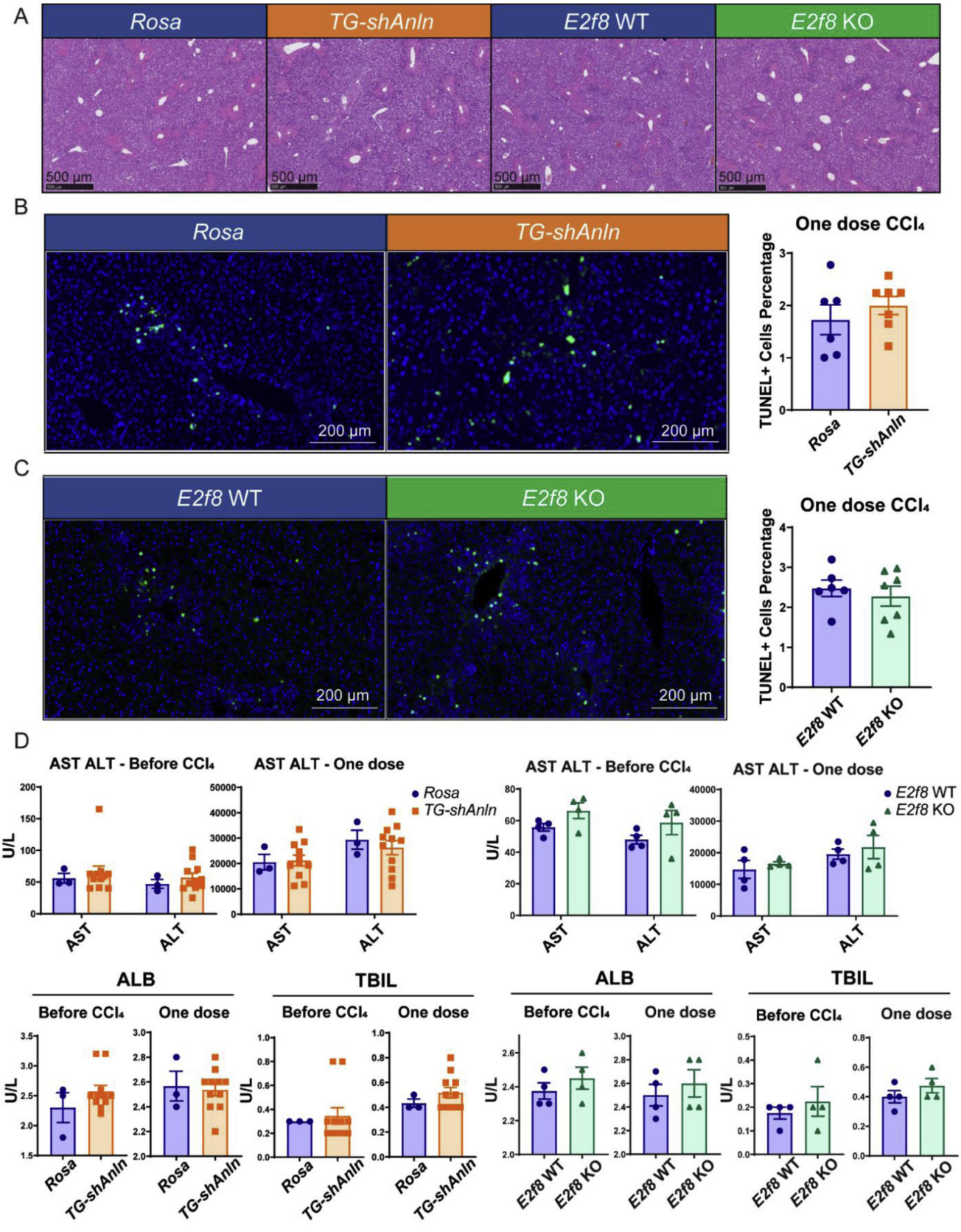
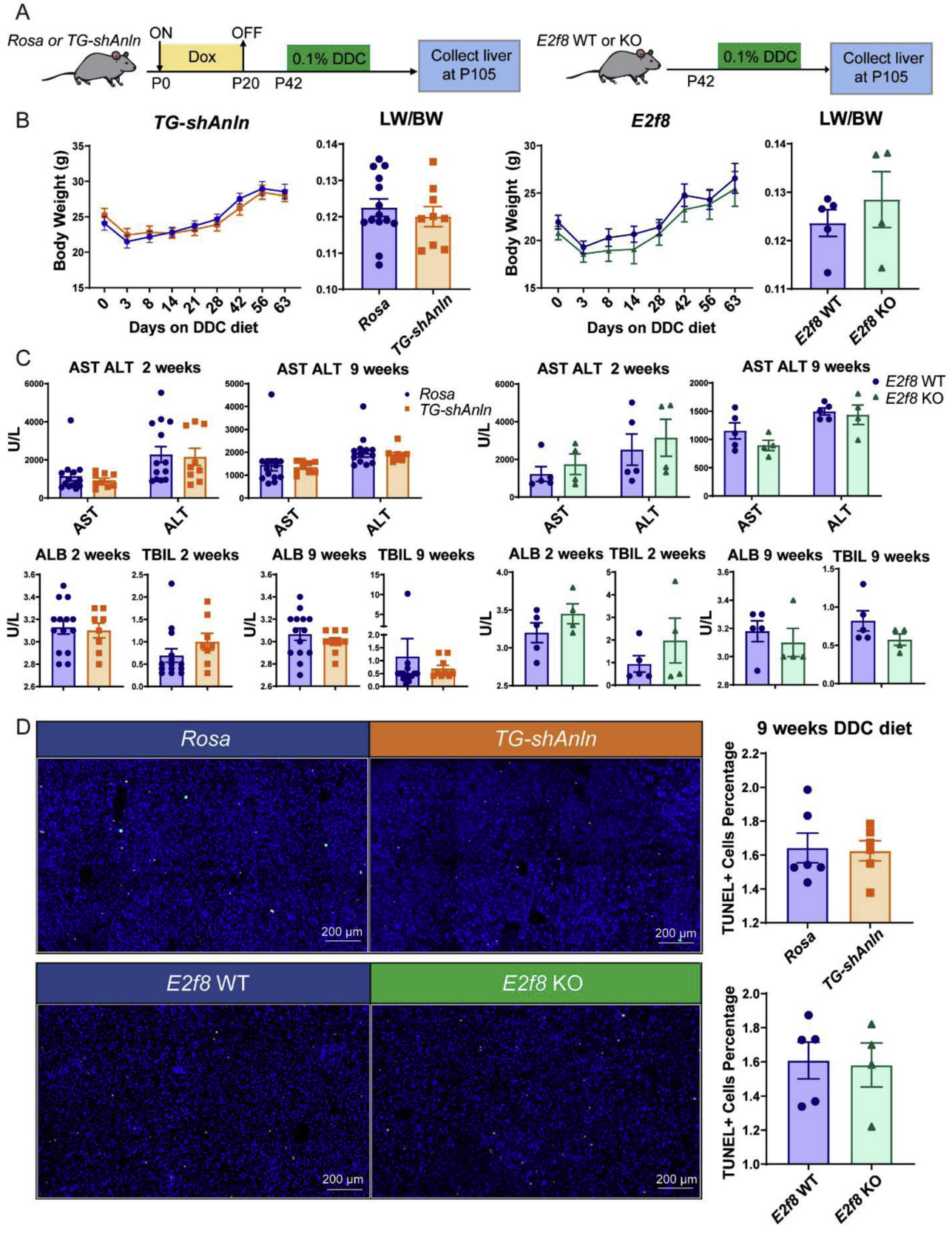
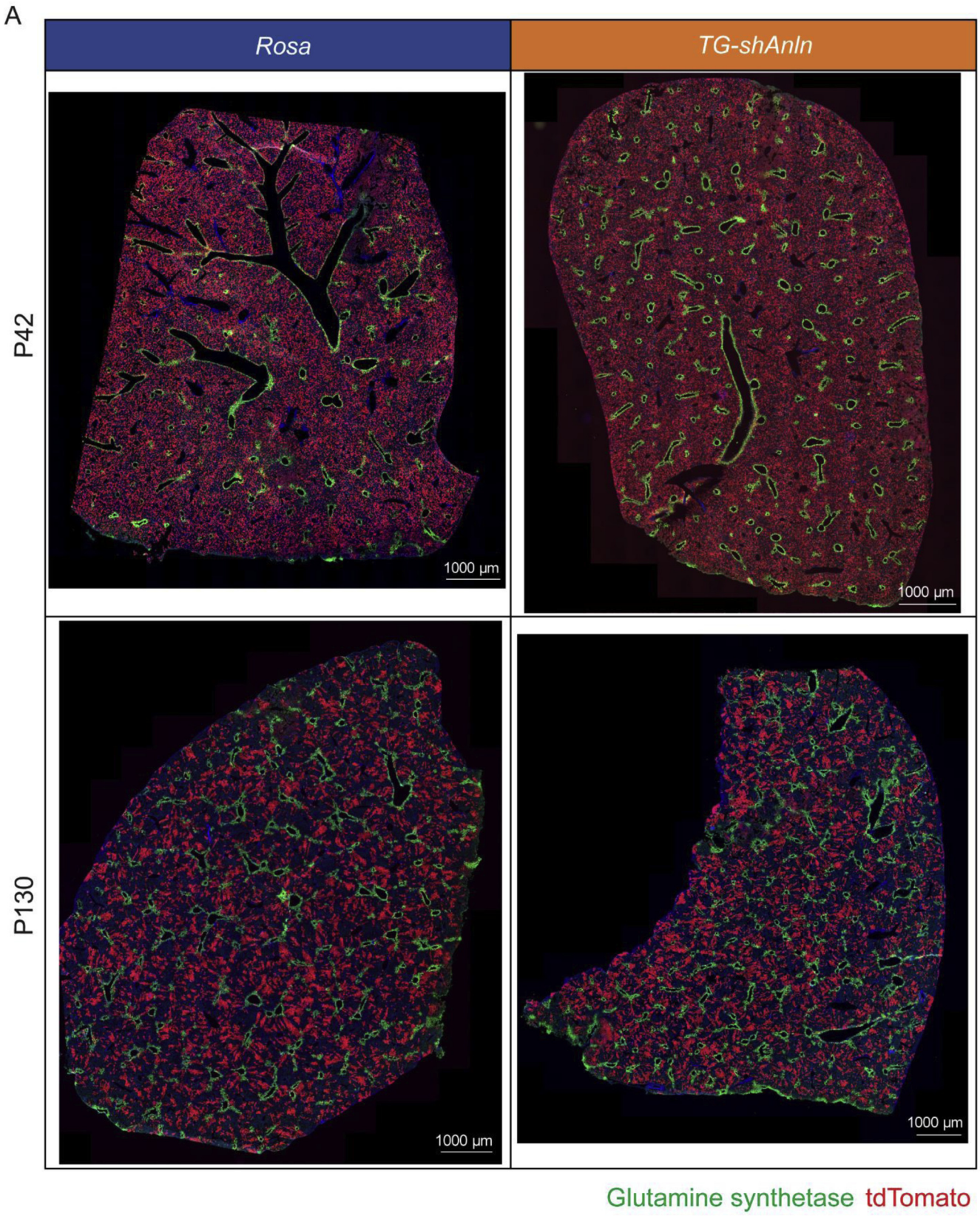

A
Rosa
TG-shAnln
E2f8 WT
E2f8 KO
500 μm
B
Rosa
TG-shAnln
200 μm
One dose CCl4
TUNEL+ Cells Percentage
Rosa
TG-shAnln
C
E2f8 WT
E2f8 KO
200 μm
One dose CCl4
TUNEL+ Cells Percentage
E2f8 WT
E2f8 KO
D
AST ALT - Before CCl4
AST ALT - One dose
