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Adipocyte Phospholipid Transfer Protein and Lipoprotein Metabolism

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Abstract

Objective—Phospholipid transfer protein (PLTP) is highly expressed in adipose tissues. Thus, the effect of adipose tissue PLTP on plasma lipoprotein metabolism was examined.

Approach and Results—we crossed PLTP-Flox-ΔNeo and adipocyte protein 2 (aP2)-Cre transgenic mice to create PLTP-Flox-ΔNeo/aP2-Cre mice that have a 90 and a 60% reduction in PLTP mRNA in adipose tissue and macrophages, respectively. PLTP ablation resulted in a significant reduction in plasma PLTP activity (22%) and in high-density lipoprotein (HDL), cholesterol (21%), phospholipid (20%), and apolipoprotein A-I (apoA-I; 33%) levels, but had no effect on non-HDL levels in comparison with those of PLTP-Flox-ΔNeo controls. To eliminate possible effects of PLTP ablation by macrophages, we lethally irradiated PLTP-Flox-ΔNeo/aP2-Cre mice and PLTP-Flox-ΔNeo mice, and then transplanted wild-type mouse bone marrow into them to create wild-type (WT)→PLTP- Flox-ΔNeo/aP2-Cre and WT→PLTP-Flox-ΔNeo mice. Thus, we constructed a mouse model (WT→PLTP-Flox-ΔNeo/aP2-Cre) with PLTP deficiency in adipocytes but not in macrophages. These knockout mice also showed significant decreases in plasma PLTP activity (19%) and cholesterol (18%), phospholipid (17%), and apoA-I (26%) levels. To further investigate the mechanisms behind the reduction in plasma apoA-I and HDL lipids, we measured apoA-I-mediated cholesterol efflux in adipose tissue explants and found that endogenous and exogenous PLTP significantly increased cholesterol efflux from the explants.

Conclusions—Adipocyte PLTP plays a small but significant role in plasma PLTP activity and promotes cholesterol efflux from adipose tissues.

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Disclosure

None.

Keywords

Adipose tissue; adipocyte; macrophage; bone marrow transplantation; PLTP; HDL; non-HDL; lipoprotein production; explant culture; cholesterol efflux

Introduction

Phospholipid transfer protein (PLTP) belongs to a family of lipid transfer/ lipopolysaccharide-binding proteins that includes lipopolysaccharide-binding protein, bactericidal/permeability-increasing protein, and cholesteryl ester-transfer protein[1]. Although cholesteryl ester-transfer protein[1] can also transfer phospholipids, there is no redundancy in the functions of PLTP and cholesteryl ester-transfer protein[2]. PLTP mRNA is most abundant in adipose tissue, followed in descending order by lung, brain, muscle, kidney, liver, small intestine, macrophage, and spleen[3].

Unexpectedly, PLTP deficiency causes significant impairment in hepatic secretion of apoB-containing lipoprotein (BLp) in mouse models[4]. Likewise, it has been reported that animals overexpressing PLTP exhibit hepatic over-production of very low-density lipoproteins[5, 6]. Masson et al.[7] found that human PLTP-transgenic rabbits showed a significant increase in BLp but not in high-density lipoprotein (HDL) in the circulation. This might reflect the real situation in humans because rabbits, like humans, are a low-density lipoprotein (LDL) mammal. Okazaki et al. reported that, in concert with an increase in triglyceride synthesis, an increased PLTP activity permits triglyceride incorporation into large very low-density lipoproteins[8]. More importantly, genome-wide association and other studies in humans have shown that PLTP levels are positively associated with plasma triglyceride levels[9, 10]. Thus, we believe that PLTP activity is involved in promoting BLp lipidation.

PLTP is also involved in HDL metabolism. Human plasma PLTP activity is inversely associated with HDL levels[11–13]. Moreover, human genome-wide association studies also suggest that plasma HDL levels are associated with variation in the PLTP locus[9]. Transgenic mice overexpressing human PLTP at high levels show a 30–40% reduction in plasma HDL cholesterol levels[14]. PLTP deficiency also results in a marked decrease in HDL cholesterol, phospholipid, and apoA-I levels[15]. In other words, for still unknown reasons, both PLTP overexpression and PLTP deficiency cause significant reduction in circulating HDL levels.

We previously showed that liver-specific PLTP expression in a PLTP-null background dramatically affects plasma BLp levels, but has a marginal effect on plasma HDL levels[16]. Liver-specific PLTP knockout (KO) mice, on the other hand, showed significant reduction in HDL and BLp levels. Thus, we speculated that extrahepatic tissue-generated PLTP may strongly affect HDL metabolism.

There is accumulating evidence that adipose cholesterol imbalance is closely associated with adipocyte dysfunction and obesity-mediated metabolic complications, including low levels of HDL cholesterol[17–19]. It has been reported that the adipocyte scavenger receptor BI (SR-BI) and ATP-binding cassette transporter A1 (ABCA1), but not the ABCG1, are involved in cholesterol transfer to HDL *in vivo*[19]. It has been shown that adipocyte protein 2 (aP2)-Cre

recombinase (Cre)-mediated adipose tissue-ABCA1 deficiency significantly decreases systemic HDL biogenesis *in vivo*[20]. In addition, as noted earlier, PLTP expression in adipose tissue is much larger than in the liver[3], and PLTP not only transfers phospholipids but also free cholesterol[15]. In this study, we specifically evaluated the effects of adipocyte PLTP on HDL production. We hypothesized that adipocyte PLTP-mediated lipid transfer activity provides an additional pathway for HDL biogenesis.

