The incidence of obesity-associated disorders, such as type 2 diabetes and the metabolic syndrome, is continuously increasing worldwide. These disorders are characterized by abnormalities in glucose and lipid metabolism, putting patients at increased risk for macro- and microvascular complications. Although statin treatment, which primarily targets elevated plasma low-density lipoprotein (LDL)-cholesterol levels, lowers cardiovascular morbidity and mortality in patients with type 2 diabetes, it is increasingly clear that a significant residual cardiovascular risk remains in these patients, which is partly attributable to the typical atherogenic lipoprotein profile (ALP) characterized by hypertriglyceridemia and low-high density lipoprotein (HDL)-cholesterol concentrations. Post hoc analysis of statin trials, such as PROVE-IT TIMI 22, have identified plasma triglycerides as a determinant of cardiovascular risk in patients achieving LDL-cholesterol goals.

Plasma triglyceride concentrations are determined by the balance between clearance/uptake and production of triglyceride (TG)-rich lipoproteins. Dysregulation of this balance results in the development of hypertriglyceridemia. Triglycerides in very-low-density lipoproteins (VLDL) and chylomicrons are hydrolyzed by lipoprotein lipase, thus allowing their conversion to remnant and subsequently to LDL particles. This process is controlled by specific apolipoprotein (apo) constituents, such as apoCII and apoAV, which facilitate TG-rich lipoprotein clearance/lipolysis, whereas apoCIII delays it.

ApoCIII is a 79-aa glycoprotein synthesized in the liver and the intestine and a major component of the apoB-containing TG-rich lipoproteins and HDL. Plasma apoCIII levels are positively correlated with plasma triglycerides over the entire spectrum from normo- to hypertriglyceridemia. ApoCIII deficiency results in hypertriglyceridemia both in humans and mice, whereas overexpression of apoCIII in mice results in hypertriglyceridemia. The functions of apoCIII in lipoprotein metabolism are multiple. First, apoCIII inhibits lipoprotein lipase activity and hence delays lipoprotein triglyceride lipolysis. Second, apoCIII impairs glycosaminoglycan–lipoprotein interactions and receptor-mediated uptake of TG-rich remnant lipoproteins. Moreover apoCIII stimulates VLDL assembly and secretion. In the Cholesterol and Recurrent Events (CARE) clinical trial, apoCIII-containing apoB lipoproteins (LpB:CIII) emerged as an independent predictor of recurrent coronary events.

More recently, a series of articles have identified novel, unexpected functions of apoCIII, which exerts direct proatherogenic activities resulting in endothelial dysfunction and monocyte activation and adhesion. ApoCIII-enriched lipoproteins induce endothelial cell expression of the adhesion molecules vascular cell adhesion molecule-1 and intercellular adhesion molecule-1. ApoCIII also impairs insulin signaling in vitro and in vivo in endothelial cells, leading to a decrease of nitric oxide (NO) production and an increase of endothelin-1 synthesis and secretion, effects that enhance vasoconstriction. Moreover, LpB:CIII particles increase protein kinase Cα and RhoA-mediated β-integrin activation in monocytes. Finally, apoCIII-mediated nuclear factor (NF)-κB activation in monocytes further enhances the inflammatory response. All these actions result in enhanced monocyte adhesion to endothelial cells. Altogether, these results identified a direct vascular activity of apoCIII to induce endothelial dysfunction. However, the molecular and cellular mechanisms involved in these responses to apoCIII were unresolved.

In this issue of Circulation Research, Kawakami et al identify a direct molecular target of apoCIII. The authors demonstrate that apoCIII-induced monocyte activation is mediated by Toll-like receptor (TLR)2 activation in vitro and in vivo. TLRs were initially identified as major sensors of the innate immune response (for instance in case of microbial infection). TLRs are principal sensors of the innate immune system and provide a molecular link between infection, inflammation, and, more recently, atherosclerosis development. The authors show that incubation of human THP-1 monocytes or human peripheral blood monocytes with a blocking antibody against TLR2, but not TLR4, reduces apoCIII-induced monocyte adhesion to HUVEC cells. Incubation of monocytes with the TLR2 antibody also reduced protein kinase Cα and NF-κB activation and induction of β1-integrin expression by apoCIII. Most interestingly, the authors showed by a combination of in vitro and in cellulo experiments that apoCIII binds directly to TLR2. Moreover, overexpression of TLR2 enhanced apoCIII-mediated activation of NF-κB and induction of β1-integrin expression. ApoCIII induced the same pathways in monocytes isolated from wild type, but not from TLR2-deficient mice. Finally, intravenous administration of apoCIII-rich VLDL, but not apoCIII-deficient VLDL, in wild-type mice led to an increase...
of monocyte adhesion, which was reduced by pretreatment with apoCIII or TLR2 antibodies, an effect that appears to be mediated by NF-κB activation. These results indicate that TLR2 mediates at least part of the apoCIII-induced proinflammatory signals in monocytes.

The results from Kawakami et al.17 together with the previous data published by the laboratories of Sacks and Yoshida13–16 demonstrate that apoCIII has a direct effect on endothelial functions and provide insights on the molecular mechanisms of apoCIII actions on monocytes. Endothelial dysfunction is a causal factor in the initiation of atherosclerosis and among the earliest abnormalities that can be detected clinically in people with metabolic disorders at risk for atherosclerosis.19 Although the exact pathophysiological relevance of the apoCIII/TLR2 pathway remains to be studied using appropriate animal models, TRL2-deficient mice bred on the atherosclerosis-susceptible LDL receptor–deficient genetic background displayed a significant protection against atherosclerosis development.18 However, it should be noted that isolated hypertriglyceridemia, which is accompanied by elevated plasma apoCIII concentrations, is not a major cardiovascular risk factor. Hence, it is unlikely that apoCIII induction of endothelial cell dysfunction is the sole event precipitating atherosclerosis but likely acts in cooperation with other proatherogenic stimuli present in patients with an ALP. Altogether, these novel findings13–17 identify apoCIII as a molecular link between dyslipidemia and endothelial dysfunction, 2 features of cardiovascular disease (Figure).

These findings reinforce the concept that drugs inhibiting apoCIII production or activity may be useful in the treatment and prevention of cardiovascular disease, especially in patients with ALP. Peroxisome proliferator-activated receptor α agonists, such as the currently used fibrates, are drugs used in the treatment of hypertriglyceridemia.3 These compounds are potent downregulators of apoCIII expression.11 Interestingly, fibrates have been found to be most efficacious in those patients with the ALP associated with the metabolic syndrome and type 2 diabetes,3 and these novel findings regarding apoCIII may provide a mechanistic explanation for these effects of peroxisome proliferator-activated receptor α ago-
nists. Moreover, the findings reported in the present study suggest that modulators of the apoCIII/TLR2 pathway could be useful in the treatment of atherosclerosis.

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**References**


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