U/L
AST
ALT
Rosa
TG-shAnln
E2f8 WT
E2f8 KO
ALB
TBIL
Before CCl4
One dose

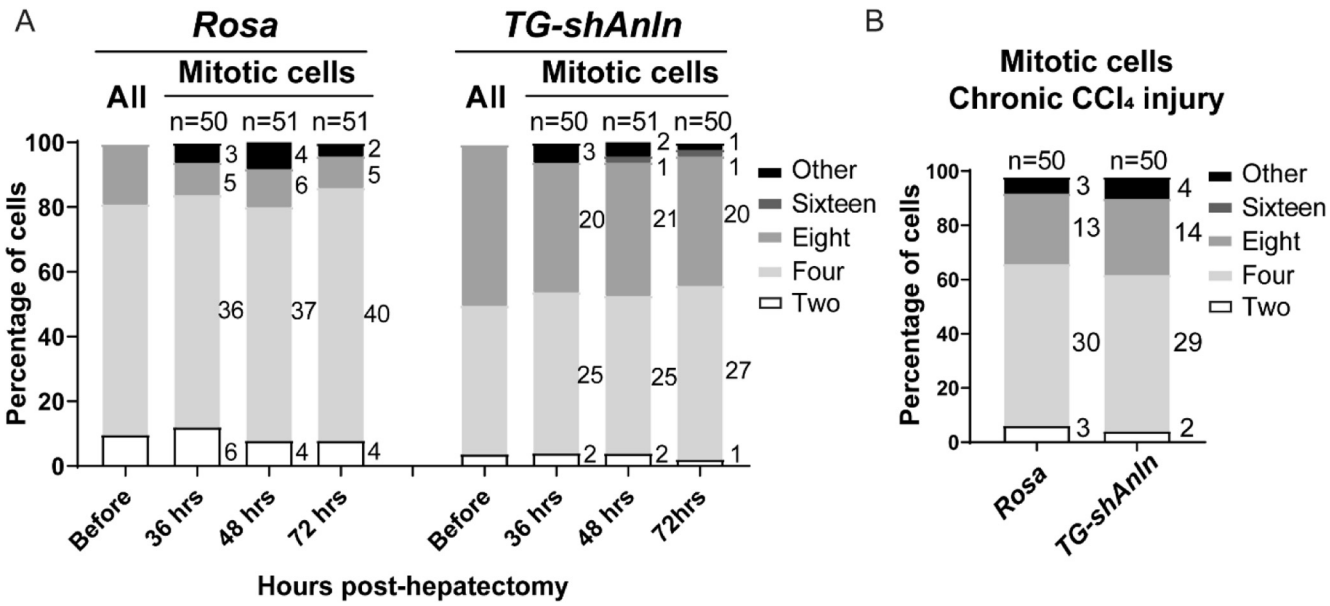
Supplementary Figure 5. Polyploidy does not have a differential impact after 1 dose of CCl_4. Related to Figure 3. (*A*) Hematoxylin-eosin staining of *Rosa*, *TG-shAnln*, *E2f8* WT, and KO livers 48 hours after 1 dose of CCl_4. (*B*) Apoptosis in *Rosa* and *TG-shAnln* livers 48 hours after 1 dose of CCl_4 as measured by terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick-end labeling (TUNEL) staining. The percentage of TUNEL-positive cells was quantified in whole slide images, shown on the right (n = 6 for *Rosa*, n=7 for *TG-shAnln*). (*C*) Apoptosis of *E2f8* WT and KO livers 48 hours after 1 dose of CCl_4 as measured by TUNEL staining. The percentage of TUNEL-positive cells was quantified in whole slide images, shown on the right (n = 6 for *E2f8* WT, n = 7 for *E2f8* KO). (*D*) Liver function tests performed before and after 1 dose of CCl_4 (n = 3 for *Rosa* and n = 11 for *TG-shAnln*, n = 4 for *E2f8* WT and KO).