Materials and Methods

Materials and Methods are available in the online-only Supplement.

Results

Adipose Tissue PLTP Deficiency Decreases Plasma PLTP Activity

We prepared homozygous PLTP-Flox-ΔNeo mice and found that these animals have normal plasma PLTP activity, and plasma cholesterol and phospholipid levels[21]. Next, we crossed these PLTP-Flox-ΔNeo mice with aP2-Cre transgenic mice (Figure 1A and B) to obtain a mouse model with 90 and 60% reduction in PLTP mRNA levels in adipose tissue and macrophages, respectively (Figure 2). We observed that mouse adipose tissue had three-fold higher PLTP mRNA levels than did the bone marrow-derived macrophages (Figure 2A). PLTP ablation resulted in a ~22% reduction in plasma PLTP activity in comparison with that of the controls (Figure 1B), indicating that both adipose tissue- and macrophage-expressed PLTP make significant contributions to the PLTP activity in the blood.

PLTP Deficiency Mediated by aP2-Cre Significantly Decreases Plasma HDL Lipid Levels

We found that aP2-Cre-mediated PLTP deficiency in male mice significantly decreased plasma levels of cholesterol (21%, $P < 0.01$; Figure 2C) and phospholipids (20%, $P < 0.05$; Figure 2D), but had no significant effect on the triglyceride level (Figure 2E). We observed the same phenotypes in female mice (data not shown).

Plasma lipid distributions were also examined by FPLC using pooled plasma. We observed that plasma cholesterol levels decreased in the HDL fraction but not in the non-HDL fraction from male PLTP-deficient mice compared with controls (Figure 3A). This was also true for total phospholipid distribution (Figure 3B). The same phenomena were also observed in female mice, as compared with male controls (data not shown).

Next, we assessed plasma apolipoprotein levels by reducing SDS-PAGE and western blotting and found that the PLTP-deficient mice had a significant reduction in apoA-I (33%, $P < 0.01$) but not in total apoB and apoE, compared with the control group (Figure 3C and D), suggesting that PLTP deficiency in the adipose tissue and macrophages impacted apoA-I-containing lipoprotein (HDL) levels but not BLp (non-HDL) levels.

When the mice were fed a high-fat, high-cholesterol diet for 2 weeks, we found that aP2-Cre-mediated PLTP deficiency also significantly decreased plasma levels of PLTP (20%, $P < 0.05$; Supplemental Figure IA), cholesterol (22%, $P < 0.05$; Supplemental Figure IB), and apoA-I (38%, $P < 0.01$; Supplemental Figure IC and D).

Adipocyte-Specific PLTP Deficiency Decreases Plasma PLTP Activity

To eliminate the potential effects by PLTP deficiency in macrophages, eight male PLTP-Flox-ΔNeo/aP2-Cre mice and eight male PLTP-Flox-ΔNeo mice were lethally irradiated and then transplanted with WT mouse bone marrow cells to create adipocyte KO mice (WT →PLTP-Flox-ΔNeo/aP2-Cre) and control mice (WT →PLTP-Flox-ΔNeo). In the WT→PLTP-Flox-ΔNeo/aP2-Cre group, the peripheral cells did not express Cre (the 100-bp transgene fragment had disappeared) after bone marrow transplantation (Figure 4), suggesting that macrophages had normal PLTP expression. Indeed, primary macrophages isolated from WT →PLTP-Flox-ΔNeo/aP2-Cre mice had similar levels of PLTP mRNA as control mice, whereas adipose tissues from WT →PLTP-Flox-ΔNeo/aP2-Cre were deficient in PLTP (Figure 5A).

We next determined plasma PLTP activity and lipid levels in the WT →PLTP-Flox-ΔNeo/aP2-Cre and WT →PLTP-Flox-ΔNeo mice. We found that adipocyte PLTP-KO mice also showed significant decreases in plasma PLTP activity (19%, $P < 0.05$; Figure 5B), cholesterol (18%, $P < 0.05$; Figure 5C), and phospholipid (17%, $P < 0.05$; Figure 5D) levels, but had no significant change in triglyceride levels (data not shown). We also assessed plasma apolipoprotein levels and found that the PLTP-deficient mice showed a significant reduction in apoA-I (26%, $P < 0.01$) but not in total apoB levels compared with the control group (Figure 5E), indicating that PLTP deficiency in adipose tissue has an impact on apoA-I-containing lipoprotein (HDL) but not BLp (non-HDL) levels.

We also fed the WT →PLTP-Flox-ΔNeo/aP2-Cre and WT →PLTP-Flox-ΔNeo mice a high-fat, high-cholesterol diet for 5 weeks and found that the PLTP deficient mice showed significant decreases in plasma levels of PLTP (23%, $P < 0.05$), cholesterol (26%, $P < 0.05$) and phospholipid (28%, $P < 0.01$), compared with the controls (Supplemental Figure IIA–C).

