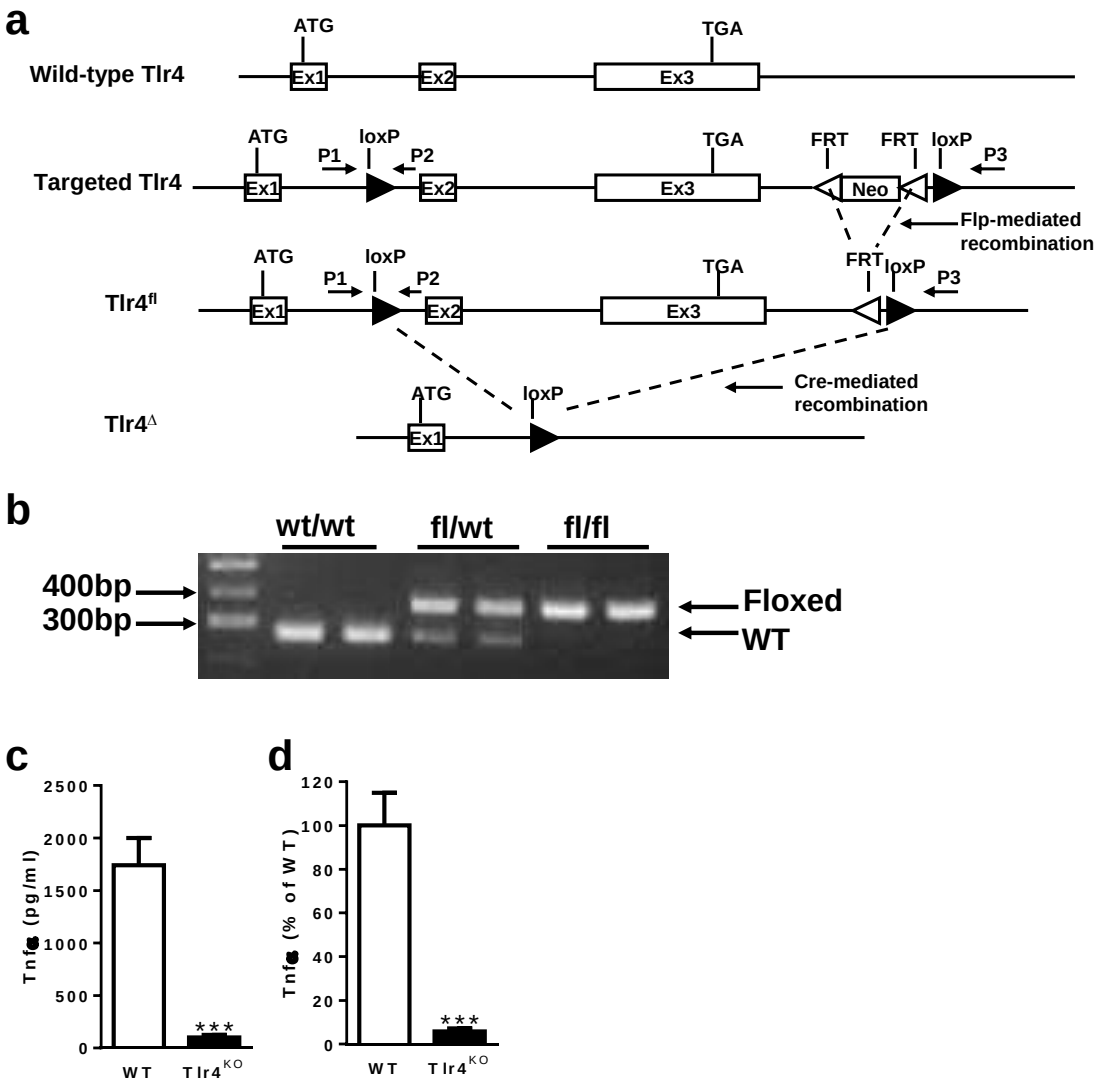
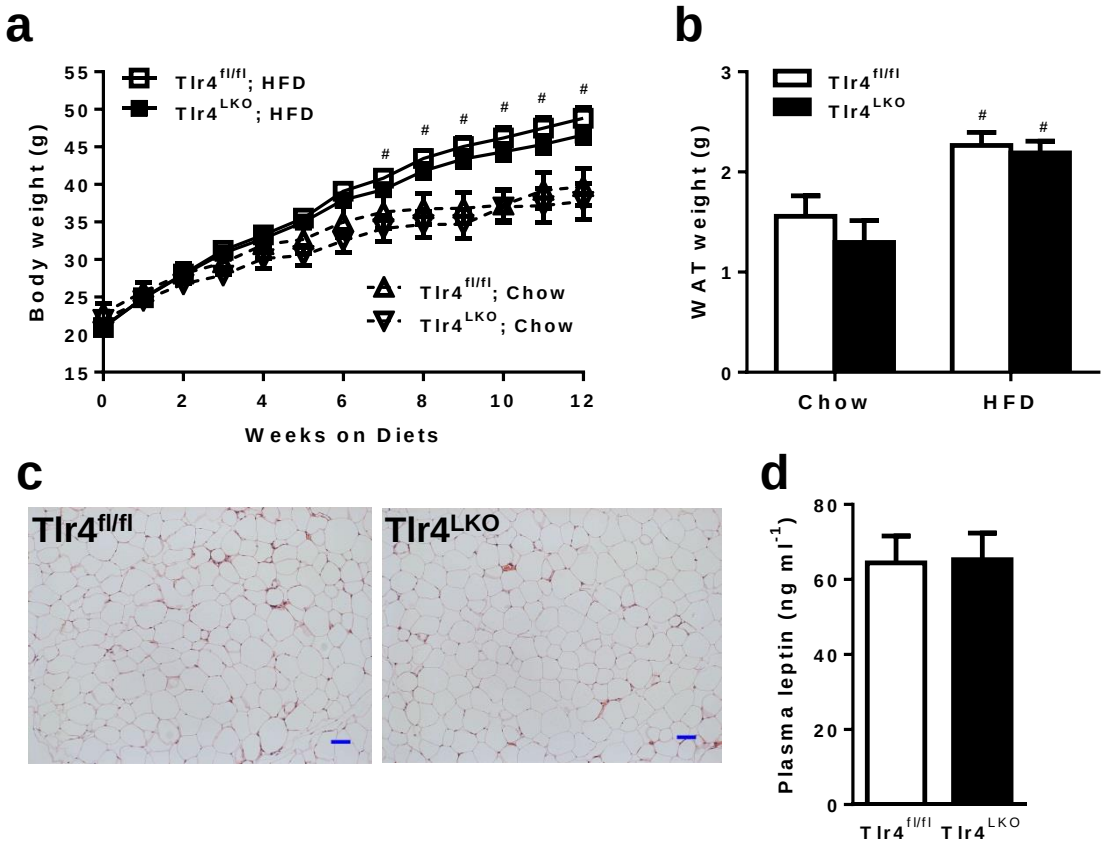
Supplementary Figure 1



