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**New Therapeutic Horizons for Plasma Phospholipid Transfer Protein (PLTP):
Targeting Endotoxemia, Infection and Sepsis**

By

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Abstract

Phospholipid Transfer Protein (PLTP) transfers amphiphilic lipids between circulating lipoproteins and between lipoproteins, cells and tissues. Indeed, PLTP is a major determinant of the plasma levels, turnover and functionality of the main lipoprotein classes: very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). To date, most attention has been focused on the role of PLTP in the context of cardiometabolic diseases, with additional insights in neurodegenerative diseases and immunity. Importantly, beyond its influence on plasma triglyceride and cholesterol transport, PLTP plays a key role in the modulation of the immune response, with immediate relevance to a wide range of inflammatory diseases including bacterial infection and sepsis. Indeed, emerging evidence supports the role of PLTP, in the context of its association with lipoproteins, in the neutralization and clearance of bacterial lipopolysaccharides (LPS) or endotoxins. LPS are amphipathic molecules originating from Gram-negative bacteria which harbor major pathogen-associated patterns, triggering an innate immune response in the host. Although the early inflammatory reaction constitutes a key step in the anti-microbial defense of the organism, it can lead to a dysregulated inflammatory response and to hemodynamic disorders, organ failure and eventually death. Moreover, and in addition to endotoxemia and acute inflammation, small amounts of LPS in the circulation can induce chronic, low-grade inflammation with long-term consequences in several metabolic disorders such as atherosclerosis, obesity and diabetes. After an updated overview of the role of PLTP in lipid transfer, lipoprotein metabolism and related diseases, current knowledge of its impact on inflammation, infection and sepsis is critically appraised. Finally, the relevance of PLTP as a new player and novel therapeutic target in the fight against inflammatory diseases is considered.

Key Words: plasma phospholipid transfer protein, lipoprotein, lipopolysaccharides, endotoxemia, infection, bacteria, sepsis

Abbreviations: PLTP, phospholipid transfer protein; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; TRL, triglyceride-rich lipoprotein; LPS, lipopolysaccharide; LT/LBP, lipid transfer/lipopolysaccharide binding protein; BPI, bactericidal permeability increasing protein; LBP, lipopolysaccharide binding protein; TULIP, tubular lipid binding protein; CETP, cholesteryl ester transfer protein; apo, apolipoprotein; ABCA1, ATP-binding cassette A1; MTP, microsomal triglyceride transfer protein; CAD, coronary artery disease; T2DM, type2 diabetes mellitus; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; STAT3, signal transducer and activator

of transcription 3; AD, Alzheimer disease; Th, T helper; IL, interleukin; TLR4, toll-like receptor 4; SR-B1, scavenger receptor B1; FXR, farnesoid X-activated receptor; PPAR, peroxisome proliferator-activated receptor; LXR, liver X receptor; Tg, transgenic; rhPLTP, recombinant human PLTP; WAP, whey acidic protein; S1P, sphingosine-1-phosphate; SNP, single nucleotide polymorphism.

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Introduction

PLTP is a member of the lipid transfer/lipopolysaccharide-binding protein (LT/LBP) or BPI-like gene family, which also includes cholesteryl ester transfer protein (CETP), lipopolysaccharide-binding protein (LBP) and bactericidal permeability increasing protein (BPI). All are members of the tubular lipid-binding (TULIP) superfamily which has emerged in recent years as a major mediator of lipid sensing and transport in eukaryotes (Alva & Lupas, 2016; Wong & Levine, 2017). Being born somewhere is always a coincidence, and the origins of each LT/LBP family member have greatly guided the first steps in Science and Medicine. Thus, and as for CETP, PLTP was initially described by lipidologists and primarily studied in the field of lipid metabolism, metabolic disorders and cardiovascular diseases (Masson et al., 2009). In contrast, LBP and BPI were first described by immunologists and studied in the field of LPS metabolism and innate immunity to bacteria. However, after years of intense research, new insights, for instance concerning the roles of LBP and BPI in lipid metabolism and cardiovascular diseases (Yu & Song, 2020), or of CETP and PLTP in LPS metabolism and innate immunity (Alva & Lupas, 2016; Dusuel et al., 2020), suggested that LT/LBP family members, among them PLTP, should rather be considered henceforth in a broader way, extending far beyond the original reason for study (**Figure 1**). The present article aims to shed light on the complex and unique trajectory of PLTP, which has emerged over the years as a bridge between the field of lipidology and that of innate immunity against gram-negative bacteria.

