

Supplemental Figure 1. Adenovirus-mediated targeting of HSCs (A-C)

Immunofluorescence analysis of liver sections of adult C57BL/6 wild type mice injected with GFP-expressing adenoviruses (Ad-GFP). Pictures of liver cells co-expressing GFP and the HSCs marker desmin (A), the hepatocyte marker HNF4 (B) and Lectin from *Bandeiraea simplicifolia* (C). Arrowheads indicate cells co-expressing both markers. (D) Quantification of double labelled cells for GFP and Desmin, GFP and HNF4, and GFP and lectin (percentage per total cells) in liver of adult mice C57BL/6 wild type injected with Ad-GFP (n=3 each group). (E) PCR using specific primers for *Gata4* on genomic DNA from liver of wild type (+/+), *Gata4* floxed mice injected with *Cre*-expressing adenovirus (*Gata4*^{flx/flx}; Ad-Cre) or GFP-expressing adenovirus (*Gata4*^{flx/flx}; Ad-GFP) demonstrates *Cre*-mediated excision of the *Gata4* floxed alleles. Polarized light microscopy pictures of Sirius-red-stained liver sections of *Gata4*^{+/+} control mice injected with *Cre*-expressing adenovirus (Ad-Cre) (F) or with GFP-expressing adenovirus (Ad-GFP) (G) and *Gata4*^{flx/flx} mice injected with GFP-expressing adenovirus (Ad-GFP) (H). (I) Quantification of Sirius red-stained area of liver per total tissue area in each experimental group (n=3 each group). Scale bars= 25µm for A-B; 100µm for C, F-H. Statistical analyses was performed using two-tailed Student Test. Error bars represent mean ± SEM.

Supplemental Figure 2. Labelling of *G2Cre*-targeted cells. (A) Immunofluorescence analysis of YFP and Desmin accumulation in liver sections of adult *G2-Cre*; *ROSA26ReYFP* mice. (B) Quantification of cells coexpressing YFP and Desmin relative to total Desmin-positive cells in liver of *G2-Cre*; *ROSA26ReYFP* mice (n=3). Scale bars: 25µm.

Supplemental Figure 3. CCl₄-treatment induce liver fibrosis similarly in male and female mice. (A) Relative quantification of Sirius red-stained area per total liver area in

CCl₄-treated and control-treated (oil) adult male and female C57BL/6 mice. Polarized light microscopy pictures of Sirius-red-stained liver sections from CCl₄-treated male (D) and female mice (E) and control-treated (oil) (B) male and female mice (C) (n=3). (F) Serum AST levels in CCl₄-treated and control-treated (oil) male and female adult mice (n=3 oil; n=6 CCl₄). (G) Serum ALT levels in CCl₄-treated and control-treated (oil) male and female adult mice (n=3 oil; n=6 CCl₄). Scale bars: 100μm. Statistical analyses was performed using two-tailed Student Test. Error bars represent mean ± SEM. **p < 0.01.

Supplemental Figure 4. *Gata4* expression during liver fibrosis regression. (A)

Quantitative RT-PCR analysis of *Gata4* expression and relative quantification of Sirius red-stained area per total liver area (B) (n=3-4) of mice treated with vehicle (oil), CCl₄ and two-three and 4-weeks after CCl₄ treatment (recovery phase) (n=3-4). Statistical analyses was performed using one-way ANOVA test. Error bars represent mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001.

Supplemental Figure 5. Vascular hemorrhage in *G2-Cre;HIF2dPA* embryos.

Representative pictures of whole E13.5 *G2-Cre;HIF2dPA* (B) and control littermate embryos (A). (C, D) Immunostaining for HIF2α in E13.5 embryonic hearts of control and *G2-Cre;HIF2dPA* embryos. Note the accumulation of HIF2α protein in the epicardium of *G2-Cre;HIF2dPA* embryos (arrows in D) compared with control embryos. Hematoxylin-eosin staining of heart sections of E13.5 *G2-Cre;HIF2dPA* (F) and littermate control embryos (E). (G, H) Higher magnification images of panels E and F. The hearts of E13.5 *G2-Cre;HIF2dPA* embryos display a thinner ventricular septum and a more compacted myocardium (marked by double arrows) compared to control embryonic hearts. The hearts of E13.5 *G2-Cre;HIF2dPA* embryos show lack of

myocardial compaction, ventricular trabeculae close to the epicardium (J, arrowheads) and epicardium distended from the underlying myocardium (J, arrows) compared to control hearts (I). At least 4 embryos per experimental group (from two independent litters) were analyzed. Scale bars: 500 μ m for A, B, E and F; 100 μ m for C, D, G and H; 25 μ m for I and J.

