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PLTP deficiency-mediated atherosclerosis regression could be related with sphinogosine-1-phosphate reduction

Jiao Zhen[1], **Ke Zhang**[1], **Zhiqiang Li**[1], **Tilla S. Worgall**[3], **Xian-Cheng Jiang**[1,2]

[1]SUNY Downstate Health Sciences University, Brooklyn, New York, USA

[2]Molecular and Cellular Cardiology Program, VA New York Harbor Healthcare System, Brooklyn, New York, USA

[3]Department of Pathology and Cell Biology, Columbia University Medical Center, New York, New York, USA.

Dear Editor,

We appreciate the positive comment, from Drs. Menno Hoekstra Ezra J. van der Wel, and Miranda Van Eck, on our recent work of PLTP deficiency-mediated atherosclerosis regression [1]. We agree that the lesion regression effect observed by us can also be attributed to the effect of PLTP deficiency specifically in macrophages, although the mechanism remains unclear.

There are certain important mechanisms are involved in atherosclerosis regression through macrophages in mouse models[2]: 1) suppression of monocyte infiltration into the atherosclerotic plaques. 2) depletion of M1 and enrichment of M2 microphages; 3) upregulation of macrophage CCR7 and increase of CCR7-dependent egress of resident macrophages from atheroma; 4) increasing cholesterol efflux from macrophages on the lesions. The results reported Hoekstra M et al. have enriched the existing mechanisms. They found that 1) treatment of hypercholesterolemia could facilitate CCR7-positive macrophage polarization and migration; and 2) new macrophages continuously infiltrate regressing atherosclerotic lesions.

In fact, PLTP deficiency can effectively reverse diet-induced or LDL receptor deficiency-mediated hypercholesterolemia [1]. *Pltp* knockout (KO) mice have lower circulating levels of interleukin-6 (IL-6)[3, 4] and less infiltrating macrophages in aortic tissue [5], compared with controls. All these effects could contribute to promote the regression of atherosclerosis, although PLTP activity has no effect on macrophage cholesterol efflux in mouse models [6].

Previously, it was reported that global PLTP deficiency not only greatly reduced plasma HDL-cholesterol and apoAI levels but also greatly reduced plasma sphingosine 1 phosphate (S1P) levels (60%), compared with controls [7]. Recently, we confirmed that both male and female *Pltp* KO mice significantly reduced S1P in the circulation (about 45%) (Fig. 1A) and we also found that inducible male and female *Pltp* KO mice, under a high fat and

Full contact details Phone: (718)-270-6701, xjiang@downstate.edu.

high cholesterol diet, had about 50% reduction of plasma S1P (Fig. 1B), respectively. This PLTP deficiency-mediated S1P reduction could contribute to reduction of atherosclerosis progression and induction of regression[1].

S1P is a potent lipid mediator composed of one long hydrophobic chain and one phosphoric acid group. S1P in blood is produced primarily by red blood cells (RBC), platelets, and endothelial cells[8], and secreted by major facilitator superfamily transporter 2b (Mfsd2b) [9] and S1P transporter spinster homolog 2 (Spns2) [10], respectively. S1P acts on macrophages to alter their functional phenotype[11]. S1P activates NF-κB [12], promotes chemotaxis, and stimulates the production of TNF-α in macrophages and/or monocytes[13]. S1P exerts potent physiological effects through five S1P receptors (S1PR1–5) located on cell membranes. The order of S1P receptor expression levels in macrophages are as follows: S1PR2 > S1PR1 >>S1PR3 and SIPR4 and there is no detectable S1PR5 [14]. The association between S1PR1 and CCR7 has been reported [15]. Activation of S1PR1 by a specific compound, KRP-203, can inhibit atherosclerosis by modulating macrophage and lymphocyte function [16]. S1PR2 signaling in macrophages is sufficient to promote atherosclerosis in the apolipoprotein (Apo) E KO mice [14]. Moreover, S1P promotes inflammatory M1 polarization of macrophage and promotes macrophages chemotaxis [17]. These studies provides support for S1P-mediated proatherogenic property.

