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Phospholipid transfer protein (PLTP) depletion in adults reduces sphingosine-1-phosphate (S1P) through reducing high-density lipoprotein (HDL) in the circulation

Background: Plasma phospholipid transfer protein (PLTP) is an independent risk factor for human coronary artery disease (CAD), however, the mechanism is still not fully understood. Sphingosine-1-phosphate (S1P), mainly carried by high-density lipoprotein (HDL) in the circulation, is a potent lipid mediator and also associated with CAD. Besides phospholipids, plasma PLTP efficiently transfers sphingolipids, including S1P. Previous studies indicated that PLTP whole body knockout (KO) mice (starting from embryo stage) have decreased circulating S1P levels without influencing apoM, a major S1P carrier in HDL. We then hypothesized that, like apoM, PLTP is another S1P carrier in the blood. PLTP and apoM double deficiency should have an additive or synergistic effect on plasma S1P levels, thus influencing CAD. Method and Results: We established an inducible whole body PLTP KO, whole body apoM KO, and PLTP/apoM double KO (dKO) mice and measured plasma lipoprotein and S1P levels in them. We found that PLTP deficiency and the double deficiency have a similar level of HDL reduction, while apoM deficiency has no such an effect. Unexpectedly, we found that all mice have about 50% reduction of S1P, indicating that there is no additive effect of the double deficiency. Further, we found that PLTP deficiency significantly reduces apoM levels (about 40%), while apoM deficiency has no effect on PLTP activity, suggesting that PLTP deficiency-mediated S1P reduction could be related to its effect on HDL but not to apoM. Furthermore, we found that albumin (another reported S1P carrier in the circulation) deficiency has no effect on plasma S1P levels. Conclusion: Both apoM and PLTP but not albumin influence plasma S1P levels. Plasma PLTP depletion in adults dramatically reduce S1P through HDL reduction. The significance of this phenomenon, in terms of CAD treatment, deserves further investigation.