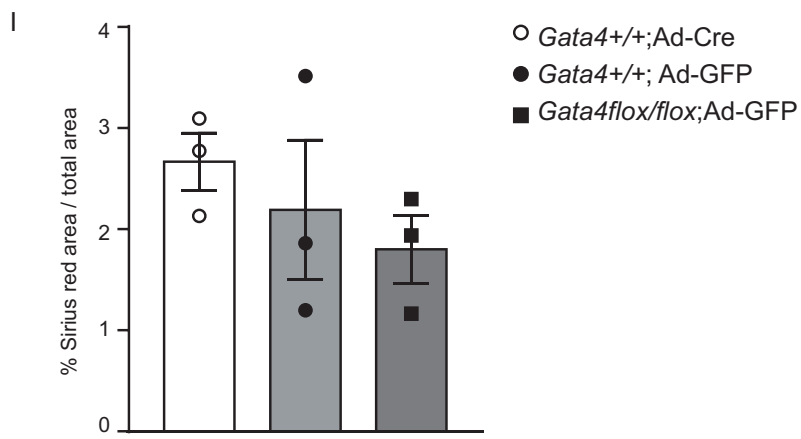
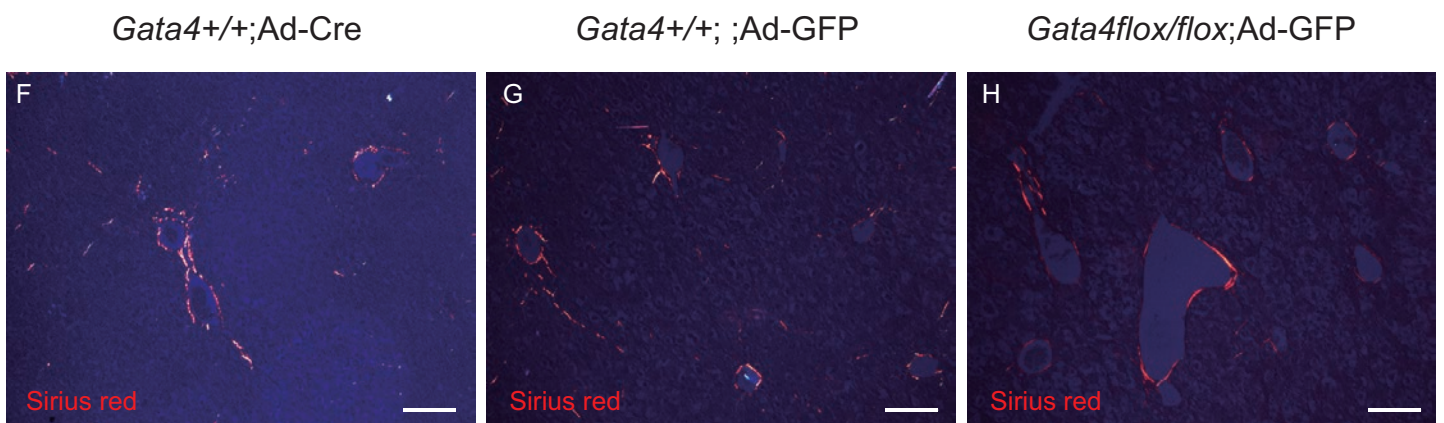
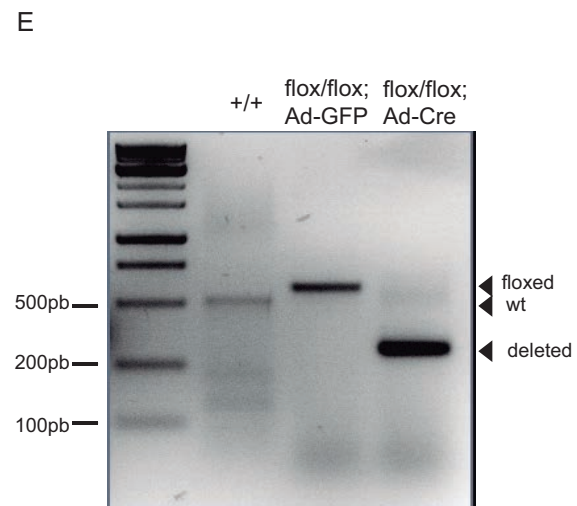
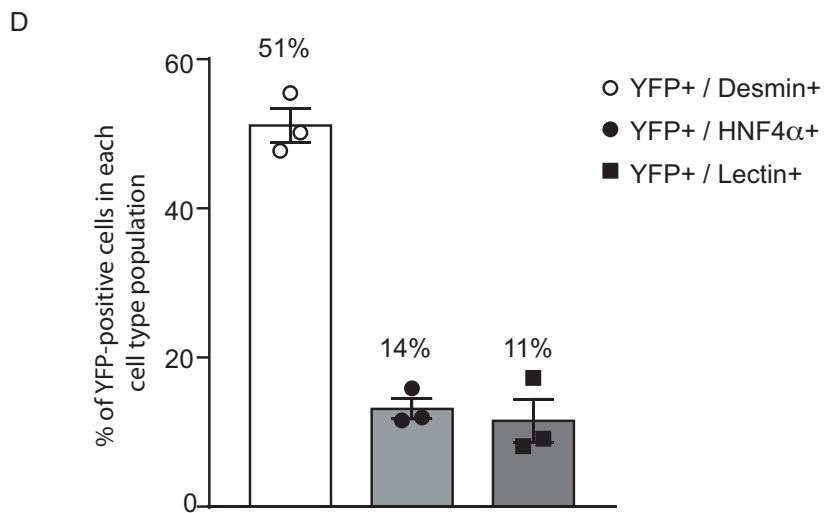
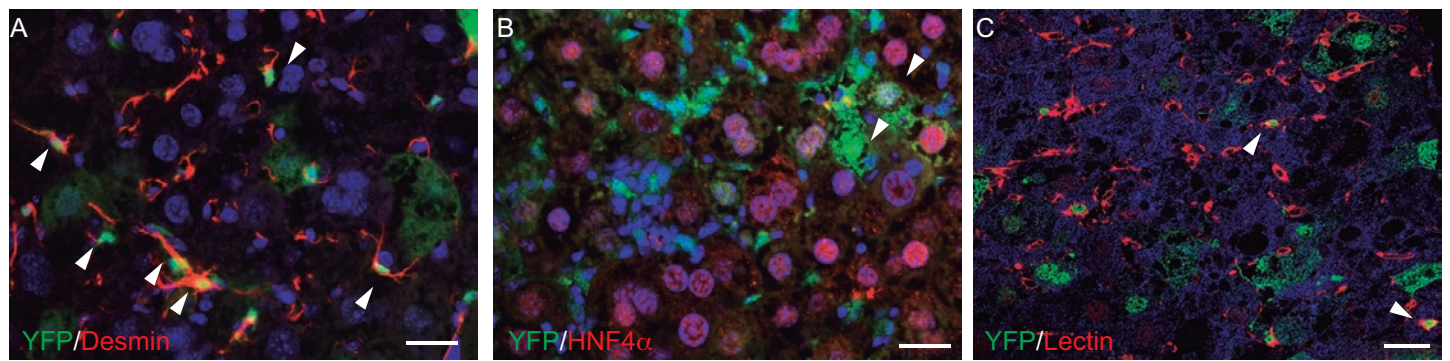
Supplemental Figure 6. Proliferation analysis in *G2-Cre;HIF2dPA* liver embryos.

