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Review

Lipid transfer proteins: Past, present and perspectives

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ABSTRACT

Lipid transfer proteins (PLTP and CETP) play roles in atherogenesis by modifying the arterial intima cholesterol content via altering the concentration and function of plasma lipoproteins and influencing inflammation. In this regard, endotoxins impair the reverse cholesterol transport (RCT) system in an endotoxemic rodent model, supporting a pro-inflammatory role of HDL reported in chronic diseases where atherosclerosis is premature. High PLTP activity related to atherosclerosis in some clinical studies, but the mechanisms involved could not be ascertained. In experimental animals the relation of elevated plasma PLTP concentration with atherosclerosis was confounded by HDL-C lowering and by unfavorable effects on several inflammatory markers. Coincidently, PLTP also increases in human experimental endotoxemia and in clinical sepsis. Human population investigations seem to favor low CETP as atheroprotective; this is supported by animal models where overexpression of huCETP is atherogenic, most likely due to increased concentration of apoB-lipoprotein-cholesterol. Thus, in spite of CETP facilitating the HDL-C-mediated RCT, the reduction of apoB-LP-cholesterol concentration is the probable antiatherogenic mechanism of CETP inhibition. On the other hand, experimental huCETP expression protects mice from the harmful effects of a bacterial polysaccharide infusion and the mortality rate of severely ill patients correlates with reduction of the plasma CETP concentration. Thus, the roles played by PLTP and CETP on atherosclerosis and acute inflammation seem contradictory. Therefore, the biological roles of PLTP and CETP must be carefully monitored when investigating drugs that inhibit their activity in the prevention of atherosclerosis.

Contents

1. Introduction

Several plasma proteins have long been known to share common roles in atherosclerosis and inflammation (including the acute phase of inflammation), although to various degrees [1–5], likely

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due to their structural similarities. Among others, these plasma proteins include bactericidal/permeability increasing protein (BPI), lipopolysaccharide binding protein (LBP), phospholipid transfer protein (PLTP), cholesteryl ester transfer protein (CETP), C reactive protein (CRP), and soluble CD14 molecules [1–4]. LBP, PLTP and CETP in plasma are associated with lipoproteins. BPI and PLTP bind, transfer and neutralize LPS [4,5] whereas LBP binds LPS, transfers it to lipopoproteins and also presents it to the CD14 receptor bringing on the release of pro-inflammatory cytokines [6]. On the other hand, PLTP activity is consistently elevated in systemic inflammation, neutralizes LPS but does not present it to CD14. In the inflammatory stress PLTP may improve the delivery of energy substrates to tissues [7,8]. Furthermore, PLTP [9] and CETP protect mice against lethal doses of bacterial endotoxins [10,11].

Because PLTP and CETP have been extensively investigated, we will review these proteins in detail raising questions on their interactions with atherosclerosis and inflammation. Both lipid transfer proteins are involved in responses to acute inflammation and possibly in chronic inflammation causing modifications in the concentration and function of the plasma lipoproteins that have direct impact on the development of atherosclerosis that will be dealt with in detail. However, this review should not distract the readers from the excellent reviews published in the last decade describing other metabolic and genetic aspects of these transfer proteins [12–17].

2. Does plasma PLTP activity relate to atherosclerosis in humans?

In humans, the relationship of plasma PLTP as an independent correlate of premature atherosclerosis is unclear, primarily due to the influence of confounding variables as well as the fact that PLTP is present in human atherosclerotic lesions [18]. An example of this is the recently published Atherogene Study [19], where statins were administered to angiographically documented coronary artery disease patients. The study concluded that the serum PLTP activity was not associated with the combined endpoint in all patients. However, in a subgroup of participants receiving statins at baseline, PLTP was a significant predictor of cardiovascular outcomes that were not modified by the classical risk factors such as HDL-C plasma concentration. Under statin treatment, high plasma PLTP activity was related to fatal and nonfatal cardiovascular events in CAD patients in this report. However, considering that statin treated cases consisted of a subgroup analysis this interpretation should be viewed with caution.