Due to its hydrophobic nature, S1P is poorly water soluble and requires carrier proteins for efficient transport and circulation. Based on previous reports, plasma S1P is carried by HDL and albumin[18]. HDL-bound apoM as a physiologically-relevant S1P chaperone [19], which is defined as S1P carrier protein that facilitates specific receptor activation and biological response. despite the potential of the apoM-S1P axis as an endothelium-protective mechanism, the effect of apoM-S1P on atherosclerosis is still controversy [20, 21]. Moreover, global apoM deficiency causes about 45% reduction of plasma S1P [19, 21], global albumin deficiency has no significant impact on S1P in the circulation [22], and global apoM/albumin double deficient mice still have sufficient amount of plasma S1P [22]. These observations suggested that there are other S1P chaperones exist to mediate S1P functions, such as apoA4 [22]. Thus, PLTP (as a lipid carrier) depletion and PLTP deficiency-mediated HDL dramatical reduction could be two potential reasons for the dramatical reduction of S1P in the circulation. This effect of PLTP deficiency is independent from apoM, since global PLTP deficiency has no significant impact on plasma apoM (Fig. 2A) [7], and apoM deficiency has no effect on plasma PLTP activity (Fig. 2B). Unlike apoM, it is known that PLTP deficiency prevents and PLTP overexpression promotes atherosclerosis in animal models. Thus, we hypothesize that there is a PLTP-S1P axis, which is different from apoM-S1P axis, affecting atherosclerosis regression through influencing macrophages.

We agree that more detailed mechanistic studies are warranted into the possible effect of (inducible) PLTP deficiency on atherosclerosis regression. In particular, we would like to investigate the effect of PLTP deficiency-mediated S1P reduction on monocyte migration and macrophage differentiation and polarization as well as emigration of macrophages from atherosclerotic lesions.

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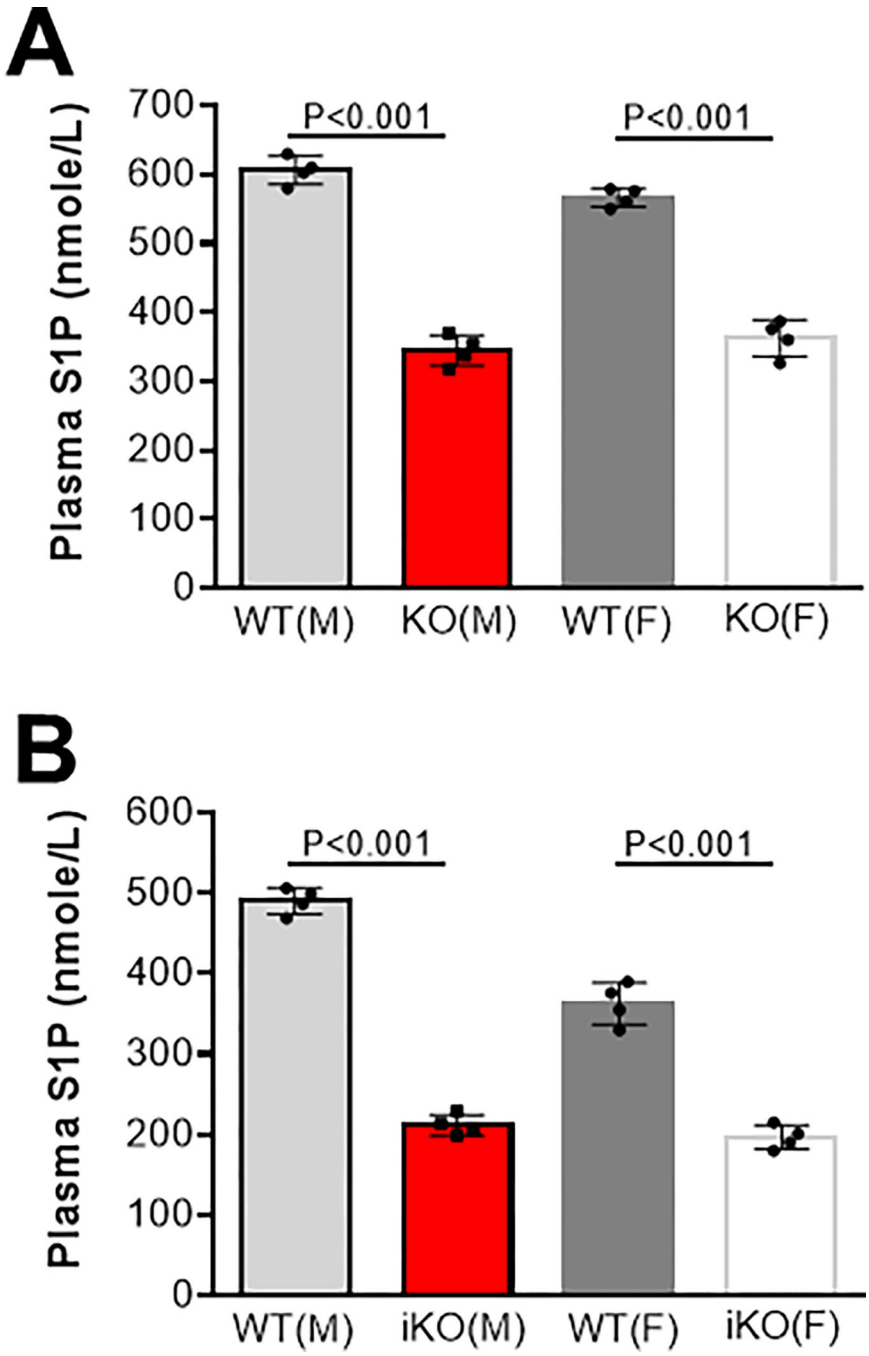

