Commentary

The Link Between Human and Transgenic Animal Studies Involving Postprandial Hypertriglyceridemia and CETP Gene Polymorphisms

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During last decades a considerable attempt has been made to prevent cardiovascular disease (CVD). Nevertheless, CVD remains a leading cause of death world wide [1]. The guidelines of medical scientific societies for primary and secondary prevention of CVD are directed towards established CVD risk factors (dyslipidemia, diabetes mellitus, hypertension, obesity, smoking and others). As far as dyslipidemia is concerned, the first priority, according to the guidelines [2], is to achieve optimal low density lipoprotein cholesterol (LDL-C) levels. Many clinical trials have shown that hypolipidemic treatment besides lowering LDL-C also significantly reduces CVD-related morbidity and mortality [3, 4]. Nevertheless, a considerable number of treated subjects still have CVD events. Thus, the need for additional therapeutic treatment such as increasing high density lipoprotein cholesterol (HDL-C) levels and decreasing levels of triglycerides (TG) has been suggested [5]. In this context, torcetrapib, an inhibitor of cholesteryl ester transport protein (CETP), increased HDL-C levels and decreased LDL-C levels [6-8]. However, the drug was withdrawn due to side effects.

Another potential target to reduce CVD risk is postprandial hypertriglyceridemia [9, 10]. In 1979, Zilversmit [11] proposed that TG are involved in development of atherosclerosis. Since then, many research teams, including ours, [12-15] have examined the role of the exaggerated and delayed clearance of postprandial lipoprotein particles in various diseases [16, 17] including CVD. The mechanisms involved in postprandial lipemia were reviewed [18]. Considering all the above, the ideal gene associated with all 3 (TG, HDL and postprandial hypertriglyceridemia) is the one encoding for CETP.

The mechanisms by which the CETP controls lipid metabolism have attracted many investigators, especially when plasma CETP concentration was found to be associated with the increased risk for premature atherosclerosis [19]. CETP activity depends on several factors such as environmental components (e.g. diet [20], alcohol consumption [21] and smoking [22]) gender [23] and genetic influence (e.g. polymorphisms of CETP) [24-26].

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Few months ago, Salerno *et al*. examined the association between CETP and postprandial hypertriglyceridemia in transgenic mice [27]. They performed functional studies to show that plasma CETP activity modifies postprandial response of TG-rich lipoproteins. They assessed the TG response to fat load in rats with introduced human CETP gene (mice and rats are naturally CETP deficient). They found that elevated levels of CETP were associated with fat intolerance.

Genetically, engineered mice have proven to be valid models for the study of CETP function and its relation with atherosclerosis. Introduction of the human CETP gene into mice results in a dose-related reduction of HDL-C levels and, as a consequence, these animals have significantly more early atherosclerotic lesions in the proximal aorta than control mice [28]. CETP variants have a strong impact on CETP activity and thus on HDL-C levels [29]. Several polymorphisms have been identified in the coding sequence of the CETP gene including I405V [30]. The I405V polymorphism has been associated with reduced CETP mass, increased HDL-C levels and increased CVD risk [31, 32]. Another widely studied CETP polymorphism is TaqIB which seems to influence HDL-C levels [33]. In normolipidemic subjects, the absence of the TaqIB restriction site (B2 allele) is associated with decreased CETP activity, increased HDL-C levels and reduced risk of CVD in males compared with B1 subjects [19]. The CETP TaqIB polymorphism has been found to account for 5.8% of the variance in HDL-C, which is important since the 1 mg/dl increase of HDL-C leads to 2% decrease in CVD risk [33, 34]. Subjects with the B2 allele usually have lower levels of CETP, higher levels of HDL-C and reduced risk of CHD compared with B1 subjects [33]. Our group also analyzed the association between TaqIB polymorphism and fasting as well as postprandial TG levels in heterozygote familial hypercholesterolemia (hFH) patients [35]. The B1 allele carriers with exaggerate TG response to fat loading had higher fasting and postprandial TGs compared with B2 allele carriers. Also, patients with the B1B2 genotype had significantly higher HDL-C levels compared with the B1B1 genotype. Noone *et al.* found that B1 allele carriers had increased mass and activity of CETP at 6 h after fat loading compared with B2 allele carriers [36]. This finding is similar to our results (higher TG 6 and 8 h after fat loading in B1 allele carriers compared with B2;

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$p<0.05$ and $p<0.042$, respectively). This was in accordance with other studies as well. Tall *et al.* found a 1.1–1.7-fold increase in CETP in response to a 135-g fat meal [37]. It has been shown by others [38, 39] and by us that carriers of the B1 allele have a more atherogenic fasting and non fasting lipid profile (low HDL-C, increased TGs, exaggerated and delayed clearance of TGs postprandially) than carriers of the B2 allele, which should lead to increased cardiovascular risk. Furthermore, Hogue *et al.* reported that a high plasma CETP concentration was associated with higher risk of having small-diameter particles of LDL in hFH patients, suggesting that CETP-induced remodeling of LDL is dependent on the number of TG-rich lipoproteins [40]. Also, in a previous study of ours [41] a significant gender association between TG response after oral fat loading and TaqIB polymorphism of the CETP gene in subjects with a exaggerate response was found. Specifically, men carrying the B2 allele of the TaqIB polymorphism showed a higher postprandial TG peak and a delayed return to baseline values compared with women carrying the B2 allele. The mechanisms of this observation were explained by Salerno *et al.* [27]. They reported that CETP expression in transgenic mice delays plasma clearance and liver uptake of TG-rich lipoproteins firstly, by transferring TGs to HDLs and increasing cholesteryl ester concentration of the remnant particles, and secondly by decreasing lipoprotein lipase (LPL) expression. Similarly, Zhou *et al.* [42] also found that adipocytes from adipose tissue of transgenic mice (CETP expressing) presented reduced LPL expression. The mechanisms underlying the differential lipemic responses confirmed in CETP expressing and non-expressing transgenic animals could also be applicable for humans expressing high or low CETP activities. Thus, the human studies performed by our group presented similar positive associations between CETP and TG levels [35]. Two other studies have also shown similar results [43, 44].

A new aspect linked to the effects of CETP expression contribute to a better understanding of the influence of a precise gene on lipids and lipoproteins responsiveness to nutritional fat. This research carried out in either humans or transgenic animals may have clinical implications in the near future. The understanding of postprandial lipemia is important, since postprandial hypertriglyceridemia is involved in endothelial dysfunction, oxidative stress, small dense LDL and small dense HDL particles [45].

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