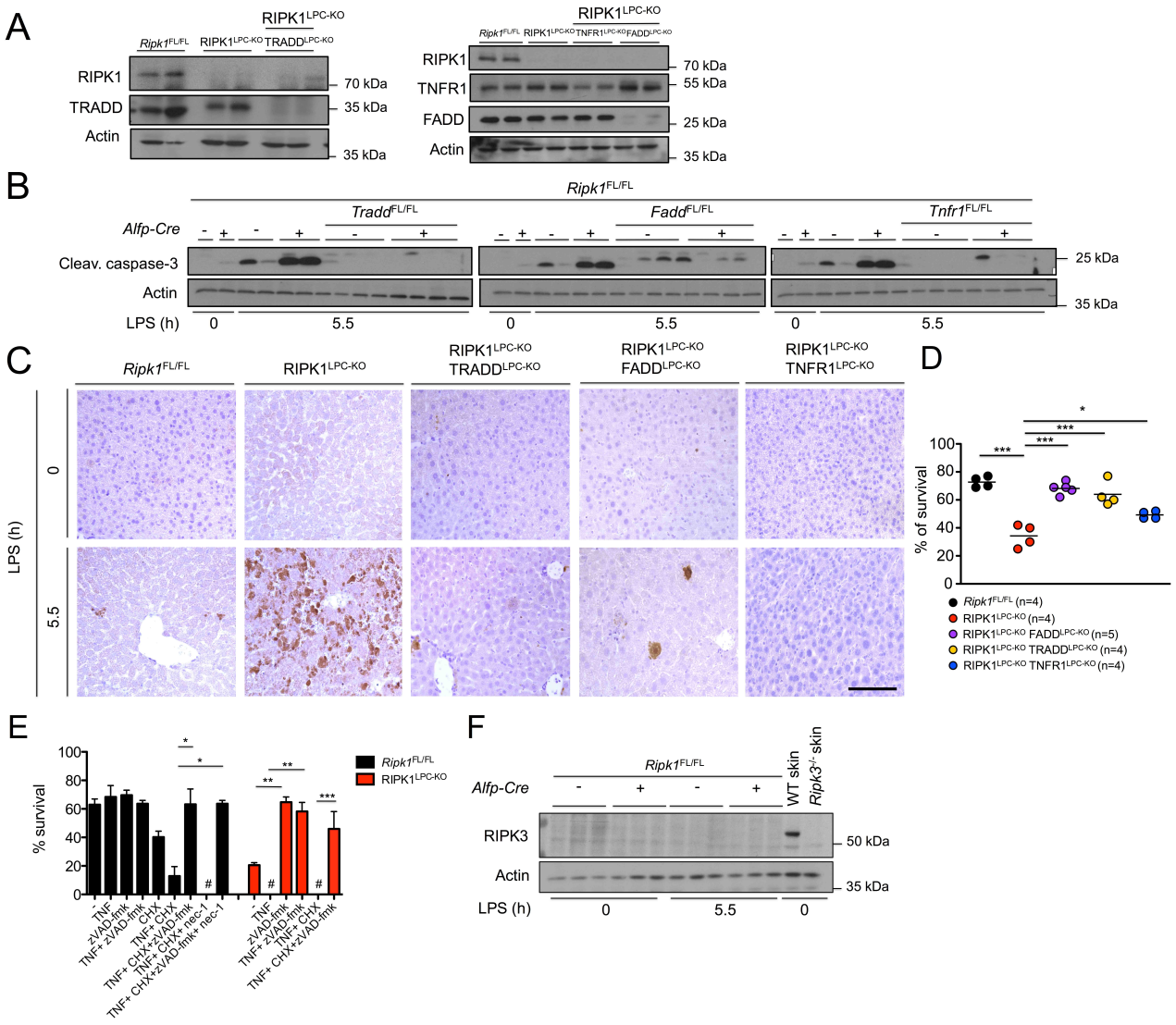