PLTP Promotes Cholesterol Efflux from Adipose Tissues

It has been reported that adipose tissue ABCA1 contributes to cholesterol efflux, which is involved in nascent HDL production from the tissue[20] and that PLTP assists ABCA1 in cholesterol efflux[21, 22]. To further investigate the mechanisms behind reduction of apoA-I and HDL lipids in plasma, we measured cholesterol efflux directly from adipose tissue. We isolated epididymal fat pats from PLTP-Flox-ΔNeo/aP2-Cre and control mice for explant culture (Figure 6A). The explants were labeled with ^{3}H-cholesterol and then incubated with apoA-I and with rPLTP or BSA. We then measured radioactivity in lipids extracted from the medium. We found that PLTP KO adipose tissue explants had a lesser level of cholesterol efflux compared with control adipose tissue explants (Figure 6B) under LXR agonist stimulation, indicating that adipose tissue PLTP is involved in nascent HDL production. To eliminate the possible involvement of macrophages, we also carried out explant culture using epididymal fat pats from WT →PLTP-Flox-ΔNeo/aP2-Cre mice and WT →PLTP-Flox-ΔNeo controls. We found that adipocyte-specific PLTP deficient explants had a decreased cholesterol efflux compared with controls (Figure 6C). Next, we examined the effect of exogenous rPLTP on efflux and found that rPLTP significantly increased cholesterol efflux from control and PLTP KO (Figure 6D) adipose tissue explants.

Because PLTP deficiency appeared to have an effect on HDL function, in terms of cholesterol efflux, we then isolated HDL from both PLTP-Flox-ΔNeo/aP2-Cre and control mice. We measured cholesterol efflux in WT adipose explants incubated with the two HDL fractions and found no significant difference between the two (Supplemental Figure III). We also utilized liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) to measure subspecies of phospholipids (sphingomyelin and phosphatidylcholine) in HDL isolated from PLTP deficient and control mice and we did not find significant differences between two groups of animals (Supplemental Table I).

For further characterization, we performed NMR analysis (LipoScience, Inc.) on HDLs from wild type (WT), systemic PLTP KO[4], adipocyte PLTP KO, and PLTP transgenic[5, 6] mice. The order of the size is systemic PLTP KO > adipocyte PLTP KO = wile type (WT) > PLTP Tg (Fig. 6E). We further measured inflammatory index (derived by dividing net antioxidant activity in the presence of HDL by that observed in the absence of HDL) using HDLs from WT, systemic PLTP KO, and PLTP transgenic mice. They are 0.42±0.03, 0.69±0.05, and 1.27±0.090, for systemic PLTP KO, WT, and PLTP Tg HDL, respectively (Fig. 6F). The differences are significant ($P<0.05$). We did LDL conjugated diene formation in the presence of WT or adipocyte PLTP KO HDL, a way to evaluate HDL function of anti-oxidation, and we did not observe a significant difference (data not shown). Thus, although systemic PLTP KO HDL has an anti-LDL-oxidation effect [23], HDL isolated from adipocyte PLTP KO mice has a marginal effect. Finally, we performed HDL fractional catabolic rate (FCR) analysis using ^{3}H-cholesterol ether-HDL isolated from WT and adipocyte LTP KO mice, and we did not find a significant difference, between the two HDLs in mice (Supplemental Figure IV).

We previously reported that liver PLTP accounts for 20–25% of plasma PLTP activity. In the current study, we show that adipose tissue PLTP-deficient mice have ~20% less plasma PLTP activity than do the controls. Thus, extrahepatic tissues likely contribute to plasma PLTP activity. To investigate the effect of lung PLTP on plasma PLTP activity and lipid levels, adenovirus (AdV)-Cre and AdV-GFP were intratracheally delivered to PLTP-Flox-Neo mice[24] and GFP was expressed in the lungs (Supplemental Figure VA). AdV-Cre treatment caused an 18% reduction in PLTP activity ($P < 0.05$), a 23% reduction in cholesterol levels ($P < 0.05$), and a 20% reduction in phospholipid levels ($P < 0.05$) in the circulation (Supplemental Figure VB–D). Thus, the lungs also appear to contribute to PLTP activity in the blood.

Discussion

In this study, we used the aP2-Cre approach because we found that mouse adipose tissue expresses ~three-fold more PLTP than do macrophages (Figure 2A), and, therefore, the phenotypic effect of aP2-Cre-mediated PLTP deficiency on plasma lipid levels, is mainly caused by PLTP deficiency in the adipose tissue. Moreover, by eliminating potential PLTP contributions from hematopoietically derived cells, including macrophages, by transplanting WT bone marrow into lethally irradiated PLTP-Flox-ΔNeo/aP2-Cre mice, we were able to see that PLTP in hematopoietically derived cells has negligible (if any) effect on plasma cholesterol, phospholipid, and apolipoprotein levels.

Adipose tissue PLTP appears to play a small but significant role in plasma PLTP activity. We previously reported that liver PLTP accounts for 20–25% of plasma PLTP activity[16, 21]. In the current study, we showed that adipose tissue PLTP-deficient mice have a ~20% lower plasma PLTP activity level than do control mice. In other words, extrahepatic tissues[3] contribute >50% of plasma PLTP activity.

Adipose tissue PLTP also plays a small but significant role in plasma HDL levels. Previously, we showed that systemic PLTP deficiency results in a 60–70% reduction in plasma HDL lipid and apoA-I levels[15], which may be related to decreased HDL production and increased HDL catabolism. We have reported that liver PLTP deficiency-mediated reduction of HDL levels is partially related to decreased cholesterol efflux from the liver[21]. In this study, we provide *in vivo* evidence that adipose tissue-PLTP deficiency causes a ~15–20% reduction in HDL-cholesterol (Figures 3A and 5C), which appears to be a consequence of decreased cholesterol efflux by adipose tissue.

