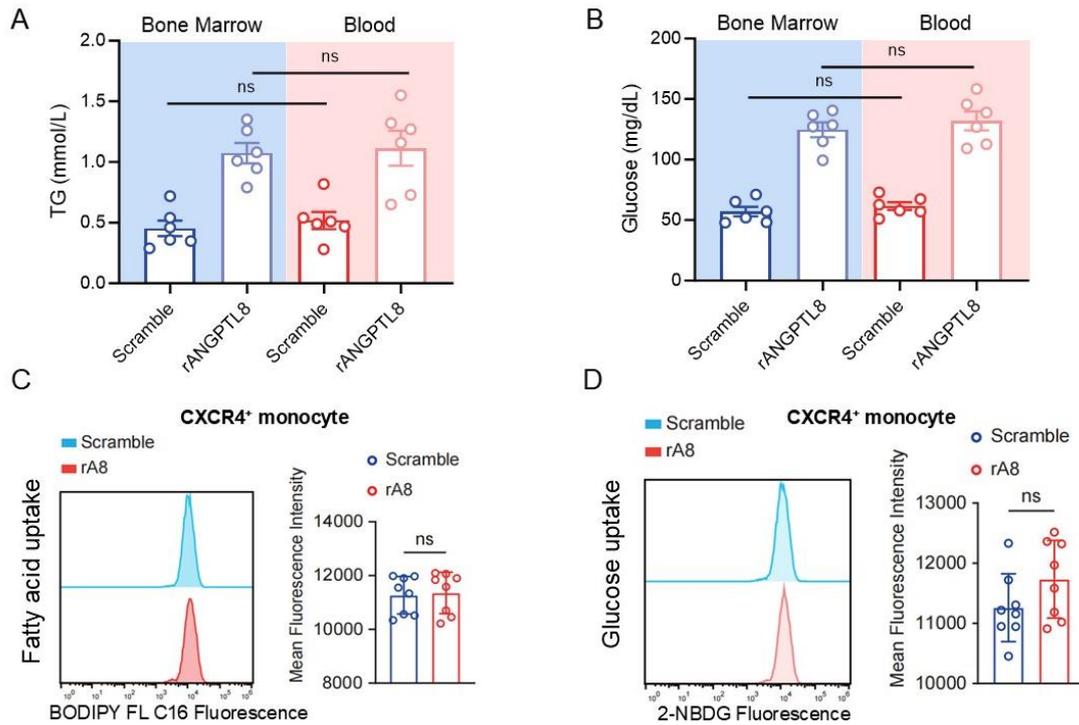


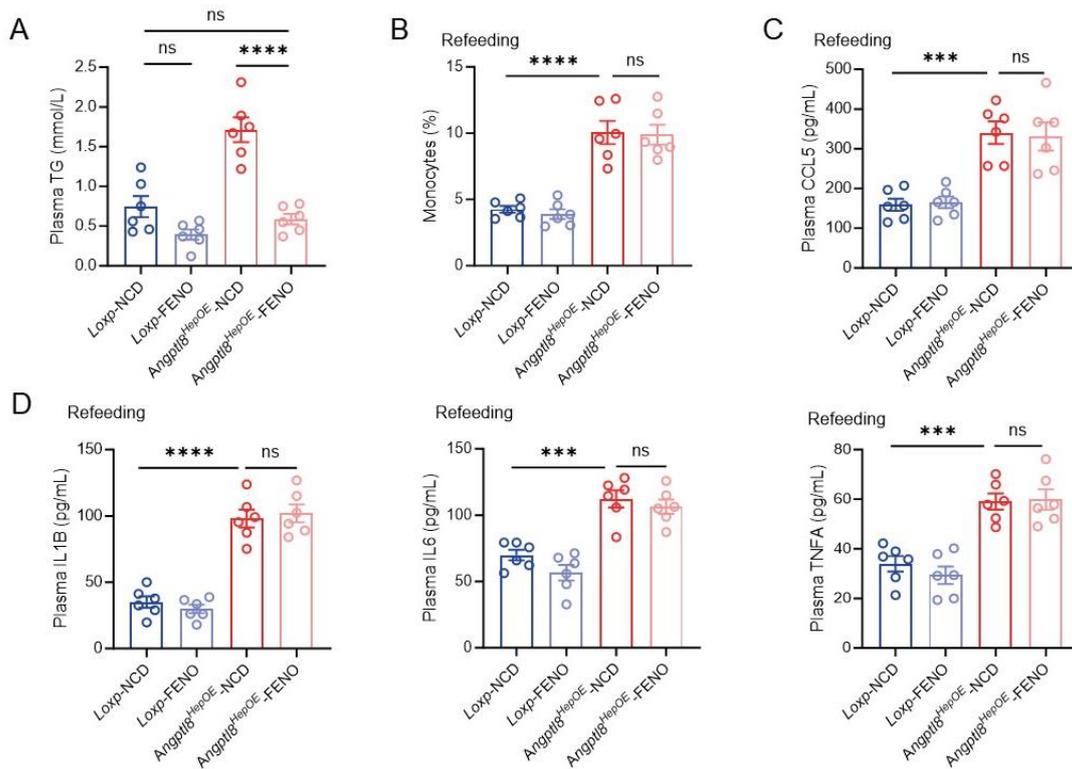
**Fig. S1**



**Figure S1. ANGPTL8 does not alter nutrient availability in the bone marrow microenvironment or nutrient uptake in monocyte precursors.**

(A) Triglyceride and (B) glucose concentrations were measured in paired samples of plasma and bone marrow flush fluid ( $n = 6$  mice per group). (C) Representative flow cytometry histograms and quantitation of MFI of BODIPY FL C16 in CXCR4<sup>+</sup> monocytes ( $n = 8$  mice per group). (D) Representative flow cytometry histograms and quantitation of MFI of 2-NBDG in CXCR4<sup>+</sup> monocytes. All samples are biologically independent replicates and  $n$  indicates the number of biologically independent samples examined. Data are mean  $\pm$  SEM ( $n = 8$  mice per group). Statistical significance was determined by paired two-tailed t-test (A, B) or unpaired two-tailed t-test (C, D). ns, not significant. rA8, recombinant ANGPTL8; MFI, mean fluorescence intensity.

