CORRESPONDENCE

# Plasma phospholipid transfer protein (PLTP) as an emerging determinant of the adaptive immune response

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Plasma phospholipid transfer protein (PLTP) is a multifunctional lipid transporter. In addition to phospholipids, PLTP transports various amphipathic compounds, such as cholesterol, alpha-tocopherol, diacylglycerides, and lipopolysaccharides. In addition to its impact on lipid metabolism and atherosclerosis development, PLTP has recently been reported to modulate inflammation and immune responses. It modulates the phagocytic activity of macrophages and microglial cells[1,2] and increases the production of the pro-inflammatory cytokine interleukin 6 (IL-6).[3–5] In further support of the pro-inflammatory effect of PLTP, the expression level of IL-6 and the number of infiltrating macrophages in aortic tissue after experimental aneurysm induction were shown to be lower in PLTP-deficient mice than in wild-type mice;[6] additionally, recombinant PLTP was shown to exert a direct pro-inflammatory effect on rheumatoid arthritis fibroblast-like synoviocytes, independent of its lipid transfer activity.[7] Notably, despite its direct pro-inflammatory actions, PLTP can exert indirect anti-inflammatory actions through its ability to transport and detoxify lipopolysaccharides in gram-negative bacteria.[8,9] In humans, the majority of PLTP-associated proteins are involved in innate immunity and/or the inflammatory response in plasma, and PLTP activity is significantly increased in patients with bacterial infections and systemic inflammation. In addition to the key roles of PLTP in innate immunity, a recent publication from our group entitled "Plasma phospholipid transfer protein (PLTP) modulates adaptive immune functions through alternation of T-helper-cell polarization"[10] demonstrated for the first time that PLTP can also modulate adaptive immune responses. This modulation occurred through a profound effect on CD4+ T-cell polarization toward the pro-inflammatory Th1 subtype. This novel property also supports the pro-inflammatory and pro-atherogenic effects of PLTP (Fig. 1).

The function and regulation of helper T-cell subsets (Th1, Th2, and Th17) are critical to both normal and pathophysiological host responses. Th1 cells are mainly responsible for phagocyte-mediated host defenses and are the main effectors of cell-mediated immunity, delayed-type hypersensitivity reactions, and chronic inflammation. In contrast, Th2 cells promote humoral immunity, allergic reactions, and eosinophil recruitment. In PLTP-deficient animals, an impaired Th1 response and an increased Th2 response were observed in isolated spleen mononuclear cells. The in vivo relevance of these observations was demonstrated through (i) the measurement of Th1 and Th2 cytokine plasma levels and (ii) the assessment of ear swelling and T-cell orientation in a delayed-type contact hypersensitivity model.

In our study, the total white blood cell count and the CD3+ cell subpopulations were not modified in a PLTP-deficient context, suggesting that PLTP does not induce modifications in leukocyte generation or egress from secondary lymphoid tissues; instead, PLTP specifically modulates the balance between Th1 and Th2 subtypes. Since no difference in T-cell polarization was observed when comparing isolated spleen CD4+ T cells to the total spleen mononuclear cell population, which was activated in vitro, the impact of PLTP deficiency on the Th1/Th2 balance is unlikely to be related to altered intrinsic properties of CD4+ T cells; instead, the effects likely result from cytokine milieu modifications caused by accessory cell secretions.

Most of the mechanisms driving naive CD4+ T-cell differentiation are linked to the conditions during the initial or repeated encounters with the allergen via antigen-presenting cells (APCs). The different types of APCs and their ability to display particular cytokine production profiles, pattern recognition receptors, costimulatory molecules, and specific HLA haplotypes are key determinants of Th1 and Th2 cell polarization. In particular, the ability of APCs to induce Th1 differentiation has been linked to the production of high levels of interleukin-12 (IL-12) and/or interleukin 18 (IL-18). In our study, we found no difference in IL-12 production in isolated accessory cells from wild-type and PLTP-deficient animals. In contrast, IL-18 production was markedly reduced in PLTP-deficient mice. IL-18 promotes Th1 immune responses through its promotion of IFN-γ expression in lymphocytes, as well as through IFN-γ-independent pathways, and it acts synergistically with IL-12. Our results suggest that the alteration of IL-18 expression by APCs may account at least in part for the switch in Th1/Th2 balance in PLTP-deficient mice.