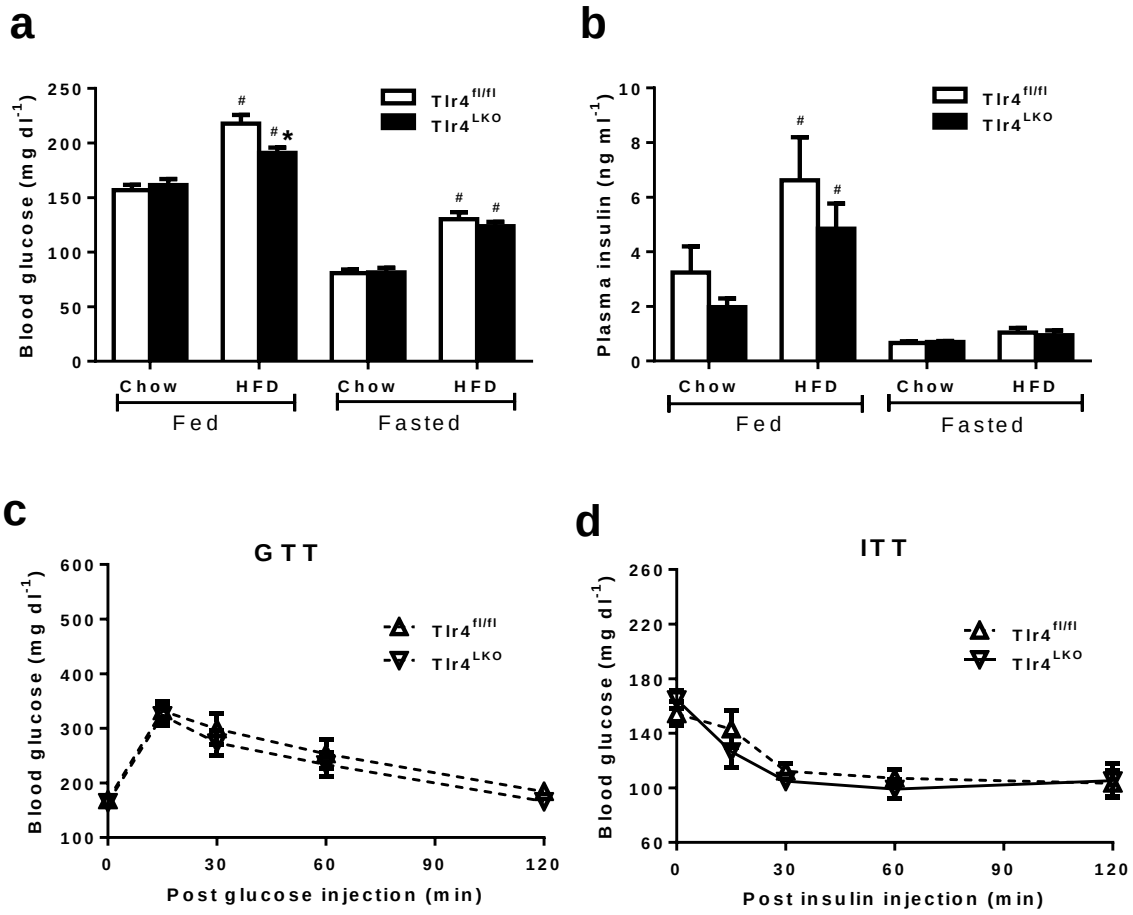
Supplementary Figure 1. Generation of mice bearing a Cre-conditional Tlr4 null allele ($Tlr4^{fl}$). (**a**) Schematic diagram of the targeting strategy. (**b**) PCR analysis of tail-genomic DNA of mice bearing wild-type (WT) and/or floxed allele. PCR products of WT and floxed allele are 260 bp and 343 bp, respectively. (**c**) Circulating levels of Tnfα were measured in wild-type (WT) and $Tlr4^{KO}$ mice (6-8 weeks of age, n = 4-6) 1.5 h after intraperitoneally injection of lipopolysaccharide (LPS, 1mg kg^{-1} body weight). (**d**) Levels are presented as a percentage relative of $Tlr4^{fl/fl}$ levels. ***$p<0.001$, compared between WT and $Tlr4^{KO}$ mice (Student's t-test). All data are presented as means ± s.e.m.