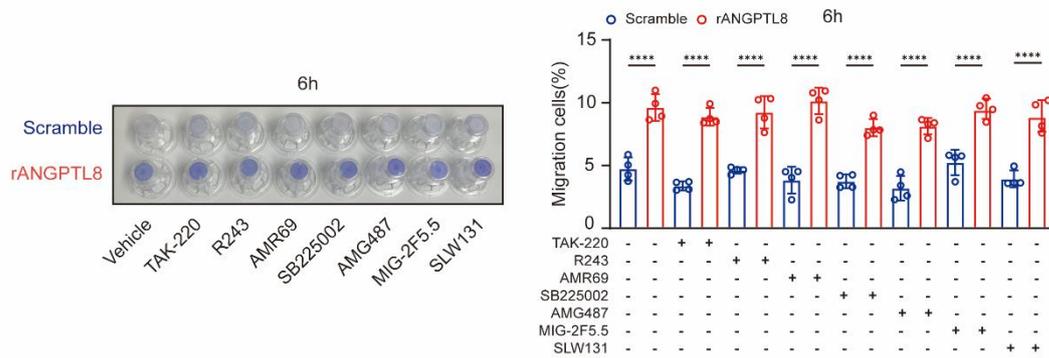
**Fig. S2**



**Figure S2. ANGPTL8-driven monocytois and inflammation are independent of its hyperlipidemic effect.**

(A) Plasma TG levels in *Angptl8<sup>HepOE</sup>* mice and *LoxP* littermate controls after two weeks of treatment with fenofibrate (200 mg/kg in chow) or control chow (n = 6 mice per group). (B) Circulating monocyte populations and (C) Plasma CCL5 levels in the same groups (n = 6 mice per group). (D) Plasma pro-inflammatory cytokines in the indicated groups (n = 6 mice per group). All samples are biologically independent replicates and n indicates the number of biologically independent samples examined. Data are mean  $\pm$  SEM. Statistical significance was determined by one-way ANOVA with Tukey's test. ns, not significant; \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001, \*\*\*\* p < 0.0001. TG, triglyceride; NCD, normal chow diet; FENO, fenofibrate.