Hepatocytes (marked by HNF4 α immunoreactivity) of E15.5 embryonic *G2-Cre;HIF2dPA* livers (B) show decreased proliferation (assessed by Ki-67 immunofluorescence) compared with control embryonic livers (A). Arrowheads in A and B indicate double labelled cells for HNF4 α and Ki-67. (C) Quantification of proliferating hepatocytes (positive for HNF4 α) in E15.5 embryonic livers (n=3 each group). Reduced hepatic stellate cell (marked by desmin immunofluorescence) proliferation in E15.5 embryonic *G2-Cre;HIF2dPA* livers (E) compared with control embryonic livers (D) (n=3 each group). Arrows in D and E indicate double labelled cells for Desmin and Ki-67. (F) Quantification of proliferating hepatic stellate cells (positive for desmin) in E15.5 embryonic livers (n=3 each group). Immunostaining for cleaved Caspase 3 in control liver (G) or *G2-Cre;HIF2dPA* (H) of E15.5 embryos. Scale bars: (A, B, D, E, G, H): 10 μ m. Statistical analyses was performed using two-tailed Student Test. Error bars represent mean \pm SEM. *p < 0.05.

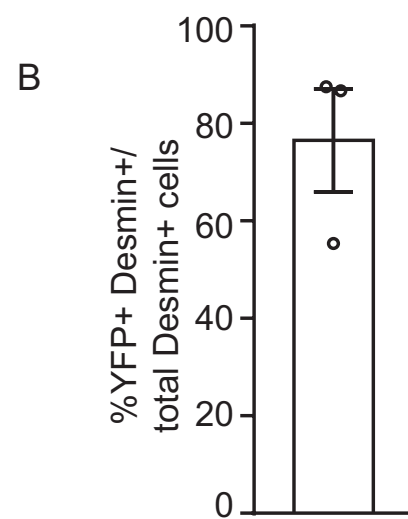
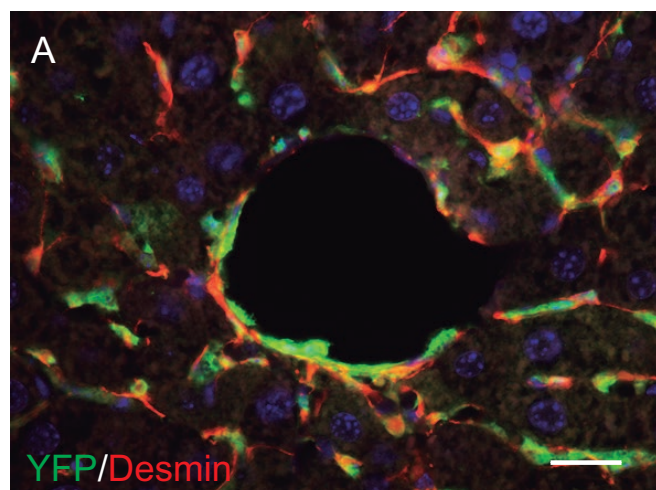
Supplemental Table 1: List of primers used for RT-PCR

