thematic review series

Thematic Review Series: Lipid Transfer Proteins

Phospholipid transfer protein: its impact on lipoprotein homeostasis and atherosclerosis

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Abstract Phospholipid transfer protein (PLTP) is one of the major modulators of lipoprotein metabolism and atherosclerosis development in humans; however, we still do not quite understand the mechanisms. In mouse models, PLTP overexpression induces atherosclerosis, while its deficiency reduces it. Thus, mouse models were used to explore the mechanisms. In this review, I summarize the major progress made in the PLTP research field and emphasize its impact on lipoprotein metabolism and atherosclerosis, as well as its regulation.—Jiang, X-C. **Phospholipid transfer protein: its impact on lipoprotein homeostasis and atherosclerosis. *J. Lipid Res.* 2018.** 59: **764–771.**

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PHOSPHOLIPID TRANSFER PROTEIN

Phospholipid transfer protein (PLTP) belongs to the lipid transfer protein family, including cholesteryl ester transfer protein (CETP), lipopolysaccharide-binding protein, and bactericidal/permeability increasing protein (BPI) (1). It is a monomeric protein of 81 kDa (2). Besides phospholipids, PLTP efficiently transfers diacylglycerol, α-tocopherol, cerebroside, and lipopolysaccharides (3). Therefore, plasma PLTP is also a nonspecific lipid transfer protein. It has also been reported that there are two forms of lipoprotein-associated PLTP proteins. Active plasma PLTP is associated with apoA-I-containing lipoproteins (about 160 kDa in size) and the form with low activity is associated with apoE-containing lipoproteins (about 520 kDa in size) (4–6). However, we still do not know why there should be two forms of PLTP in the circulation. Also, it is unknown whether animals, such as mouse and rabbit, have two forms of PLTP. It is possible that PLTP may have lipid transfer-independent activity.

PLTP is expressed ubiquitously (2, 7). The highest expression levels in human tissues were observed in ovary, thymus, placenta, and lung (2). Taking into account the organ size involved, liver and adipose tissue appear to be important sites of PLTP expression. It was also shown that PLTP is highly expressed in macrophages (8–10) and in atherosclerotic lesions (11, 12).

The liver is one of the major sites of lipoprotein production and degradation, as well as of PLTP expression. To address the impact of liver-expressed PLTP on lipoprotein metabolism, we created a mouse model that expresses PLTP in the liver acutely and specifically, with a PLTP-null background. We found that liver-expressed PLTP mice have about 25% plasma PLTP activity compared with that of WT mice (13). We also created liver-specific KO mice and found that the KO mice have 20% less plasma PLTP activity than that of controls (14). These results indicated that liver-generated PLTP makes about a 20% contribution to the PLTP activity in the circulation.

Adipose tissue expresses significantly higher PLTP than that in the liver (7). PLTP not only transfers phospholipids but also unesterified cholesterol (15), which is more abundant than cholesteryl esters in adipose tissue (16). We prepared adipose tissue-specific PLTP KO mice and found that the mice showed significant decreases in plasma PLTP activity (20%) and cholesterol (18%), phospholipid (17%), and apoA-I (26%) levels (17). 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 (17). Thus, adipocyte-derived

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Abbreviations: AdV, adenovirus; BLp, apoB-containing triglyceride-rich lipoprotein; CETP, cholesteryl ester transfer protein; LXR, liver X receptor; NAFLD, nonalcoholic fatty liver disease; PLTP, phospholipid transfer protein; RCT, reverse cholesterol transport; S1P, sphingosine-1-phosphate.

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PLTP, like hepatically derived PLTP (14), plays a small but significant role in plasma PLTP activity.

The lung is one of the major organs to produce PLTP (18). 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 mice (19). Lung-specific PLTP deficiency caused an 18% reduction in PLTP activity, a 23% reduction in cholesterol levels, and a 20% reduction in phospholipid levels in the circulation. Thus, the lungs also appear to contribute to PLTP activity in the circulation (17).