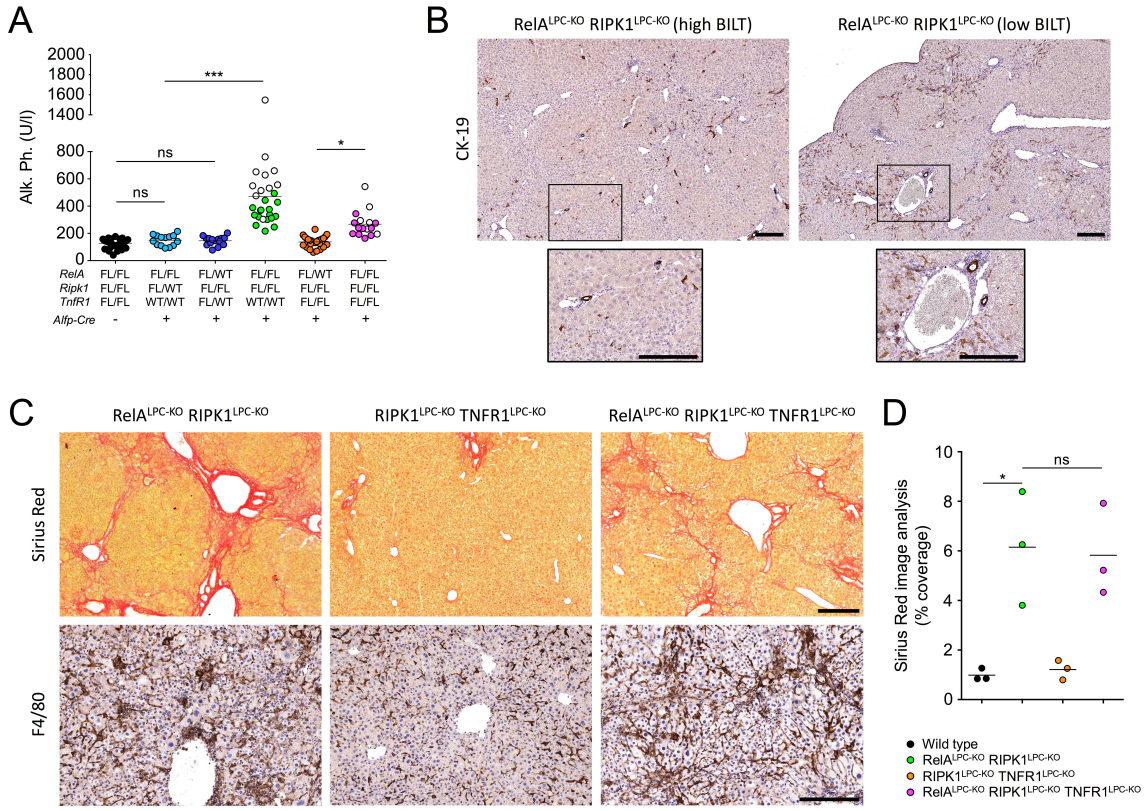