GENE	SEQUENCES
mouse <i>Gata4</i> deletion floxed alleles	Rec2: TCCATGAGACCCCAGAGTGTGCCTGAG Rec4: ACCCTGGAAGACACCCCAATCTCGG Rec5: TGTCATTCTTCGCTGGAGCCGC
mouse TIMP1	Forward ACC TGG TCA TAA GGG CTA AA Reverse ATT TCC CAC AGC CTT GAA TC
mouse IL-6	Forward CAG AGT CCT TCA GAG AGA TAC A Reverse GTG ACT CCA GCT TAT CTG TTA G
mouse TGFBR1	Forward TGC CAT AAC CGC ACT GTC A Reverse AAT GAA AGG GCG ATC TAG TGA TG
mouse TGFBR2	Forward GAG TCG TTC AAG CAG ACG GA Reverse GAA CCA AAT GGG GGC TCG TA
mouse PDGFRA	Forward GGA AGG CAC AGA AGC AAT A Reverse GGC TCA GTC TTC ACA CTT AC
mouse PDGFRB	Forward GTC CTT ACC GTC ATC TCT CT Reverse CAC AGA CTC AAT GAC CTT CC
mouse TLR4	Forward CAA CAT CAT CCA GGA AGG C Reverse GAA GGC GAT ACA ATT CCA CC
mouse SMAD7	Forward GGG CTT TCA GAT TCC CAA CTT Reverse CAC GCG AGT CTT CTC CTC C
mouse STAT1	Forward GAT CTC TAA CGT CTG TCA GCT G Reverse GAG GTC CAG GAT TCC TTC GA TC
mouse TCF21	Forward AGG TCA TTC TCT GGT TTG CC Reverse GCT ACA TCG CTC ACT TAA GGC
mouse GATA4 EX2	Forward GTG GCC CTG GCG CCT TCA TG Reverse TCC CAG GCC CTG CAC CCG AC
mouse β -ACT	Forward TCC TGT GGC ATC CAC GAA ACT Reverse ACC AGA CAG CAC TGT GTT GGC
human TGFBR1	Forward GGA CCA TTG TGT TAC AAG A Reverse CCA TGC TCA TGA TAA TCT G
human TGFBR2	Forward GTA GCT CTG ATG AGT GCA A Reverse CAG ATA TGG CAA CTC CCA G
human PDGFRA	Forward AAA GAA GTT CCA GAC CAT C Reverse AGG TGA CCA CAA TCG TTT CC
human PDGFRB	Forward CAG CAA GGA CAC CAT GCG G Reverse GGG GCT CCT GGG ACA TCC GT
human SMAD7	Forward AGA AGG TGC GGA GCA AAA T Reverse GTG TGG CGG ACT TGA TGA
human STAT1	Forward CTA GTG GAG TGG AAG CGG A Reverse CAC CAC AAA CGA GCT CTG AA
human TCF21	Forward TCC TGG CTA ACG ACA AAT AC Reverse TTT CCC GGC CAC CAT AAA GG
human β -ACT	Forward GAT CAG CAA GCA GGA GTA TG Reverse AAG GGT GTA ACG CAA CTA AG

