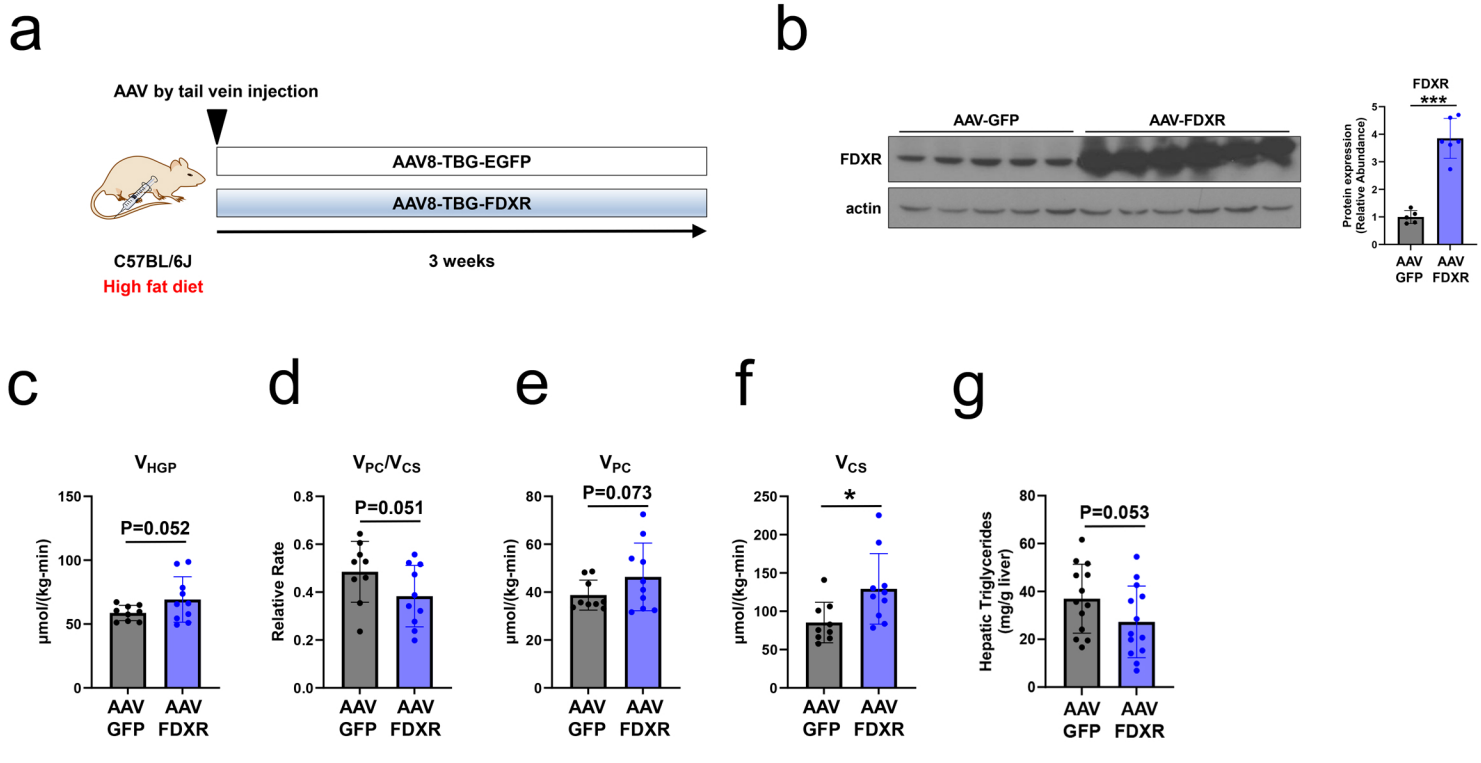