The brain expresses PLTP; however, the potential roles of PLTP in the brain are still poorly understood (20, 21). PLTP may play a role in the maintenance of the functional and structural integrity of myelin; and PLTP may be an important regulator of signal transduction pathways in human neurons (22). PLTP deficiency significantly reduces brain vitamin E content and has been associated with increased anxiety in mice (23). Interestingly, PLTP levels are altered in brain tissue of patients suffering from Alzheimer's disease (20, 21). PLTP deletion was demonstrated to increase amyloid-β-induced memory deficits in mice (24). Compared with the whole brain, the PLTP mRNA expression level is 6.8-fold higher in cerebral vessels (25) and PLTP may play a role in maintaining blood-brain barrier integrity, possibly through its ability to transfer vitamin E and modulate cerebrovascular oxidative stress (26). These findings collectively suggest a significant role of PLTP in both physiological and pathophysiological processes in the brain.

PLTP AND CETP

Although PLTP and CETP show moderate homology of sequence (2) and similar structural features (1, 27), they show no overlap in their in vivo functions. This was demonstrated in our study by preparing CETP transgenic/PLTP KO mice; the expression of CETP had an additive effect on HDL lowering, resulting in markedly reduced HDL levels in the CETP transgenic/PLTP KO mice (28). However, there is an interaction between PLTP and CETP. It has been reported that purified PLTP enhances cholesteryl ester transfer from HDL_3 to VLDL (29), even though PLTP has no such transfer activity of its own. Moreover, CETP transgenic/PLTP KO mice have significantly lower CETP activity than that of CETP transgenic mice (28).

PLTP REGULATION

PLTP activity and mRNA can be regulated by many factors. A high-fat high-cholesterol diet causes a significant increase in PLTP activity and in mRNA levels (7). After lipopolysaccharide injection, plasma PLTP activity is significantly decreased, and this is associated with a similar decrease in PLTP mRNA levels in the liver and adipose tissues (7). PLTP expression and activity can be upregulated by glucose (30) and downregulated by insulin (31, 32). It has been reported that diacylglyceride can also regulate PLTP activity (33).

PLTP promoter contains farnesoid X-activated receptor and PPAR binding motifs. The promoters of human and mouse PLTP genes show five consensus sequences for the transcription factors Sp1 and AP2 that are necessary for PLTP transcription (34, 35). The transcriptional activity of the PLTP gene was significantly increased by chenodeoxycholic acid and fenofibrate, suggesting that farnesoid X-activated receptor and PPAR are probably involved in the process (34). We (8) and another group (36) independently showed that PLTP expression can also be upregulated by liver X receptor (LXR). The PLTP promoter contains a high-affinity LXR response element that is bound by LXR/RXR heterodimers in vitro, and is activated by LXR/RXR in transient-transfection studies (36). A recent report indicated that LXR agonists activate triglyceride synthesis and PLTP transcription by activating SREBP-1c (37).

It has been found that AdV-mediated hepatic profurin, prodomain of furin, dramatically reduce plasma lipoprotein levels (38). Recently, we found that hepatic profurin overexpression resulted in a significant reduction of atherosclerotic lesion development and plasma LDL cholesterol in LDL receptor KO mice (39). This could be due to profurin-mediated PLTP degradation in hepatocytes, thereby inhibiting VLDL production (Y. Yu et al., unpublished observations).

PLTP AND HDL METABOLISM

Plasma PLTP mediates net transfer of phospholipids from apoB-containing triglyceride-rich lipoprotein (BLp) into HDL, and also exchanges phospholipids between lipoproteins (40, 41). Additionally, it has been shown that PLTP can act like a putative fusion factor to enlarge HDL particles (41). Huuskonen et al. (42) reported that phospholipid transfer activity is a prerequisite for efficient PLTP-mediated HDL enlargement. Rye et al. (43) reported that enrichment of triglyceride in the HDL core could promote such fusion.

Overexpression of PLTP in mice using AdV and AdV-associated virus resulted in a 10- to 40-fold increase in plasma PLTP activity (44, 45). These mice were characterized by increased preβ-HDL levels, but decreased α-HDL cholesterol levels. PLTP expression mediated by AdV-associated virus showed a prolonged pattern of overexpression that resulted in a significant decrease in total cholesterol and HDL cholesterol in C57BL/6 mice (45). We prepared PLTP transgenic mice and found that the preβ-HDL is significantly increased (46). Transgenic mice that overexpress human PLTP at high levels were also generated. Compared with WT mice, they showed a 2.5- to 4.5-fold increase in PLTP activity in plasma. This resulted in a 30–40% reduction of plasma HDL cholesterol levels, but a 2- to 3-fold increase in the formation of preβ-HDL (47). Overall, PLTP overexpression causes a significant reduction in plasma HDL levels, but increases preβ-HDL.