Supplemental Figure 1

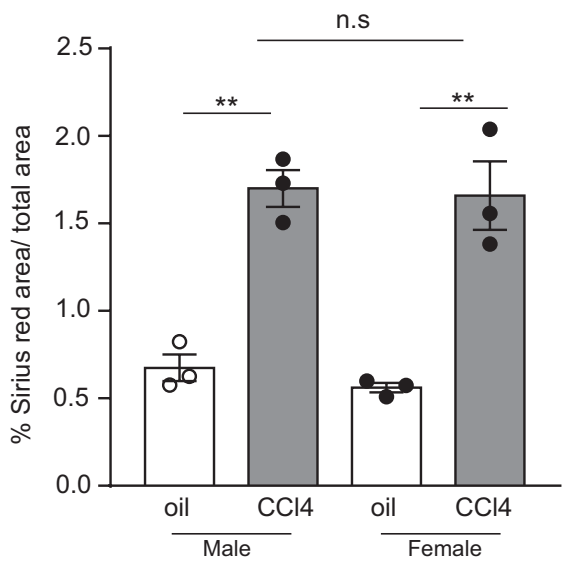


Supplemental Figure 2



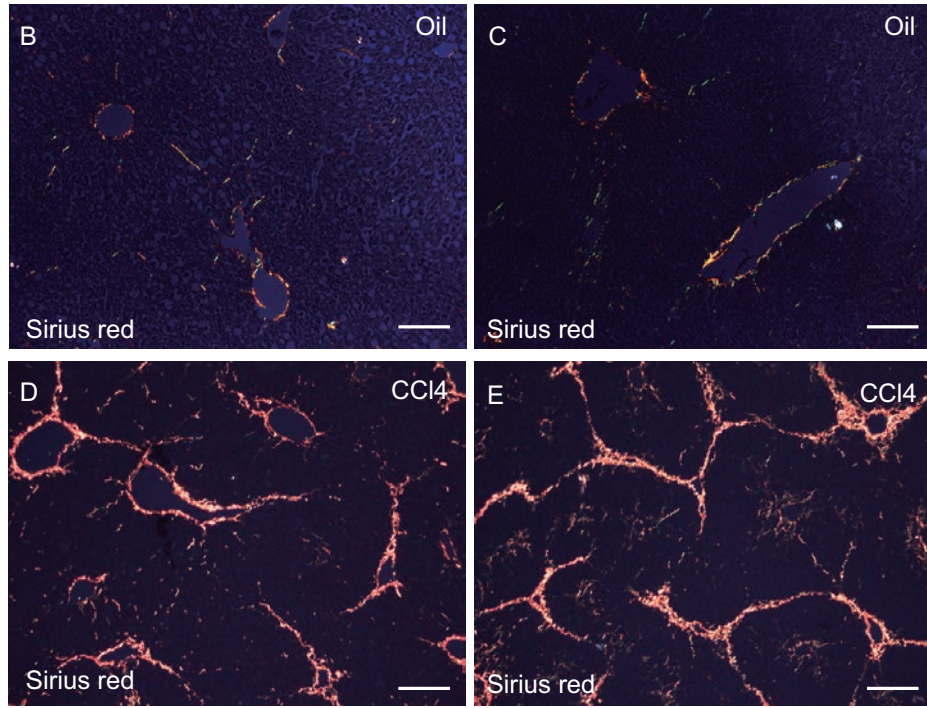
Supplemental Figure 3

A

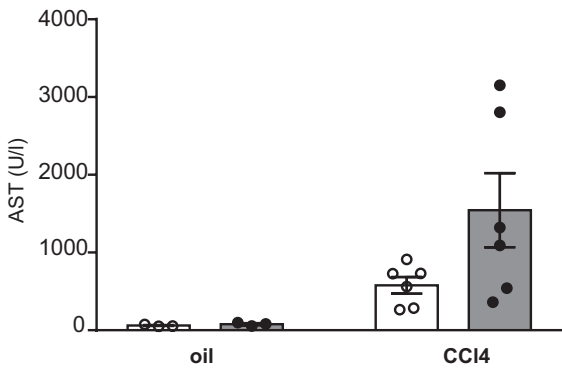