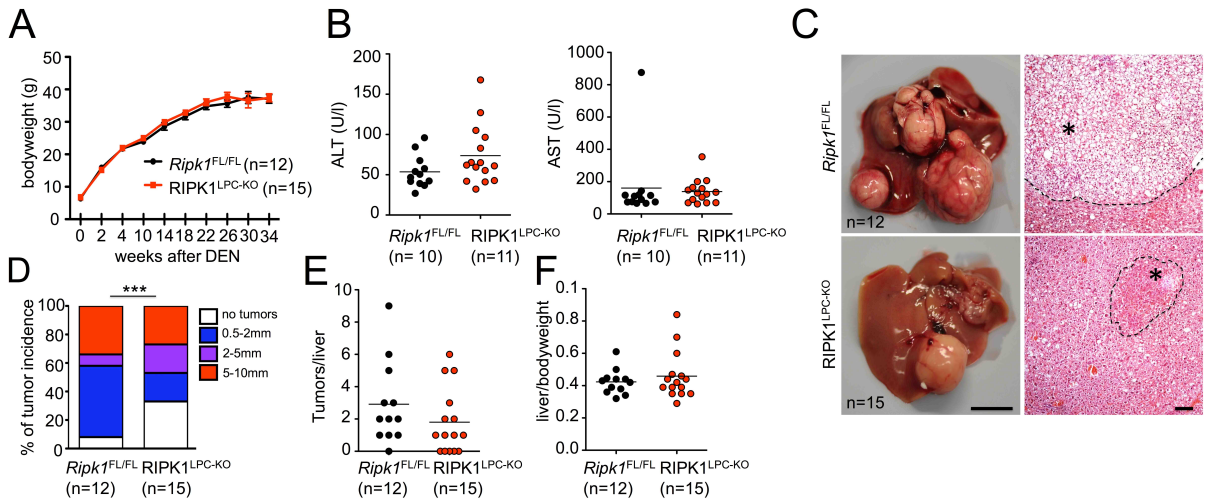
Supplementary Figure 1. RIPK1 prevents endotoxin-induced liver damage by inhibiting TNFR1-mediated hepatocyte apoptosis.