So far, no PLTP deficiency has been found in humans. The most useful information about PLTP deficiency was obtained from PLTP KO mice. These mice show a complete loss of phosphatidylcholine, phosphatidylethanolamine,

phosphatidylinositol, and sphingomyelin, but a partial loss of free cholesterol transfer activities (15). Moreover, the in vivo transfer of [^{3}H]phosphatidylcholine from VLDL to HDL does not occur in PLTP KO mice. On a chow diet, these mice showed a marked decrease in HDL phospholipid, HDL cholesterol, and apoA-I, demonstrating the important role of PLTP-mediated transfer of surface components of triglyceride-rich lipoprotein in the maintenance of HDL levels (15). Additionally, the HDL from the PLTP KO mice was enriched in protein, but was deficient in phosphatidylcholine. Turnover studies showed a 4-fold increase in the catabolism of HDL protein and cholesterol in PLTP KO mice compared with WT mice (48, 49). Overall, PLTP deficiency causes a significant reduction in plasma HDL cholesterol levels.

We compared HDL isolated from transgenic (a gift from Dr. Rini de Crom, Department of Cell Biology and Genetics, Erasmus Medical Center, The Netherlands), WT, and KO mice and found that: *1*) HDLs isolated from different mice have different sizes, the order being as follows: PLTP transgenic > WT > PLTP KO (17); *2*) the HDLs have a different inflammatory index, the order being as follows: PLTP transgenic > WT > PLTP KO (17); and *3*) the HDLs have different lipid compositions. The order of HDL cholesterol levels is WT > PLTP transgenic > PLTP KO; the order of HDL total phospholipids is WT > PLTP transgenic = PLTP KO (**Table 1**). These studies indicate that PLTP plays an important role in determining plasma HDL size, inflammatory index, and lipid composition (17). We also found that liver-specific PLTP deficiency significantly decreases HDL and apoA-I levels (14).

Sphingosine-1-phosphate (S1P) is an important bioactive lipid that plays a critical role in numerous physiological and cellular processes (50, 51). Recent research has focused on S1P and HDL metabolism because S1P is an important constituent of HDL. Many studies (52–55) have indicated that, in fact, HDL-carrying S1P mediates many of the physiological effects of HDL in different cells. We found that PLTP is the key factor that maintains HDL-S1P level, and lack of PLTP decreases HDL-S1P significantly; moreover, PLTP transfers S1P from erythrocytes to HDL, which constitutes the mechanism by which PLTP affects S1P content in plasma and HDL (56).

PLTP IN CHOLESTEROL EFFLUX/REVERSE CHOLESTEROL TRANSPORT

PLTP is highly expressed and regulated in macrophage cells and this suggests its potential involvement in lipid efflux. However, the role of PLTP in reverse cholesterol transport (RCT) (most of the studies were based on a mouse macrophage cholesterol efflux model) is controversial. There are reports which indicate that PLTP might promote (57, 58) or inhibit (59, 60) or have no effect (8) on cell cholesterol efflux. Differences in various published reports might be because these studies did not compare the same amounts of HDL.

Oram et al. (57) reported that exogenous PLTP can promote HDL-mediated cholesterol efflux through the ABCA1 pathway. We also found that recombinant PLTP (50 ng/ml) together with 0.8 nmol/ml HDL promotes HDL-mediated cholesterol efflux (A. Yazdanyar and X. C. Jiang, unpublished observations). PLTP appears to function as an intermediary in the transfer of excess cellular lipids to lipoproteins through its interaction with ABCA1 (57) and we confirmed this observation (14). It was also indicated that an amphipathic helical region of the N-terminal barrel of PLTP is critical for ABCA1-dependent cholesterol efflux (58). Furthermore, Lee-Rueckert et al. (10) studied the ABCA1-dependent efflux of cholesterol from peritoneal macrophages derived from PLTP KO mice and compared it with cholesterol efflux from WT macrophages. They found that cholesterol efflux from PLTP-deficient macrophage foam cells is defective and that the defect can be corrected by robust stimulation of the ABCA1-dependent pathway. These results support an intracellular role for endogenous macrophage PLTP in ABCA1-mediated cholesterol efflux from macrophage foam cells (10).