Male

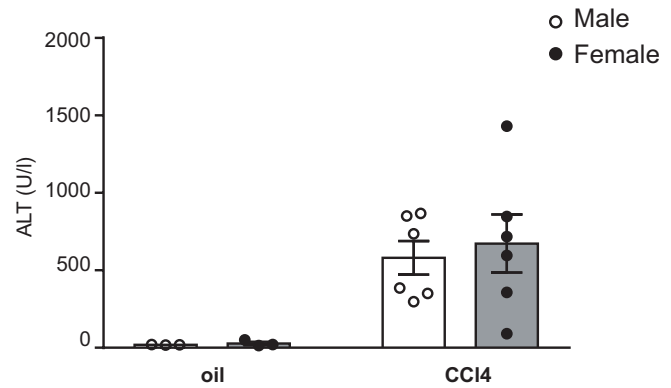
Female



F

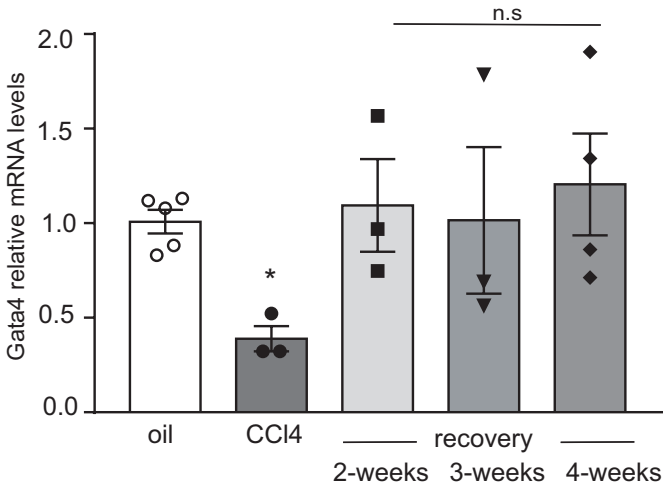


G

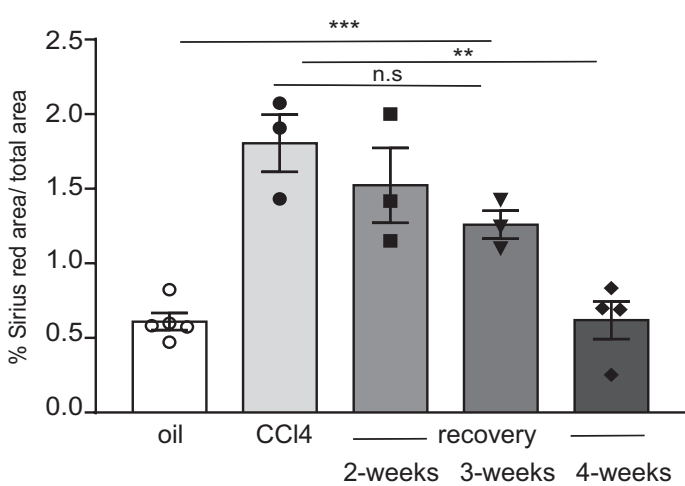


Supplemental Figure 4