(A) Immunoblot analysis for FADD, RIPK1, TNFR1, TRADD in liver lysates of mice with indicated genotypes (n=2 per genotype). Actin was used as loading control. (B) Immunoblot analysis for cleaved caspase-3 in liver lysates of 9-week-old mice with indicated genotypes. Same liver lysates of *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ mice were used for indicated immunoblots. Actin was used as loading control. (C) Representative images of liver sections from non-injected or LPS injected mice with depicted genotypes stained for cleaved caspase-3 (n=4 per genotype). Scale bar 100µm. (D) Survival assay of primary hepatocytes with indicated genotypes cultured for 24h (One-way Anova, ***P<0.005, *P<0.05). (E) Graph depicting survival of primary hepatocytes from *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ mice cultured in presence or absence of zVAD-fmk, cycloheximide (CHX), necrostatin-1 (nec-1) and TNF for 24h (n= 3 per genotype) (One-way Anova, ***P<0.005, **P<0.01, *P<0.05). (F) Immunoblot analysis for RIPK3 in whole liver lysates of 9-week-old non-injected or LPS injected *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ mice. Actin was used as loading control.



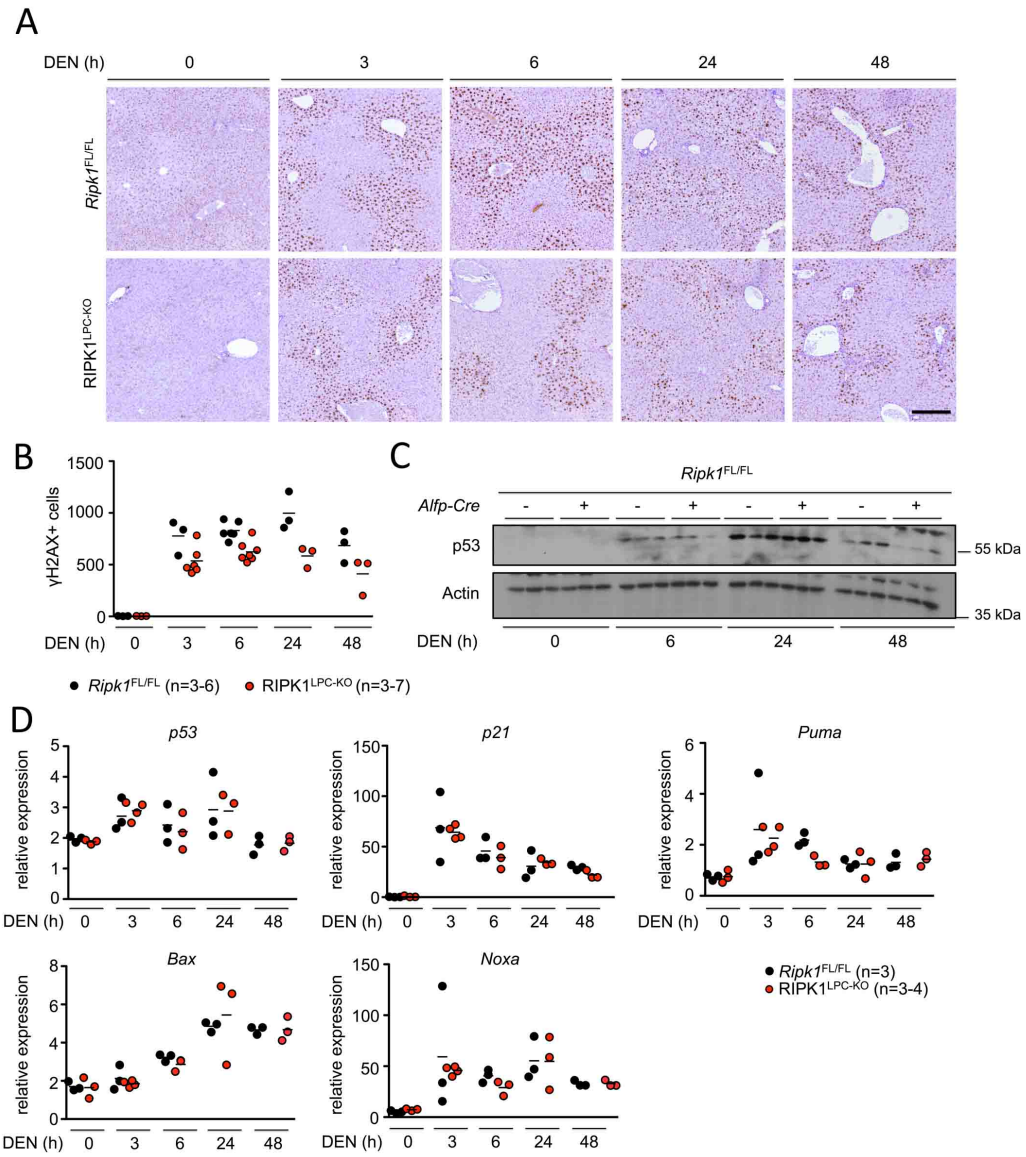
Supplementary Figure 2. RIPK1 and RelA cooperate to prevent spontaneous development of liver inflammation and fibrosis independently of TNFR1 signaling.