Supplementary Figure 2



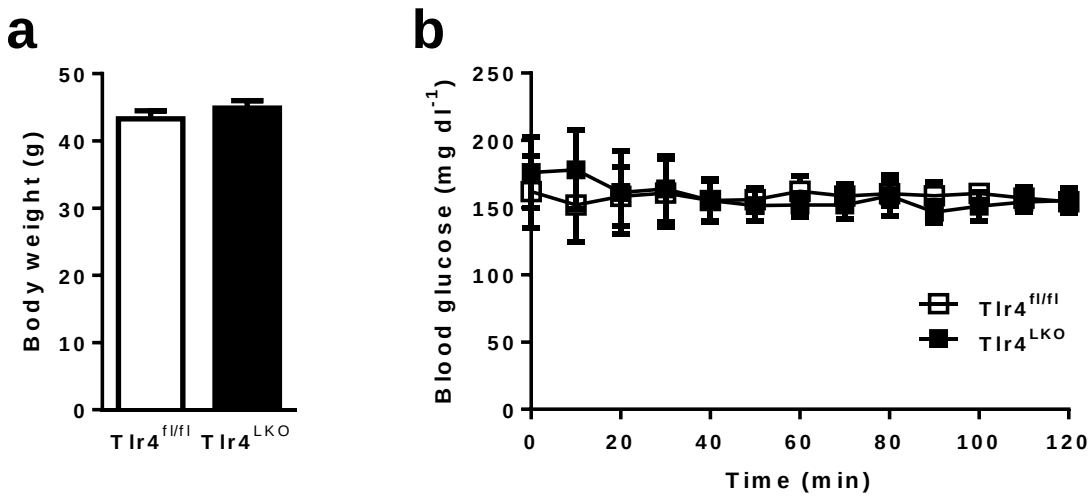
Supplementary Figure 2. Tlr4$^{fl/fl}$ and Tlr4^{LKO} mice showed similar adiposity and comparable plasma leptin concentrations. (**a**) Body weight curves in Tlr4$^{fl/fl}$ and Tlr4^{LKO} mice on a chow (n = 8) or HFD (n = 10-11) for 12 weeks. (**b**) Epididymal fat pad weight in mice after either chow (n = 8) or HFD (n = 10-11) for 12 weeks. (**c**) H&E staining of epididymal adipose tissue sections from HFD-fed mice. Scale bars, 200 μm. (**d**) Plasma leptin concentrations (n = 9) in mice on HFD. $^{\#}p < 0.05$, compared between different diets for mice of the same genotype (Student's t-test). All data are presented as means ± s.e.m.