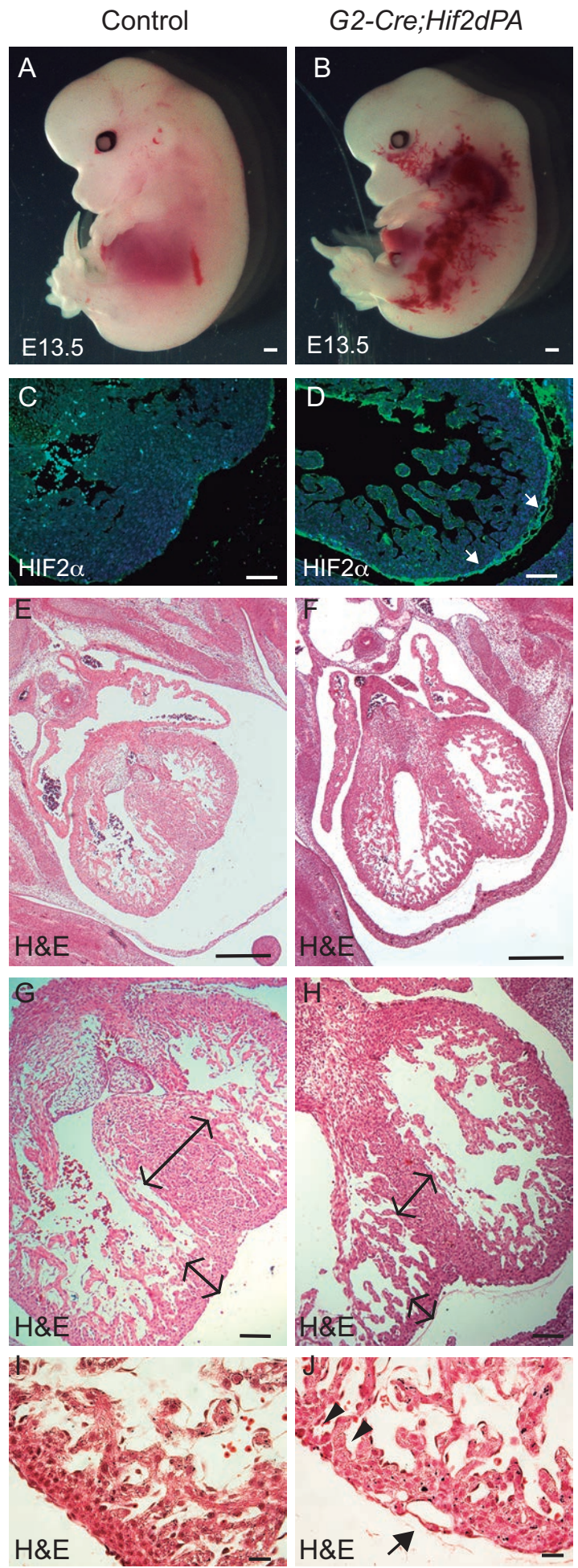
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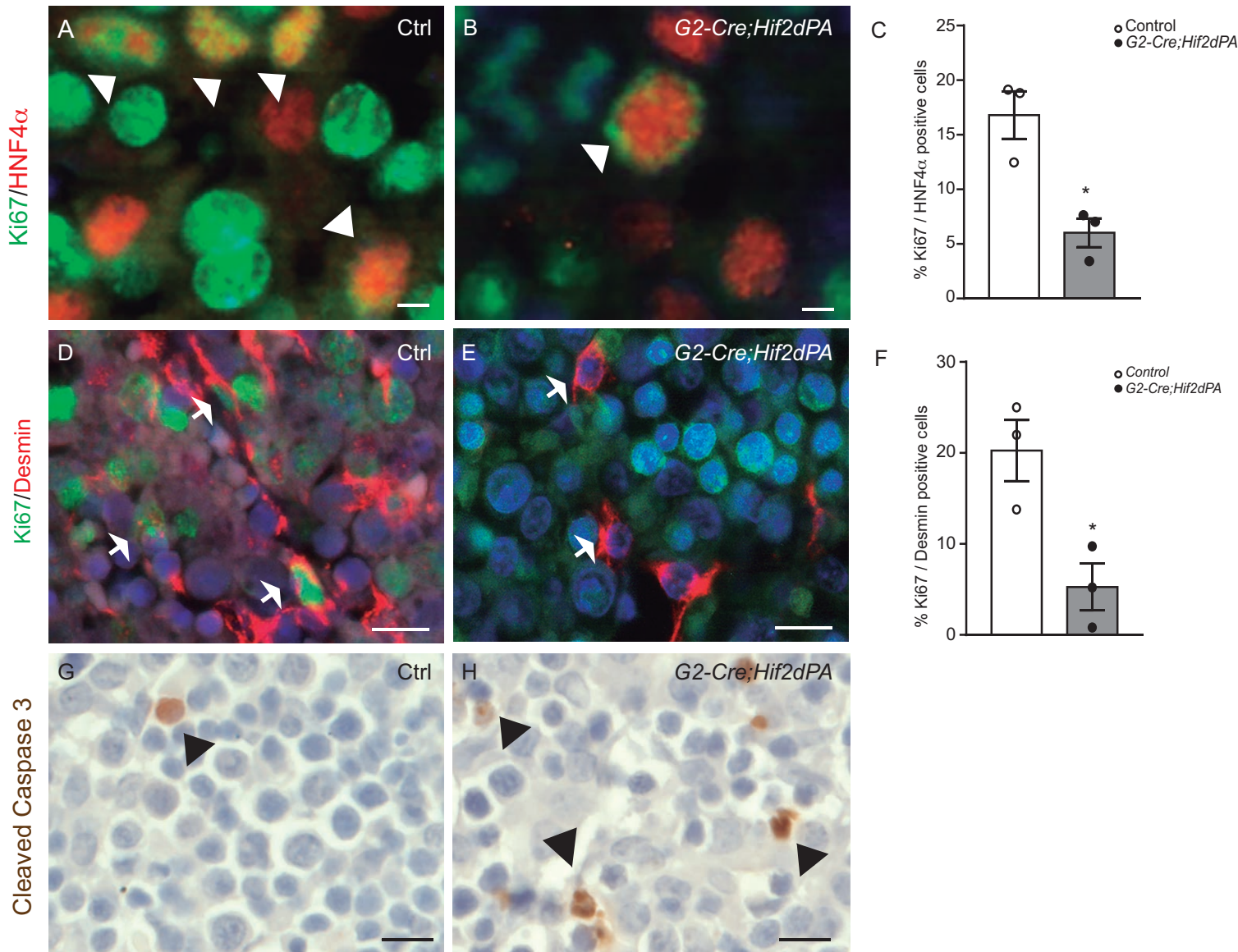
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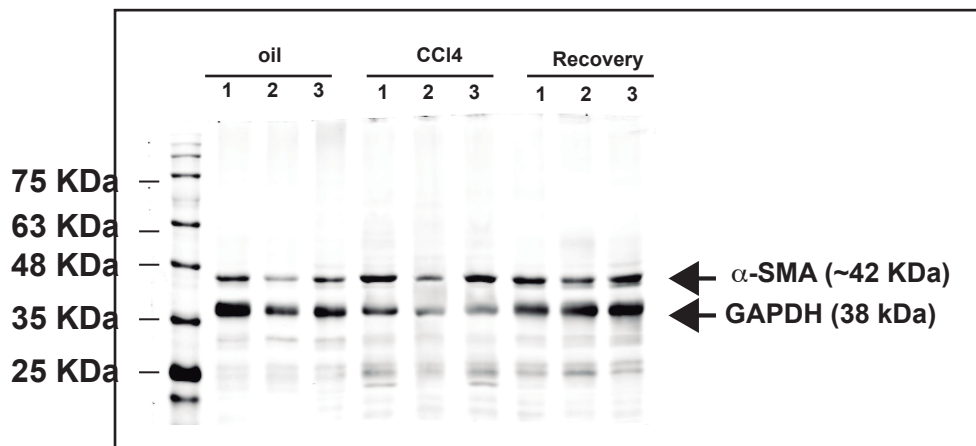