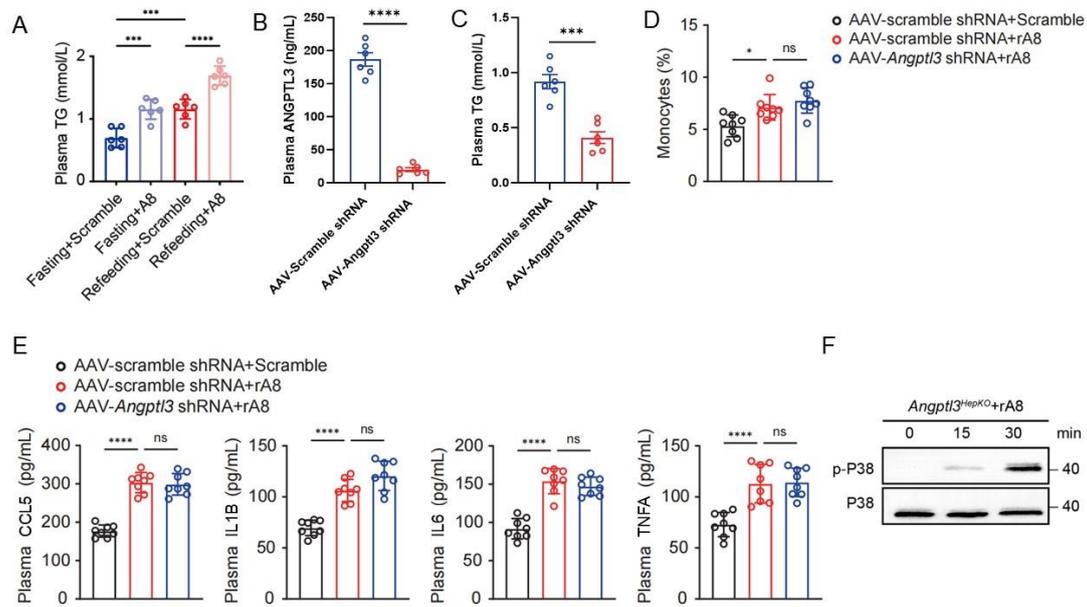
**Fig. S3**



**Figure S3. Effects of chemokine inhibitors on the 6-hour ANGPTL8-induced migration of BMDMs.**

Representative image and quantification of BMDMs migration with rA8 over time (n = 3 independent experiments). TAK-220 CCR5 antagonist, R243 CCR8 antagonist, AMR69 CCL12 inhibitor, SB225002 CXCR2 antagonist, AMG487 CXCR3 antagonist, MIG-2F5.5 anti-CXCL9 antibody, SLW131 CCR7 antagonist. Migrated cells were fixed and stained with 0.1% crystal violet. The data are shown as the mean  $\pm$  SEM. and were statistically analyzed by one-way ANOVA. All samples are biologically independent replicates and n indicates the number of biologically independent samples examined. All the p values were two-sided and adjustments were made for multiple comparisons. \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001, \*\*\*\* p < 0.0001. BMDMs bone marrow-derived macrophages.

