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Cholesteryl Ester Transfer Protein: A Potential Target for the Treatment of Coronary Artery Disease

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High-density lipoprotein cholesterol levels have a strong inverse association with a risk of cardiovascular disease. Even patients on statin therapy whose low-density lipoprotein cholesterol levels are well controlled may be at high risk for developing cardiovascular disease if their high-density lipoprotein cholesterol levels are below 40 mg/dl. Consequently, current guidelines recognize low levels of high-density lipoprotein cholesterol as a major risk factor and suggest that treatment should be considered for isolated low level of high-density lipoprotein cholesterol. Unfortunately, only a few therapies are particularly effective at increasing high-density lipoprotein cholesterol, one promising new approach targets cholesteryl ester transfer protein. In healthy subjects with mild dyslipidemia, treatment with JTT-705 decreased cholesteryl ester transfer protein activity, increased high-density lipoprotein cholesterol and decreased low-density lipoprotein cholesterol. Similarly, another cholesteryl ester transfer protein inhibitor, torcetrapib, has recently been shown to increase high-density lipoprotein cholesterol by 46%. Increasing high-density lipoprotein cholesterol with inhibitors of cholesteryl ester transfer protein represents a new approach to dyslipidemia that requires further investigation, especially in patients with coronary artery diseases. The goal of this review is therefore to discuss the potential clinical relevance of cholesteryl ester transfer protein inhibition in hyperlipidemic subjects at elevated cardiovascular risk.

Key words: Cholesteryl ester transfer protein, high density lipoprotein cholesterol, coronary artery disease, CETP inhibitor

Historically, atherosclerosis has been considered a chronic, slowly progressive disease for which the treatments are largely preventive in nature and exert their effects over long periods. Over the last decade, investigators have found that coronary atherosclerosis may be much more dynamic in nature; as many acute coronary events are caused by the rupture of an inflammatory unstable plaque[1]. Indeed, aggressive cholesterol-lowering therapy with statins appears to have clinical benefit within 4 to 6 mo of initiation of therapy, suggesting rather rapid effects on the stability of preexisting coronary lesions. Large-scale clinical trials in which inhibitors of statins have been used to reduce low-density lipoprotein (LDL) cholesterol levels have shown marked improvements in clinical outcomes[2,3]. Despite the favorable effects of statins on the risk of coronary heart disease, many cardiovascular events are not prevented by statin therapy. Hence, there is a great deal of interest in identifying therapies capable of further reducing the risk of coronary heart disease. One such potential therapeutic target is a low level of high-density lipoprotein (HDL) cholesterol. Plasma levels of high-density lipoprotein cholesterol (HDL-C) and its major protein apolipoprotein A-I are consistently inversely associated with coronary heart disease (CHD) risk in observational studies. There are two different approaches to increasing the HDL cholesterol level that are currently under development. Firstly an HDL cholesterol raising strategy actively being explored is the inhibition of cholesteryl ester transfer protein (CETP)[4]. Secondly, short-term HDL-infusion therapy, whereby patients with cardiovascular disease would receive infusions of HDL for six to eight weeks in conjunction with lipid therapy in order to reduce atherosclerosis and the risk of cardiac events in the short term. Additional approaches to short-term HDL therapy that are under development include the infusion of synthetic peptides[5-7].

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Role of CETP in reverse cholesterol transport:

Cholesterol homeostasis is maintained through a specific multistep pathway termed reverse cholesterol

transport (RCT), whose action results in the net movement of cholesterol from peripheral tissues via the plasma compartment to the liver for excretion (fig. 1). Among the key actors involved in this potentially antiatherogenic pathway is the cholesteryl ester transfer protein (CETP), which plays a fundamental role in mediating the transfer of CE from cardioprotective high density lipoprotein (HDL) particles to atherogenic apolipoprotein (apo)-B-containing lipoproteins (very low density lipoprotein, VLDL, VLDL remnants, intermediate density lipoprotein, IDL, and low density lipoprotein, LDL). Indeed, the CETP-mediated transfer of CE to these particles, which may subsequently be taken up by both receptor-dependent and receptor-independent pathways in the liver, may represent up to 70% of total cholesterol flux to the liver in some animal species, such as rabbit.