Since PLTP can transfer a variety of amphipathic lipids, variations in the membrane lipid composition of T cells and/or accessory cells in PLTP-deficient conditions may account for the observed changes in T-cell polarization. Cholesterol levels can modulate T-helper-cell orientation through both direct effects on signaling pathways and cytokine secretion modification by dendritic cells. As second messengers and activators of protein kinase C, diacylglycerides play an important role at the immunological synapse in the crosstalk between T cells and APCs and T-cell activation. Last but not least, the lipid-soluble antioxidant alpha-tocopherol, whose distribution is largely dependent on PLTP activity,[11–14] is one of the key nutrients

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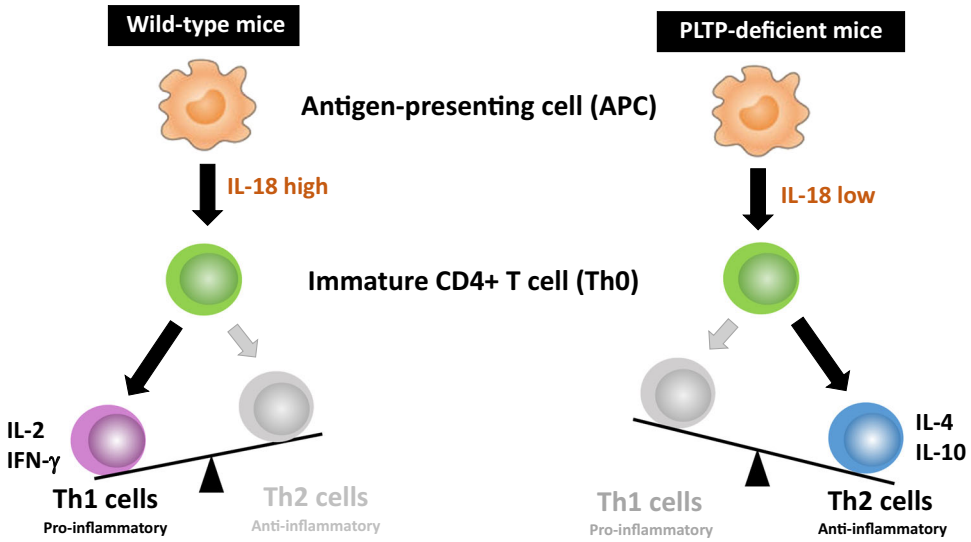


**Fig. 1** PLTP modulates T-helper-cell polarization. In wild-type mice, APCs secrete high levels of IL-18 that drive immature CD4+ T cells toward the Th1 phenotype. In PLTP-deficient mice, APCs secrete lower levels of IL-18, leading to T-helper-cell polarization toward the Th2 phenotype

affecting immune cell function. Regarding T lymphocytes, studies conducted in old mice and in the elderly suggested that alpha-tocopherol could act as an immunostimulating factor through its ability to reduce PGE2 production in accessory cells. Moreover, alpha-tocopherol has a direct effect on T-cell function because it increases IL-2 production and naive T-cell proliferation. Notably, compared to wild-type cells, spleen mononuclear cells from PLTP-deficient mice have a two-fold increase in their alpha-tocopherol concentration (unpublished data). This finding suggests that alpha-tocopherol enrichment in the total splenocyte population from PLTP-deficient mice might contribute to the orientation of CD4+ T cells toward the anti-inflammatory Th2 phenotype, a hypothesis that deserves further attention.

The role of PLTP in the polarization of CD4+ T cells toward the pro-inflammatory Th1 phenotype might be an additional contributor to its pro-atherogenic potency. Recent in vivo studies in mice and rabbits identified plasma PLTP as a potent pro-atherogenic factor.[15,16] Atherosclerosis is a multifactorial disease, and the classical view that it depends solely on lipid deposition has been challenged by studies showing that the activation of inflammatory and immune responses (both innate and adaptive) plays a central role in plaque initiation and progression. The majority of T cells in atherosclerotic plaques are CD4+ T cells, and the Th1/Th2 balance can determine the evolution and complication of plaques. While animal studies have helped establish that Th1 responses have a potent pro-atherogenic effect, there is still no clear evidence that Th2 responses have an anti-atherogenic effect, and it is currently accepted that a Th1/Th2 switch is protective because it alleviates the pro-atherogenic effects of Th1. As mentioned above, APCs are instrumental in defining the type of effector T cell formed, and both IL-12 and IL-18 are central in Th1 differentiation. The significant decreases in the expression and circulating levels of IL-18 in monocytes observed in PLTP-deficient mice may contribute to the pro-atherogenic effects of PLTP as numerous studies conducted in animals have shown that IL-18 has pro-atherogenic effects. In humans, IL-18 and its receptors are highly expressed in all types of cells in atherosclerotic plaques and are located preferentially in unstable symptomatic plaques. Moreover, epidemiological data from case/control studies showed that elevated blood levels of IL-18 are associated with an increased risk of acute coronary syndrome, restenosis, cardiac arrest, and myocardial infarction. The serum concentration of IL-18 was connected to cardiovascular mortality in the prospective follow-up of patients in a cohort including 10,600 healthy European men.[16]

In conclusion, our data provide the first evidence that PLTP plays a role in modulating the adaptive immune response toward a pro-inflammatory phenotype, which may well be an additional contributor to its pro-atherogenic effects.

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