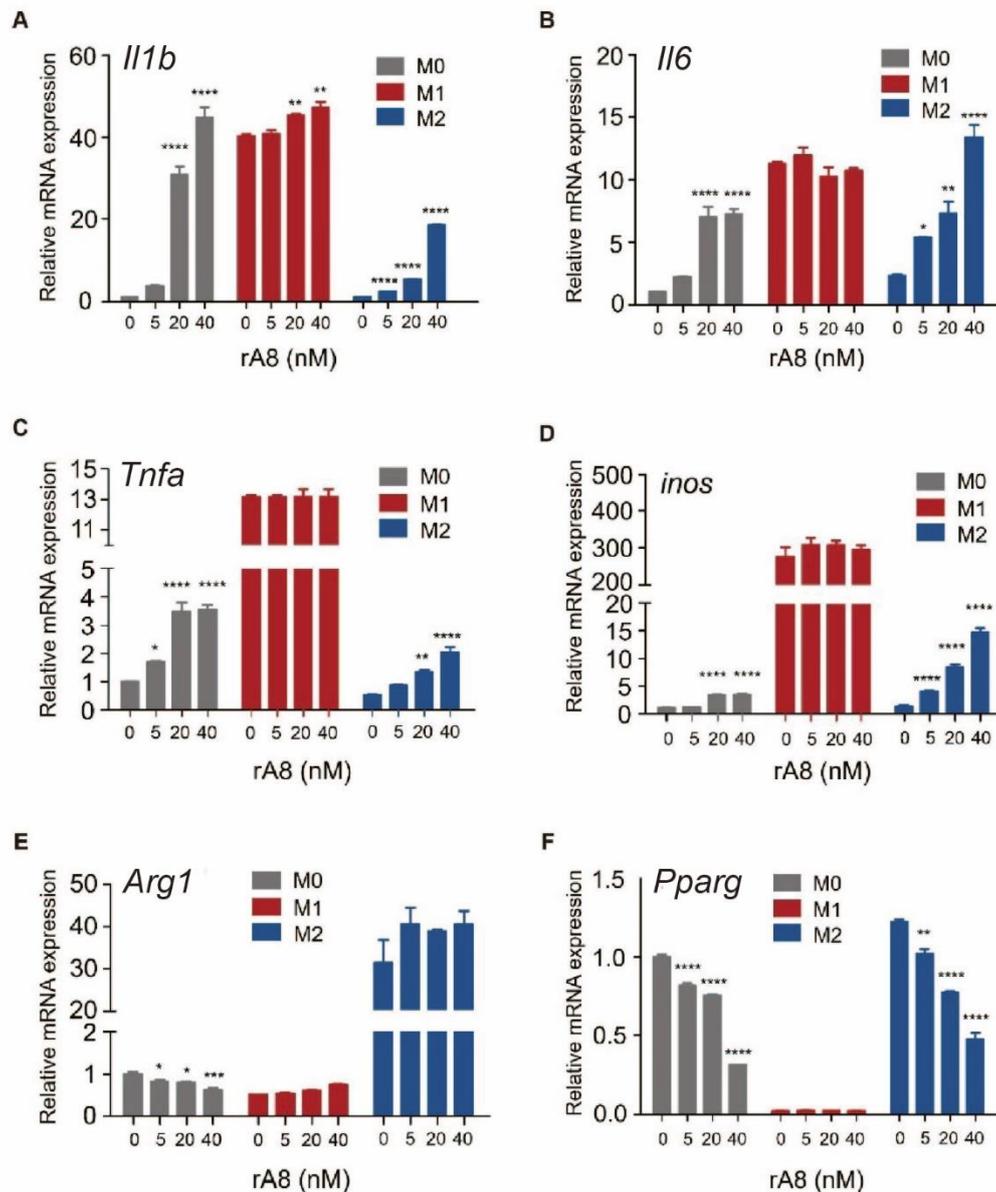
**Fig. S4**



**Figure S4. ANGPTL8 induces inflammation independently of ANGPTL3.**

(A) Plasma triglyceride levels in mice under fasting or refeed conditions after injection with scramble or recombinant ANGPTL8 ( $n = 6$  mice per group). (B) Plasma ANGPTL3 levels and (C) plasma triglyceride levels in *Angptl3* knockdown mice ( $n = 6$  mice per group). (D) Circulating monocyte populations in mice injected with AAV8-*shAngptl3* and recombinant ANGPTL8 compared to the scramble control group ( $n = 8$  mice per group). (E) Plasma levels of CCL5 and pro-inflammatory cytokines of indicated groups. (F) Phospho-P38 and total P38 protein levels in BMDMs. All samples are biologically independent replicates and  $n$  indicates the number of biologically independent samples examined. Data are mean  $\pm$  SEM. Statistical significance was determined by (A) two-way ANOVA with Tukey's test, (B, C) unpaired two-tailed t-test, and (D, E) one-way ANOVA with Tukey's multiple-comparison test. ns, not significant; \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ , \*\*\*\*  $p < 0.0001$ . TG, triglyceride; rA8, recombinant ANGPTL8.

