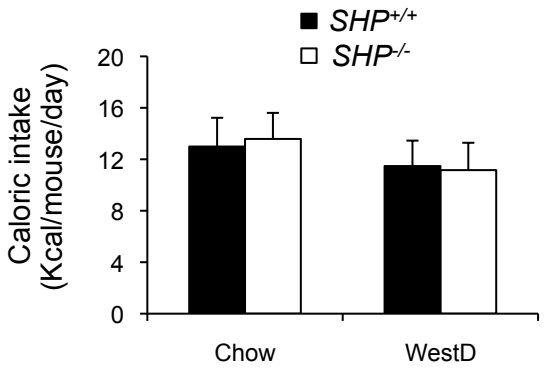
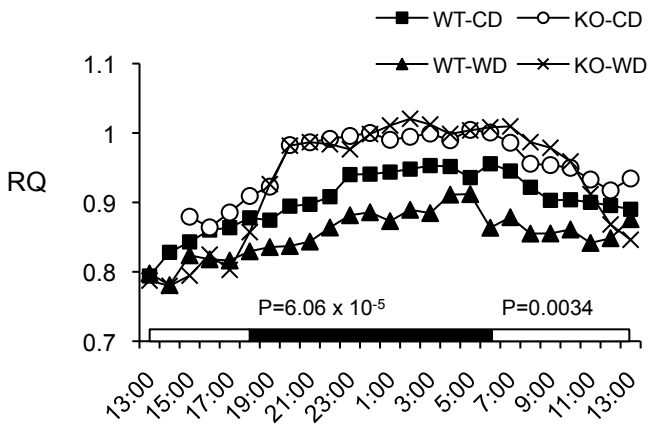
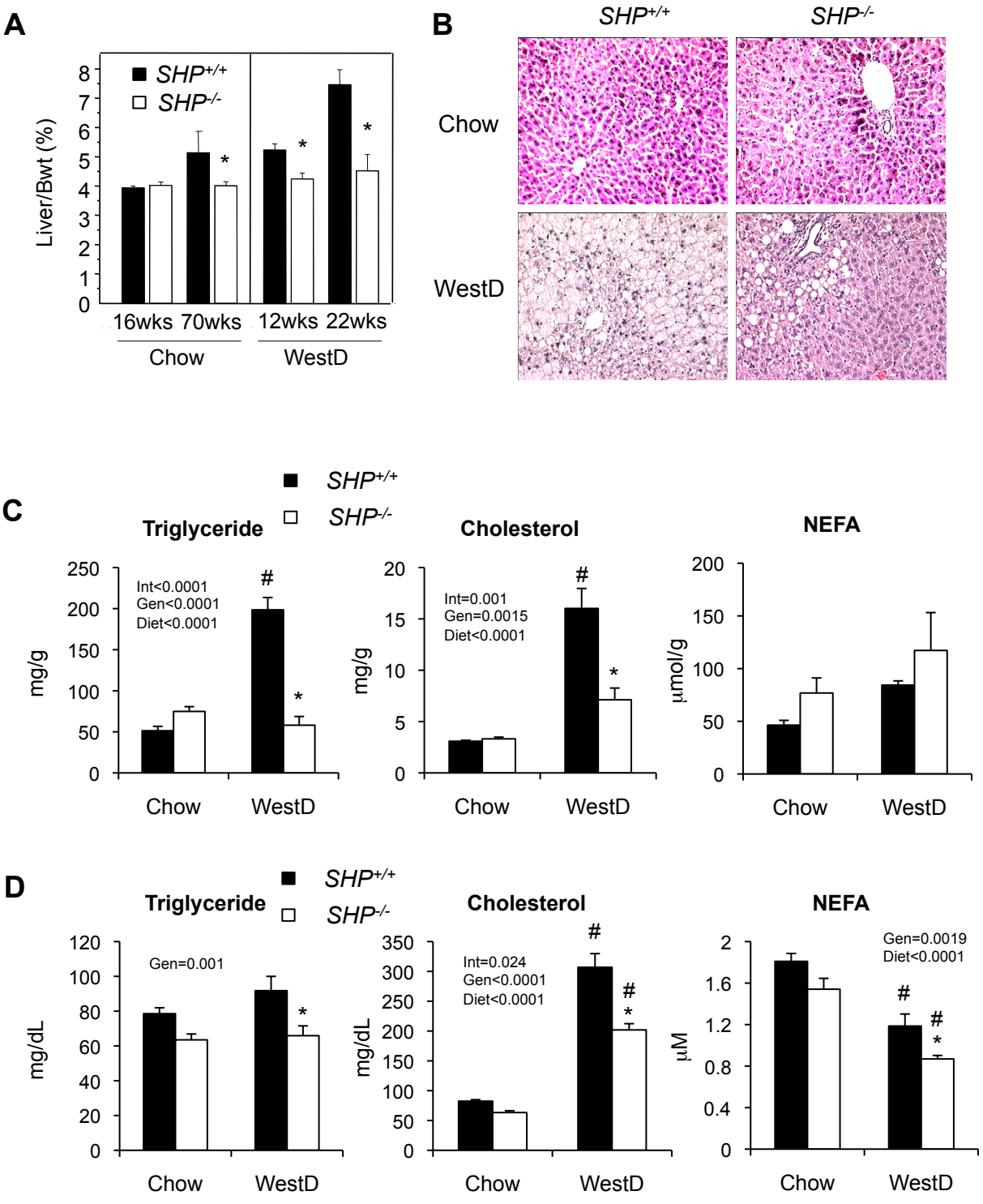