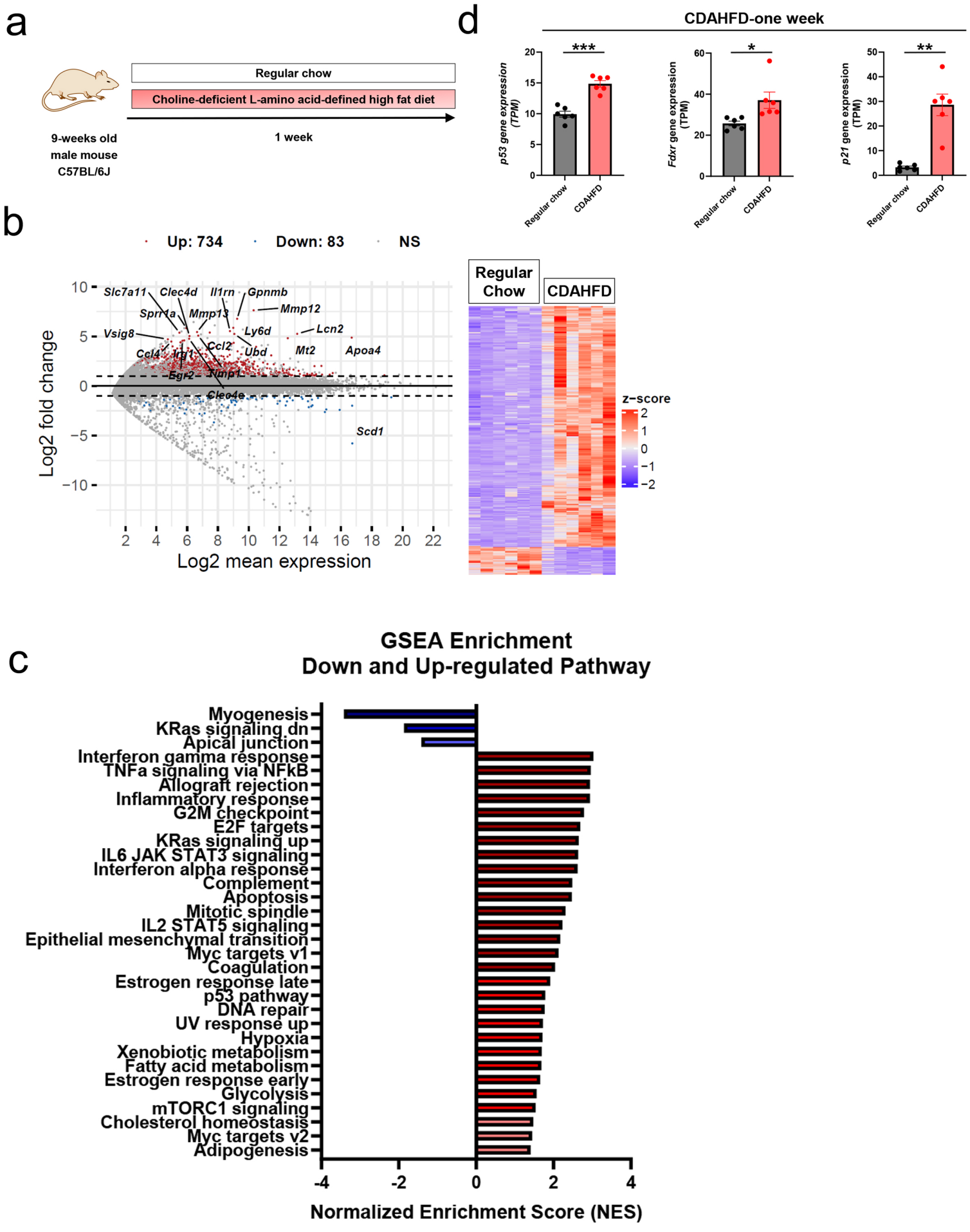
Figure S1


