Shared terms between tissues:

-FA, triacylglycerol & ketone body metabolism
-Cell cycle, mitotic cell cycle
-ECM glycoproteins & ECM organization terms
-Core matrisome
-mRNA and capped intron containing pre mRNA processing

Adipose

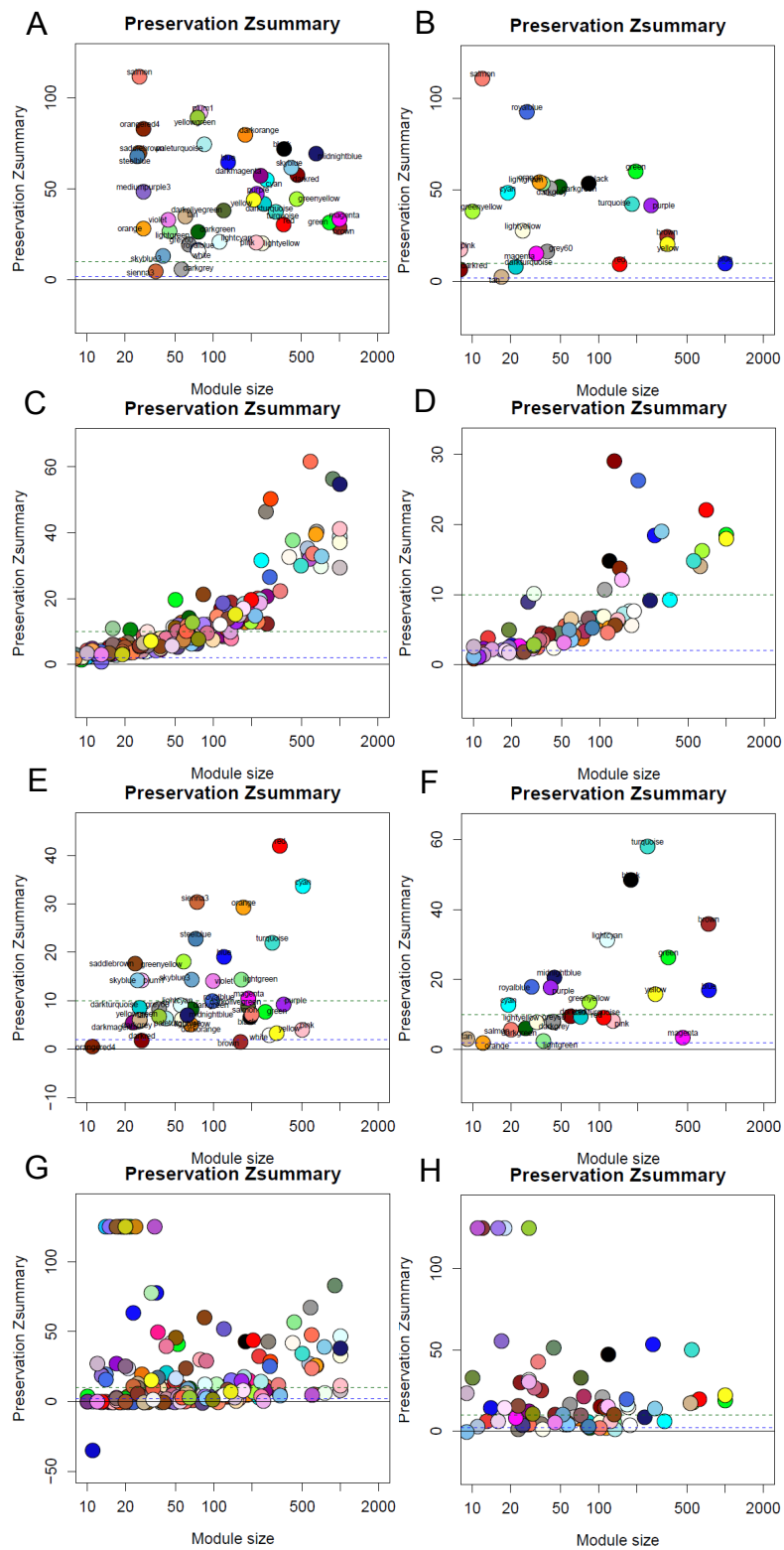-Immune system
-Interferon (alpha/beta) signaling
-Cytokine signaling in immune system, IL12
 pathways
-TCA cycle and respiratory electron transport
-Diabetes pathways
-Insulin signaling pathway
-Valine, leucine, isoleucine degradation
-Glycosaminoglycan & glycosphingolipid
-Sphingolipid metabolism
-TGF beta signaling pathway
-Toll like receptor signaling & related terms
-Metabolism of vitamins & cofactors and aa
 & derivatives
-PDGF pathway
-HIF2
-IGF1
-Lysosome
-Tight junction related terms