Supplementary Fig. 1. Caloric intake in WT and *SHP*$^{-/-}$ mice.
Caloric intake (food intake (g diet/mouse/day) x caloric value of diet (kcal/g diet)) was determined from 4 month old mice (n=8) on the diet regimen for 8 weeks and plotted with STD. Their average body weights at the time of experiment were 27.58 ± 1.20, 28.53 ± 1.87, 38.77 ± 1.84, and 31.26 ± 2.89 g for WTC, KOC, WTWD, and KOWD, respectively.

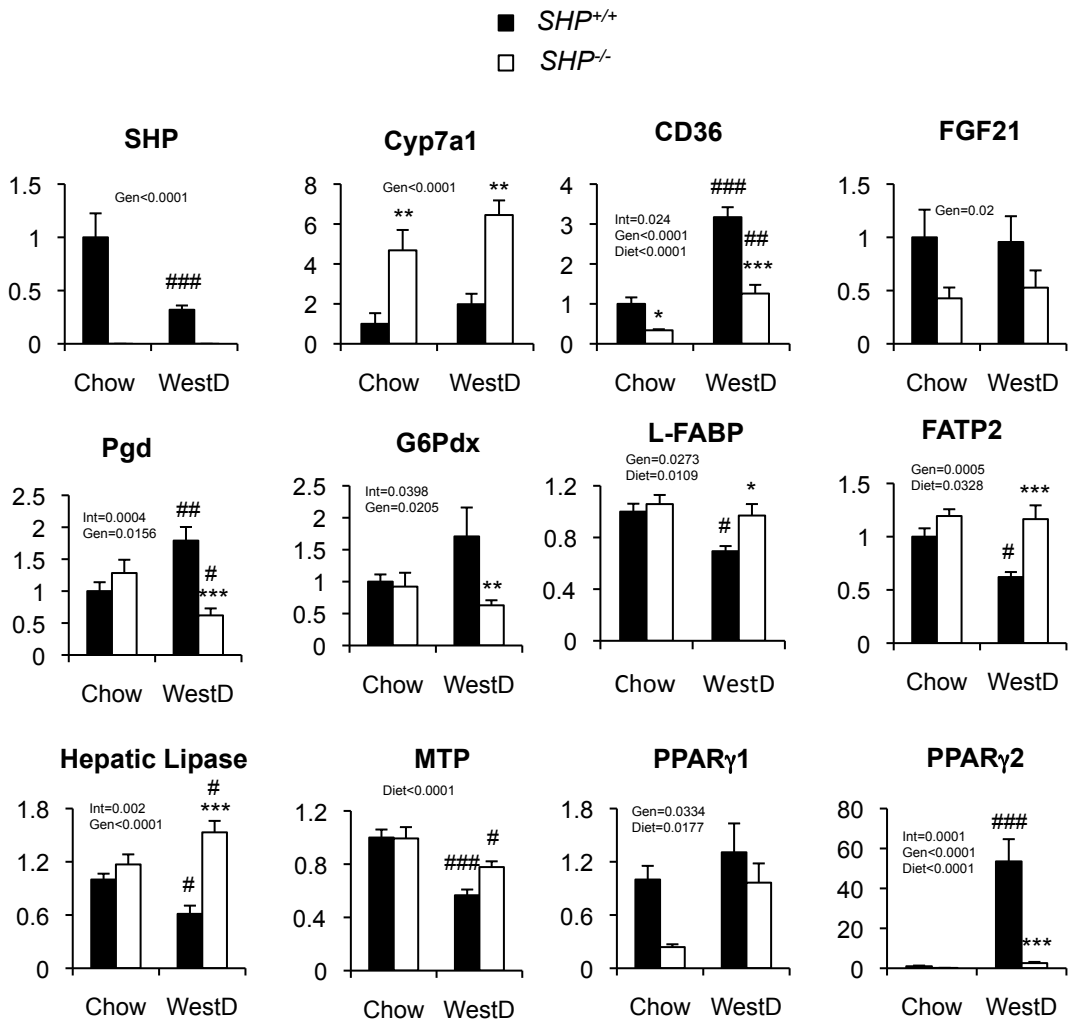


Supplementary Fig. 2. RQ values obtained indirect calorimetry analysis from WT and *SHP*$^{-/-}$ mice fed chow (CD) or western diet (WD)
RQ values from Fig. 2B were combined and re-plotted. Error bars were intentionally omitted to compare the curves clearly. P values are obtained from WT-CD and WT-WD values.



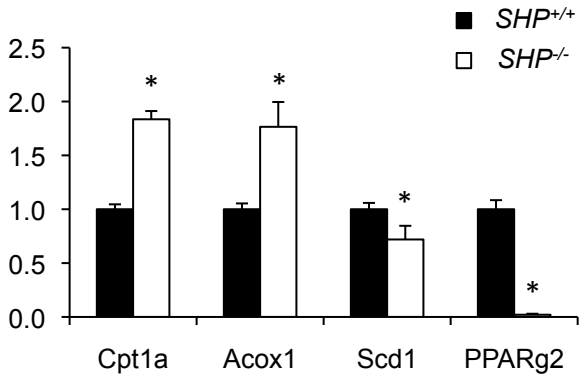
Supplementary Fig. 3

Supplementary Fig. 3. *SHP*$^{-/-}$ mice were protected from development of diet induced hepatic steatosis.