Supplementary Figure 3



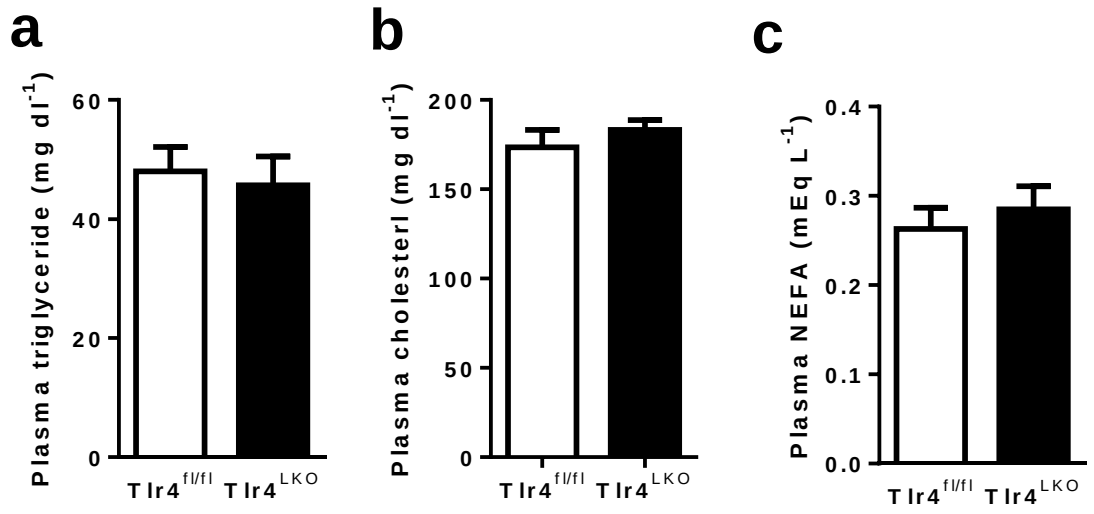
Supplementary Figure 3. HFD-fed Tlr4^{LKO} mice had reduced blood glucose levels under fed condition. (**a-b**) Blood glucose levels (**a**, n = 19-22) and plasma insulin concentrations (**b**, n = 5) in Tlr4$^{fl/fl}$ and Tlr4^{LKO} mice after 8 weeks of chow or HFD collected under either fed or overnight fasting states. (**c-d**) Chow-fed Tlr4$^{fl/fl}$ and Tlr4^{LKO} mice (n = 8) were fasted for 5 h for (**c**) glucose tolerance test (GTT, 1.2 mg g^{-1} BW) and (**d**) insulin tolerance test (ITT, 1.5 mU g^{-1} BW). *$p < 0.05$, compared between Tlr4$^{fl/fl}$ and Tlr4^{LKO} mice on the same diet; $^{\#}p < 0.05$, compared between different diets for mice of the same genotype (Student's t-test). All data are presented as means ± s.e.m.