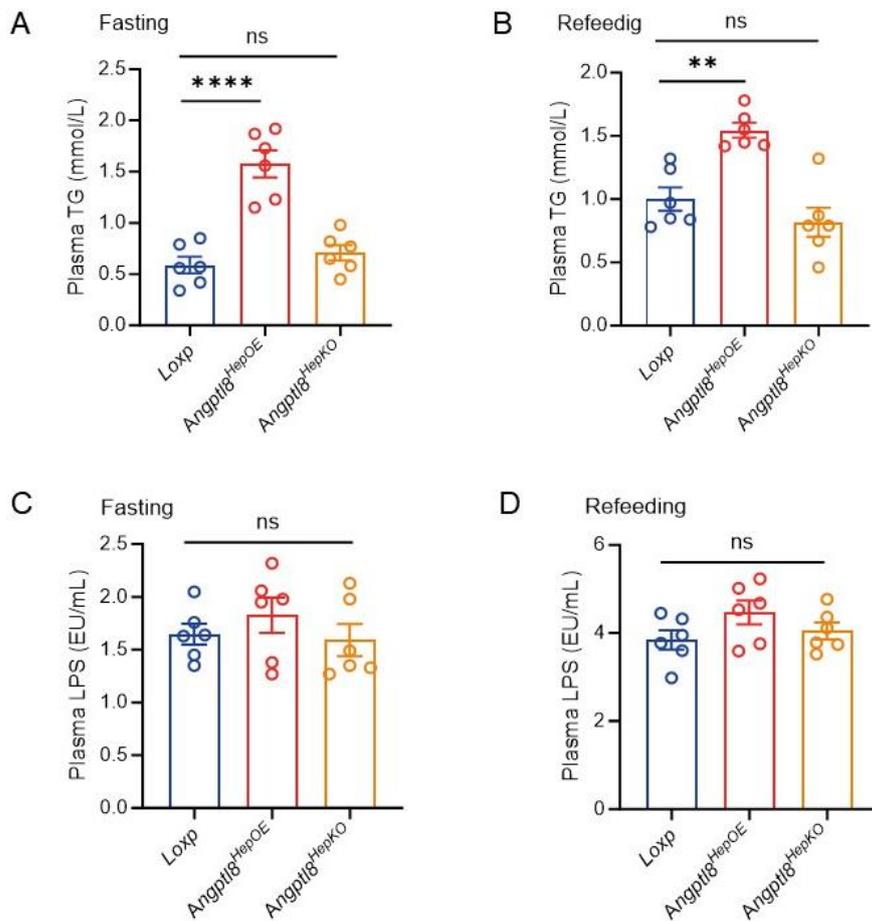
**Fig. S5**



**Figure S5. ANGPTL8 differentially regulates inflammatory gene expression in pre-polarized macrophage subsets.**

(A-D) mRNA expressions of M1 marker genes (including *Il1b*, *Il6*, *Tnfa*, and *inos*) in pre-polarized BMDMs with rA8 at different doses (n = 6 cells examined over three independent experiments). (E, F) mRNA expressions of M2 marker genes (including *Arg1* and *Pparg*) in pre-polarized BMDMs with rA8 at different doses (n = 6 cells examined over three independent experiments). The data are shown as the mean  $\pm$  SEM, and were statistically analyzed by two-way ANOVA. All samples are biologically independent replicates and n indicates the number of biologically independent samples examined. All the p values were two-sided and adjustments were made for multiple comparisons. \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001, \*\*\*\* p < 0.0001. BMDMs bone marrow-derived macrophages, M0 initial macrophages, M1 proinflammation macrophages, M2 anti-inflammation macrophages.

