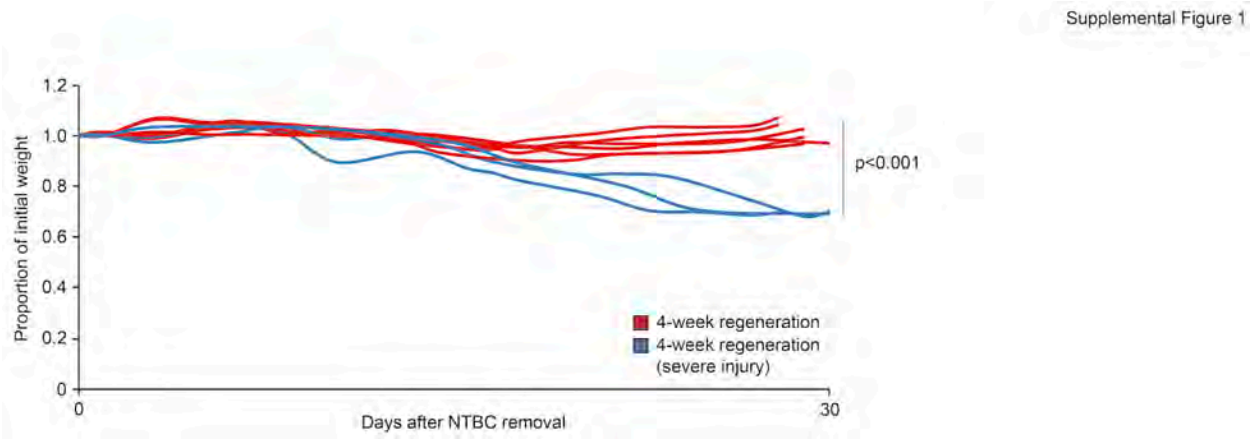
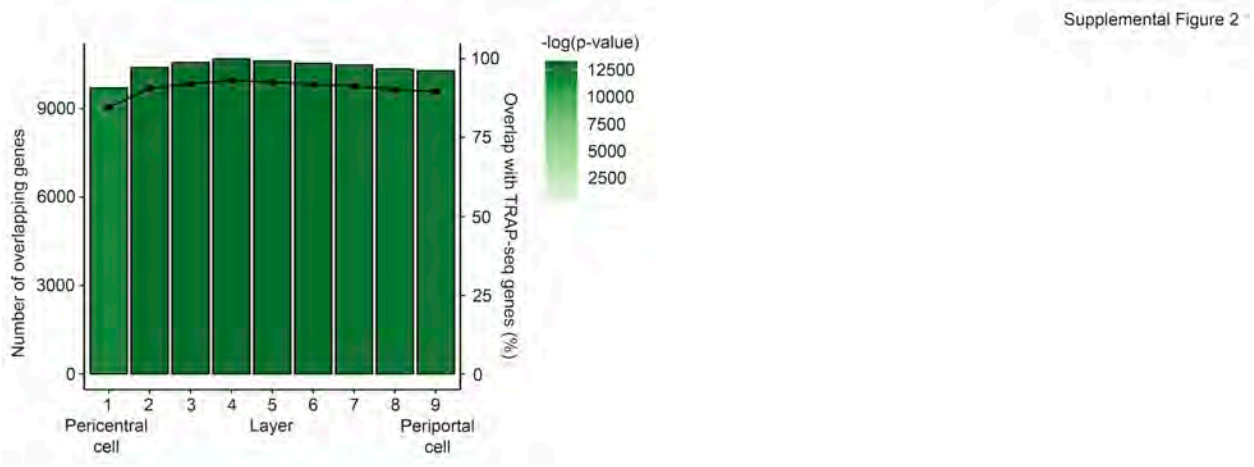
SUPPLEMENTAL DATA