(A) Graph depicting the serum Alkaline phosphatase level in 8-week-old mice with the indicated genotypes. Empty data points in the graph correspond to mice with mildly elevated BILT levels (>0.7mg/dl). (One-way Anova, ***P<0.005, *P<0.05, ns= not significant) (B) Representative images of liver sections from 8-week-old RelA^{LPC-KO} RIPK1^{LPC-KO} mice with mildly elevated or normal BILT levels that are immunostained for CK-19 (Scale bar, 200µm). (C) Representative liver images from 8-week-old mice with the indicated genotypes stained with Sirius Red or immunostained for F4/80 (Scale bar, 200µm). (D) Image quantification of Sirius red staining depicted in C (n=3 per genotype, One-way Anova, *P<0.05, ns= not significant).



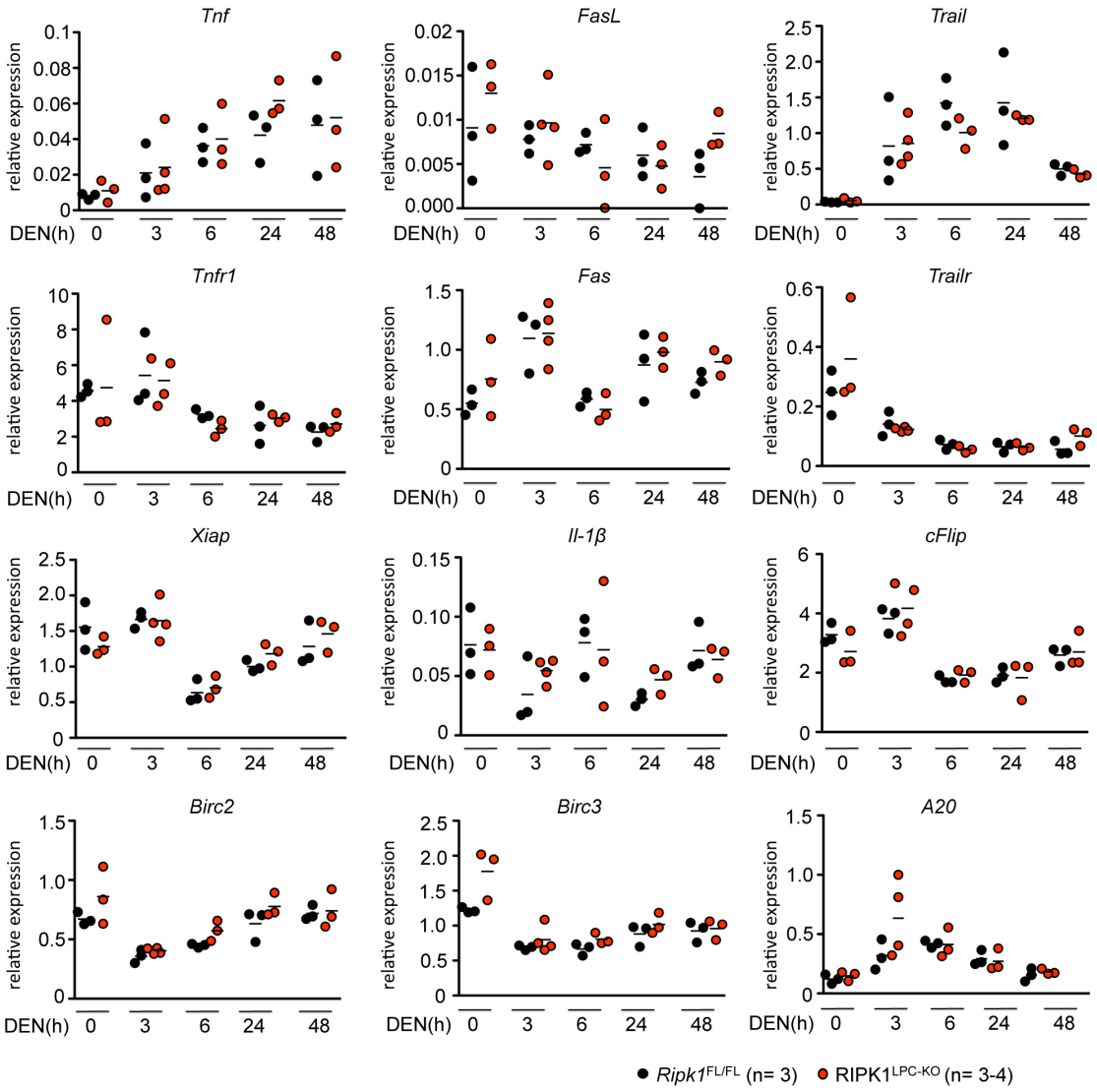
Supplementary Figure 3. RIPK1 promotes DEN-induced liver carcinogenesis.

(A) Graph depicting the bodyweight of DEN-injected *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ mice starting from DEN injection until the age of 36 weeks (mean± SEM). (B) Graph depicting serum ALT and AST levels of DEN-injected *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ mice at 36 weeks of age. (C) Representative pictures of livers and HE stained liver sections from DEN-injected *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ mice at the age of 36 weeks. (D-F) Graphs depicting the size distribution of tumors found in livers of DEN-injected *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ mice at the age of 36 weeks (Chi-square test, ***P<0.005) (D), number of tumors (E) or liver to body weight ratio (F).