PLTP in lipoprotein metabolism

PLTP was initially studied in the context of its role in HDL metabolism. HDL represent a highly heterogeneous lipoprotein population encompassing nascent discoidal, lipid-poor particles as well as mature spherical particles with a neutral lipid core which themselves can vary in size, lipid and protein content. These different HDL subclasses are tightly related with each other through constant remodeling phenomena occurring during their intravascular transit. As for CETP, PLTP is involved in the different steps of HDL remodeling, function and turnover as demonstrated by several *in vitro* and *in vivo* studies. Interestingly, the net effects of PLTP and CETP in lipoprotein remodeling in humans are quite different (Lagrost et al., 1996). First, and unlike CETP, PLTP promotes the conversion of small HDL (HDL3) into larger HDL (HDL2) together with lipid-poor apoA1 (Jauhainen et al., 1993; Tu et al., 1993) via a complex fusion/dissociation pathway (Rye & Barter, 2014) involving its phospholipid transfer activity (Huuskonen et al., 2000). Secondly, PLTP favors the generation of nascent HDL by promoting the shedding of redundant surface components of triglyceride-rich lipoprotein remnants (Jiang et al., 1999; Tall et al., 1985) or directly by stimulating the secretion of lipid-poor apoA1 from enterocytes (Liu et al., 2007). Thirdly, PLTP contributes to HDL maturation by stimulating ABCA1-mediated phospholipid and cholesterol efflux from peripheral cells (Lee-Rueckert et al., 2006; Oram et al., 2003). These multiple roles of PLTP in HDL remodeling lead to complex effects on HDL profile and functionality *in vivo*. In transgenic mouse models, while a moderate increase in PLTP activity results in either increased nascent or mature HDL levels (Albers et al., 1996; Jiang et al., 1996), strong overexpression of PLTP rather leads to decreased amounts of circulating HDL. By contrast, PLTP-deficient mice consistently display markedly reduced amounts of nascent and mature HDL (Jiang et al., 1999; Qin et al., 2000; Siggins et al., 2007). These discrepancies might be explained by an altered balance between the different remodeling effects of PLTP, depending on the metabolic context and differential levels of PLTP activity. In humans, the relationship between HDL-cholesterol, HDL particle size and PLTP activity was observed in different populations (Cheung et al., 1996; Elchebly et al., 1996; Lagrost et al., 1996). This finding was confirmed in genetic studies dealing with single nucleotide polymorphisms as well as in GWAS studies (Davis et al., 2017; Kaess et al., 2011; Kathiresan et al., 2009). Beside its role in phospholipid transfer, PLTP equally influences the amounts of highly bioactive lipids in HDL, such as vitamin E (Kostner et al., 1995) and sphingosine-1-phosphate (S1P) (Yu et al., 2014), two factors which influence oxidative and inflammatory

status in tissues and cell types interacting with HDL (Desrumaux, et al., 1999a; Desrumaux et al., 2010; Potì et al., 2014).

PLTP has also been shown to play a key role in the production of triglyceride-rich lipoproteins. *In vivo* experiments in genetically engineered mice showed that PLTP-deficient animals display lower apoB and triglyceride secretion by the liver (Jiang et al., 2001; Yazdanyar et al., 2013) and that this phenotype could be reversed when restoring PLTP expression in hepatocytes (Jiang et al., 2001; Yazdanyar et al., 2013). Accordingly, transgenic mice expressing high levels of PLTP ubiquitously or specifically in the liver have increased production of triglyceride-rich lipoproteins (Lie et al., 2002; van Haperen et al., 2002). *In vitro* experiments conducted on isolated hepatocytes deciphered the mechanisms involved and showed that PLTP plays a role in the early steps of apoB-containing lipoprotein assembly by allowing early lipidation (especially involving phospholipids) of the N-terminal residues of apoB, thereby avoiding degradation of apoB in the endoplasmic reticulum (Jiang et al., 2005; Manchekar et al., 2015). PLTP-mediated inhibition of apoB proteolysis might be due to its direct effect on apoB lipidation but also to an indirect effect on oxidative stress dependent on cellular vitamin E content (Jiang et al., 2005). Interestingly, the facilitating effect of PLTP on the secretion of triglyceride-rich lipoproteins might not be restricted to the liver and hepatocytes since it was also shown that enterocytes from PLTP-deficient mice produce fewer chylomicrons and display decreased MTP activity (Liu et al., 2007). However, the impact of PLTP on plasma triglyceride levels is not restricted to the production of apoB-containing lipoproteins. It was shown indeed that PLTP deficiency in mice also leads to exacerbated postprandial triglyceride response resulting from impaired VLDL/chylomicron catabolism (Hoekstra et al., 2020). Altogether, these observations in animal models suggest that the net impact of PLTP on plasma triglyceride levels and apoB-containing lipoproteins is complex and would depend on the metabolic context. This complexity was reflected in genetic studies in human populations. On the one hand a single-nucleotide polymorphism linked with increased PLTP activity in humans was reported to be positively correlated with circulating levels of apoB (Jarvik et al., 2010). On the other hand, human genome-wide association studies, reported SNPs associating with higher levels of PLTP transcript which were found to relate to lower triglyceride concentrations (Kathiresan et al., 2009; Teslovich et al., 2010).

PLTP in atherosclerosis and cardiometabolic diseases

Importantly, it must be borne in mind that different methods, based either on PLTP mass measurements or on PLTP activity assays, were used to evaluate PLTP levels in human studies, possibly accounting in part for some apparently discrepant results. Firstly, plasma PLTP mass assay does not correlate constantly with actual PLTP activity. It is likely to reflect the presence of active and inactive forms of PLTP when associated with distinct lipoprotein fractions (Oka T. et al., 2000; Kärkkäinen M 2002, Cheung et al., 2011). Consequently, even at constant PLTP mass, the ratio between inactive and inactive form might vary according to differences in plasma lipoprotein profile, thus modulating phospholipid transfer rates. Secondly, measurement of PLTP activity itself might lead to different results depending on whether the assay relies on phospholipid transfer measurement between endogenous plasma lipoproteins or between exogenous phospholipid donors and acceptor particles (Lagrost L., et al., 1999; Jauhiainen M. & Ehnholm C., 2005). While the former method would reflect the influence of both the amounts of active PLTP and the ability of endogenous lipoproteins to serve as substrates for the phospholipid transfer reaction, the latter would rather reflect the amounts of active PLTP only.