A
Rosa or TG-shAnln
ON
OFF
Dox
P0
P20
P42
0.1% DDC
Collect liver at P105
E2f8 WT or KO
P42
0.1% DDC
Collect liver at P105
B
TG-shAnln
LW/BW
E2f8
LW/BW
Body Weight (g)
Days on DDC diet
Rosa
TG-shAnln
E2f8 WT
E2f8 KO
C
AST ALT 2 weeks
AST ALT 9 weeks
Rosa
TG-shAnln
E2f8 WT
E2f8 KO
U/L
AST
ALT
ALB 2 weeks
TBIL 2 weeks
ALB 9 weeks
TBIL 9 weeks
D
Rosa
TG-shAnln
E2f8 WT
E2f8 KO
200 μm
9 weeks DDC diet
TUNEL+ Cells Percentage

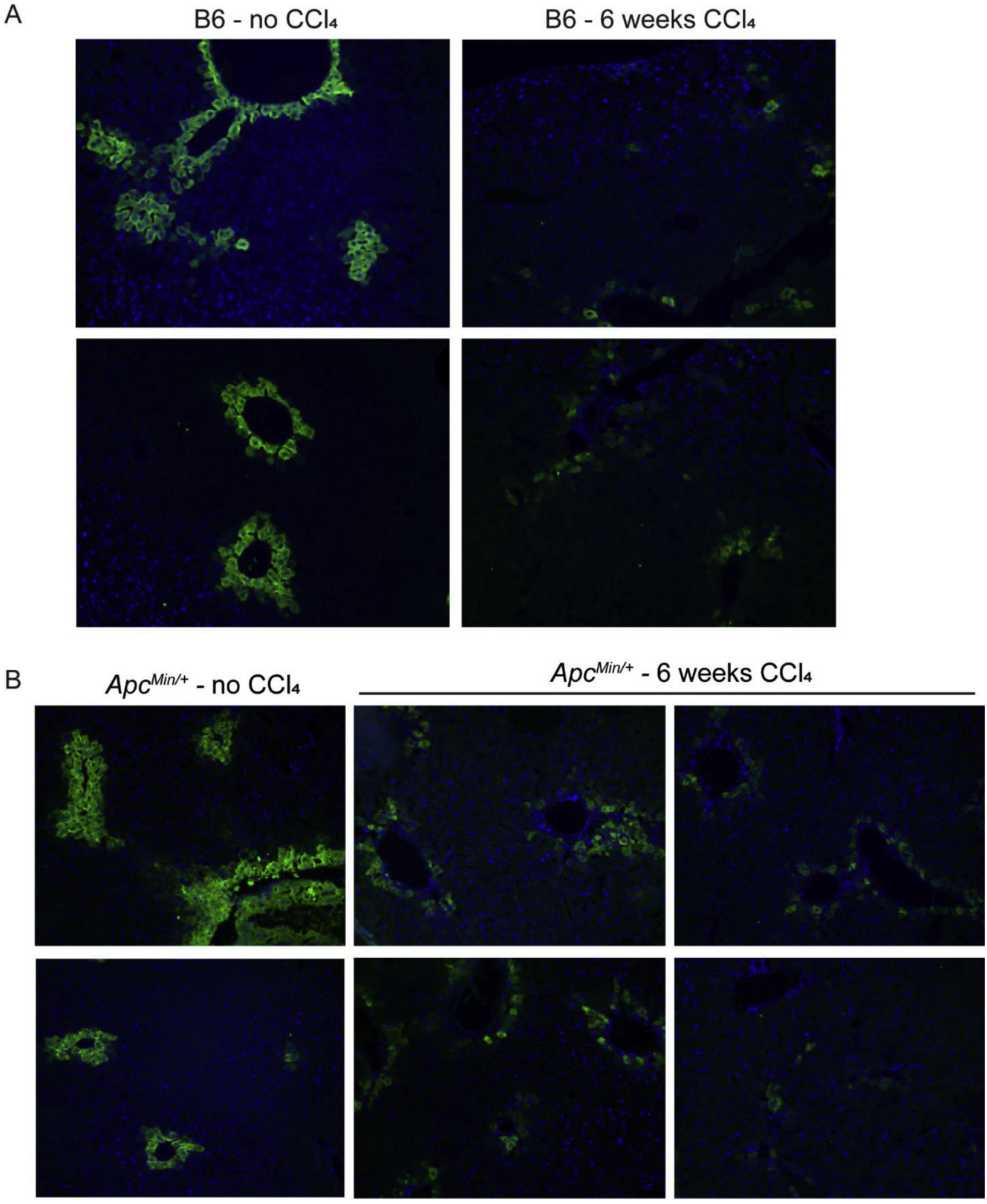
Supplementary Figure 6. Polyploidy does not influence liver damage mediated by DDC. Related to Figure 3. (*A*) Schema for the DDC experiment in inducible short hairpin RNA mice (left) and *E2f8* KO mice (right). Transient doxyclyclin treatment from P0 to P20 in *Rosa-rtta* or *TG-shAnln* mice established ploidy differences. DDC diet was started at P42. The body weights were monitored and livers were harvested after 9 weeks of the DDC diet. (*B*) Body weight over a 9-week period and the liver and body weight ratios after 9 weeks of DDC diet (n = 14 for *Rosa*, n = 9 for *TG-shAnln*, n = 5 for *E2f8* WT, and n = 4 for *E2f8* KO). (*C*) Liver function tests after 2 weeks and 9 weeks of DDC diet (n = 14 for *Rosa*, n = 9 for *TG-shAnln*, n = 5 for *E2f8* WT, and n = 4 for *E2f8* KO). (*D*) Apoptosis after 9 weeks of DDC as measured by TUNEL staining. The percentage of TUNEL positive cells was quantified in whole slide images, shown on the right (n = 6 for *Rosa* and *TG-shAnln*, n = 5 for *E2f8* WT, and n = 4 for *E2f8* KO).