These findings raise the possibility that adipose tissue PLTP-mediated lipid transfer activity may provide an additional pathway for cholesterol efflux. Adipose tissue ABCA1-dependent cholesterol efflux and nascent HDL particle formation contribute to systemic HDL biogenesis, and adipose tissue ABCA1 expression plays an important role in adipocyte cholesterol homeostasis[20]. Exogenous PLTP can promote cholesterol and phospholipid removal from cells by the ABCA1 pathway[22]. In contrast, PLTP had no effect on lipid efflux from fibroblasts isolated from a patient with Tangier disease[25]. An amphipathic helical region (amino acids 144–163) of PLTP has been shown to be critical for ABCA1-dependent cholesterol efflux[26], and PLTP can stabilize ABCA1 on the cell plasma membrane[22]. In line with these reports, we found that liver PLTP is an important player in ABCA1-mediated cholesterol efflux[21]. Based on our observation that PLTP ablation significantly reduces (Figure 6B and C) and PLTP supplement significantly induces cholesterol efflux towards apoA-I in explant cultures (Figure 6D), we believe that, as proposed for macrophages[22], PLTP may function to stabilize adipocyte ABCA1 and to shuttle lipids between cells and existing HDL particles (formed through the action of ABCA1)[27]. Because scavenger receptor BI (SR-BI) is also involved in adipocyte cholesterol efflux[19], we assessed SR-BI mRNA (data not shown) and SR-BI (Supplemental Figure VI) levels in PLTP deficient and control adipose tissue and found no significant differences.

PLTP appears to have an anti-atherogenic function, as PLTP overexpression promotes[28] and deficiency prevents[4] atherosclerosis in mice, and PLTP promotes nascent HDL production. However, an increase in plasma HDL may not uniformly translate into reduction in coronary heart disease. HDL particles are heterogeneous in size and composition[29]. Thus, understanding the origins of and characterizing the different subclasses of HDL particles will be important in clarifying how plasma concentrations lead to atherosclerotic lesion development. PLTP has the ability to remodel and enlarge mature[30, 31] and nascent HDL[32]. In this study, we found that the reduction (about 20%) of HDL in adipocyte KO mice is most likely due to the decrease of apoA-I-mediated cholesterol efflux from the adipocytes (Figures 6B–C). The deficiency has marginal effect on HDL, in terms of phospholipid composition (Supplemental Table I), cholesterol efflux (Supplemental Figure III), size (Figure 6E), catabolic rate (Supplemental Figure IV), and anti-inflammatory functions (data

not shown). However, systemic PLTP deficient HDL has smaller size (Figure 6E), higher catabolic rate [33], and lower inflammatory index than that of WT HDL (Figure 6F).

The adiponectin-Cre system may allow for better adipocyte-specific expression than the aP2-Cre construct used in this study. According to the supplier (Jackson Laboratory), adiponectin-Cre transgenic mice express Cre recombinase effectively in white and brown adipose tissue, but not in macrophages. However, although adipocytes appear to be the primary site of synthesis and secretion of adiponectin, there is some recent evidence that adiponectin is also expressed in certain areas of the brain[34] and, therefore, the adiponectin-Cre approach may have some unintended effects in the brain.

In conclusion, we established adipose tissue-PLTP KO mice through the Cre-LoxP system and bone marrow transplantation; although we still cannot claim that the PLTP deficiency is entirely adipose tissue-specific. Adipose tissue PLTP can be secreted into the circulation and makes a small but significant contribution to plasma PLTP activity and HDL lipid levels. Thus, PLTP joins the growing list of molecules secreted by adipose tissue that have more widespread systemic effects than previously thought. PLTP in the adipose tissue appears to exert its effect on cholesterol efflux from the tissue. The relationship between PLTP expression in adipose tissue and the development of diseases, such cardiovascular disease, diabetes, and insulin resistance, warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PLTP	phospholipid transfer protein
aP2	adipocyte protein 2
Cre	Cre recombinase
HDL	high-density lipoprotein
BLp	apolipoprotein B-containing lipoprotein particles
FPLC	fast protein liquid chromatography
KO	knockout

rPLTP	recombinant PLTP
WT	wild type

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Significance

Our knowledge of atherosclerosis is still limited, and more extensive investigation is necessary to better understand this disease, including exploring the effect of PLTP on lipid metabolism, because PLTP is a risk factor for the development of atherosclerosis. Although HDL levels are generally a negative risk factor in human populations, we have previously shown that PLTP KO mice with low HDL have decreased levels of lesion development, suggesting that other characteristics of HDL, including its origins, may be just as important as plasma concentration in atherosclerotic lesion development. The current study is the first to indicate that adipose tissue-PLTP deficiency can reduce PLTP activity in the blood and can suppress adipose tissue apoA-I-mediated cholesterol efflux, a requisite step for nascent HDL production. Therefore, PLTP may increase nascent HDL production by promoting ABCA1-mediated lipid efflux.