Supplementary Figure 4



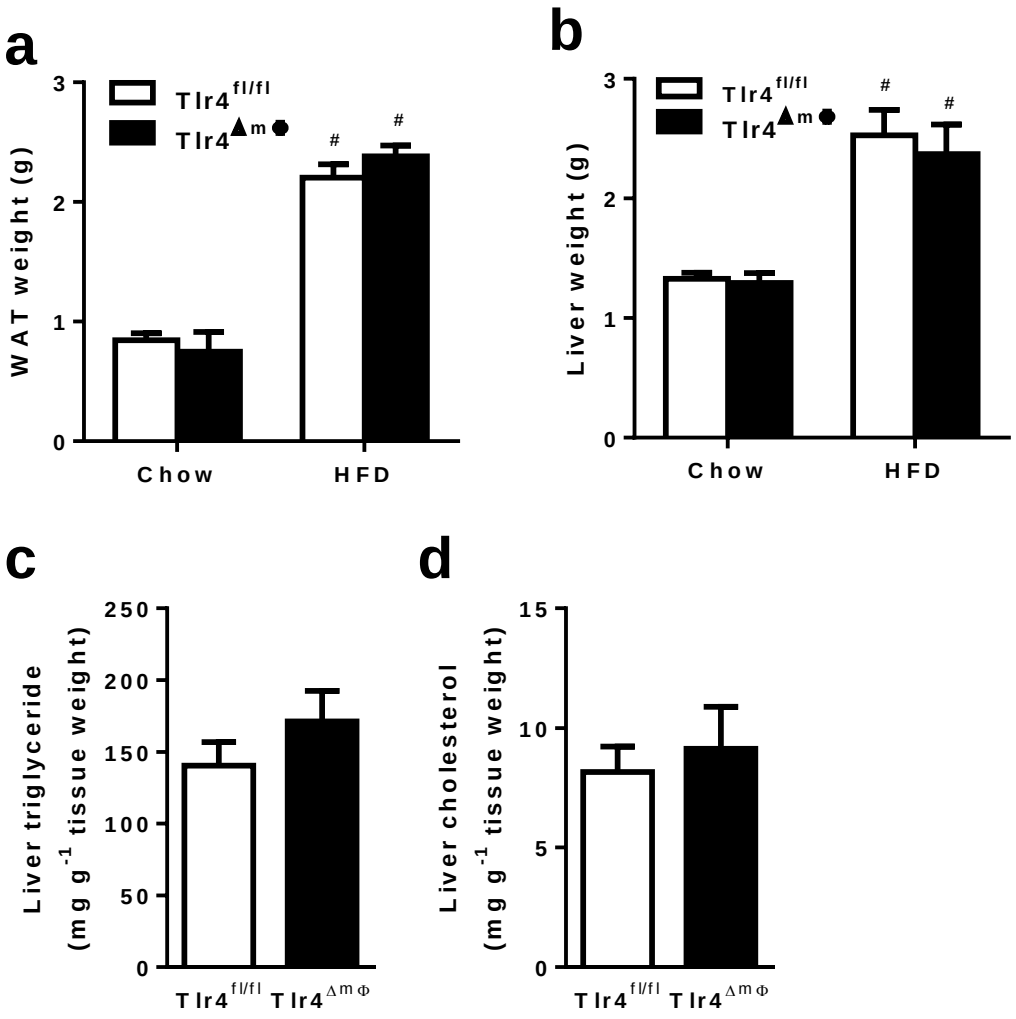
Supplementary Figure 4. $Tlr4^{fl/fl}$ and $Tlr4^{LKO}$ mice had similar body weight and comparable blood glucose levels during hyperinsulinemic-euglycemic clamp experiment. After 16 weeks HFD feeding, hyperinsulinemic-euglycemic (10 mU kg^{-1} min^{-1}, 150 mg dl^{-1}, respectively) clamps of 120 minutes were performed in conscious, chronically catheterized, 4- to 5-hour-fasted $Tlr4^{fl/fl}$ and $Tlr4^{LKO}$ mice (n = 6-7). (**a**) Body weight. (**b**) Blood glucose levels during the clamps. All data are presented as means ± s.e.m.