The action of CETP is however equally implicated in the intravascular remodeling of lipoproteins, which favors HDL particle recycling and thus the formation

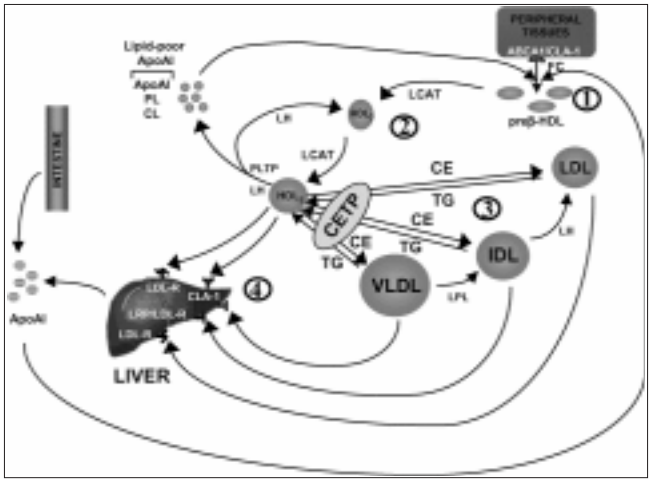

Fig. 1: The key role of CETP in RCT
RCT can be divided into 4 major steps. (1) Cellular FC efflux, during which intracellular FC traverses the plasma membrane by passive diffusion or via the intermediary of a specific transporter, such as ABCA1 or a receptor such as SR-BI/CLA-1. FC is then taken up by a lipid-poor complex containing PL and apoAI to form pre-HDL. (2) Pre particles are transformed to HDL3 particles and subsequently to HDL2; such transformation involves esterification of FC by LCAT, thereby generating CE-enriched HDL2. (3) CETP redistributes CE from HDL particles to apoB-containing lipoproteins (VLDL, VLDL remnants, IDL, and LDL), enhancing their CE content but also favoring the formation of TG-enriched HDL2 particles. (4) The final step of RCT involves the return of CE to the liver, where HDL-CE may be taken up via a selective process involving SR-BI/CLA-1, while the intact particles can be taken up by HDL receptors and the LDL receptors (LDL-R). Finally, TG in CE-depleted HDL2 may be hydrolyzed by HL, thereby reducing HDL size and permitting the recycling of HDL particles and apoAI; this step potentially involves the action of PLTP and CETP.

of pre-HDL, thereby leading to enhanced cellular free cholesterol (FC) efflux and plasma lecithin: cholesterol acyltransferase (LCAT) activity (fig. 1). Such actions are synonymous with an antiatherogenic role for CETP. Nevertheless, by depleting plasma HDL-cholesterol levels and by increasing CE content in all apoB-containing lipoproteins in both fasting and postprandial states, CETP can potentially contribute to the establishment of an atherogenic lipoprotein profile. Indeed, when circulating concentrations of apoB-containing particles are elevated, as occurs typically in the major forms of hyperlipidemia associated with premature atherosclerosis (hypercholesterolemia, mixed hyperlipidemia, and hypertriglyceridemia), then both CETP activity and mass are typically elevated significantly (up to 3-fold) as compared with the normolipidemic state and Paradoxically then, CETP possesses the potential to simultaneously exert both proatherogenic and antiatherogenic effects, the balance between them clearly depending primarily on the metabolic context. Plasma CETP activity and mass should clearly be sufficient to facilitate generation of optimal amounts of small HDL particles to ensure the initial step of RCT (fig. 1) but should not exceed such an optimal level so as to limit the overall cholesterol load in atherogenic apoB-containing lipoproteins.

From the foregoing discussion, it is evident that pharmacological inhibition of CETP in hyperlipidemic subjects at high cardiovascular risk can be envisaged with the goal of attenuating CETP-mediated CE enrichment of apoB-containing lipoproteins. In this way, HDL-cholesterol levels may be raised at the expense of reduction in the CE content of atherogenic VLDL, IDL and LDL[8,9].

Physiological function of CETP:

The analysis of the CETP primary sequence (476 amino acids) indicates that the mature protein is composed of 45% of nonpolar residues, suggesting it to be highly hydrophobic in nature. However, the fact that CETP is readily soluble in water implies that such hydrophobic residues are mainly inaccessible to the aqueous phase; indeed, they form a hydrophobic pocket that permits the binding of neutral lipids[10]. Study of structure-function relationships in CETP revealed that the C-terminal region plays a crucial role in neutral lipid binding[11]. However, the binding of phospholipids seems to require a distinct site. Recently, the crystallographic structure of the bactericidal/ permeability-increasing protein (BPI), a protein

presenting high sequence homology to CETP (~20%), has been reported[12]. Thus, BPI is a boomerang-shaped molecule whose conformational structure displays 2 similar domains (N and C termini), each possessing a hydrophobic pocket that can bind a phospholipid molecule. Based on the structure of BPI, a model for CETP has been proposed, in which C-terminal residues 461-476 form an amphipathic helix that covers the opening of the N-terminal pocket. Lipid transfer thus implies disordering of lipids in the lipoprotein surface followed by the flipping open of the hydrophobic pocket with subsequent entry of a neutral lipid molecule.

In normolipidemic subjects, CETP concentration varies from ~1 to 3 g/ml plasma[13]. However, plasma CETP levels are typically increased by 2 to 3 fold in subjects displaying hypercholesterolemia or mixed forms of hyperlipidemia involving elevated triglyceride (TG) levels[14,15]. Circulating CETP is associated with VLDL, LDL, and HDL particles[16]. Nevertheless, while the affinity of CETP is greater for VLDL and LDL than for HDL, when the relative plasma concentration of each lipoprotein is considered, then some 74% of CETP are associated with the HDL fraction, 24% with LDL, and 1% with VLDL. Only ~1% of plasma CETP is present in free form[17]. Among the different HDL particle subspecies, CETP is mainly associated with HDL particles containing apoAI alone and with preβ-HDL; only a minor proportion of CETP is associated with HDL particles containing both apoAI and apoAII[18]. Nevertheless, in humans, CETP distribution among lipoproteins varies according to sex and the hyperlipidemic state. Indeed, in females, CETP is mainly associated with LpAI, while in normolipidemic males, CETP is equally distributed between LpAI and LpAI:AII. By contrast, the majority of plasma CETP in hyperlipidemic males is bound to LpAI:AII particles.

In human plasma, CETP facilitates exchange and net transfer of neutral lipids, principally CE and TG, between different plasma lipoprotein particles and of phospholipids to a lesser degree. Thus, CETP assures the totality of the transfer of esterified cholesterol (EC) and TG but only one-third of that of phospholipid; the remaining two-thirds of phospholipid transfer is mediated by the phospholipid transfer protein (PLTP). In contrast to PLTP, CETP exclusively mediates phospholipid exchange with no net mass transfer between lipoproteins. In addition, CETP cannot facilitate exchange of phospholipids between liposomes and HDL3 particles. Studies on transgenic mice expressing the human CETP gene, but in which the PLTP gene has been invalidated, indicate that the function of these 2 proteins is not redundant[19]. Homoexchange of neutral lipids involves the bidirectional exchange of CE or TG between lipoprotein acceptor and donor particles. By contrast, when CETP is involved in transfer of CE from CE-rich lipoproteins to TG-rich lipoproteins (TRL), and when such transfer occurs simultaneously with reciprocal TG transfer in the opposite direction, then such neutral lipid exchange is termed heteroexchange. Thus, although each plasma lipoprotein particle species may act as a potential donor or acceptor of neutral lipid, the relative concentration and lipid content of EC and TG (expressed as the EC/TG ratio) constitutes a major determinant of its specific contribution to net neutral lipid mass transfer. Thus, the net mass transfer of TG is typically observed from VLDL to both LDL and HDL, with a reciprocal transfer of CE from both HDL and LDL to VLDL. Such differences in transfer patterns are reflected in the ratio of EC/TG content of VLDL, LDL, and HDL. Nevertheless, in the absence of the lipid transfer inhibitor protein (LTIP), both HDL and LDL represent equivalent substrates for CETP in their capacity to transfer EC to other lipoprotein particles. Although no net mass transfer of neutral lipids was initially observed between HDL and LDL, it is now well established that a net mass transfer of CE indeed occurs from HDL to LDL in human plasma. In addition, LDL particles of the intermediate size and density subclass appear to represent the preferential acceptors for CE among the major LDL subclasses[20]. Moreover, it is important to note that CETP can equally mediate exchange of neutral lipids between distinct HDL subspecies.