a
AAV by tail vein injection
AAV8-TBG-EGFP
AAV8-TBG-FDXR
C57BL/6J
High fat diet
3 weeks
b
AAV-GFP
AAV-FDXR
FDXR
actin
FDXR
***
Protein expression (Relative Abundance)
AAV GFP
AAV FDXR
c
V_HGP
P=0.052
µmol/(kg-min)
d
V_PC/V_CS
P=0.051
Relative Rate
e
V_PC
P=0.073
µmol/(kg-min)
f
V_CS
*
µmol/(kg-min)
g
P=0.053
Hepatic Triglycerides (mg/g liver)

Supplementary Figure 1. FDXR increases TCA cycle flux in the liver and alleviates steatosis. **(a)** Study design. AAV8-TBG-EGFP (AAV-GFP) or AAV8-TBG-FDXR (AAV-FDXR) was administered to C57BL6J mice, which were then fed a high-fat diet for 3 weeks. **(b)** FDXR protein levels in the liver. AAV-FDXR (n = 5) induced FDXR protein expression in the liver compared to AAV-GFP (n = 6). ***P < 0.001 (Unpaired one-sided Student's t-test). **(c–f)** Hepatic mitochondrial flux measured using the positional isotopomer NMR tracer analysis (PINTA) in AAV-FDXR-treated mice (n = 10) and AAV-GFP-treated mice (n = 9). **(c)** Hepatic glucose production (V_{HGP}). **(d)** Mitochondrial pyruvate carboxylase flux relative to citrate synthase flux (V_{PC}/V_{CS}). **(e)** Absolute rates of V_{PC}. **(f)** Absolute rates of V_{CS}. V_{CS} was significantly increased in AAV-FDXR-treated mice compared to that in AAV-GFP-treated mice. *P < 0.05 (Unpaired one-sided Student's t-test).

Figure S2


a
Regular chow
Choline-deficient L-amino acid-defined high fat diet
1 week
9-weeks old male mouse C57BL/6J
b
Up: 734
Down: 83
NS
Log2 fold change
Log2 mean expression
Slc7a11
Clec4d
Il1rn
Gpnmb
Sprr1a
Mmp13
Mmp12
Vsig8
Ly6d
Lcn2
Ccl4
Irg1
Ccl2
Ubd
Mt2
Apoa4
Egr2
Jun1
Clec4e
Scd1
Regular Chow
CDAHFD
z-score
d
CDAHFD-one week
p53 gene expression (TPM)
Fdxr gene expression (TPM)
p21 gene expression (TPM)
Regular chow
CDAHFD
c
GSEA Enrichment
Down and Up-regulated Pathway
Myogenesis
KRas signaling dn
Apical junction
Interferon gamma response
TNFa signaling via NFkB
Allograft rejection
Inflammatory response
G2M checkpoint
E2F targets
KRas signaling up
IL6 JAK STAT3 signaling
Interferon alpha response
Complement
Apoptosis
Mitotic spindle
IL2 STAT5 signaling
Epithelial mesenchymal transition
Myc targets v1
Coagulation
Estrogen response late
p53 pathway
DNA repair
UV response up
Hypoxia
Xenobiotic metabolism
Fatty acid metabolism
Estrogen response early
Glycolysis
mTORC1 signaling
Cholesterol homeostasis
Myc targets v2
Adipogenesis
Normalized Enrichment Score (NES)

Supplementary Figure 2. CDAHFD induces steatohepatitis and activates the p53–FDXR pathway in the liver. (a) Study design. Male C57BL/6J mice were fed either regular chow or a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for one week. **(b)** MA plot showing differentially expressed genes (DEGs) between CDAHFD-fed and regular chow-fed mice, based on RNA-seq analysis. **(c)** Gene set enrichment analysis (GSEA) demonstrating significant enrichment of inflammatory and metabolic pathways in the CDAHFD group. Enrichment of the “p53 pathway” was also observed. **(d)** Expression levels of *p53*, *Fdxr*, and *p21* quantified from RNA-seq data in CDAHFD-fed livers compared to regular chow-fed controls.