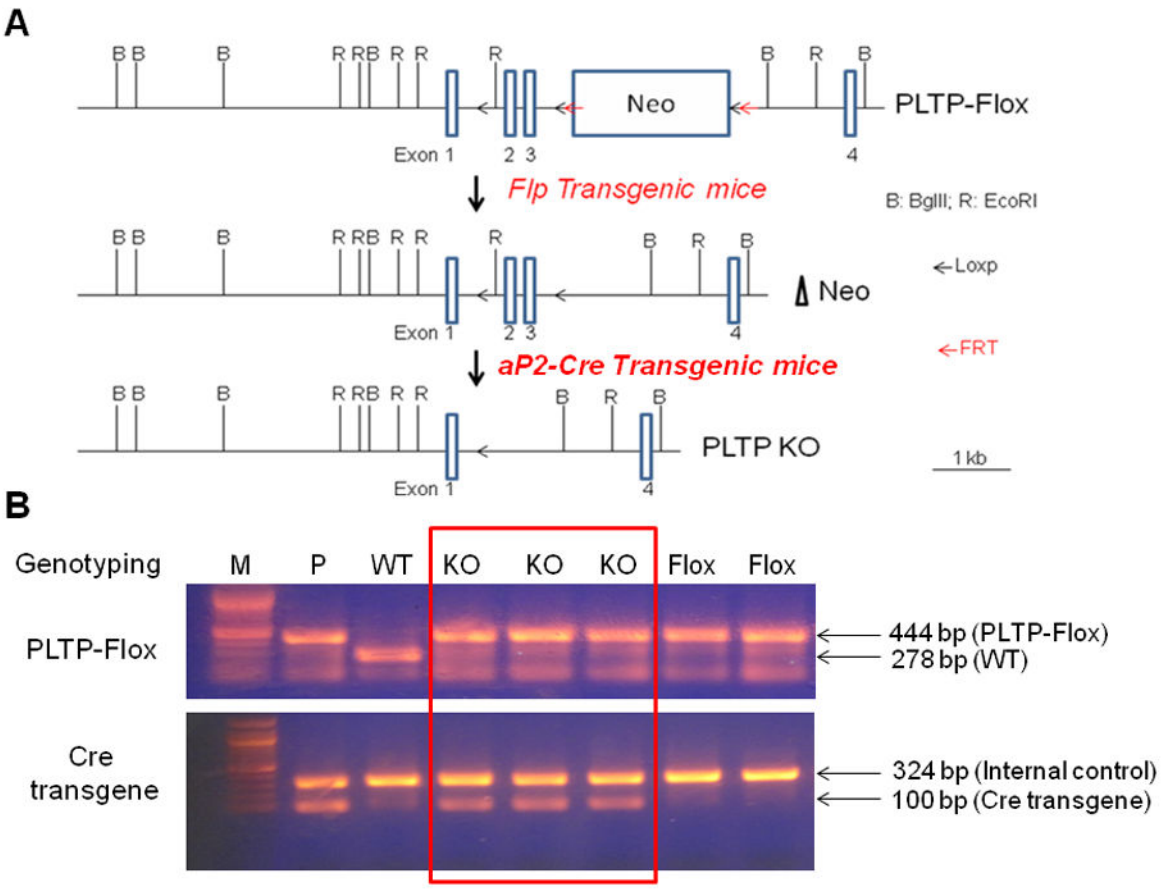

Figure 1. PLTP-Flox-ΔNeo/aP2-Cre mouse characterization

Panel A, Strategy for PLTP-Flox-ΔNeo/aP2-Cre mouse preparation. One LoxP site was located in intron 1, and a Neo cassette double flanked with flippase (flp) recognition target (FRT)/LoxP sites was placed in intron 3. The Flp transgene mediates Neo cassette deletion. AP2-Cre recombinase-mediated exon 2 and 3 deletion results in deficient PLTP expression, specifically in adipose tissue and macrophages. Panel B, Genotyping using mouse tail tip DNA. Top, PLTP-Flox-ΔNeo, and WT are detected by a 444 bp and a 278 bp fragment, respectively. Bottom, the Cre transgene is detected by a 100 bp fragment. The 324 bp internal control fragment was provided by the Jackson Laboratory. M, molecular weight markers; P, positive control.

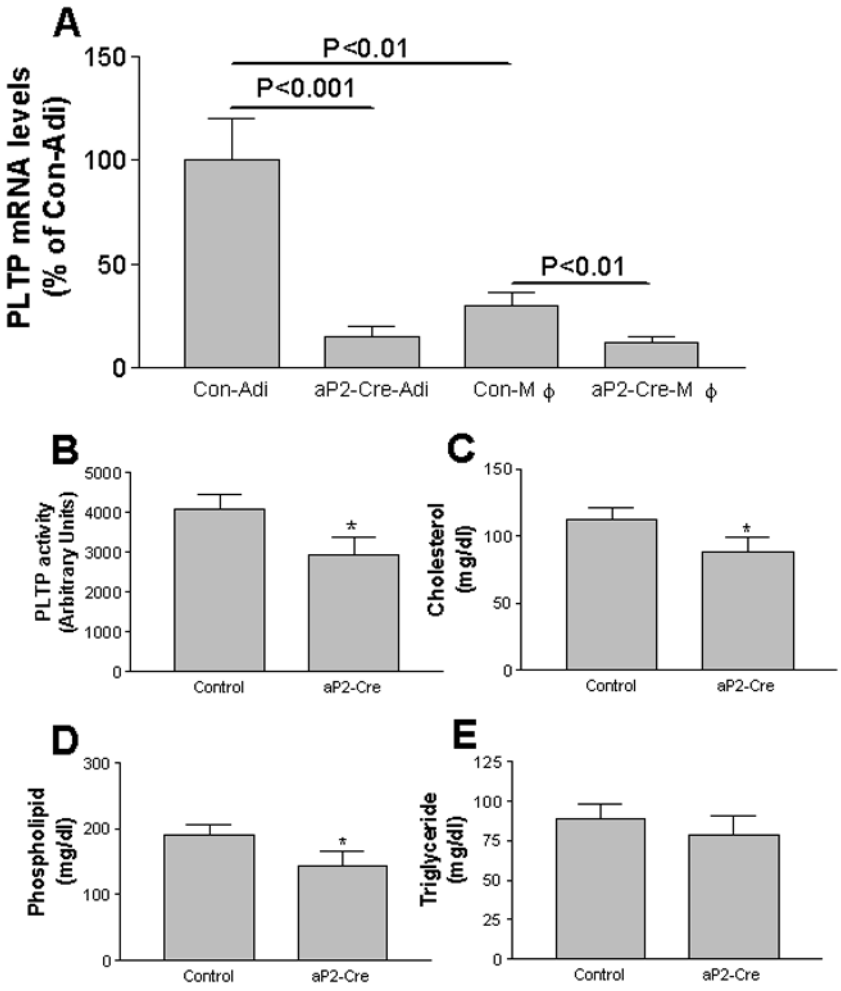

Figure 2. PLTP mRNA and activity, and plasma lipid measurements in PLTP-Flox-ΔNeo/aP2-Cre (aP2-Cre) and control (Con) mice