(A) Ratio of liver weight to body weight of WT and *SHP*$^{-/-}$ mice fed CD (16 wks; n = 8, and 70 wks; n = 3) or WestD (n = 8). (B) Hematoxylin-eosin staining of representative liver paraffin sections. (C) Hepatic lipid contents in mice after 21 week WestD regimen were presented as means (n=5) ± SEM. (D) Fasting serum lipid concentrations obtained from mice (n=8 to 10) on 22 wk-WestD regimen. 2-way ANOVA with were used to calculate significance of overall effect of genotype (Gen), diet, and their interactions (Int). Boneferroni post hoc test results were presented to compare significance between groups (* for between genotypes, # for between diets). All the p values were < 0.001 except serum NEFA *, which is < 0.05.



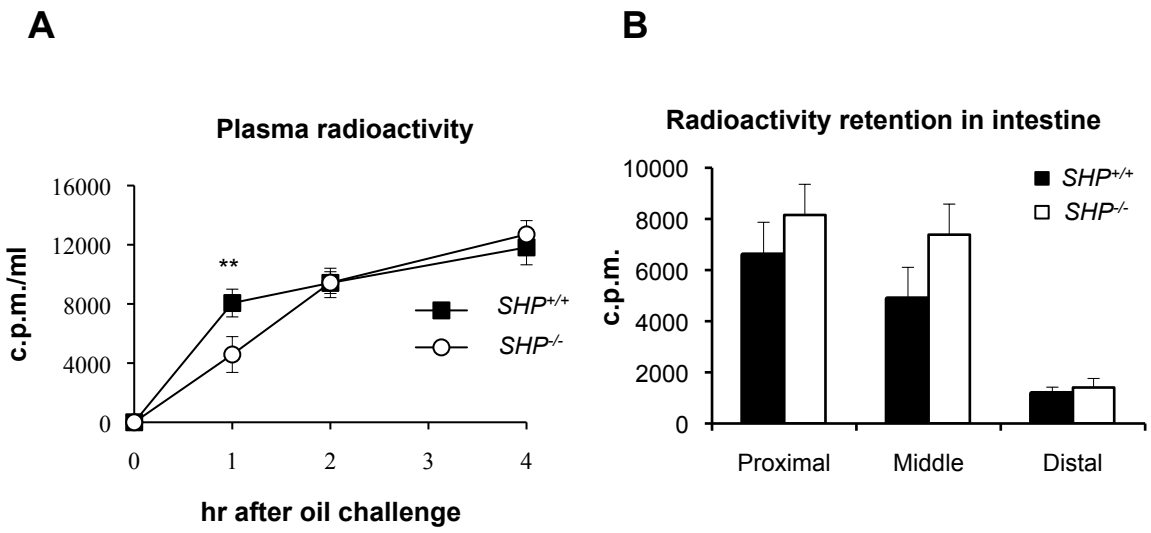
Supplementary Fig. 4. qPCR analysis of expression of hepatic genes involved in lipid metabolism