On the other hand, Moerland et al. (59) reported that in cholesterol efflux studies from macrophages, HDL isolated from human PLTP/human apoA-I double transgenic mice was less efficient than HDL isolated from human apoA-I transgenic mice. Furthermore, it was found that the largest subfraction of the HDL particles present in the double transgenic mice was markedly inferior as a cholesterol acceptor, as no labeled cholesterol was transferred to this fraction. These data demonstrate that the action of human PLTP in the presence of human apoA-I results in the formation of a dysfunctional HDL subfraction, which is less efficient in the uptake of cholesterol from cholesterol-laden macrophages (61). The same group of researchers investigated the role of systemic and peripheral PLTP in macrophage cholesterol efflux and RCT in vivo. They found that macrophage cholesterol efflux and RCT to feces is impaired in PLTP transgenic mice, and that elevation of macrophage-PLTP does not affect RCT, indicating that higher systemic PLTP levels may promote atherosclerosis development by decreasing the rate of macrophage RCT (60). Based on the above results, PLTP may inhibit macrophage

TABLE 1. The influence of PLTP expression on HDL

	PLTP Transgenic	WT	PLTP KO
HDL size (nm)	$9.65 + 0.15^a$	$9.25 + 0.15^b$	$8.85 + 0.10^c$
HDL inflammatory index	$1.22 + 0.29^a$	$0.52 + 0.13^b$	$0.39 + 0.19^c$
HDL cholesterol (mg/dl)	$57 + 10^a$	$92 + 8^b$	$35 + 7^c$
HDL phospholipid (mg/dl)	$79 + 12^a$	$135 + 15^b$	$62 + 8^a$

Value displayed are mean ± SD, n = 5. Values labeled with different superscript lowercase letters are statistically different ($P < 0.05$). HDL size and HDL inflammatory index were adapted from (17).

cholesterol efflux. A most recent mouse study indicated that overexpression and deletion of PLTP reduce HDL mass and cholesterol efflux capacity, but not macrophage RCT (62).

PLTP AND BLp PRODUCTION

We have unexpectedly found that PLTP deficiency causes a significant impairment in hepatic secretion of VLDL in mouse models (63). Likewise, it has been reported that animals overexpressing PLTP exhibit hepatic VLDL overproduction (64, 65). Largrost's group found that human PLTP transgenic rabbits showed a significant increase of LDL, but not of HDL, in the circulation (66). This might reflect the real situation in humans, because rabbits, like humans, are LDL mammals. Okazaki et al. (38) reported that, in concert with the increase in TG synthesis, the increased PLTP activity permits triglyceride incorporation into large VLDLs. It has been suggested that PLTP plays a major role in the initiation of BLp assembly in mouse primary hepatocytes (first step of lipidation) (67). We also found that, from liver-specific PLTP expressed (in PLTP-null background) mice, the major function of liver PLTP is to drive VLDL production and we proposed a model for PLTP activity-mediated BLp lipidation (**Fig. 1**) (13). Hepatocyte-specific PLTP deficiency showed the opposite results (14). More importantly, human genome-wide association studies and many others have shown that human PLTP levels are positively associated with plasma triglyceride and apoB levels (68, 69).

