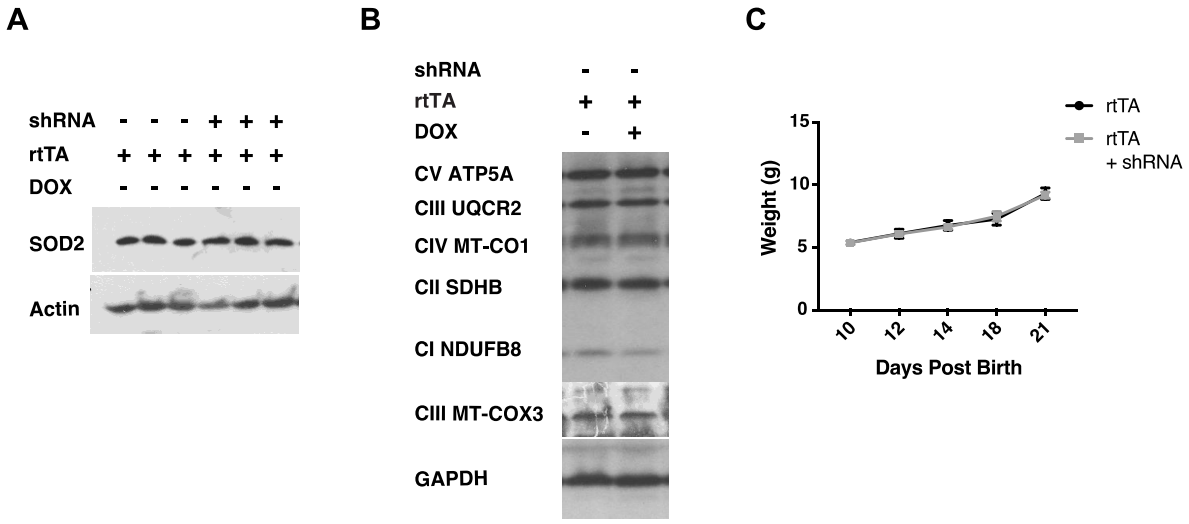

Figure S1. Additional Analysis of SOD2 Knock-down in iSOD2 Embryos and Mice, Related to Figure 1.

A) Western blot of iSOD2-KD embryos (with both rtTA and shRNA transgenes) compared to negative-control embryos (rtTA transgene only) without doxycycline (DOX). Actin was probed as a loading control.

B) Western blot for mitochondrial OXPHOS components, including mtDNA-encoded COX1 and COX III in negative-control mice (with rtTA transgene only) with (+) and without (-) doxycycline (DOX). GAPDH was probed as a loading control.

C) Body weight (grams) of iSOD2-KD mice that had SOD2 knocked down from day 0.5 to day 12.5e in utero is plotted as a function of time (days post birth through weaning). Error bars represent +/- SEM.

All calculations for statistical significance were completed using a non-parametric, unpaired, two- tailed t-test. n=3-7.

A

PPARα-PPARγ-PGC1α	NRF2
UCP2	AKR1C18
MPC1	GST3
MAOB	GST1
CISD3	CHGB
Slc25a4	TCN2
PMVK	CdC34
IDH3B	NFE2L3
PDK1	BGLAP
Slc25a11	
MDH2	
ECHS1	
MUP1	
HNF4A	
GST1	
GCK	
ARHGDIA	
AKR1C18	
ACSS2	
GOT1	
PTGR1	
HPGD	
GAPDH	
SLC2A2	
IRF1	
LTB4R	
DOK1	
C4A/C4B	

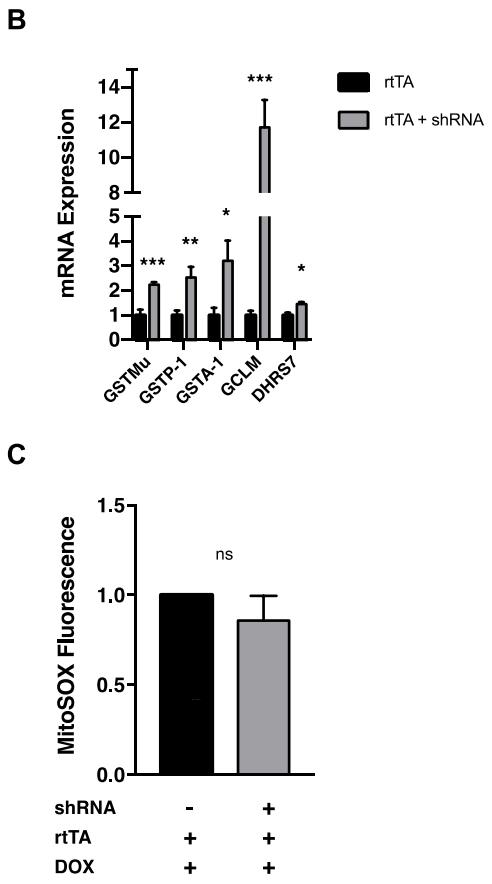

Figure S2. A**dditional Analysis of "A**dapted**" Liver from iSOD2 mice that** experienced embryonic SOD2 knock-down, Related to Figure 2.