Panel A, PLTP mRNA in adipose tissues (Adi) and macrophages (Mφ) measured by real-time PCR. Panel B, Plasma PLTP activity. Panels C, Plasma cholesterol; Panel D, Phospholipids; and Panel E, Triglyceride measurements. Values are the mean ± SD, n = 5, *P < 0.05.

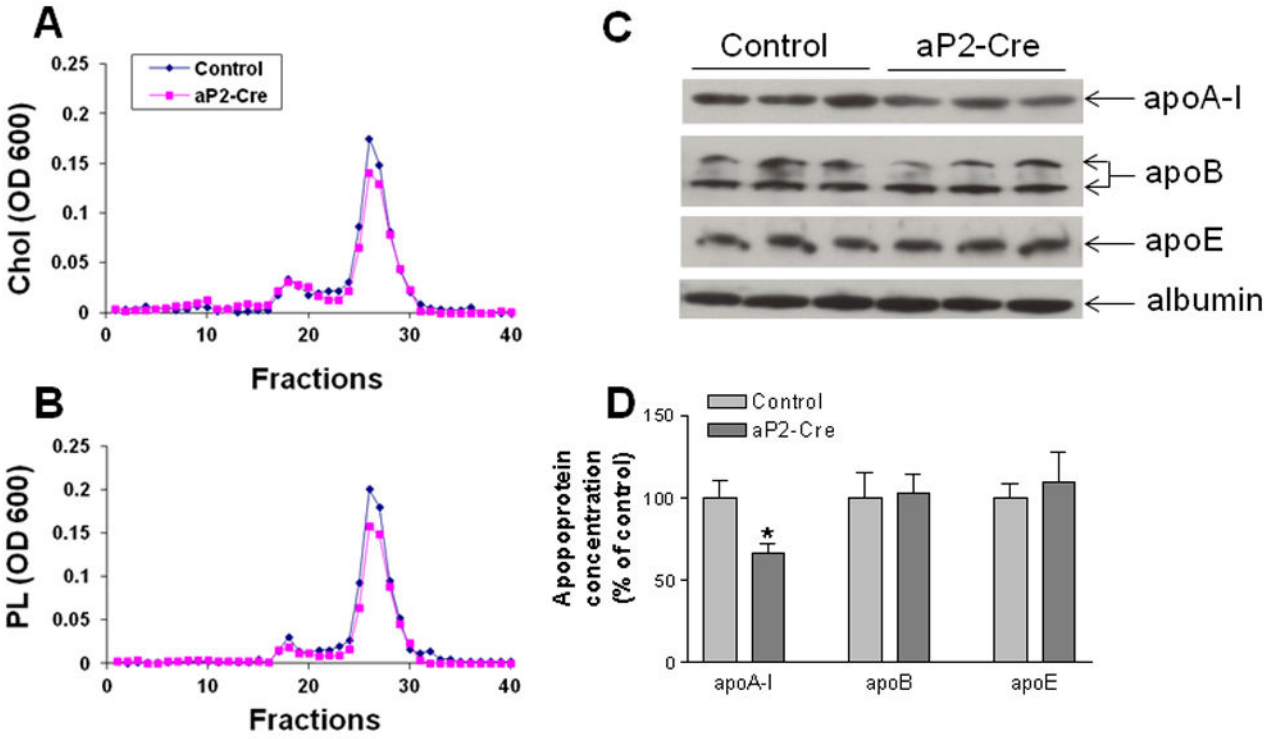

Figure 3. Lipid distribution and apolipoprotein measurements in PLTP-Flox-ΔNeo/aP2-Cre (aP2-Cre) and control mice

Plasma lipid distribution was analyzed by FPLC of pooled plasma from five male animals. Panel A, Cholesterol (Chol) distribution. Panel B, Phospholipid (PL) distribution. Panel C, Western blot of plasma apolipoproteins with polyclonal antibodies against apoA-I, apoB, apoE, and albumin. Panel D, Quantification of plasma apoA-I, apoB, and apoE. Values are the mean ± SD, n = 5, *P < 0.01.