State of the art knowledge of the role of PLTP in the development of atherosclerosis and cardiovascular diseases has been recently presented in the light of human and animal studies (Jiang & Yu, 2021). Most studies support a role of PLTP as a risk factor for coronary heart disease and stroke (Jiang & Yu, 2021). In mouse models, a direct relationship between plasma PLTP activity and atherosclerosis could be established, in particular in a pioneering study showing that complete PLTP deficiency attenuates atherogenesis in hyperlipidemic mice (Jiang et al., 2001). In addition, PLTP deficiency in mice was shown to be associated with a reduced thrombotic response to acute intravascular oxidative stress (Desrumaux et al., 2010; Klein et al., 2006), impaired platelet aggregation (Zhao et al., 2018) as well as with reduced development of abdominal aortic aneurysm (Deckert et al., 2013). However, and as concerns lipoprotein metabolism, atherosclerosis susceptibility and thromboembolic events, the mouse model may not reproduce human pathophysiology faithfully, particularly as unlike humans, the mouse model is naturally CETP-deficient and displays very low levels of apoB-containing lipoproteins. Moderate expression of human PLTP in hypercholesterolemic rabbits with natural endogenous CETP activity, elevated apoB-containing lipoprotein levels, and high atherosclerosis susceptibility, was associated with increased fatty streak formation in the aorta (Masson et al., 2011). Such enhanced fatty streak formation occurred independently of quantitative changes in HDL cholesterol or antioxidative protection of lipoproteins, and was

primarily related to increased atherogenic apoB-containing lipoprotein levels and to larger LDL and HDL particle size (Masson et al., 2011). Overall, these data indicate that the atherogenic potential of PLTP may derive from its ability to foster apoB-containing lipoprotein production in the liver. In humans, while high PLTP activity has been associated with the risk of CAD (Schlitt et al., 2003), the underlying molecular mechanisms appear complex. Indeed, while PLTP activity has also been positively associated with LDL-cholesterol levels (Murdoch et al., 2000), GWAS studies have shown that genetic variations at the PLTP gene locus are primarily associated with HDL cholesterol and triglycerides levels, but not with LDL cholesterol levels. Indeed, higher PLTP transcript levels lead to elevation in HDL cholesterol levels and fall in triglyceride concentrations (Kathiresan et al., 2009). In addition to modulation of HDL cholesterol concentrations, remodeling of HDL particles may also account for the relationship of PLTP with CAD risk in humans. In a recent study, a single nucleotide polymorphism at the PLTP gene was positively associated with small and medium HDL particles but negatively with large HDL particles and CAD risk. Interestingly, this polymorphism was not associated with either LDL-cholesterol or apoB concentrations (Zhao et al., 2021). Finally, PLTP may also exert lipoprotein-independent effects directly within the plaque by modulating myeloid cell functions. Thus, PLTP was shown to be present in human atherosclerotic lesions and expressed by macrophages and foam cells (Desrumaux et al., 2003). Moreover, using bone-marrow transplantation, Valenta et al. demonstrated that in contrast to systemic PLTP, macrophage-derived PLTP is atheroprotective (Valenta et al., 2006). Complementary *in vitro* studies suggested that this finding could be related at least in part to PLTP's ability to reduce cholesterol accumulation in macrophages through changes in cellular vitamin E content and oxidative status (Ogier et al., 2007). More recently, single cell RNA seq analysis of human atheroma plaques confirmed that PLTP is abundantly expressed by both pro-inflammatory macrophages and foamy anti-inflammatory myeloid cells (Depuydt et al., 2020).

Atherosclerosis is present in many patients with metabolic abnormalities, including obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome. Importantly, alterations in PLTP activity may account for the elevated cardiovascular risk associated with these pathological situations. PLTP activity levels were consistently reported to be increased in obese subjects (Dullaart et al., 1994; Murdoch et al., 2000; Riemens et al., 1998) and a positive correlation between PLTP activity or mRNA levels in adipose tissue and BMI or obesity markers was observed in several clinical studies (Cheung et al., 2002; de Vries et al., 2011; Dusserre et al., 2000; Murdoch et al., 2000). Conversely, decrease in PLTP activity was observed after weight