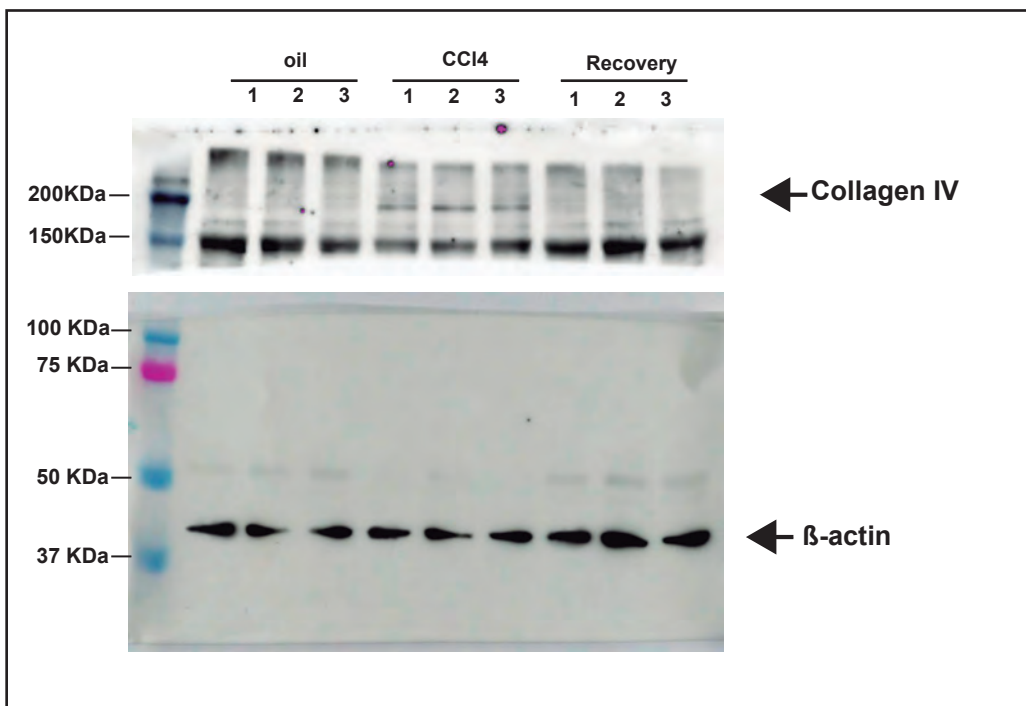
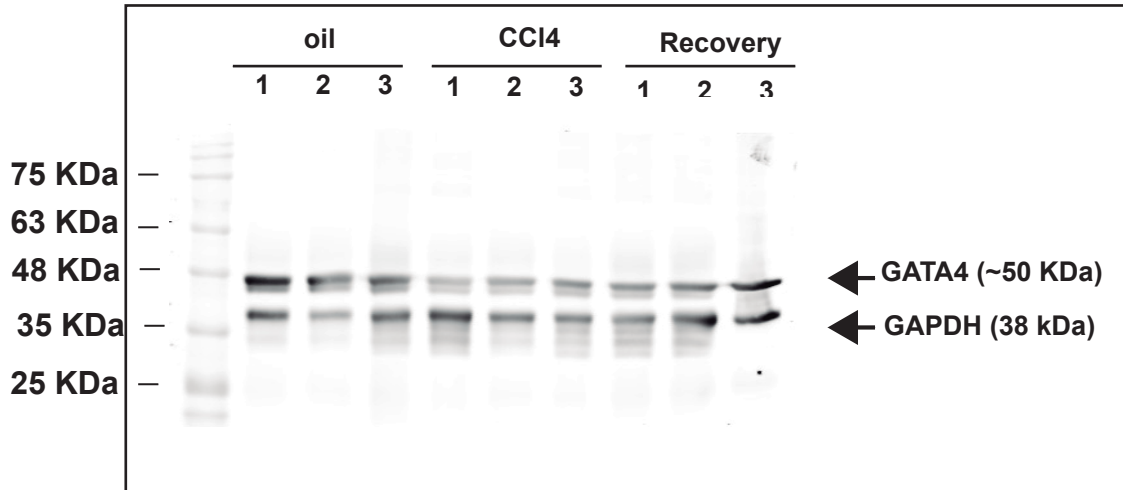
Supplemental Figure 5



Supplemental Figure 6



Uncropped gels Figure 2



Uncropped gels Figure 4