Figure 1:

Plasma S1P levels in mice. (A), WT and *Pltp* KO mice on chow diet. (B), WT and inducible *Pltp* KO mice on a high fat high cholesterol diet (0.15% cholesterol, 20% saturated fat). M, male; F, female. Values are mean ± SD.

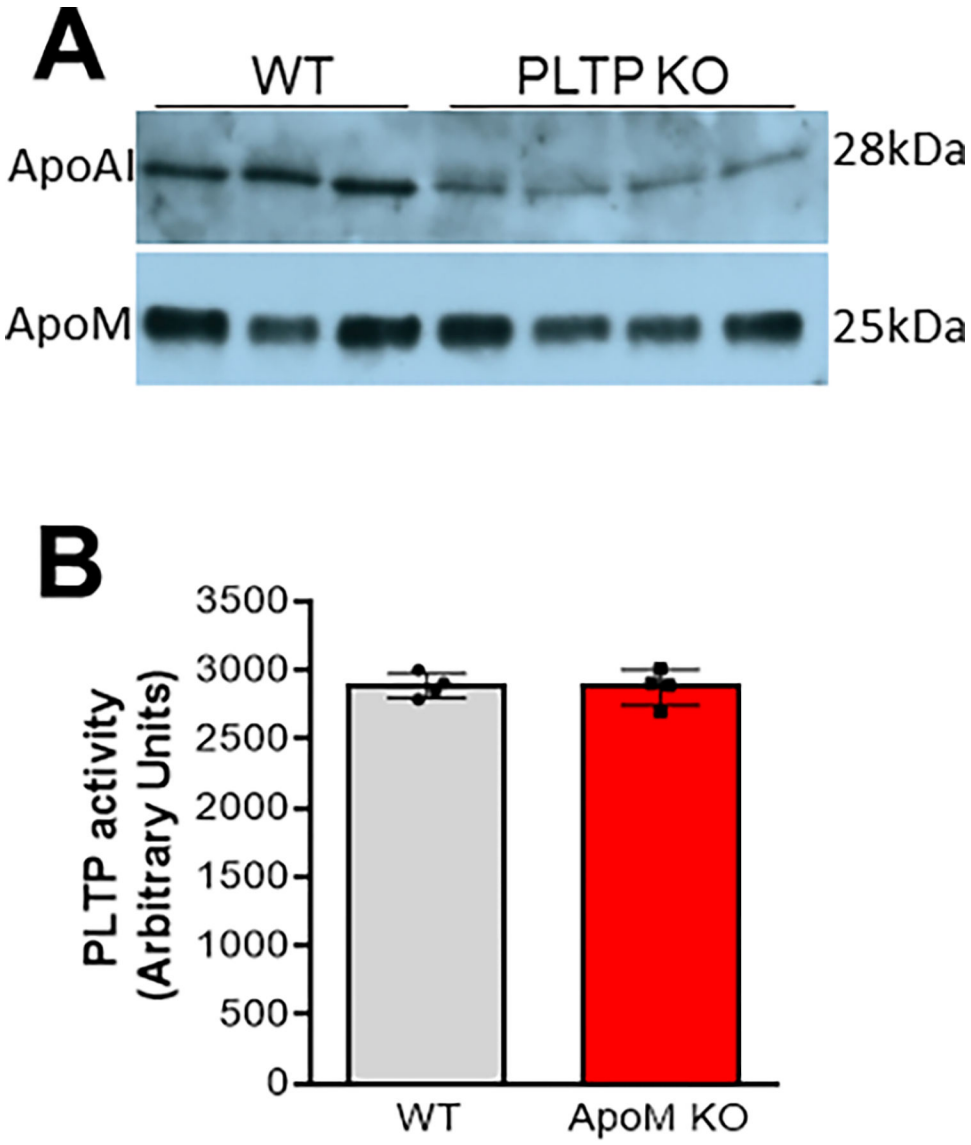

Figure 2:
Western blot analysis for plasma apoAI and apoM in WT and *Pltp* KO mice (A); Plasma PLTP activity in the WT and *Apom* KO mice (B). Values are mean ± SD.