Supplementary Figure 7. Hepatocytes contribute to liver regeneration during chronic CCl_4 injury. Related to Figure 4. Representative whole slide images from the tdTomato lineage tracing experiment. GS is shown in green and tdTomato is shown in red.



Supplementary Figure 8. Polyploid hepatocytes undergo mitosis during different stages of surgical-induced and chronic chemical injury-induced regeneration. Related to Figure 5. (*A*) Transient doxycycline treatment established ploidy differences. *Rosa* or *TG-shAnln* were subjected to 70% partial hepatectomy, and the livers were collected at different timepoints after hepatectomy. Ploidy distribution before injury is determined by flow. Ploidy of mitotic hepatocytes is estimated by centrosome number (quantified γ-tubulin foci). More than 50 mitotic cells from 2 mice were measured in each condition. (*B*) *Rosa* or *TG-shAnln* were subjected to biweekly CCl_4 for 12 weeks. Livers were harvested 48 hours after the last dosage of CCl4. Ploidy of mitotic hepatocytes is estimated by centrosome number (quantified γ-tubulin foci). Fifty mitotic cells from 4 mice were measured in each group.



Supplementary Figure 9. Chronically injured heterozygous *Apc*^{Min} livers do not readily develop *Apc* LOH. Related to Figure 5. (*A*) GS staining of WT mice without or after 6 weeks of biweekly CCl_4. (*B*) GS staining of *Apc*^{Min} mice without or after 6 weeks of biweekly CCl_4.