loss achieved by bariatric surgery (Kaser et al., 2001; Laimer et al., 2009), or by short term as well as long term dietary intervention (Murdoch et al., 2000; Tzotzas et al., 2006). This tight association between PLTP and obesity is most likely due to the significant contribution of adipose tissue to the pool of circulating PLTP (Dusserre et al., 2000). Interestingly, subcutaneous, but not visceral fat, was reported to be responsible for weight-related alterations in PLTP expression (Dusserre et al., 2000; Murdoch et al., 2000). As for obesity, a strong relationship was established between elevated PLTP activity and T2DM (Borggreve et al., 2003; Desrumaux, et al., 1999b; Tan et al., 2003). The underlying causes of this association have been extensively studied but are still debated. Firstly, although some studies suggest that insulin resistance can account for increased PLTP activity (Riemens et al., 1998, 1999), other investigations failed to demonstrate a direct effect of insulin on PLTP expression in vitro (Kaser et al., 2001) or to establish a correlation between PLTP activity and insulin sensitivity or markers of glucose tolerance in human subjects (Dullaart et al., 2004; Julius et al., 2007). By contrast, studies in PLTP-deficient mice showed that PLTP itself could modulate insulin sensitivity by modulating the expression of the insulin receptor in many tissues (Song et al., 2019). Furthermore, high levels of PLTP activity were predictive of T2DM onset in a clinical study with a 9.4-year follow-up (Abbasi et al., 2015). Secondly, as in obese subjects, alterations in fat mass contributed to increased PLTP activity in T2DM (Dullaart et al., 1994; Tan et al., 2005) and a positive correlation between leptin and PLTP activity was observed in diabetic subjects (Dullaart et al., 2007). Thirdly, some studies reported a positive correlation between PLTP and inflammatory markers such as CRP in patients with T2DM (Gruppen et al., 2018; Tan et al., 2005); PLTP was also associated with CRP and BMI in patients with CVD (Cheung et al., 2006). Importantly, inflammation plays a key role in the onset and progression of atherosclerosis (Ridker et al., 2017; Soehnlein & Libby, 2021) and both obese and diabetic subjects harbour increased inflammatory status (Pickup, 2004; Weisberg et al., 2003). Whether elevated PLTP might be a cause or a consequence of the exacerbated inflammatory status in metabolic disorders is still poorly understood. On the one hand, since PLTP is highly expressed in myeloid cells (Desrumaux et al., 2003; Vikstedt et al., 2007), macrophage accumulation in fat tissue in patients presenting with metabolic abnormalities could well account for increased PLTP activity in this context. On the other hand, several groups have investigated the pro-versus anti-inflammatory potential of PLTP, both in vitro and in genetically engineered mice. While PLTP deficiency has been shown to decrease basal inflammatory status and to improve anti-inflammatory properties of HDL in mice (Schlitt et al., 2005; Yan et al., 2004), other studies demonstrated that PLTP actually shows anti-inflammatory properties by increasing

STAT3 expression (via its interaction with ABCA1 in cultured macrophages (Vuletic et al., 2011)), and preventing neutrophil degranulation in mice (Ochieng et al., 2018). Finally, evidence for a direct effect of PLTP on inflammation in the context of cardiometabolic diseases in humans is still lacking and deserves further attention.

PLTP in neurodegenerative disease

PLTP is widely expressed in the brain (Vuletic et al., 2003), and several studies have suggested its involvement in the etiology of Alzheimer's disease (AD). Using different AD models at various stages of the pathology, contradictory findings have been obtained and, at this time, it is not clear whether PLTP rather acts as a good or a bad guy with regards to AD pathophysiology (Wang et al., 2021). On the one hand, it was shown that PLTP plays a key role in supplying vitamin E to the brain, which leads to enhanced antioxidant neuroprotection (Desrumaux et al., 2013). PLTP was also shown to lower amyloid beta peptide production and Tau hyperphosphorylation, two key mechanisms leading to neuronal and synaptic loss (Dong et al., 2009; Tong et al., 2015; Wang et al., 2014; Wang et al., 2021). On the other hand, PLTP seems to reduce microglial phagocytosis, a crucial mechanism involved in amyloid beta peptide clearance (Mansuy et al., 2018). Thus, whether the discrepancies between independent studies can be explained by stage-dependent differential effects of PLTP on AD pathology, and/or to environmental factors which may modify the immunological status of the experimental animals, warrants further investigation.

PLTP in adaptive immunity

In recent studies, PLTP modulated the polarization of T-helper-cells toward the proinflammatory Th1 subtype (Desrumaux et al., 2016); this effect was related to the ability of PLTP to stimulate IL-18 production by antigen-presenting cells, thus switching the Th1/Th2 balance towards a pro-atherogenic phenotype (Desrumaux & Lagrost, 2018).

PLTP in LPS metabolism and innate immunity: the reverse LPS transport system

All members of the LT/LBP family are able to influence the metabolism of LPS, but with significant differences in the modality, extent and consequence of their actions. As shown in

Table 1, it is noteworthy that only PLTP cumulates LPS binding, disaggregation and transfer properties without consequences on leukocyte activation. In other words, and among LT/LBP family members, PLTP is actually the only family member to cumulate virtuous detoxifying, bactericidal and anti-inflammatory properties. Thus, PLTP emerged recently as a promising weapon to fight against LPS and its harmful consequences.

Several studies reported that purified PLTP is able 1) to prevent bacterial growth (Deckert et al., 2017), 2) to extract LPS from bacterial membranes (Vesny et al., 2000), 3) to bind and transfer LPS to lipoproteins in plasma (Hailman et al., 1996; Levels et al., 2005), 4) to inhibit the ability of LPS to stimulate adhesive responses of neutrophils and to produce proinflammatory cytokines (Hailman et al., 1996), and 5) to block macrophage activation independently of lipid transfer activity (Vuletic et al., 2011). These observations were extended *in vivo* in genetically engineered mice with deficiency of the endogenous PLTP gene (Gautier et al., 2008; Yu et al., 2016). Unequivocally, the mouse studies led to the conclusion that PLTP markedly reduces LPS-induced inflammation *in vivo*, leading to the new concept of a reverse LPS transport pathway through which plasma PLTP can neutralize LPS, reduce endotoxemia and prevent endotoxic shock (Gautier & Lagrost, 2011) (**Figure 2**). This pathway is analogous with that of reverse cholesterol transport. Indeed, and as for the bulk of cholesterol, lipoprotein transport and biliary excretion is actually the major way through which LPS can be eliminated from the body. Most of the key steps of reverse LPS transport were identified through the comparison of PLTP-knock out with wild-type mice with naturally elevated PLTP expression. Briefly, and in an alternative route to the pro-inflammatory sequence of LPS-activated leukocytes expressing TLR4, the reverse LPS transport pathway encompasses disaggregation of LPS, its transfer and binding to lipoproteins, its uptake by the liver, and its terminal biliary excretion (**Figure 2**). The key roles of PLTP and lipoproteins during the early steps of the absorption and clearance of LPS originating from the peritoneal cavity was recently documented in a mouse model of peritonitis (Nguyen et al., 2021a). First, endogenous PLTP expression was found to promote the rapid and efficient binding of LPS to lipoproteins, thus promoting its transfer from the peritoneal cavity to the portal blood. Subsequently, a hepatic first pass effect could occur. We demonstrated that about half of the LPS bulk was cleared from the portal blood during its first hepatic pass in wild-type mice, resulting in a lower central LPS concentration. Clearance occurred mainly from the cholesterol-rich lipoprotein pool and such clearance was significantly reduced in the absence of PLTP (Nguyen et al., 2021a). The mechanisms involved in LPS hepatic uptake are still not completely elucidated, but it has been