The same RNAs from Fig. 4 were further assessed with indicated PCR primers to analyze the impact of SHP gene deletion on lipid metabolism. The bars are presented as means ± SEM. Two-way ANOVA was used to calculate significance of overall effect as described in supplementary Fig. 3. To compare significance between groups, we used Boneferroni post hoc tests (* for between genotypes, # for between diets). *, #, $p < 0.05$; **, ##, $p < 0.01$; ***, ###, $p < 0.001$. Pgd, phosphogluconate dehydrogenase; G6Pdx, glucose-6-phosphate dehaydrogenase



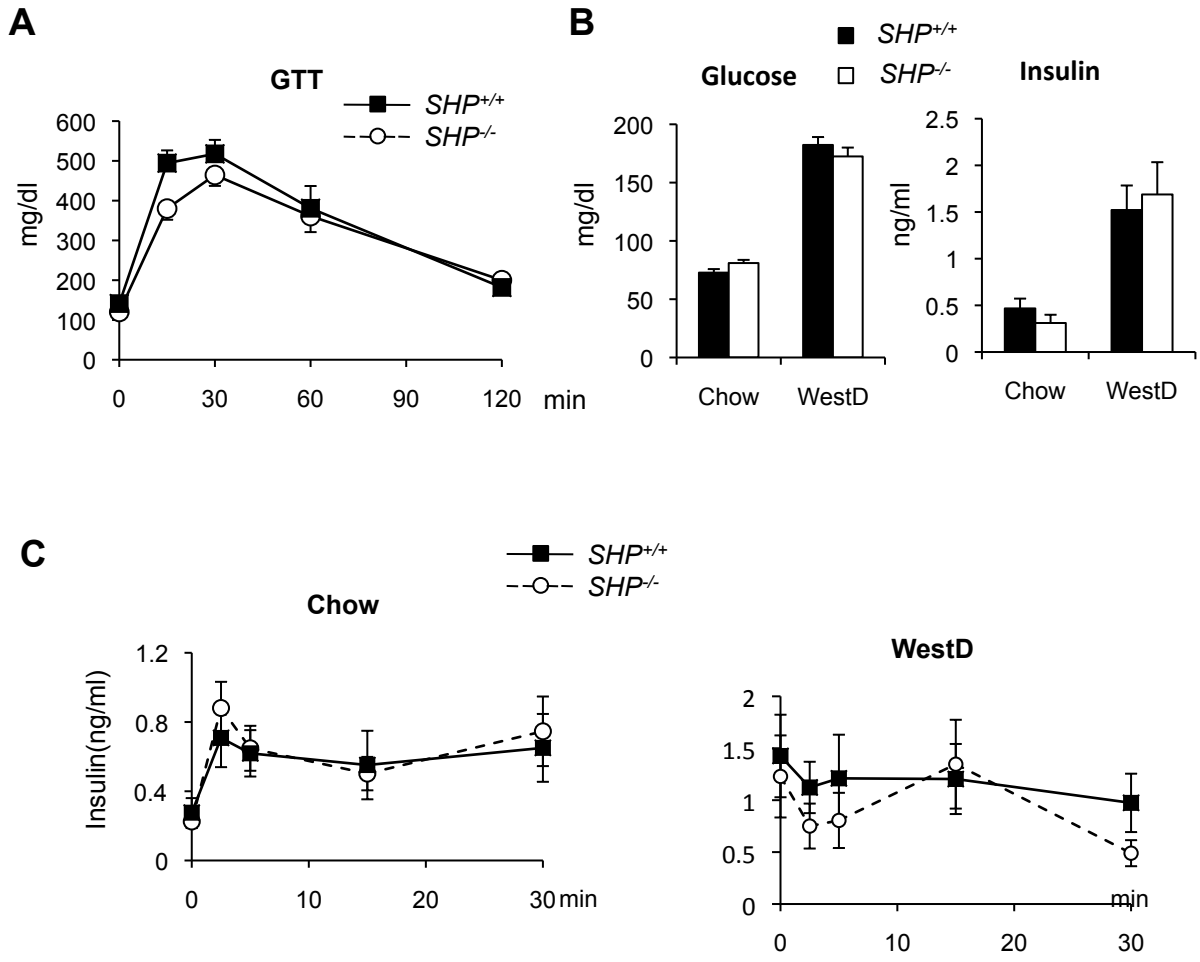
Supplementary Fig. 5. mRNA expression of hepatic genes involved in lipid metabolism upon 4 wk WestD regimen

