**
**
FF
KO
FF
KO
LFD
HFD
GSH/GSSG ratio
100
80
60
40
20
0
**
**
**
*
FF
KO
FF
KO
LFD
HFD

Supplemental Figure legends

Figure S1, related to Figure 1. Rapamycin treatment induces autophagy but also inhibits IL-10 expression. (A) Livers from mice kept on LFD or HFD with or without rapamycin (Rapa or R) treatment were collected and homogenized, and p62 and LC3 expression were analyzed by immunoblotting. The loading control tubulin blot is the same as in Figure 1D. (B) Relative amounts of IL-10 and SREBP1c mRNAs in above livers were determined by real time qPCR and normalized to cyclophilin mRNA. (C) AML12 cells were incubated with indicated concentration of rapamycin for 16hrs, and then relative hepatocyte viability/proliferation was analyzed. (D) Immunoblot analysis of hepatocyte lysates collected 16hrs after rapamycin incubation. (E) The morphorogical change of hepatocytes after rapamycin incubation. All the bar graphs in Figure S1 represent means +/- S.D.

Figure S2, related to Figure 2. Increased nuclear and cell size of Raptor-deficient hepatocytes. (A) Nuclear and cell sizes of hepatocytes in H&E stained liver sections from *Raptor*$^{F/F}$ (FF), and *Raptor*$^{\Delta hep}$ (KO) mice were determined. (n= 4) (scale bar: 100 μm). (B) Smooth muscle actin (SMA) staining of liver tissue sections from FF and KO mice (scale bar: 100 μm). SMA positive areas were quantified with Image J software and the results are depicted in the bar graphs. (n= 4). (C) The mRNA expression of fibrogenic markers, collagen α1(I) (Col1A1), collagen α1(IV) (Col4A1), actin α (Acta), and TIMP1 (Timp1) were analyzed by real time qPCR. (D) Liver cell proliferation was analyzed by immunostaining with antibodies against Ki67, p-ERK, and cyclin D1. The results were quantified and are depicted as above (n= 4). All the bar graphs in Figure S2 represent means +/- S.D.

Figure S3, related to Figure 3. Loss of Raptor inhibits hepatocyte mitosis, but enhances ERK and STAT3 activation after partial hepatectomy. *Raptor*$^{F/F}$ and *Raptor*$^{\Delta hep}$ mice were subjected to PH as described in Figure. 3. (A) High magnification images of H&E stained liver sections 48 hrs after PH (scale bar: 100 μm). White arrows indicate representative mitotic hepatocytes. (B) PAS and PAS diastase (PASD) staining of liver tissues showing glycogen accumulation (scale bar: 100 μm).

Figure S4, related to Figure 4. Loss of Raptor enhances cyclin D1 expression, IL-6 production and ROS accumulation after DEN challenge. *Raptor*$^{F/F}$ or *Raptor*$^{\Delta hep}$ were treated with 100 mg/Kg DEN as in Figure. 4. Livers were removed for analysis after 24 or 48 or 72 hrs. (A) Serum IL-6 was determined at the indicated times (n= 3). (B) Liver sections were prepared 48 hrs after DEN injection and analyzed for ROS accumulation by DHE staining. DHE positive areas were quantified and the results are exhibited in the bar graphs to the right (scale bar: 100 μm, n= 3). (C) mRNA expression of immune cell markers, cyclin D1, pro-inflammatory cytokines, and cell death mediators was quantitated by real-time qPCR at the indicated time-points after DEN injection (n= 3). (D) PAS and PAS diastase (PASD) staining of liver tissues showing glycogen accumulation (scale bar: 100 μm). All the bar graphs in Figure S4 represent means +/- S.D.

Figure S5, related to Figure 5. Genotyping of DEN-induced HCC and non-tumor tissue, and the effect of AKT inhibiton on HCC cells. (A) *Raptor*$^{F/F}$ and *Raptor*$^{\Delta hep}$ males were injected with 25 mg/Kg. Non-tumor and tumor liver tissues were isolated and subjected to *Raptor* genotyping by PCR. (B) Dih10 cells and HCC cells isolated from a *Raptor*$^{\Delta hep}$ mouse were cultured and then incubated with the AKT inhibitor MK2206. Immunoblot analysis of HCC cell lysates collected 13hrs after MK2206 incubation. (C) Relative cell viabilty/proliferation in HCC cells incubated with or without MK2206 was analyzed at the indicated times (MK-Dih10; Dih10 cells incubated with MK2206, MK-Raptor; HCC cells isolated from a *Raptor*$^{\Delta hep}$ mouse and incubated with MK2206). Results are means +/- S.D.

Figure S6, related to Figure 6. Inhibition of Raptor enhances liver damage. (A) Serum ALT and liver weight as percentage of total body weight (LW/BW) in LFD-fed and HFD-fed 7-months old *Raptor*$^{F/F}$ (FF) and *Raptor*$^{\Delta hep}$ (KO) mice. Results are means +/- S.E.M. (n= 4). (B) GSH, GSSG, and GSH/GSSG ratio in LFD-fed and HFD-fed 7 months old *Raptor*$^{F/F}$ (FF) and *Raptor*$^{\Delta hep}$ (KO) mice. Results are means +/- S.E.M. (n=4).

Supplemental Experimental Procedures

GSH and GSSG quantification.

GSH and GSSG were measured with a GSSG/GSH Quantification kit (Dojindo).