reported in animal models that both the LDL receptor and scavenger receptor B1 (SR-B1) may play a role in LPS clearance (Guo et al., 2014; Topchiy et al., 2016) (**Figure 3**).

To date, clinical insights relating PLTP to LPS detoxification in human subjects are scarce, but they are in line with animal studies. Thus, plasma PLTP activity was found to be significantly elevated in patients with a systemic inflammatory response (Barlage et al., 2001), and correlated with inflammation markers in patients with severe sepsis (Dargent et al., 2019). In addition, PLTP activity decreased upon LPS infusion in healthy volunteers (Hudgins et al., 2003; Levels et al., 2007). New evidence for a role of PLTP in adapting and acting under conditions of elevated endotoxemia and inflammatory stress have been reported in human populations. Among seventy-two patients undergoing valve surgery or coronary artery bypass graft surgery with cardiopulmonary bypass, high PLTP activity was associated with lower perioperative concentrations of LPS (Nguyen et al., 2021b). In a multicentric cohort (n=187 patients) with peritonitis-induced septic shock, the LPS to PLTP ratio in plasma (*i.e.* an index of poor capacity to neutralize LPS) was significantly higher in patients who died compared to surviving patients, and high plasma PLTP activity was associated with lower plasma levels of IL-6 in this population (Payen et al., 2021). Importantly, and in recent human studies (Nguyen et al., 2021b; Payen et al., 2021), the protective potential of PLTP was observed independently of alterations in plasma lipid and lipoprotein parameters, suggesting that PLTP, not lipoprotein pool size, would be the limiting factor for LPS neutralization and detoxification in humans. This finding is in line with earlier mouse studies which reported that this is the ability of plasma PLTP to bind LPS, rather than the lipoprotein pool size, which mostly accounts for the repression of LPS-induced inflammation (Yu et al., 2016).

Overexpressing PLTP to fight against LPS-mediated inflammation and sepsis

In view of its potential role in LPS metabolism and detoxification, PLTP came to the fore as a potential and promising therapeutic tool to fight against inflammation and sepsis. In an attempt to modulate PLTP expression, earlier studies addressed the transcriptional regulation of the PLTP gene in mouse and human. Interestingly, the transcription factors farnesoid X-activated receptor (FXR), peroxisome proliferator-activated receptors (PPARalpha and PPAR beta/delta) and liver X receptor (LXR) were alternatively proposed to be involved in the transcriptional regulation of the PLTP gene (Bouly et al., 2001; Chehaibi et al., 2015; Mak et al., 2002; Tu & Albers, 2001). However, and as far as the promoter activity of the PLTP gene is concerned,

somewhat contrasting effects were reported in mice and humans. For instance, and unlike mouse, human PLTP gene expression was found to be downregulated by fibrates (Tu & Albers, 1999), and changes in lipoprotein metabolism in patients with metabolic syndrome could only marginally be explained by changes in plasma lipid transfer activities (Watts et al., 2006).

Overall, there has been uncertainty regarding the development of nuclear receptor agonists to upregulate PLTP gene expression selectively in order to fight against endotoxemia and related inflammatory processes in humans.

The pathophysiological relevance of PLTP overexpression to fight against sepsis was documented in PLTP Tg mice (Yu et al., 2016). Interestingly, survival rate was closely related to plasma PLTP activity, confirming that plasma PLTP was indeed a key protective factor and relevant therapeutic tool for prevention of lethal endotoxemia.

Beside additive transgenesis or pharmacological upregulation of endogenous PLTP gene expression, direct infusion of recombinant human PLTP (rhPLTP) emerged as a novel and relevant strategy to enhance the LPS-detoxifying process *in vivo*. An essential step in the strategy to explore the capacity of rhPLTP as a therapeutic tool to counteract the effects of endotoxins involved access to sufficient amounts of a purified and active human protein. In this context, rabbit appeared as a well-adapted and most reliable animal model for expression of a human PLTP transgene and for production of the recombinant protein in large amounts in milk. Briefly, the human PLTP gene was placed under the control of the rabbit promoter of the WAP (whey acidic protein synthesized in the mammary gland), allowing production of the protein of interest in the milk. After extraction and purification, rhPLTP was shown to retain its biological activity, and was used as a therapeutic tool in mice with sepsis or septic shock. Even low amounts of rhPLTP were found to be sufficient to dramatically improve the health of these animals, with marked regression of both the inflammatory response and multi-organ dysfunction. These findings lead to the conclusion that rhPLTP conceals an astonishing property which might be relevant to treat sepsis in the context of an urgent and considerable medical need (Deckert et al., 2017).