Liver RNAs from mice fed WestD for 4 weeks were assessed to measure the mRNA expression of major genes involved in lipid metabolism. The bars are presented as means ± SEM. n=5, *, $p < 0.02$ vs WT

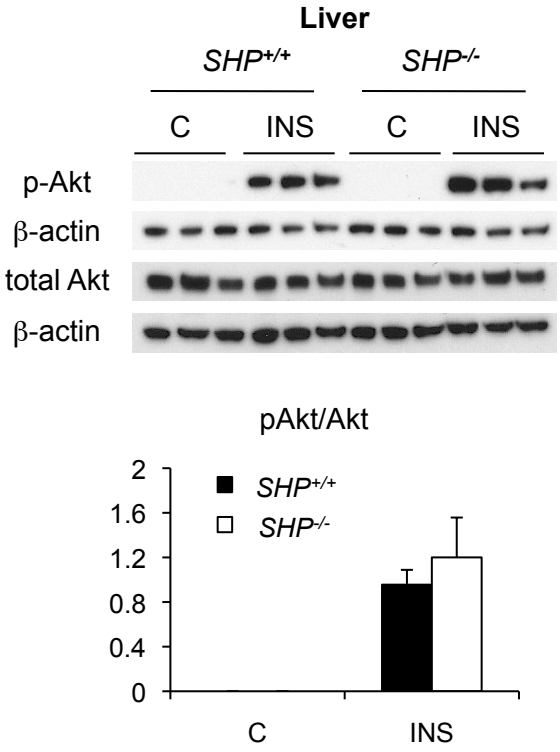


Supplementary Fig. 6. Radioactivity levels in intestine and plasma after oral challenge with radiolabeled oil

(A) Blood was collected at the indicated time points from animals after challenged with radiolabeled TG orally (Fig. 4F). (B) After final hour, intestines and their contents were collected and equally divided into 3 pieces. The radioactivity levels were measured and plotted as means (n=5) ± SEM. **, p = 0.053



Supplementary Fig. 7. Assessment of glucose metabolism in *SHP*$^{-/-}$ mice.
(A) GTT was performed on 7 month old WT and *SHP*$^{-/-}$ mice (n=6) fed chow diet after overnight fasting. Plasma glucose levels were monitored at the indicated time points after 2g/kg of glucose injection. Average values are presented as means ± SEM. (B) 10 month old mice fed chow or western diet (22 wks) were analyzed for their serum glucose and insulin levels after overnight fasting. Average values are presented as means ± SEM. n = 7 to 19. (C) 8 month old chow-fed and 10 month old western diet-fed (22 wks) mice were challenged with i.p. 2g/kg dextrose. Their insulin releases were plotted as means ± SEM. n = 6.



Supplementary Fig. 8. Hepatic insulin sensitivity in mice fed chow assessed by phospho-Akt level

Hepatic insulin sensitivities were assessed by Western blot analysis evaluating the ratio of phosphoserine Akt to total Akt as shown in Fig. 5 . 4 month old mice were challenged with 5U/kg of human insulin for 15 min. Livers were collected and processed for Western blotting (top panel). The phospho-Akt to total Akt ratio were presented after densitometry scanning (bottom panel).