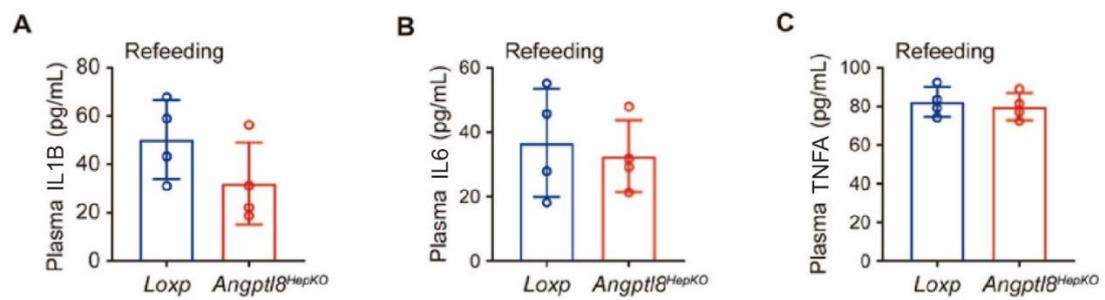
**Fig. S6**



**Figure S6. Hepatocyte-specific manipulation of *Angptl8* alters postprandial triglyceridemia without affecting plasma endotoxin levels.**

(A, B) Plasma triglyceride (TG) levels in *Angptl8<sup>HepOE</sup>* mice, *Angptl8<sup>HepKO</sup>* mice and *LoxP* controls under (A) fasting and (B) refeeding conditions (n = 6 mice per group). (C, D) Plasma LPS levels in the indicated groups under (C) fasting and (D) refeeding conditions (n = 6 mice per group). All samples are biologically independent replicates and n indicates the number of biologically independent samples examined. Data are presented as mean  $\pm$  SEM. Statistical significance was determined by one-way ANOVA with Tukey's multiple-comparison test. ns, not significant; \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001, \*\*\*\* p < 0.0001. TG, triglyceride; LPS, lipopolysaccharides.

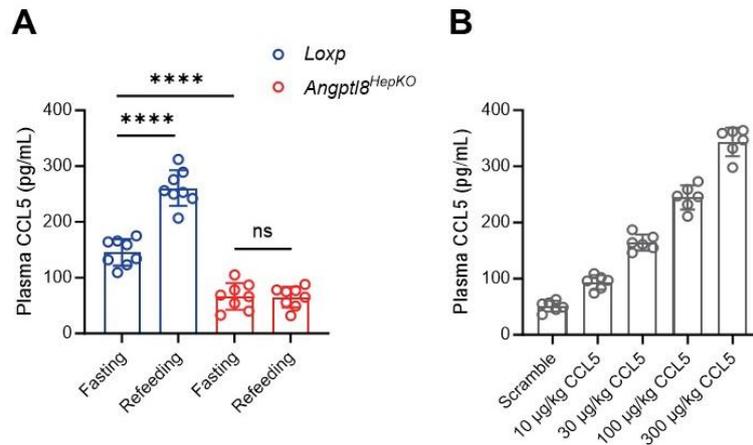
**Fig. S7**



**Fig. S7. ANGPTL8 did not impact proinflammation chemokines in refeeding mice with normal diet.**

(A-C) Plasma proinflammation cytokines levels of refeeding mice with normal diet (n = 4 mice per group). All samples are biologically independent replicates and n indicates the number of biologically independent samples examined. The data are shown as the mean  $\pm$  SEM and were statistically analyzed by two-tailed Student's test. All samples are biologically independent replicates and n indicates the number of biologically independent samples examined. All the p values were two-sided. \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001, \*\*\*\* p < 0.0001.