Conclusion

As PLTP has been historically studied for its ability to modulate lipoprotein metabolism, it has been mostly considered as a potential therapeutic target in the cardiometabolic field. However, the complexity of its mode of action and the wide variety of processes impacted by PLTP cast doubt on the benefits of modulating PLTP activity to prevent atherosclerosis. This point of view

also relies on the controversial results obtained in large clinical studies that evaluated the relevance of inhibitors aimed at its close relative, CETP, in the last two decades. In addition, PLTP inhibition could lead to adverse effects in light of its beneficial role in other physiological processes such as brain function or adaptive and innate immunity. Regarding this last point, there is now strong evidence that PLTP is a key player in protection against sepsis and endotoxemia at multiple levels, from its anti-bacterial effect to its rate-limiting role in LPS detoxification and clearance to resolution of acute inflammatory status. These observations strongly suggest that strategies that favor the action of PLTP in the context of risk for systemic inflammatory syndrome represent a new hope in a field lacking efficient therapeutic options. While studies in animal models largely support this view, human data are still inadequate and large population studies are needed to provide additional elements in support of the development of PLTP-based strategies in the field of sepsis and infectious diseases.

Conflict of Interest Statement: TG, VD, MN, CD, DM and LL have no conflict of interest to declare.

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FIGURE LEGENDS

Figure 1. The multiplicity of the molecular and cellular roles of PLTP and pathophysiological processes.

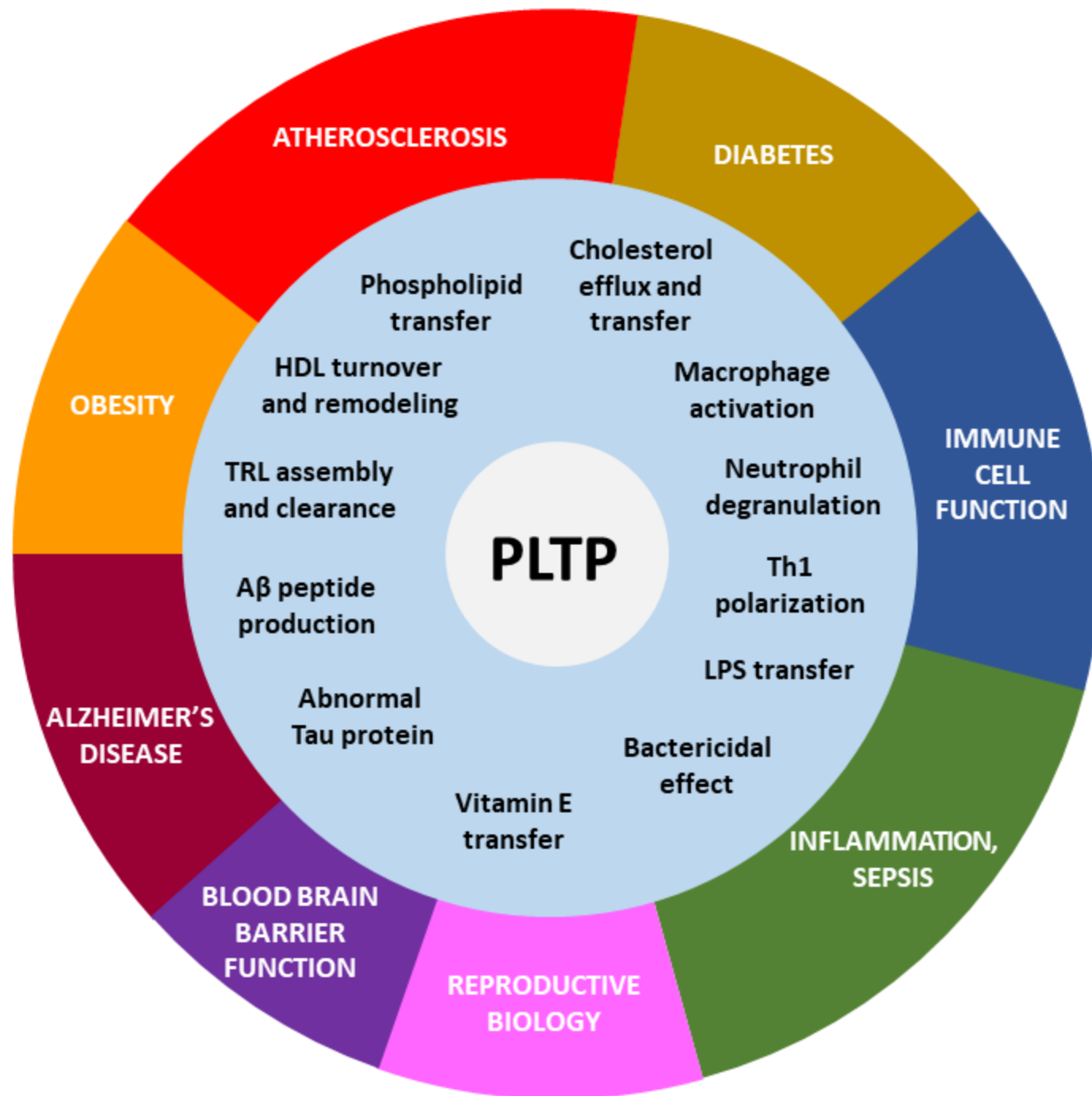
PLTP was first described for its many roles in lipid transfer (phospholipid and cholesterol) (Tollefson et al. 1988; Nishida & Nishida, 1997), lipoprotein metabolism (dealing mostly with HDL and triglyceride-rich lipoproteins, TRL) and its relationship with cardio-metabolic diseases (including atherosclerosis, obesity and diabetes) (Masson et al., 2009; Tzotzas et al., 2009; Jiang et al., 2021). The role of PLTP in vitamin E transfer between lipoproteins and tissues unveiled its impact not only in vascular biology but also in reproductive biology (Drouineaud et al., 2006) and brain physiology, in the latter case with new insights in blood-brain barrier function (Zhou et al., 2014) and Alzheimer's disease through effects on Tau protein and Amyloid- β peptide (Desrumaux et al., 2013; Wang et al., 2021). The discovery of the role of PLTP in cholesterol efflux from macrophages (Lee-Rueckert et al., 2006) is also in link with its involvement in immune cell function, with an impact on macrophage activation (Vuletic et al. 2011), neutrophil degranulation (Ochieng et al., 2018) and T-lymphocyte polarization (Desrumaux & Lagrost, 2018). The latter field is tightly connected to recent advances demonstrating that, through its ability to interact with and transfer LPS, PLTP is a key player in the resolution of inflammation and sepsis by promoting bacterial killing and LPS detoxification (Gautier et al., 2011; Deckert et al., 2017; Payen et al., 2021).