Supplemental Figures

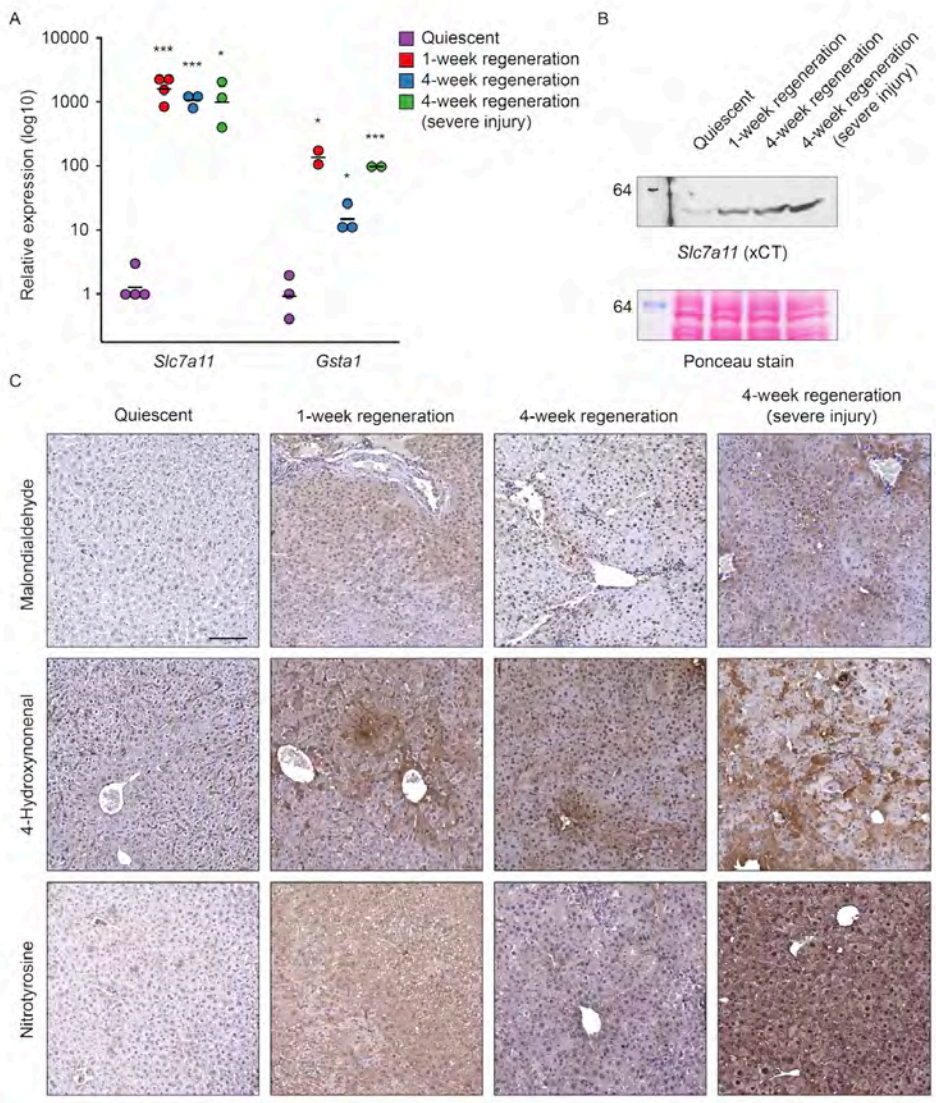


Supplemental Figure 1. Mice in the 4-week regeneration after severe injury group exhibit significant weight loss. The proportion of weight loss was normalized to the initial weight prior to plasmid injection and NTBC removal. Body weight was monitored three times per week after induction of liver injury and regeneration. After four weeks of injury and regeneration, three mice lost ~30% of the starting weight (blue), significantly different from mice in the 4-week regeneration group that underwent initial weight loss but restored body weight after four weeks (red). A two-sided, two-tailed Student's t-test was used to compare the proportion body weight in the 4-week regeneration (n=6) and 4-week regeneration after severe injury (n=3) groups.