Supplementary Figure 5

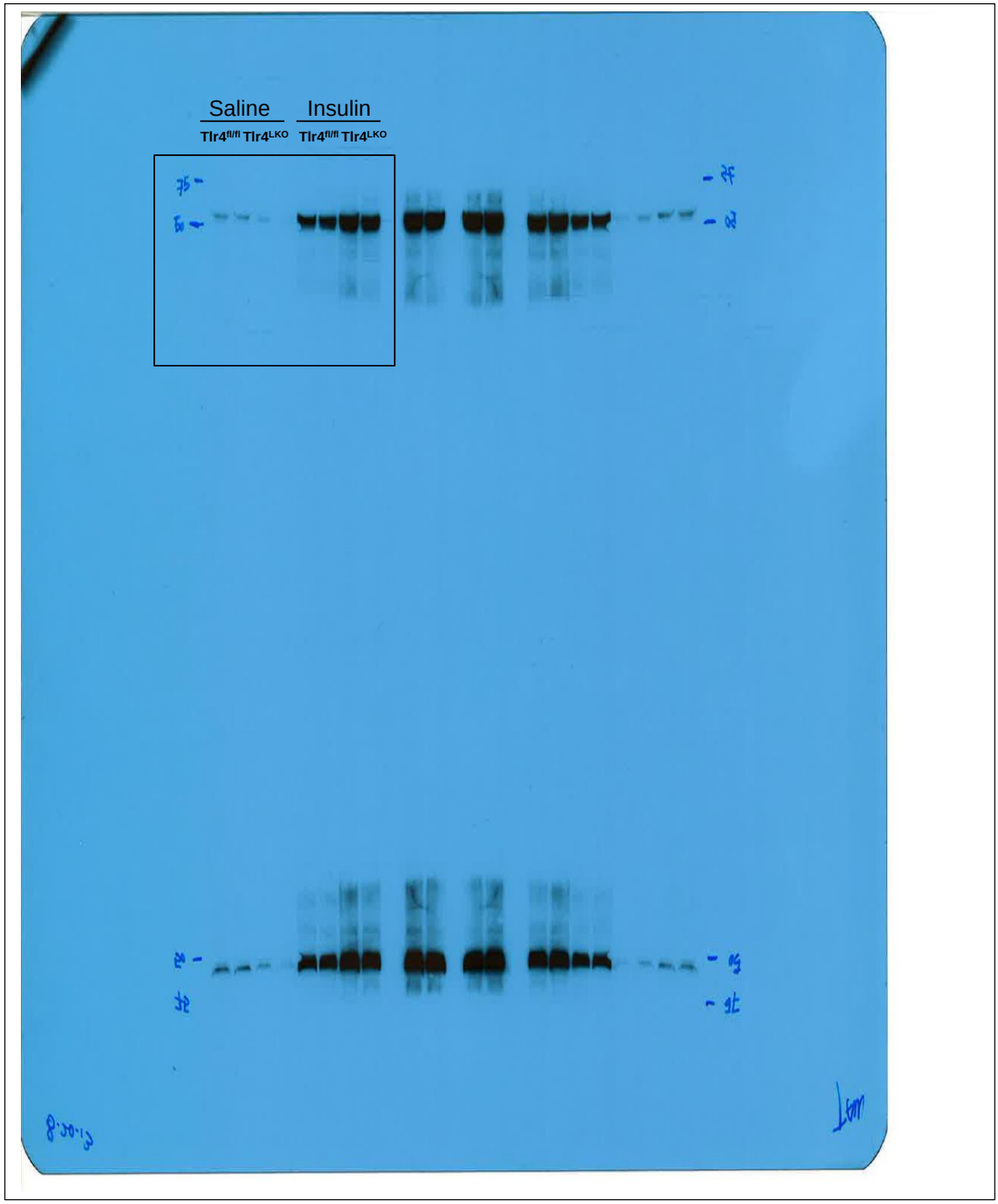


Supplementary Figure 5. HFD-fed Tlr4^{LKO} mice exhibited similar plasma lipid concentrations compared to their controls. Mice were fed HFD for 12 weeks (n = 7-9). (**a**) Plasma levels of triglyceride. (**b**) Plasma cholesterol levels. (**c**) Plasma non-esterified fatty acids (NEFA) levels. All data are presented as means ± s.e.m.

