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Review

Apolipoprotein C-III: From Pathophysiology to Pharmacology

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Apolipoprotein C-III (apoC-III) has a critical role in the metabolism of triglyceride (TG)-rich lipoproteins (TRLs). Animal models lacking the *APOC3* gene exhibit reduced plasma TG levels, whereas the overexpression of *APOC3* leads to increased TG levels. In humans, loss-of-function mutations in *APOC3* are associated with reduced plasma TG levels and reduced risk for ischemic vascular disease and coronary heart disease. Several hypolipidemic agents have been shown to reduce apoC-III, including fibrates and statins, and antisense technology aimed at inhibiting *APOC3* mRNA to decrease the production of apoC-III is currently in Phase III of clinical development. Here, we review the pathophysiological role of apoC-III in TG metabolism and the evidence supporting this apolipoprotein as an emerging target for hypertriglyceridemia (HTG) and associated cardiovascular disorders.

Trends

ApoC-III has a key role in the metabolism of TG-rich lipoproteins.

APOC3-knockout animals have reduced plasma TG levels, whereas the overexpression of the *APOC3* gene increases TG levels.

Loss-of-function mutations in the *APOC3* gene decrease plasma TG levels and cardiovascular risk.

Current Phase III trials are evaluating an antisense oligonucleotide to *APOC3* mRNA.

Introduction

ApoC-III has a critical role in the metabolism of TRLs, which are causally associated with increased cardiovascular disease (CVD) risk, independent of low-density lipoprotein cholesterol (LDL-C) or high-density lipoprotein cholesterol (HDL-C) levels [1–6]. Most recently, a large prospective analysis clearly demonstrated that the risk of ischemic vascular disease and ischemic heart disease is a function of plasma levels of TG [7]. Therefore, pharmacological therapies aimed at reducing plasma TG levels are of great interest, and strategies controlling apoC-III are currently under clinical development.

Here, we review the pathophysiological role of apoC-III in TG metabolism and the evidence supporting this apolipoprotein as an emerging target for HTG and associated cardiovascular disorders.

TRLs and CVD

TG levels are commonly measured in the fasting state, but their levels increase significantly postprandially; postprandial abnormalities in TG metabolism (i.e., increased plasma TG concentrations and prolonged postprandial response after a fatty meal) are a hallmark of patients with established coronary heart disease (CHD) [8,9]. Thus, an important role in the pathogenesis of atherosclerosis-related diseases has been postulated for postprandial lipids [10,11]. The identification of TRLs in human atheroma has provided further evidence for their direct role in atherogenesis [12]. TRLs penetrate the arterial wall and reach the subendothelial space, causing endothelial lipid deposits, monocyte adhesion, production of inflammatory markers, and oxidative stress [12]. The role of TG in atherosclerosis-mediated inflammation not only depends on their direct vascular cell effects, but is also related to profound changes in the functionality of HDL [13,14], most probably related to the enrichment in TG.

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Studies conducted in endothelial cells (ECs) indicate that TRLs activate nuclear factor (NF)-κB, a transcription factor that has an important role in the activation of ECs [15]. TRLs from HTG subjects increased the expression of interleukin (IL)-6, monocyte chemoattractant protein (MCP)-1, and adhesion molecules, including vascular cell adhesion molecule (VCAM)-1, platelet/endothelial cell adhesion molecule (PECAM)-1, and endothelial/leukocyte adhesion molecule (ELAM)-1, through the activity of p38 mitogen-activated protein kinase and nuclear factor κB (NF-κB) [16]. Although fasting TRLs increase adhesion-molecule expression, the effect observed with postprandial TRL is more pronounced [17].

The composition of TRL particles has a key role in determining the proinflammatory response to TRLs [18]. A different composition of very low-density lipoproteins (VLDL) may be responsible for the differences observed between normolipidemic and hypertriglyceridemic TRLs. Furthermore, lipolysis products from TRLs promote a pro-atherogenic environment by increasing endothelial permeability [19]. One could speculate that, in the presence of hypertriglyceridemia, the reduced activity of LPL may promote the presence of proinflammatory TRLs. All the aspects point to the relevance of increasing LPL activity to limit postprandial lipemia and reduce plasma TG levels; this process is controlled at different levels, as detailed below.

Synthesis and Catabolism of TG-rich Lipoproteins

TRLs are synthesized either in the liver (apoB100-containing VLDL) and the intestine (apoB48-containing chylomicrons) [20,21]. Newly synthesized apoB100 interacts with microsomal triglyceride transfer protein (MTP), which catalyzes the transfer of lipids to nascent apoB, generating a pre-VLDL particle that is further lipidated to VLDL2 and transferred to the Golgi apparatus [22,23]. There, VLDL2 can be either secreted or further acquires TG, generating larger, TG-rich VLDL1, which is then secreted into the hepatic vein [22,23].

MTP is also expressed in the intestine and is involved in the assembly of chylomicrons through a process similar to that described for VLDL production: MTP transfers lipids (mainly TG) to newly synthesized apoB48 and facilitates the successive lipidation of chylomicron precursors. In this phase, apoA-IV, which increases MTP activity and chylomicron lipidation, is added at the particle surface [24].

VLDL and chylomicrons leave the liver and intestine and enter the circulation, where they acquire apoC-II and apoE from HDL. In the capillaries of adipose tissue and muscle, TG are hydrolyzed by lipoprotein lipase (LPL) to produce free fatty acids, which are then taken up by the tissues. During the removal of fatty acids, a large proportion of the phospholipids and apoproteins are transferred to HDL, converting the lipoproteins to the highly atherogenic VLDL and chylomicron remnants.

The main organ involved in the clearance of remnant lipoproteins is the liver, which expresses several surface receptors that, following the action of LPL and hepatic lipase, facilitate the rapid hepatic clearance of remnants [25]. These remnants contain several proteins involved in this process, including not only apoE, apoA-V, LPL, and HL, but also apoB100 for hepatically derived remnants. By contrast, apoC-III seems to inhibit the binding of remnants to hepatic receptors [26,27].

Several factors affect TRL metabolism, such as LPL, apoC-II, and apoC-III. LPL has an essential role in the lipolytic processing of TG in VLDL and chylomicrons in peripheral tissues (Figure 1) [25]. This enzyme is localized at the luminal surface of ECs of small capillaries, where the presence of heparin sulfate proteoglycans facilitates the binding of TRLs, thus helping LPL function [25]. LPL hydrolyzes TG, releasing fatty acids that are then taken up by surrounding cells for storage or to provide energy [25]. LPL activity is regulated by several factors, including: