Apolipoprotein CIII (apoCIII) was first identified more than 40 years ago as a component of very-low-density lipoprotein (VLDL), and shortly thereafter as an inhibitor of lipoprotein lipase. More than a decade later, apoCIII was found to inhibit lipoprotein remnant uptake by the liver. Its relevance to human lipid metabolism was made clear by its absence, along with apolipoprotein AI, in 2 sisters with essentially no plasma high-density lipoprotein and very low triglyceride levels. These individuals had marked increases in the fractional removal of TG from VLDL (increased lipoprotein lipase activity) and increased conversion of VLDL to low-density lipoprotein (LDL) (less remnant removal). These findings spurred investigations at a molecular level, including demonstrations of hypertriglyceridemia in apoCIII transgenic mice and decreased TG levels in apoCIII knockout mice. In humans, apoCIII levels are associated with hypertriglyceridemia and increases in VLDL and inversely related to the size of LDL particles. ApoCIII was the first lipid-associated gene to be linked by a common polymorphism to hypertriglyceridemia.

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Studies of the regulation of apoCIII gene expression have identified responsiveness to insulin,11,12 peroxisome proliferator-activated receptor-α (PPAR-α),13 farnesoid X receptor,14 and Rev-erba. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Caron et al4 demonstrate responsiveness of the apoCIII promoter to glucose. In a series of well-designed and well-conducted studies, these investigators provide strong evidence for stimulation of apoCIII gene expression by glucose via hepatic nuclear factor-4α and carbohydrate-responsive element binding protein but not liver X receptor. In addition, the authors demonstrate a modest correlation between plasma apoCIII levels and both fasting and postglucose challenge plasma glucose levels in obese subjects. Of note, there was no correlation between apoCIII levels and either fasting or postchallenge plasma insulin levels. A polymorphism in the upstream untranslated region of the apoCIII gene had been shown to eliminate insulin responsiveness in rodents and hepatocytes. Although this finding has been confirmed in some human studies,18 the presence of this same polymorphism in type I diabetic patients had no effect on plasma apoCIII or triglyceride concentrations.8 Further uncertainty regarding the role of the insulin regulatory site in humans derives from conflicting studies in patients with nonalcoholic fatty liver disease.19,20 The absence of an association between apoCIII levels and plasma insulin in the present human studies reported by Caron et al16 is consistent with the negative gene association studies.

What is the physiological relevance of this finding and how can we fit these new data into a model of the normal role of apoCIII in the regulation of plasma lipid and lipoprotein metabolism (Figure 1A)? In other words, why would glucose stimulate apoCIII gene expression? Caron et al16 suggest that by stimulating apoCIII expression, thereby reducing lipolysis of circulating TG, glucose would increase its own utilization by peripheral tissues. However, insulin levels are usually increased at the same time glucose levels rise, and if insulin suppresses apoCIII expression in vivo, a much more complex relationship must exist between these 2 potential regulators of apoCIII expression. It is likely that any significant role of apoCIII in “nutrient switching” will depend on the quantities of glucose and TG ingested or released from organs, the timing of insulin release relative to the flux of glucose and TG, and the sensitivity of apoCIII in the liver and the small intestine to insulin. Caron et al suggest that in individuals with insulin resistance and diabetes, there is a loss of insulin-mediated suppression of apoCIII that, coupled with glucose-stimulated apoCIII expression, leads to hypertriglyceridemia. Thus, although a physiological role for glucose-stimulated apoCIII expression is not easily envisioned, a pathophysiologic role for this pathway is consistent with data from several sources, including kinetic studies in humans that have demonstrated increased secretion of apoCIII into plasma (presumably mostly from the liver) in people with hypertriglyceridemia and insulin resistance.21–23 Potentially important additions to this scheme derive from recent evidence in both liver cells24 and human kinetic studies5 that apoCIII may facilitate or enhance VLDL TG secretion and that plasma fatty acids, which are often elevated in insulin resistance and diabetes, stimulate apoCIII secretion (Figure 1B).

Why should we be interested in the regulation of apoCIII gene expression? In addition to its clear effects on lipid and lipoprotein metabolism, where increased apoCIII would lead to increased levels of VLDL TG and remnant lipoproteins, there have been an increasing number of clinical26 and preclinical27,28 suggesting a more direct proatherogenic role for apoCIII. Thus, apoCIII-enriched LDL has increased binding to proteoglycans27 and can increase monocyte bind-
A

Regulation of apoCIII synthesis and secretion from the liver

Glucose (+) apoCII apoB TG VLDL VLDL and Chylo Remnant FFA FFA Lipogenesis LpL

TPARα PPARγ Rev-erba Insulin FXR

B

Effects of Dysregulated apoCIII synthesis on lipoprotein metabolism in insulin resistant states

Glucose (++) apoCII apoB TG VLDL VLDL and Chylo Remnant FFA FFA Lipogenesis LpL

Figure. A, Under normal conditions, apoCIII gene expression and synthesis are regulated by several factors, including PPARα, PPARγ, Rev-erba, farnesoid X receptor, insulin, and—based on the report by Caron et al—glucose. All are inhibitory except for glucose, which stimulates apoCIII expression. Plasma free fatty acids (FFA) stimulate apoCIII secretion, but it is not known whether this occurs at the transcriptional or posttranslational level. ApoCIII in plasma inhibits lipoprotein lipase–mediated catabolism of VLDL (and chylomicrons) and inhibits the uptake of VLDL (and chylomicron) remnants by the liver. In addition, apoCIII may increase VLDL assembly and secretion. B, In states of insulin resistance, any inhibitory role of insulin on apoCIII expression may be lost, whereas higher glucose levels, particularly in patients with type 2 diabetes mellitus, would further stimulate apoCIII expression. Increased plasma FFA delivery to the liver would exacerbate this problem. The results of dysregulated apoCIII synthesis and secretion would be defective lipoprotein lipase–mediated lipolysis of triglyceride-rich lipoproteins and reduced remnant lipoprotein clearance. Thus, dysregulated apoCIII synthesis and secretion could play a major role in the genesis of the diabetic, insulin-resistant dyslipidemia. In addition, accumulation of apo-CIII rich apoB-containing lipoproteins might have direct atherogenic consequences.

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