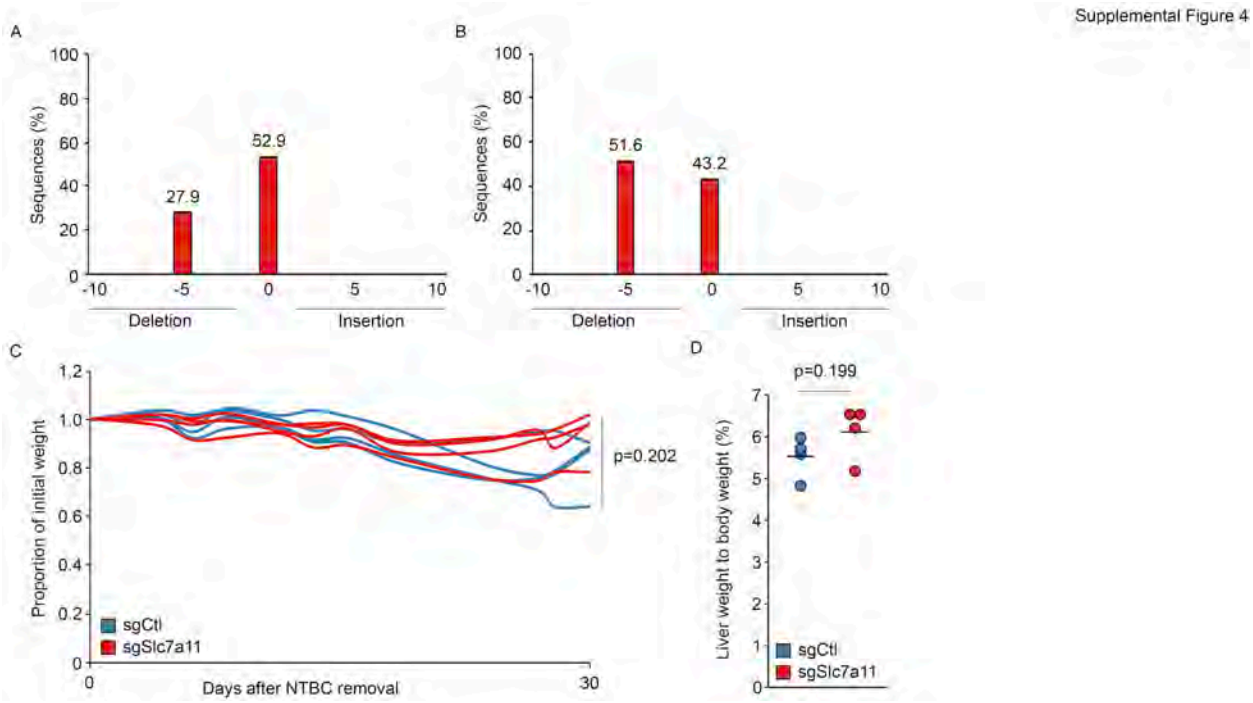
Supplemental Figure 2. Comparison of identified transcripts from single-cell RNA-seq (scRNA-seq) (41) **shows significant overlap between TRAP-seq and all nine layers of scRNA-seq.** Genes identified in the quiescent samples from TRAP-seq was compared to that from scRNA-seq. Bar height indicates the number of overlapping genes identified in two techniques. Line and data points indicate the percentage overlap from each scRNA-seq layer compared to TRAP-seq. A hypergeometric test was used to calculate the significance of overlapping genes from the two sequencing methods.

Supplemental Figure 3



Supplemental Figure 3. *Slc7a11* is activated at the transcript and protein levels under increased oxidative stress during liver regeneration. (A) Real-time reverse transcription PCR (qRT-PCR) analysis showed continuous upregulation of *Slc7a11* and *Gsta1*, both involved in GSH metabolism, in repopulating hepatocytes. A two-sample, two-tailed Student's t-test was used to compare repopulating and quiescent hepatocytes. * $p<0.05$, *** $p<0.001$ (n=4, quiescent and 1-week regeneration; n=3, 4-week regeneration and 4-week regeneration after severe injury). (B) Western blot analysis confirmed activation of xCT in the regenerating liver. (C) IHC staining of lipid peroxidation markers (malondialdehyde and 4-hydroxynonenal) and protein nitration (nitrotyrosine) showed accumulation of redox metabolites in the injured, repopulating

liver compared to healthy, quiescent livers. Scale bar: 100μm.