Figure 2. The multiple roles of PLTP in innate immunity and LPS metabolism.

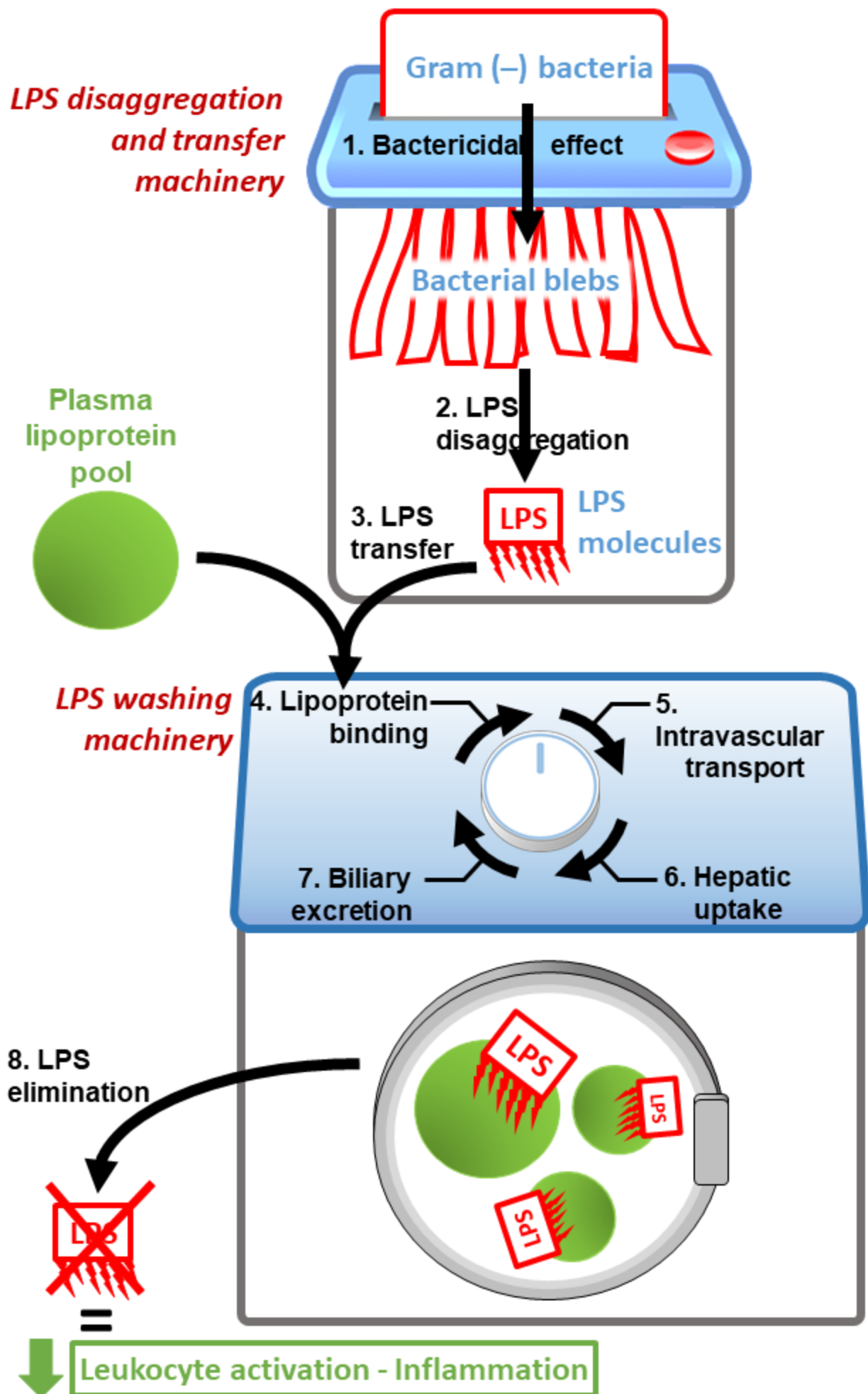
PLTP-facilitated actions are shown with black arrows. The first steps (“Disaggregation and transfer machinery”) directly involve PLTP-LPS interaction: (1.) bactericidal effect, leading to the release of bacterial blebs; (2.) LPS disaggregation from bacterial blebs; (3.) transfer of LPS molecules to plasma lipoproteins. The last steps (“LPS washing machinery”) results from (4.) PLTP-mediated binding of LPS to lipoproteins which leads to (5.) optimal intravascular transport under inactive form, (6.) increased hepatic uptake of LPS-lipoprotein complexes via lipoprotein receptors, (7.) biliary excretion and eventually (8.) LPS elimination via the feces. The overall consequences of these PLTP-facilitated actions are a reduction in the amounts of active LPS, leading to lower leukocyte activation levels and resolution of inflammation.