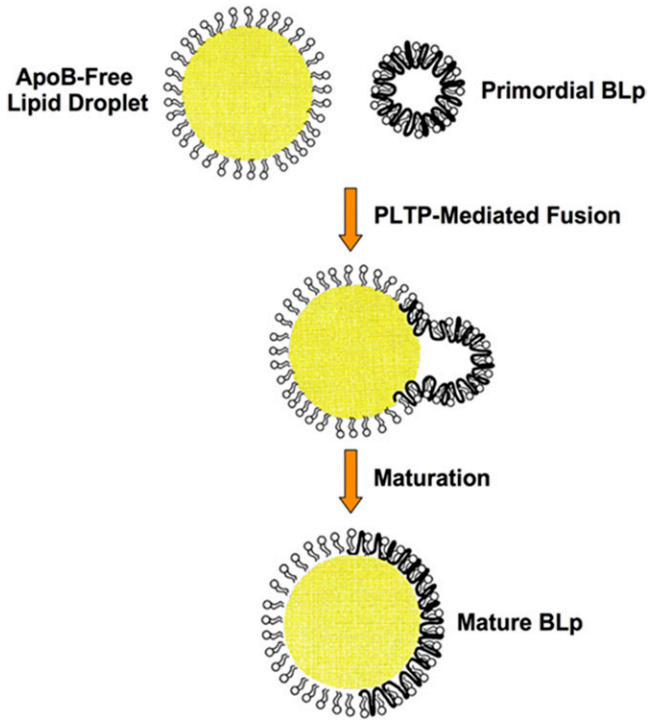

Fig. 1. A model of PLTP-involved BLp lipidation. BLp lipidation is involved in the fusion of primordial BLp and apoB-free/triglyceride-rich lipid droplets. PLTP-mediated PL transfer or exchange on both particles' surface would fuse two particles. Adapted from (13).

PLTP has vitamin E transfer activity that is important to maintain tissue and plasma vitamin E levels. It is known that vitamin E-enriched LDL from PLTP-deficient mice is resistant to oxidation and also is much less active to induce monocyte chemotactic activity (49, 70). Overexpression of PLTP decreases vitamin E content in LDL and increases its oxidation (45). Therefore, PLTP deposits vitamin E from plasma to cells. Accumulating data suggest that the function of PLTP in tissues is different from its role in plasma. Studies on macrophage-derived PLTP have demonstrated that PLTP-deficient macrophages have a more basal cholesterol level and accumulate more cholesterol in the presence of LDL (71). Supplementation of vitamin E in these animals normalizes the cholesterol phenotype (71). We have shown that PLTP-deficient hepatocytes secrete less BLp and this is related to premature degradation caused by lacking vitamin E and increasing oxidation stress (72). Hence, a major effect of PLTP on cellular physiology might be due to changes in cellular vitamin E levels and oxidative stress.

Overproduction of VLDL may be beneficial for preventing nonalcoholic fatty liver disease (NAFLD). However, plasma PLTP activity is positively associated with serum alanine aminotransferase and aspartate aminotransferase, two enzymes considered as predictors for NAFLD in diabetes patients, and it has been suggested that PLTP may be a marker for NAFLD (73). More importantly, PLTP deficiency does not cause lipid accumulation in the liver (63).

PLTP AND THROMBOSIS

Ten years ago, it was reported that PLTP KO mice exhibit a longer clotting time (tail bleeding) compared with WT mice and that this could be related to a relative decrease in PS externalization via a reduction in the vitamin E level in erythrocytes (74). Consistent with this result, Desrumaux et al. (75) reported that plasma PLTP deficiency is associated with a reduced thrombotic response to acute intravascular oxidative stress. Thus, PLTP seems to be involved in hypercoagulation. However, other research suggests that plasma PLTP has an anticoagulation effect (76, 77). Thus, it is still unknown whether PLTP is involved in hypercoagulation or hypocoagulation. A direct role of PLTP on platelets should be evaluated.

PLTP AND INFLAMMATION

Whether PLTP is a pro-inflammatory or anti-inflammatory factor is still controversial. PLTP KO mice have lower circulating levels of interleukin-6 (IL-6) (78, 79). In comparison with controls, PLTP KO mice have less expression of IL-6 and infiltrating macrophages in aortic tissue (80). Moreover, Desrumaux et al. (81) demonstrated a shift of T helper lymphocytes toward the anti-inflammatory subset, Th2, in PLTP KO mice. However, other studies, mostly using a model of LPS-induced inflammation, suggest an anti-inflammatory role of PLTP (82–84). PLTP KO mice have higher mortality after LPS injection (82). A decrease in PLTP expression or activity was

also shown to enhance the inflammatory responses in LPS and cigarette smoke exposition (83). These anti-inflammatory functions could be explained by their capacity to bind and neutralize LPS, thereby reducing activation of the innate immune system (82, 85). In addition, PLTP could also have direct anti-inflammatory properties in macrophages through direct interaction with ABCA1 and subsequent activation of the JAK2/STAT3 pathway (84).