Previous studies have also linked increased plasma activity of PLTP to premature atherosclerosis, although one study was quite small and the elevated PLTP activity in plasma was interpreted as an independent risk factor for coronary artery disease [20]. In two other studies in Type 2 diabetes mellitus, high PLTP activity coincided with the elevation of inflammatory marker C reactive protein [21,22], although atherosclerosis was not investigated in one study [22]. However, elevated plasma PLTP activity paralleled an increase in plasma TG and a decrease in plasma HDL-C. There were no studies in which the incidence of the atherosclerotic vascular disease could be ascribed solely to an increase in the PLTP activity, due to confounding factors such as low plasma concentration of HDL-C [20,21], elevated plasma TG [21] or LDL/HDL plasma ratio [20]. However, despite the fact that LDL-C and TG increased in one study [23], a high rate of atherosclerotic vascular disease has also been attributed to a reduction of the PLTP activity in two studies [23,24]. One of these studies investigated 2567 workers in Japan where PLTP mass, not activity, was found to correlate inversely with the incidence of coronary heart disease, although the result could also have been biased by a simultaneous decrease of several risk factors such as low BMI, systolic blood pressure, HbA1c, LDL-C and TG and increase in plasma HDL-C. These confounding factors are summarized in Yatsuya et al.'s report [24].

3. Does plasma CETP activity relate to atherosclerosis in humans?

Far more information is available regarding CETP's role in atherosclerosis compared to PLTP. The role of CETP in atherosclerosis was investigated in a recent meta-analysis. Thompson analyzed CETP polymorphisms from 92 studies including 113,833 healthy participants and from 46 studies including data representing 27,196 coronary disease cases and 55,338 controls, from January 1970 through January 2008 [25]. The combined per-allele odds ratios (ORs) for coronary disease were 0.95 (95% CI, 0.92–0.99) for TaqIB, 0.94 (95% CI, 0.89–1.00) for I405V, and 0.95 (95% CI, 0.91–1.00) for −629C>A, suggesting that three CETP genotypes are associated with moderate inhibition of CETP activity and modestly higher HDL-C levels, with low but weak associations with coronary risk. The ORs for coronary disease were compatible with the expected reductions in risk for equivalent increases in HDL-C concentration in available prospective studies. Thus, there is a trend for CETP activity to vary inversely with HDL-C concentration and directly with the degree of atherosclerosis. However, Thompson and co-workers concluded the study with a request "for larger studies to demonstrate the modest impact that single genetic variants have on complex outcomes such as coronary disease," and, in time, they stated that "further studies are warranted to determine the value of CETP inhibition to coronary disease prevention".

Other studies that appeared afterwards, such as the Multi-Ethnic Study of Atherosclerosis (MESA) [26], which showed that carriers of the 451Q and 373P alleles have a significantly higher CETP concentration and activity, and the observed lower HDL-C is associated with the presence of elevated coronary artery calcium (CAC), even after adjusting for CVD risk factors and HDL-C.

However, the connection between CETP concentration and atherosclerosis remains unclear in humans. A single nucleotide CETP polymorphism was associated in the Japanese population with an increase in HDL-C by 6.2 mg/dL and, surprisingly, was more prevalent in cases with myocardial infarction compared to controls [27]. The latter observation agrees with a larger Danish population study published by Regieli et al. [28] on the 10-year follow up of CAD patients of the REGRESS cohort treated with statins. Carriers of TaqIB-B2 had reduced CETP levels and higher HDL-cholesterol, although the hazard ratios per B2 copy were higher for rates of atherosclerotic disease death, ischemic heart disease death, and for all-cause mortality. As these authors conclude, this effect observed for statins "needs consideration when administering CETP inhibitors to CAD patients." One may summarize the connection of CETP concentration and atherosclerosis as a debatable issue.

4. Is PLTP involved in inflammation and atherosclerosis?

The relationship between PLTP and inflammation has been well documented in clinical conditions and has been investigated by several groups. In patients with severe acute phase response, Pussinen et al. [29] demonstrated that an increase in C reactive protein correlated negatively with lecithin cholesterol acyl transferase (LCAT) and CETP protein expression as well as with PLTP mass. However, there was an inverse correlation between CRP and PLTP activity. A decrease in LCAT and increase in PLTP activity explain the observed modifications in plasma lipoproteins (LP), such as greater conversion of HDL-3 into HDL-2 and pre-beta-HDL [29].

Human studies are supported by experimental data that indicate that PLTP facilitates inflammation and subsequent atherosclerosis. For instance, bacterial lipopolysaccharides (LPS) activate