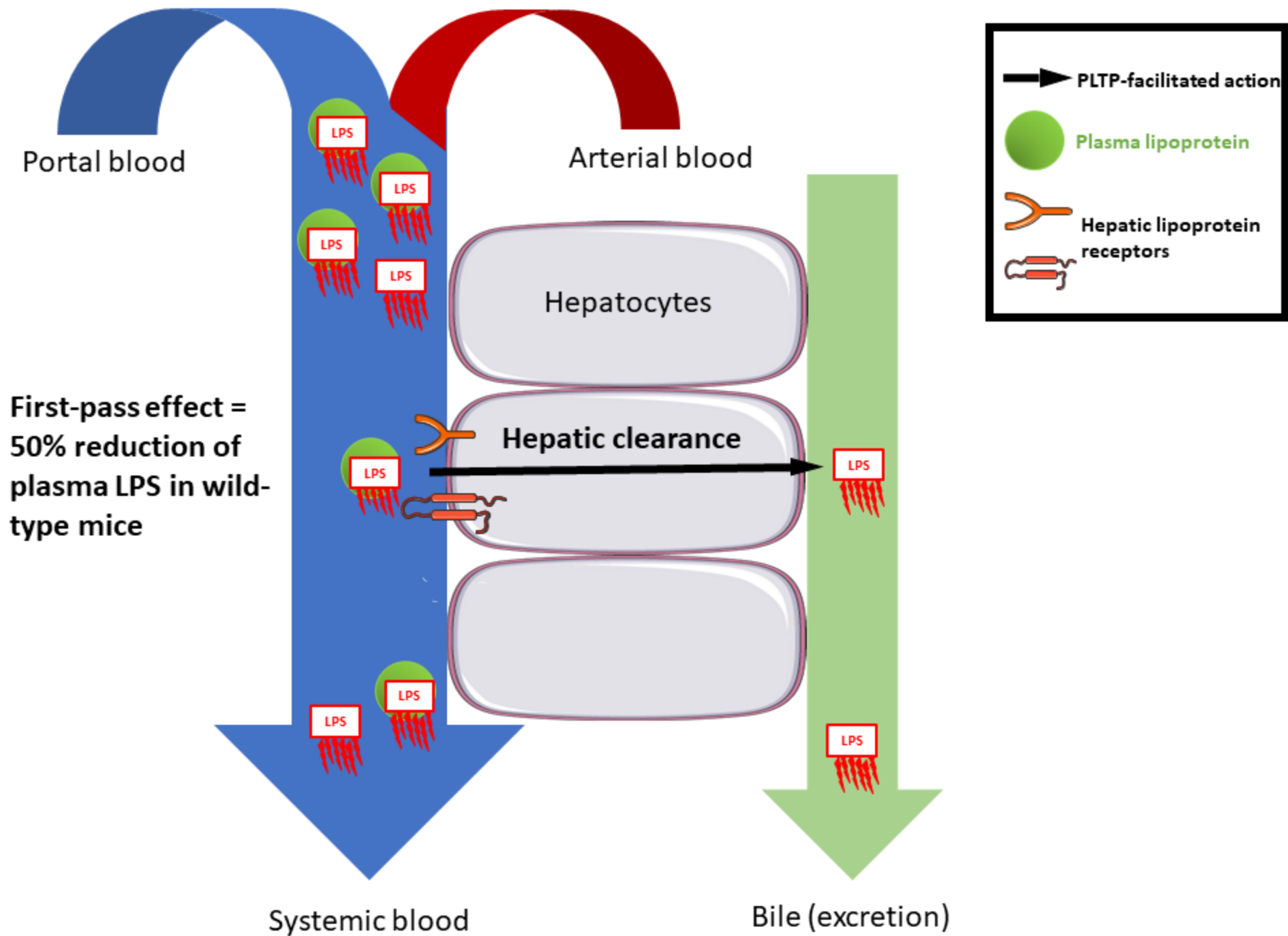
Figure 3. Impact of PLTP on early LPS clearance through the hepatic first pass effect.

PLTP efficiently associates LPS originating from the splanchnic territory (peritoneal cavity or intestine) to circulating lipoproteins. The LPS-lipoprotein complexes initially transit in the portal circulation, quickly reaching the liver which allows the clearance of a substantial fraction of these complexes through lipoprotein receptors. In wild-type mice, about 50% of LPS is cleared from plasma and excreted into the bile through this first pass effect before reaching the systemic circulation.



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Figure 3

Table 1 - Biological activities of the LT/LBP family members

	PLTP	LBP	BPI	CETP
LPS Binding	yes	yes	yes	no
LPS disaggregation	yes	yes	no	no
LPS signalling and leucocyte activation	no	yes	no	no
LPS transfer to lipoproteins	yes	yes	no	no
Biological effect of LPS	neutralization	activation	neutralization	activation
Bacteriostatic/bactericidal properties	yes	no	yes	no