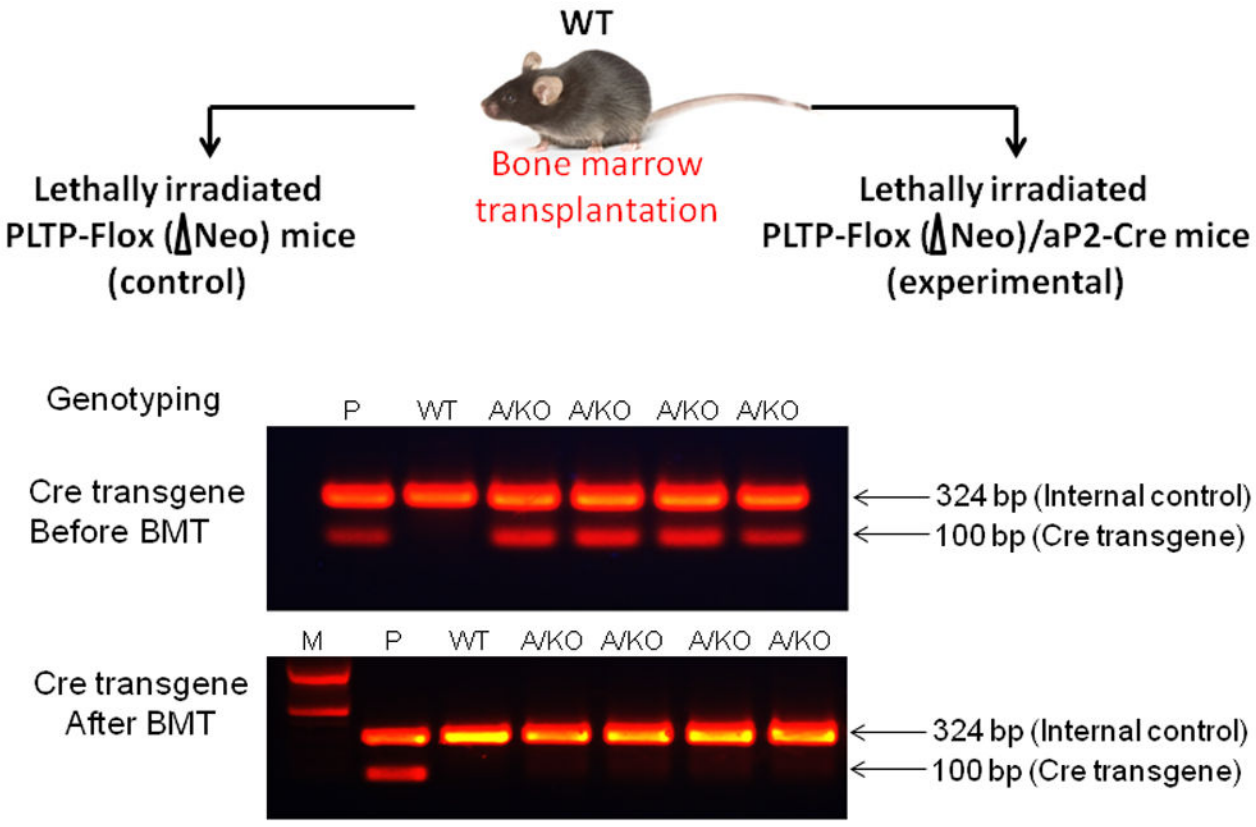

Figure 4. WT →PLTP-Flox-ΔNeo/aP2-Cre and WT →PLTP-Flox-ΔNeo mouse preparation (bone marrow transplantation, BMT)

Panel A, Strategy for bone marrow transplantation. PLTP-Flox-ΔNeo/aP2-Cre and PLTP-Flox-ΔNeo mice were lethally irradiated and then transplanted with bone marrow from the tibia of donor mice (WT; 5×10^6 cells). Panel B, Genotyping before and after bone marrow transplantation. P, positive control; M, molecular weight markers; A/KO, adipose tissue KO.