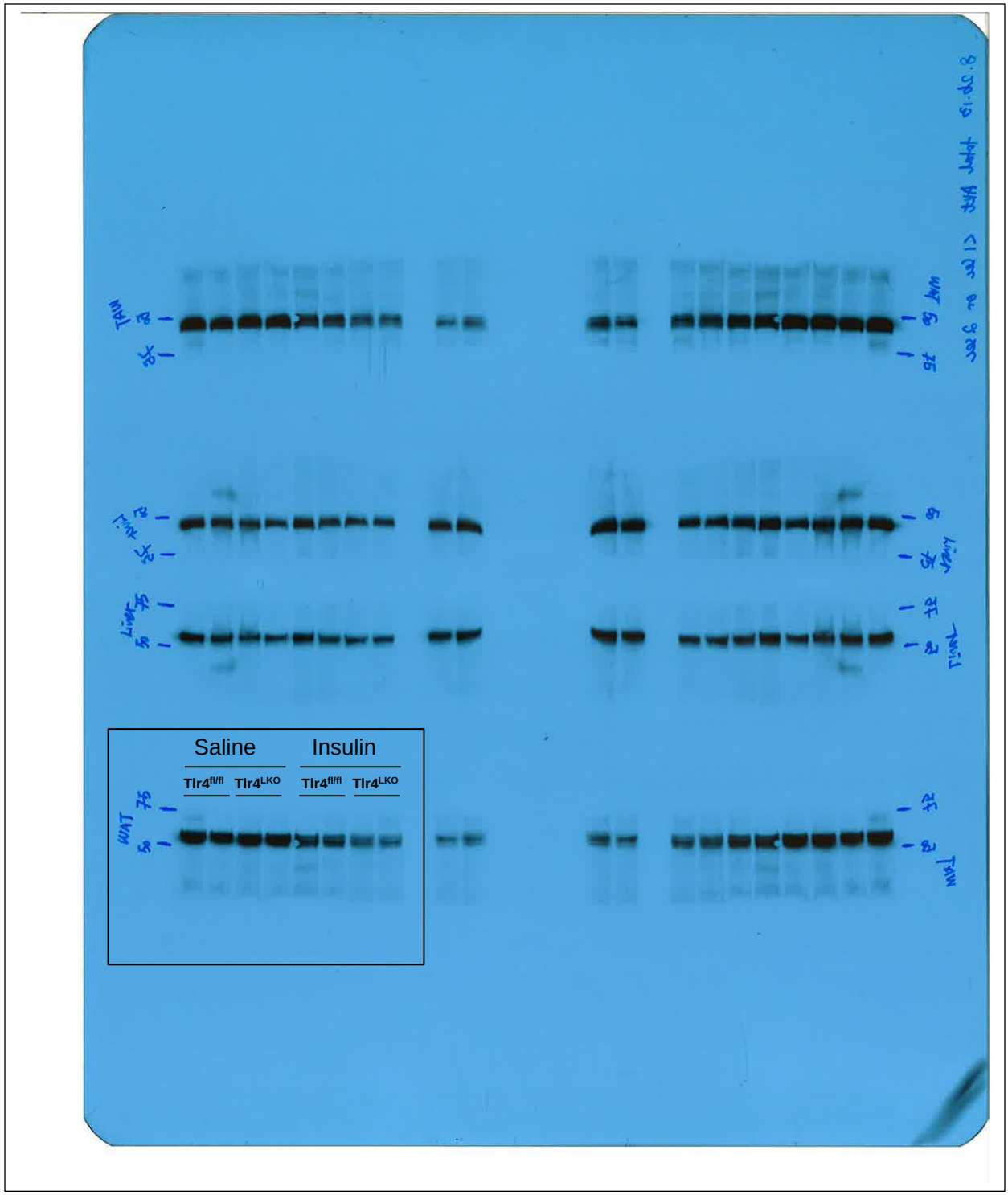
Supplementary Figure 6



Supplementary Figure 6. Macrophage Tlr4 deficiency does not protect mice from diet-induced hepatic steatosis. (**a**) Epididymal fat pad weight in mice after either chow (n = 6-10) or HFD (n = 7-8) for 12 weeks. (**b**) Liver weight in mice fed either chow (n = 7-10) or HFD (n = 13) for 12 weeks. (**c**) Liver triglyceride contents in HFD-fed mice (n = 6-7). (**d**) Liver cholesterol contents in HFD-fed mice (n = 7). $^{\#}p < 0.05$, compared between different diets for mice of the same genotype (Student's t-test). All data are presented as means ± s.e.m.



Supplementary Figure 7.Scanned western blot of p-Akt in white adipose tissue (WAT) in Figure 2g.



Scanned western blot of total Akt (t-Akt) white adipose tissue (WAT) in Figure 2g.