Dual Roles of Apolipoprotein CI in the Formation of Atherogenic Remnants

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Current Atherosclerosis Reports 2006, **8:**1–2
Current Science Inc. ISSN 1523-3804

Apolipoprotein (apo) CI is a 57–amino acid protein mainly synthesized in the liver. The apoCI gene is located together with the apoE and apoCII genes on chromosome 19. Like the other apoC family members (apoCII and apoCIII), apoCI modifies the intravascular turnover of triglyceride-rich lipoproteins (TRLs). TRLs are responsible for transporting endogenous fat from the liver (ie, very low-density lipoproteins) and dietary fat from the intestine (ie, chylomicrons). In the vascular compartment, these particles are metabolized into smaller particles, or remnants, known for their atherogenic properties. In the circulation, apoCs are distributed between TRLs and high-density lipoproteins (HDL). In the fasting state, apoCII and apoCIII are equally distributed between HDL and very low-density lipoproteins, whereas apoCI is skewed largely in favor of HDL (> 90%). Therefore, when apoCs are transferred from HDL to newly synthesized TRLs during postprandial lipemia, a relatively larger portion of apoCI is transferred than of other apoCs. The apoCI enrichment of TRLs after a fatty meal alters their metabolism and clearance and has consequences for the formation of TRL remnants.

Each of the apoCs has distinct properties and distinct effects on TRL metabolism. ApoCII is an essential cofactor for lipoprotein lipase, which sits on the endothelial surface and mediates the hydrolysis of TRLs. In contrast, apoCIII inhibits TRL hydrolysis. ApoCI, however, is not known to interfere with TRL hydrolysis. Accordingly, apoCI-enriched TRLs undergo normal hydrolysis and form smaller TRLs and eventually remnants. Because apoCI is a potent inhibitor of apoE-mediated uptake of TRL and TRL remnants by members of the low-density lipoprotein (LDL) receptor family, apoCI-enriched remnants cannot undergo receptor-mediated clearance and instead remain in the circulation. A prolonged half-life in the plasma in turn allows cholesteryl ester transfer protein (CETP) to mediate cholesterol enrichment of these remnants. These metabolic consequences of apoCI enrichment of TRLs, which have been established mostly by in vitro studies, have been confirmed in mice over-expressing apoCI. These mice suffer a familial combined hyperlipidemia–like phenotype characterized by the accumulation of cholesterol-rich remnants in plasma.

Cholesterol-rich remnants are particularly atherogenic, and delayed remnant clearance during postprandial state is a well-established feature of patients with coronary artery disease (CAD). CETP-mediated transfer of cholesterol esters from HDL to TRLs is, therefore, believed to play a crucial role in the formation of cholesterol-rich remnants. It has been suggested that apoCI, being a potent inhibitor of CETP, may prevent their formation. Although transgenic over-expression of CETP in apoCI knockout mice increased the formation of cholesterol-rich remnants, over-expression of apoCI and CETP did not reduce remnant formation. Nevertheless, initial trials with CETP inhibitors other than apoCI appear promising, shifting cholesterol away from remnants to HDL.

The consequences of alterations in the apolipoprotein and lipid composition of TRLs in humans and in patients with cardiovascular disease are less well studied. However, results from such studies indicate a central role for apoCI enrichment of TRLs in the formation of atherogenic remnants. In healthy persons, the stress of additional plasma triglycerides (eg, during postprandial lipidemia) alters the composition of TRLs and TRL remnants to favor their clearance from the circulation. In contrast, in normolipidemic patients with manifest CAD and delayed clearance of postprandial remnants, the remnants were specifically enriched with cholesterol and apoCI. Moreover, in apparently healthy men with signs of early carotid atherosclerosis but without clinical manifestations of the disease, TRL remnants were enriched with apoCI and cholesterol, suggesting that these compositional alterations are responsible for the delayed clearance.

Could the transfer of apoCI from HDL to TRLs be the key event in the generation of atherogenic remnants? In theory, this transfer would increase CETP activity by reducing the inhibitory effect of apoCI on HDL. At the same time, the transfer of apoCI to TRLs would prevent the receptor-mediated clearance of these particles from the circulation without affecting their hydrolysis. Thus, the transfer of apoCI from HDL to TRLs sets the stage for the formation atherogenic TRL remnants, suggesting a dual role of apoCI: 1) preventing remnant formation and premature atherosclerosis if attached to HDL; and 2) promoting remnant formation and atherosclerosis if transferred to TRLs. Unfortunately, the mechanisms underlying the transfer of apoCI from HDL to TRLs during triglyceridemia are largely unknown. A better understanding of this transfer may offer a therapeutic alternative to CETP inhibitors.

Regardless of whether apoCI proves to be a suitable therapeutic target to prevent remnant formation, apoCI-enriched TRLs may well be a worthwhile marker of CAD risk. In a recent study, apoCI-enriched TRLs were more powerful than conventional CAD risk markers in predicting early atherosclerosis. Prospective longitudinal studies are warranted to establish whether apoCI-enriched TRLs are indeed a useful marker of CAD risk.