To conclude, plasma CETP activity is modulated by 4 major factors: plasma CETP concentration, plasma levels and chemical composition (lipids and proteins) of lipoprotein acceptors and donors, and presence in plasma of specific inhibitors of CETP, notably LTIP and apoCI. In addition, environmental factors such as physical exercise, alcohol, and smoking can also affect plasma CETP activity.

Role of CETP in the intravascular remodeling of lipoproteins:

In vitro studies indicate that CETP influences LDL particle size by favoring a shift in LDL distribution

toward a profile composed mainly of CE-rich, buoyant LDL particles of large size. Conversely, inhibition of CETP in the hamster is associated with a shift in LDL profile toward dense particles of small size. Indeed, the presence of heterogeneous small dense LDL is a key feature in patients presenting CETP deficiency. In contrast, an increase in LDL particle size is observed in transgenic mice expressing the human CETP gene. Finally, the combined action of CETP and lipoprotein lipase (LPL) induce a shift in LDL profile from large LDL (>25.5 nm) to small dense LDL particles (<25.5 nm). CETP equally exerts major impact on the intravascular remodeling of HDL particles. Indeed, several *in vitro* studies have demonstrated that CETP induces modification in HDL particle size by favoring the formation of particles of small size including HDL3b, HDL3c, and pre-HDL. In addition, the combined action of CETP and LPL or hepatic lipase (HL), in the presence of VLDL, favors reduction in HDL size. Expression of the human CETP gene in transgenic mice induces significant reduction in plasma apoAI and HDL levels and is associated with decrease in HDL particle size and increased levels of pre-HDL[21]. The modifications induced by CETP in the remodeling of HDL particles are more pronounced in transgenic mice coexpressing the human CETP gene and human apoAI or apoCIII gene. By contrast, inhibition of CETP in hamster induces the formation of HDL particles of large size.

Finally, the role of CETP in the remodeling of HDL particles has been confirmed in patients with CETP deficiency. Such subjects are characterized by an elevated HDL2/HDL3 ratio, reflecting an increased proportion of large HDL particles enriched in CE and apoE. The presence of such large HDL particles suggests that CETP is a key factor in modulating the recycling of large HDL, and CETP thus favors reduction in HDL size[22].

Antisense and antibodies against CETP:

Mice and rats do not possess CETP and have metabolic pathways that make them resistant to diet-induced atherosclerosis. Thus, these rodents are not good models for human atherosclerosis. On the other hand, cholesterol-fed rabbits do develop atherosclerosis and can be used as a model of human atherosclerosis. In this model, antisense oligodeoxynucleotides against CETP decreased total cholesterol while increasing HDL cholesterol, and these changes were associated with decreased aortic cholesterol content and the percentage of lesions[23]. Similarly, in cholesterol-fed rabbits, an antibody to CETP reduced plasma CETP activity, increased HDL cholesterol and decreased LDL cholesterol and the atherosclerotic lesions[24,25].

Chemistry of small molecule CETP inhibitors (fig. 2):

An ideal drug candidate would likely be specific for CETP and not disrupt the integrity of other lipoproteins. While the available biochemical data indicates human CETP contains independent binding sites for neutral and phospholipids. The exact stochiometry, affinity and three dimensional structutal details of the protein interactions defining binding for these substrates are currently unknown[26].