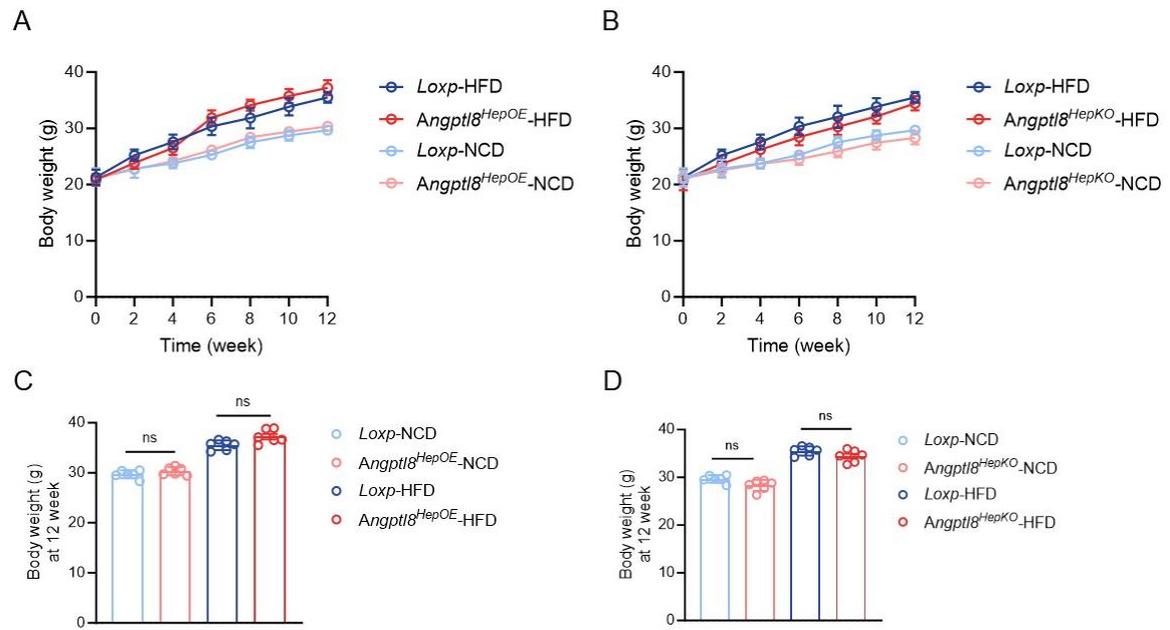
**Fig. S8**



**Figure S8. ANGPTL8 deficiency abolishes refeeding-induced CCL5 upregulation and determination of recombinant CCL5 dose.**

(A) Plasma CCL5 protein levels in *Loxp* and *Angptl8<sup>HepKO</sup>* mice under fasted and refeed conditions (n = 8 mice per group). (B) Plasma CCL5 levels following intraperitoneally injection of increasing doses of CCL5 protein (n = 6 mice per group). Data are presented as mean  $\pm$  SEM and were statistically analyzed by one-way ANOVA with Tukey's multiple-comparison test (A). All samples are biologically independent replicates and n indicates the number of biologically independent samples examined. All the p values were two-sided and adjustments were made for multiple comparisons. \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001, \*\*\*\* p < 0.0001.

**Fig. S9**



**Figure S9. Body weight gain in *Angptl8<sup>HepOE</sup>* and *Angptl8<sup>HepKO</sup>* mice under normal and high-fat feeding.**

(A) Body weight growth curves of *Angptl8<sup>HepOE</sup>* mice (n = 6 mice per group). (B) Body weight growth curves of *Angptl8<sup>HepKO</sup>* mice (n = 6 mice per group). (C) Final body weight of *Angptl8<sup>HepOE</sup>* mice and *Loxp* controls measured at the endpoint of the 12-week feeding period. (D) Final body weight of *Angptl8<sup>HepKO</sup>* mice and *Loxp* controls measured at the endpoint of the 12-week feeding period. All samples are biologically independent replicates and n indicates the number of biologically independent samples examined. Data are presented as mean  $\pm$  SEM. Statistical analysis was performed by two-way ANOVA with Tukey's multiple-comparison test (C, D). HFD, high-fat diet; NCD, normal chow diet.