Liver

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-Metabolism of lipids and lipoproteins
-Fatty acyl coa biosynthesis
-Triglyceride biosynthesis
-Lysophospholipid pathway
-Biological oxidations
-Complement and coagulation cascades
-Circadian rhythm related terms
-Collagen formation
-Carbohydrates metabolism
-Drug metabolism cytochrome p450
-FOXM1pathway
-G2-M checkpoints
-Peroxisome & peroxisomal lipid metabolism
-EGFR signaling
-Transmembrane transport of small molecules

Figure S1. Summary of the gene ontology terms assciated with coexpression modules. *Related to STAR Methods, Figure 2, and Table S2.* We annotated each module with top 5 most associated GO terms.

Figure S2. Z-summary scores of the module preservations. *Related to STAR Methods.* Preservation of the WGCNA modules in MEGENA modules for (A) Liver and (B) Adipose tissues. Preservation of MEGENA modules in WGCNA modules for (C) Liver and (D) Adipose tissues. Preservation of HF diet coexpression modules in chow diet expression data for (E) WGCNA liver, (F) WGCNA adipose, (G) MEGENA liver, (H) MEGENA adipose modules. A Z-summary score <2 shows no preservation, 2<Z-summary<10 (dashed blue line) means weak to moderate evidence, and Z-summary>10 (dashed green line) shows strong evidence for the preservation (A Z-summary score<2 shows no preservation, 2<Z-summary<10 (dashed blue line) means weak to moderate evidence for the preservation, and Z-summary>10 (dashed green line) shows strong evidence for the preservation). (I) Mutual preservation ratios of the HF and chow diet coexpression modules for both methods and both tissues.
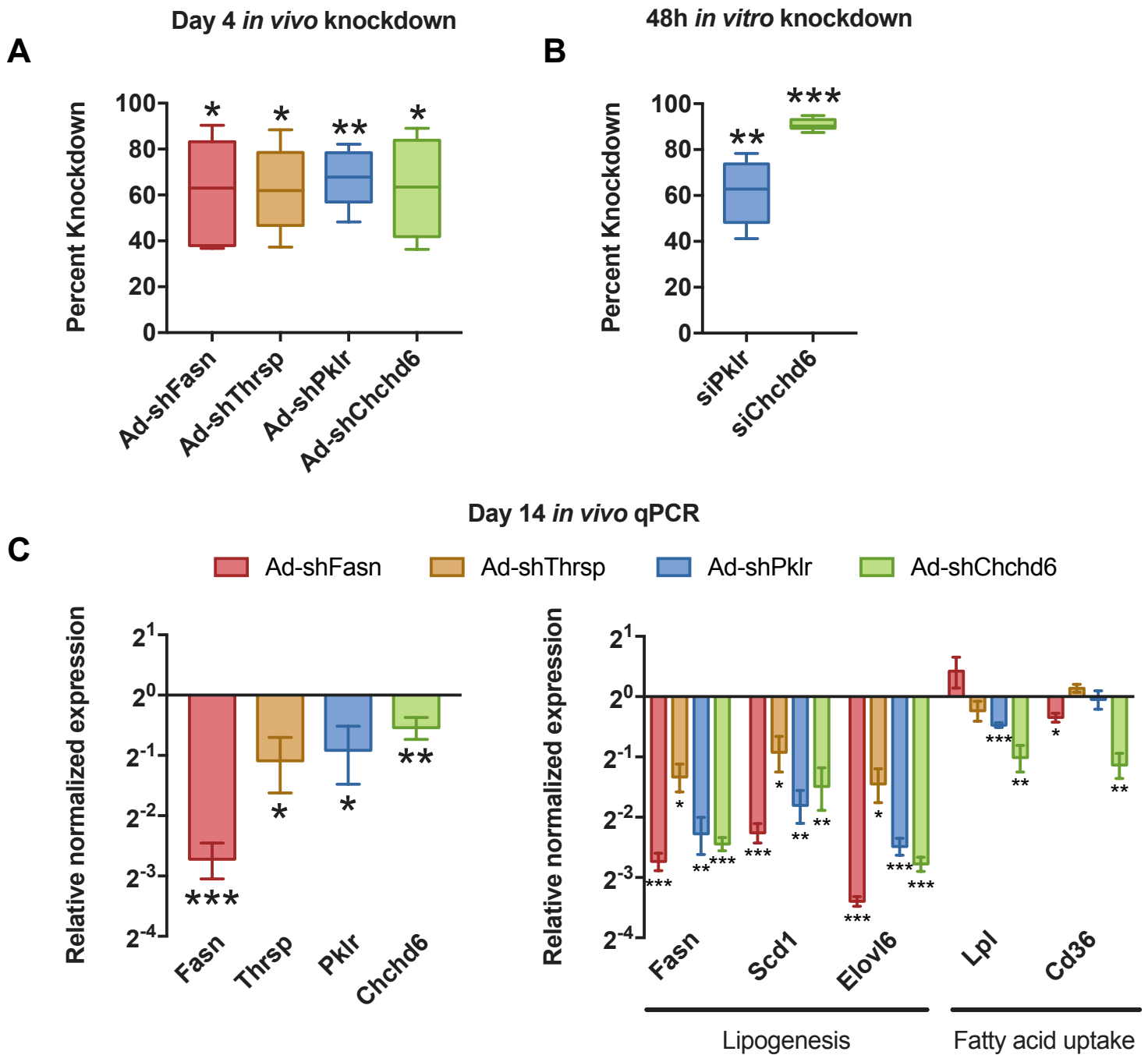
Figure S3. Quantitative PCR measurement. *Related to STAR Methods, Figures 4, 5, and 6.* Percent knockdown of KD genes (A) 4 day after adenovirus mediated shRNA infection (n = 4-5 mice per group) and (B) 48h after siRNA transfection of AML12 cells (experiment was repeated three independent times with n = 4 wells per group each time). Data are represented as median and interquartile range. (C) Relative normalized expression values of KD genes and genes involved in de novo lipogenesis and lipid uptake after 14 days of infection. Data are represented as mean ± SEM (n = 4-5 mice per group). P values were calculated by unpaired student's t-test. *P < 0.05, **P < 0.01, ***P < 0.001
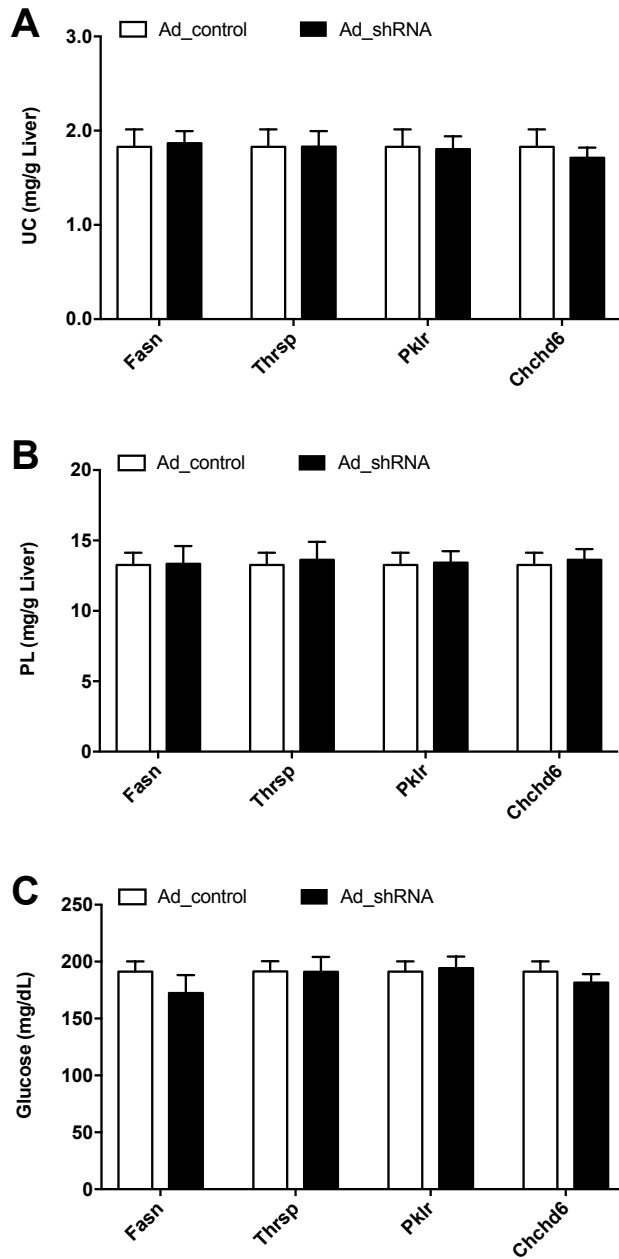
Figure S4. Effects of shRNA knockdown of KD genes on mouse phenotypes. *Related to Figure 4.* Comparisons of (A) hepatic unesterified cholesterol (UC) levels, (B) hepatic phospholipid (PL) levels (C) plasma glucose levels between the control and shRNA groups. Data are represented as mean ± SEM (n = 7-12 mice per group).