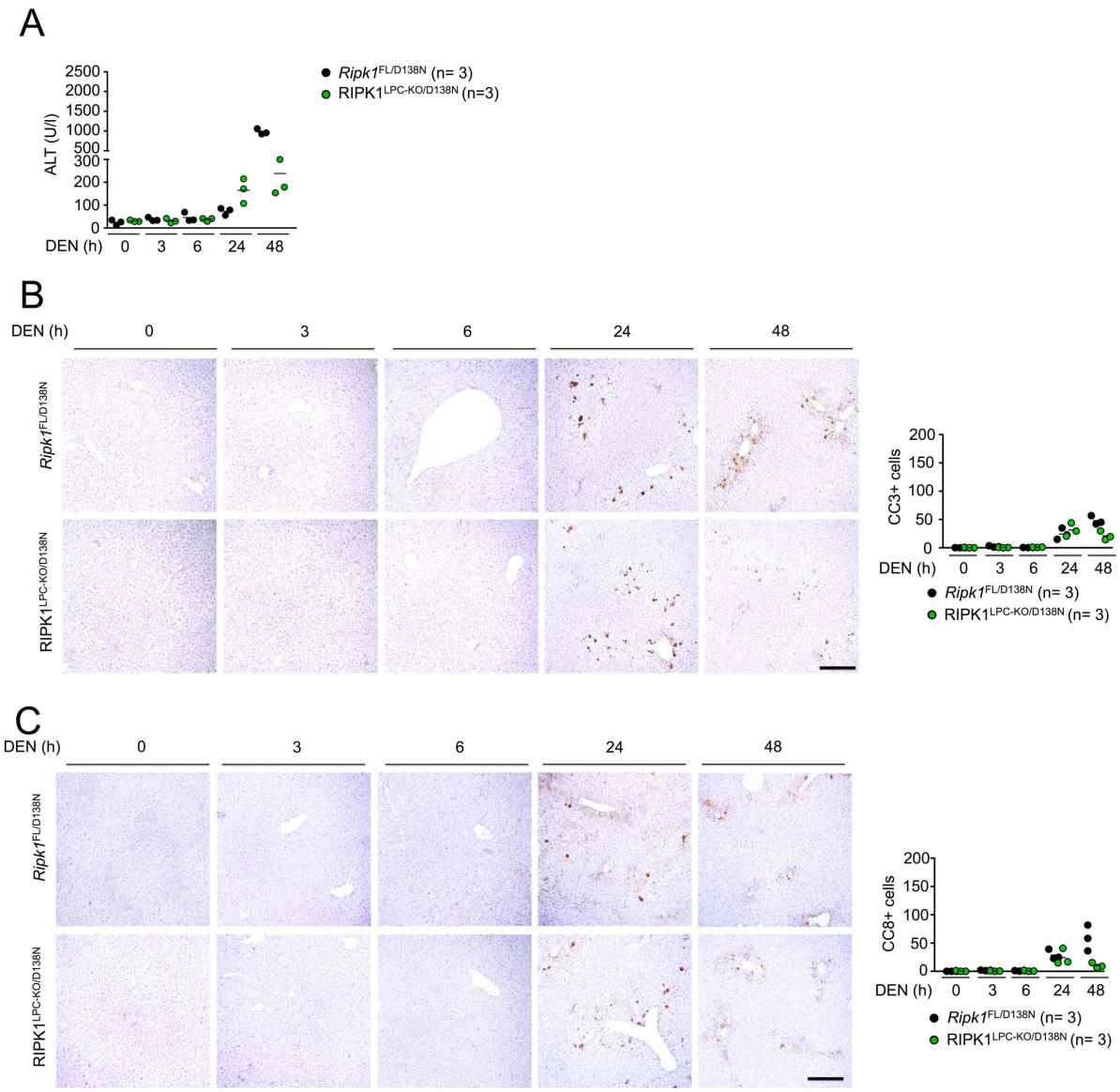
Supplementary Figure 4. RIPK1 deficiency does not affect DEN-induced DNA damage responses in the liver.

(A) Representative images of liver sections from non-injected or with 100mg/kg BW of DEN injected 6-week-old *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ mice stained for γH2AX (n=3-7). Scale bar, 100 µm. (B) Quantification of γH2AX positive cells was performed on 5 fields per animal/genotype/time point. (C) Immunoblot analysis for p53 in liver lysates of non-injected or DEN-injected *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ mice (n=3 per genotype per time point). (D) qRT-PCR analysis of p53 target gene expression in *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ livers. Graphs show relative mRNA expression normalized to *Tbp*.



Supplementary Figure 5. Expression of genes regulating cell survival and death in the liver of DEN-injected mice.

qRT-PCR analysis of the mRNA expression levels of death receptors and their ligands, as well as of pro-survival NF-κB target genes in *Ripk1*$^{FL/FL}$ and RIPK1$^{LPC\text{-}KO}$ livers. Graphs show relative mRNA expression normalized to *Tbp*.



Supplementary Figure 6. RIPK1 kinase activity is not required for DEN-induced hepatocyte apoptosis.

(A) Graph depicting serum ALT level of 6-week-old *Ripk1*$^{FL/D138N}$ and RIPK1$^{LPC\text{-}KO/D138N}$ mice injected with 100mg/kg BW of DEN for the indicated time periods. (B, C) Representative pictures of livers of non-injected or with 100mg/kg BW of DEN injected 6-week-old *Ripk1*$^{FL/D138N}$ and RIPK1$^{LPC\text{-}KO/D138N}$ mice stained for cleaved caspase-3 (B) and cleaved caspase-8 (C) Scale bar, 100 μm. Quantification of cleaved caspase-3 and caspase-8+ cells per field (mean of 5 fields per animal).