A) Top upregulated PPARα, PPARγ, PGC1α, and NRF2 driven genes as predicted by gene expression profiling of liver from iSOD2 adapted animals.

B) RNA expression (normalized to tubulin) of redox-related genes in adapted liver normalized to that in negative controls. Error bars represent +/- SEM. GSTMu, glutathione s-transferase mu; GSTP-1, glutathione s-transferase pi-1; GSTA-1, glutathione s-transferase alpha 1; GCLM, glutamate cysteine ligase; DHRS7, dehydrogenase/reductase 7.

C) MitoSox staining in adapted hepatocytes compared to negative controls, which were given a value of 1.0.

All calculations for statistical significance were completed using a non-parametric, unpaired, two- tailed t-test. n=3-6.

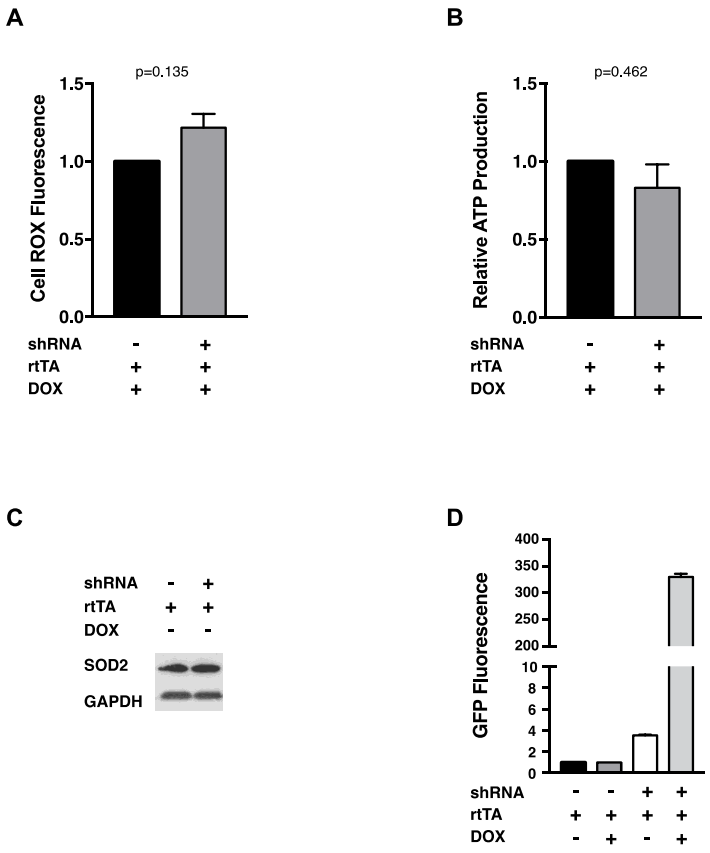

Figure S3. Additional Analysis of SOD2 Knock-down in MEFs from iSOD2-KD Mice, Related to Figure 3.

A) CellROX staining in iSOD2 MEFs in the presence of doxycycline (DOX) relative to that in negative controls, which were given a value of 1.0.

B) ATP levels in iSOD2 MEFs in the presence of doxycycline (DOX) relative to that in negative controls, which were given a value of 1.0 that equates to an ATP concentration of 1.2 nmol/μl.

C) Western blot for SOD2 in iSOD2 MEFs in the absence of doxycycline (DOX). GAPDH was probed as a loading control.

D) IRES-GFP expression from the shRNA construct in iSOD2 and negative-control MEFs with (+) and without (-) doxycycline (DOX). Error bars represent +/-SEM.

All calculations for statistical significance were completed using a non-parametric, unpaired, two- tailed t-test. n=4-6.