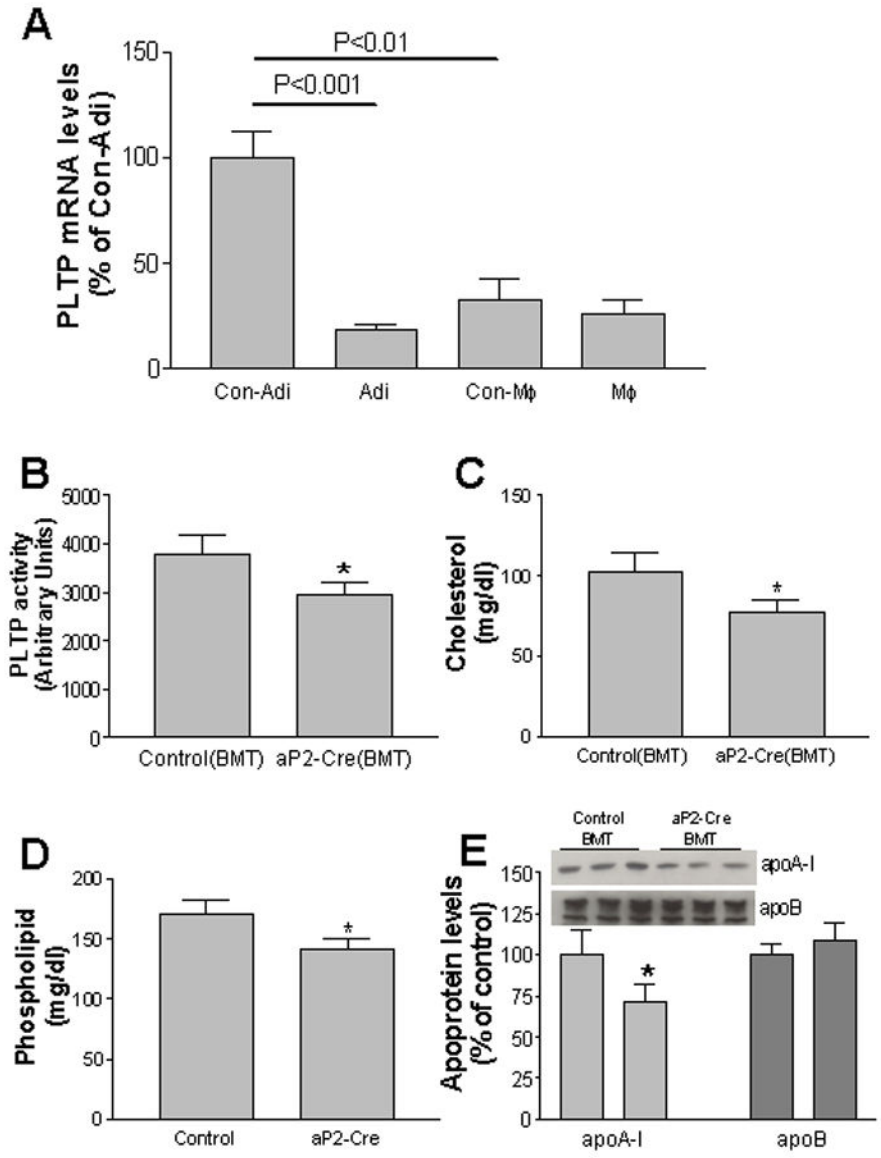

Figure 5. PLTP mRNA and activity and plasma lipid measurements in WT →PLTP-Flox-ΔNeo/ aP2-Cre (aP2-Cre(BMT)) and control (Con) mice

Panel A, PLTP mRNA in adipose tissues (Adi) and macrophages (Mφ) was measured by real-time PCR. Panel B, Plasma PLTP activity measurement. Panel C, Plasma cholesterol. Panel D, Phospholipid measurements. Panel E, Western blot with quantification of plasma apoA-I and apoB. Values are the mean ± SD, n = 5, *P < 0.05.

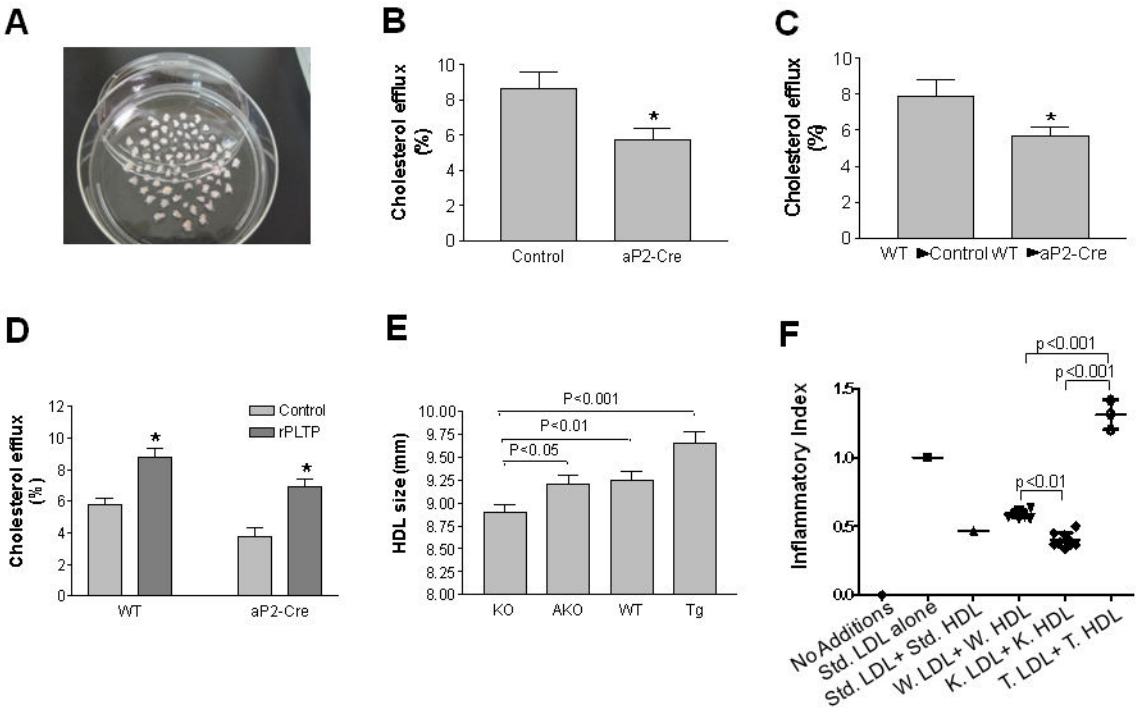

Figure 6. Adipose tissue explant culture, cholesterol efflux, HDL size, and inflammatory index measurements

Epididymal adipose tissues were isolated from PLTP-Flox-ΔNeo/aP2-Cre (aP2-Cre) or PLTP-Flox-ΔNeo (WT) mice. Panel A, The adipose tissues were minced and placed into culture dishes. The explants were loaded with [^{3}H]cholesterol then incubated with apoA-I. [^{3}H]cholesterol in the medium was determined 5 h after incubation. Panel B, Comparison of cholesterol efflux between KO and control explants under LXR agonist stimulation. Panel C, Comparison of cholesterol efflux between WT →aP2-Cre and WT → control explants under LXR agonist stimulation. Panel D, WT and the KO adipose tissue explants cultures with or without rPLTP. Values are the mean ± SD, n = 5, *P < 0.05. Panel E, HDL size measured by NMR (LipoScience, Inc.). Values are the mean ± SD, n = 5. KO, knockout; AKO, adipocyte PLTP KO; WT, wild type; Tg, transgenic. Panel F, inflammatory index was determined as described in “Materials and Methods”. Std, standard; W, wild type; K, knockout; T, transgenic. Values are the mean ± SD, n = 5.