CGS-25159, the isoflavon inhibited CETP with an IC_{50} value of approximately 10 μM. After oral administration to normolipidemic hamsters, CGS-25159 (10 mg/kg/day for 4 d) reduced CETP activity by 35-60%. Treatment with CGS-25159 at 30 mg/kg for 7 d increased HDL cholesterol by 19%. In 0.2% cholesterol-fed hamsters, CGS-25159 (30 mg/kg for 14 d) increased HDL cholesterol by about 29%, while decreasing total cholesterol and triglycerides[27]. Despite these interesting results showing that an inhibitor of CETP increases HDL chol-esterol *in vivo*, there have been no further reports of development of CGS-25159 by Novartis. SC-71952, a substituted analogue of nicotinic acid methyl ester was identified at Pharmacia (now Pfizer) as an inhibitor of CETP with an IC_{50} value of about 1 μM in a random screen of a chemical library[28]. The effects of SC-71952 on HDL cholesterol or models of atheroma have not been published to date. Using a lead disulfide compound, systematic chemistry was used by Japan Tobacco to

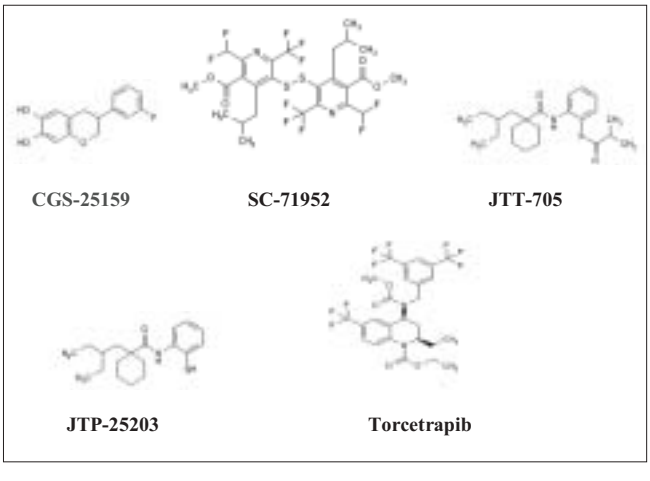

Fig. 2: Structure of some CETP inhibitors in development

obtain the small- molecule CETP inhibitor JTT-705[29]. *In vitro*, JTT-705 inhibited plasma CETP activities of humans, rabbits, hamsters, cynomolgus monkeys and marmosets with IC_{50} values in the range of 1-12 μM. The thiol and orally active form JTP-25203 also inhibited CETP activities with IC_{50} values in the range of 0.4-2.8 μM[30,31]. Pfizer is developing torcetrapib (CP-529414) as a new CETP inhibitor. Torcetrapib evolved from a series of inhibitors identified by high-throughput screening for inhibition of cholesteryl ester activity in an assay using native human plasma CETP. The IC_{50} values for torcetrapib were 52 and 65 nM, respectively; in HDL cholesterol and LDL cholesterol cholesteryl ester transfer assays[32-34]. CETP inhibition with torcetrapib retards atherosclerosis in rabbits, and the reduced lesion area is associated with increased levels of HDL-C[35].

Conclusions:

The impact of CETP-mediated lipid transfer reactions on atherogenesis remains controversial, probably reflecting the complexity of CETP activity *in vivo*. Animal studies have confirmed the dual and indeed chameleon-like action of this protein. At present, the fibrates are used to increase HDL cholesterol levels and their benefits have been demonstrated in a large clinical trial. However, greater increases in HDL cholesterol have been reported with the CETP inhibitors than with the fibrates. On the other hand, triglycerides are independent risk factors for CAD (coronary artery disease), especially in the presence of diabetes. While the fibrates cause a major reduction in triglyceride levels, JTT-075 and the lower dose of torcetrapib alone had no effect on triglyceride levels, and in one study JTT-075 was shown to increase triglyceride levels. The CETP inhibitors therefore may have both advantages and disadvantages over the fibrates, depending on the type of dyslipidemia, and this will need to be tested both experimentally and clinically. For instance, in the presence of high levels of triglycerides and marginally low HDL cholesterol, the fibrates may have advantages over the CETP inhibitors. Although there is not as yet a clear indication as to whether CETP inhibitors can reduce or prevent atherosclerosis in humans, it is nonetheless evident that CETP inhibition is a powerful therapeutic tool for induction of elevation in plasma levels of antiatherogenic HDL. Raising HDL cholesterol with inhibitors of CETP is a new approach to treating dyslipidemia that requires further investigation, especially in patients with CAD[36].

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