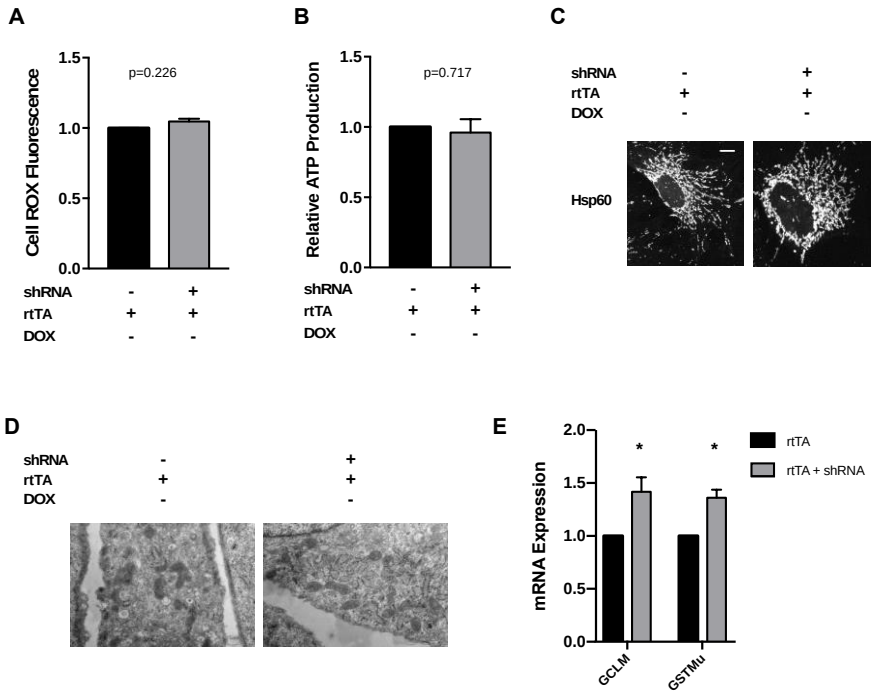

Figure S4. Additional analysis of adapted MEFs from iSOD2 mice, Related to Figure 4.

A) CellROX staining in adapted iSOD2 MEFs compared to negative controls, which were given a value of 1.0.

B) ATP levels in iSOD2 knock-down MEFs compared to negative controls, which were given a value of 1.0 that equates to an ATP concentration of 1.8 nmol/μl.

C) Grayscale image of mitochondria in adapted MEFs (day 12) compared to negative controls. Images are z-stack projections of representative cells, fixed and stained with anti-HSP60 to visualize mitochondria. Scale bar represents 10 μm.

D) Electron microscopy of adapted iSOD2 MEFs compared to negative controls. Scale bar = 2 μM.

E) RNA expression of redox-related genes (normalized to tubulin) in iSOD2 adapted MEFs relative to negative controls. Error bars represent +/- SEM. GCLM, glutamate cysteine ligase; GSTMu, glutathione s-transferase mu.

All calculations for statistical significance were completed using a non-parametric, unpaired, two- tailed t-test. n=3-9.

Table S2. Additional Oligonucleotides Used in the Study, Related to Figures 1-4

Oligonucleotides		
GCLM Forward 5'-3' TTGGGAACTCCATTCATTCA	This paper	N/A
GCLM Reverse 5'-3' CGGGAACCTGCTCAACTG	This paper	N/A
NQO1 Forward 5'-3' GTCTTCTCTGAATGGGCCAG	This paper	N/A
NQO1 Reverse 5'-3' CCAATCAGCGTTCGGTATTA	This paper	N/A
GRX Forward 5'-3' ATCGTGCATGAATTCCGAGT	This paper	N/A
GRX Reverse 5'-3' GGTGGTGGAGAGTCACAAGC	This paper	N/A
UCP2 Forward 5'-3' CAGCGCCAGATGAGCTTTG	This paper	N/A
UCP2 Reverse 5'-3' GGAAGCGGACCTTTACCACA	This paper	N/A
PGC1α Forward 5'-3' TGAGGACCGCTAGCAAGTTT	This paper	N/A
PGC1α Reverse 5'-3' TGAAGTGGTGTAGCGACCAA	This paper	N/A
GSTmu Forward 5'-3' AACACAGGTCTTGGGAGGAA	This paper	N/A
GSTmu Reverse 5'-3' CGTATGTTTGAGCCCAAGTG	This paper	N/A
GSTP1 Forward 5'-3' GGGCCTTCACGTAGTCATTC	This paper	N/A
GSTP1 Reverse 5'-3' ATGGGAAAAACCAGAGGGAG	This paper	N/A
GSTA1 Forward 5'-3' CTCTTCAAACTCCACCCCTG	This paper	N/A
GSTA1 Reverse 5'-3' TGGAGAAGAAGCCAGGACTC	This paper	N/A
Col1A1 Rev45 Reverse 5'-3' CACCCTGAAAACTTTGCCCC	This paper	N/A
ROSA C 5'-3' GGAGCGGGAGAAATGGATATG	This paper	N/A
ROSA B 5'-3' GCGAAGAGTTTGTCCTCAACC	This paper	N/A
ROSA D 5'-3' TCAGTAAGGGAGCTGCAGTGG	This paper	N/A
shRNA 835 Forward 5'-3' AAGCCACAGATGTATCTTTCAGTAA	This paper	N/A
shRNA 582 Forward 5'-3' AAGCCACAGATGTATTAAACTTCTC	This paper	N/A
Sod2_835 shRNA 1, 5'GAAGGCTCGAGAAGGTATATTGCTGTTGACAGTGAGCGA TGGGAGAATGTTACT GAAAGATAGTGAAGCCACAGATGTATCTTTCAGTAACATTC TCCCAGTGCCTACTG CCTCGGACTTCAAGGGGCTAGAATTCGAGCA-3'	This paper	N/A

Sod2_582 shRNA 2, 5′GAAGGCTCGAGAAGGTATATTGCTGTTGACAGTGAGCGC TGGGTCTTTTGAGAA GTTTAATAGTGAAGCCACAGATGTATTAAACTTCTCAAAAGA CCCAATGCCTACTGC CTCGGACTTCAAGGGGCTAGAATTCGAGCA-3’	This paper	N/A