PLTP AND ATHEROSCLEROSIS

PLTP expression is increased in different pathologies associated with increasing risk of CVD, such as obesity (86, 87), insulin resistance (88), and type II diabetes (89). Ten years ago, we reported that serum PLTP activity is increased in CVD patients (90). Despite many unresolved questions, we have since suggested that PLTP might be a therapeutic target for CVD. In the last decade, the majority of human studies showed a positive association between plasma PLTP activity and atherosclerosis (69, 91–93). Using a PLTP gene score constructed by a combination of two PLTP tagging SNPs, Vergeer et al. (94) reported that PLTP gene variation, which confers lower hepatic PLTP transcription and plasma PLTP activity, leads to decreased risk of cardiovascular events among five cohorts comprising a total of 4,658 cases and 11,459 controls. In another report, PLTP tagging SNPs were suggested to be associated with carotid artery disease (95). In the Framingham Heart Study, which comprised a total of 2,679 participants with 187 first events being ascertained during 10.4 years of follow-up, Robins et al. (96) found that higher plasma PLTP activity predicted a first cardiovascular event, defined as fatal or nonfatal coronary heart disease and stroke, among men. Moreover, PLTP activity is also positively correlated with left ventricular systolic dysfunction (97, 98). Recently, we investigated the long-term prognostic significance of plasma PLTP activity levels in a cohort of 170 high-risk diabetic men with known or suspected CVD who were referred for cardiac catheterization. We found that, after controlling for a variety of baseline variables, plasma PLTP activity levels were a strong and independent predictor of all-cause mortality in 5 years and higher PLTP activity had higher mortality (99). One potential mechanism relating PLTP-mediated CVD is that plasma PLTP activity is positively associated with triglyceride and apoB levels (68, 69). Contradictorily, PLTP mass was lower in a small group of CVD patients compared with controls (100), although it seems clear that the plasma PLTP protein concentration does not represent the preferred marker of PLTP-associated risk (101, 102). In addition, reported effects of PLTP on peripheral artery disease are both limited and inconsistent (103, 104).

In mouse models, it has been demonstrated that global PLTP deficiency reduces atherosclerotic lesion size (63) and the plaque stability (105), while its overexpression shows the opposite effect (106). Global PLTP deficiency in mice is also associated with abdominal aortic aneurysm (80). In rabbits, overexpression of PLTP increases atherosclerotic lesions after a high-fat diet feeding, compared with controls (66). In general, PLTP is a proven risk factor of atherosclerosis in animal models.

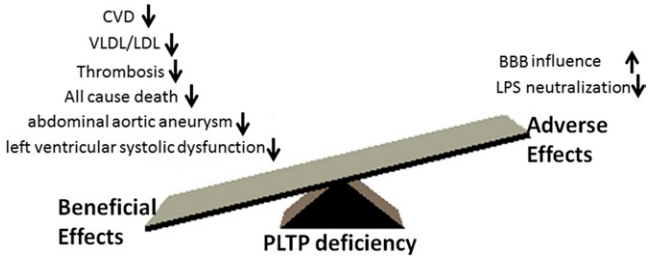

Fig. 2. Beneficial and adverse effects of PLTP inhibition. BBB, blood-brain barrier.

CONCLUSIONS

PLTP clearly has a notable role in the development of atherosclerosis, and this could be related with hyperlipidemia, hypercoagulation, obesity, insulin resistance, and type II diabetes. The effect of PLTP activity on inflammation is still controversial. Our knowledge about PLTP activity regulation, intracellularly or extracellularly, is also very limited. More epidemiological studies are needed to gain insights into the role of PLTP in atherosclerosis. Further, discovery of humans with genetic PLTP deficiency would be a major step toward the elucidation of the role of this transfer protein in human lipoprotein metabolism and atherosclerosis. A very obvious question is: should we inhibit PLTP for the treatment of hyperlipidemia and atherosclerosis? The answer is "Yes". Given the adverse effects of the new acetyl-CoA carboxylase 1/2 inhibitors in clinical trials to treat nonalcoholic steatohepatitis resulting in plasma hypertriglyceridemia due to elevation of SREBP-1c activity driving VLDL secretion (107), and given that PLTP is also a SREBP1 target gene (38) and inhibition of PLTP reduces VLDL secretion, dual inhibition of PLTP and acetyl-CoA carboxylase 1/2 would be therapeutic for nonalcoholic steatohepatitis patients. However, we have to be aware of some adverse effects of such an inhibition, for instance it could have an impact on impairment of the blood-brain barrier, impairment of LPS neutralization (**Fig. 2**), and so on.

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