Supplemental Figure 4. No significant differences in weight of mice with *Slc7a11* inhibition compared to control after 4 weeks of repopulation. (A and B) Mutation analysis of *Slc7a11* exon one identified differential indel rates introduced by two single guide RNAs (sgRNA), sgSlc7a11-1 (A) and sgSlc7a11-2 (B). The x-axis indicates the number of nucleotides that were inserted or deleted and the y-axis indicates the percentage of mutation. (C) No weight differences during and after 4 weeks of repopulation, and no changes in liver weight to body weight ratio (D) in mice treated with sgRNA against *Slc7a11* (n=4) compared to control mice (n=4). A two-sample, two-tailed Student's t-test was used to compare mice treated with *Slc7a11* and control sgRNAs.

Supplemental Tables

Supplemental Table 1. Sequencing and alignment summary of the results from TRAP-seq in *Fah*$^{-/-}$ mice.

Supplemental Table 2. Top ten abundant transcripts identified in the quiescent livers.

Gene	Transcript	Quiescent	1-week regeneration	4-week regeneration	4-week regeneration after severe injury
Apoc3	NM_023114	22258.99	8284.08	16707.52	10378.80
Apoa2	NM_013474	18465.14	8906.01	8600.62	10388.86
Fabp1	NM_017399	14824.00	15222.48	10529.91	1586.67
Apoc1	NM_001110009	12632.39	14177.49	6945.49	15360.81
Apoe	NM_009696	12418.85	6753.43	5936.13	10505.54
Apoc1	NM_007469	11083.99	12446.11	6094.25	13496.84
Alb	NM_009654	10481.08	5141.19	2962.66	9602.19
Trf	NM_133977	6906.36	1267.84	1930.87	3292.12
Gpx1	NM_008160	6150.21	4540.07	5258.64	5562.72
Apoc4	NM_007385	5028.13	4193.01	4623.31	2596.70

Numbers represent the average fragments per kilobase of transcript per million (FPKM) reads in each regeneration group.

Supplemental Table 3. FPKM of cell type-specific transcripts detected by TRAP-seq

Gene	Quiescent	1-week regeneration	4-week regeneration	4-week regeneration after severe injury	Cell type
Alb	10481.08	5141.19	2962.66	9602.19	Hepatocyte
Ttr	2639.60	3072.59	1212.62	5454.57	Hepatocyte
Cyp2e1	2424.01	588.72	1418.17	380.48	Hepatocyte
Asgr1	1190.04	865.69	1375.35	654.07	Hepatocyte
Krt19	0.18	0.16	0.15	1.97	Cholangiocyte
Pkd2	1.28	0.71	0.79	1.56	Cholangiocyte
Krt7	0.22	0	0.22	0.89	Cholangiocyte
Cftr	0	0	0.02	0	Cholangiocyte
Des	1.09	0.33	0.43	0.86	Stellate cell
Acta2	0.41	0.35	0.27	0.34	Stellate cell
Col1a1	0.04	0.42	0.26	1.22	Stellate cell
Cd68	0.92	0.71	0.36	5.90	Kupffer cell
Emr1	0.67	0.28	0.27	0.84	Kupffer cell
Cd163l1	0	0	0.00	0.00	Kupffer cell
Clec5a	0	0	0.02	0.05	Kupffer cell

Supplemental Table 4. Fold change and read counts of transcripts identified with TRAP-seq.

Supplemental Table 5. Genes enriched in the KEGG pathway 'metabolic pathway' that were upregulated and downregulated, respectively.

Supplemental Table 6. Top congruently upregulated and downregulated genes ranked from the *Fah*$^{-/-}$ model viewpoint and comparison with the PHx model.

Supplemental Table 7. A list of oligos used in this study.