ApoE in Atherosclerosis
A Protein With Multiple Hats

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Apolipoprotein (apo) E, which is present in plasma lipoproteins that carry dietary and liver-derived cholesterol, plays a protective role in atherosclerosis. ApoE plays a requisite role in remnant lipoprotein clearance by the liver, and although hepatic LDL receptors can clear both LDL and apoE-containing lipoproteins, LDL receptor–related protein–mediated clearance of remnants is dependent on apoE. Compared with wild-type mice, apoE–deficient mice have high levels of plasma cholesterol as a result of this impaired clearance of cholesterol–enriched lipoproteins. Moreover, these apoE–deficient mice develop complex atherosclerotic lesions that are a direct result of the plasma accumulation of cholesterol–rich lipoproteins. Addition of apoE to apoE–deficient mice (by either expression of apoE transgenes, intravenous injection of synthetic mimics of apoE, or administration of adenovirus to achieve hepatic expression of apoE) reduces plasma cholesterol levels and provides protection against the progression of atherosclerosis. Thus, apoE plays a requisite role in maintenance of plasma cholesterol levels.

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Although most plasma apoE is made by the liver, other tissues also make apoE. For example, in the absence of any hepatic production of apoE, apoE–deficient mice can participate in liver–mediated uptake of cholesterol–rich lipoproteins. Importantly, there is an optimal level of plasma apoE that is required for lipoprotein clearance. Overexpression of human apoE3 in apoE–deficient mice at levels of >30 mg/dL leads to a hypertriglyceridemia due to both an apoE–dependent increase in hepatic VLDL triglyceride production and interference with apoC–II–dependent VLDL lipolysis. Furthermore, only a small amount of apoE is actually needed to lower plasma cholesterol. Thus, heterozygous apoE–deficient mice do not have elevated plasma cholesterol, and plasma apoE concentrations of only 40 μg/dL generated solely by bone marrow–transplanted macrophages can effectively lower plasma cholesterol levels.

Elsewhere in this issue, Thorngate et al report their studies of apoE–deficient mice that express only adrenal apoE. Their examination of multiple transgenic founder lines reveals that apoE plasma levels of up to 3% of wild-type levels can be achieved by adrenal expression and that this level is sufficient to normalize total plasma cholesterol levels. Thus, remnant clearance can be mediated by circulating plasma apoE made by the liver, bone marrow–derived macrophages, or adrenal cells. These researchers also identified transgenic lines of mice that express <1% to 2% of wild-type plasma apoE, a systemic amount of adrenal expression that has no effect on plasma cholesterol levels. Yet, in the absence of any observed effects on plasma cholesterol, the progression of atherosclerosis is reduced even in the low-expressor founder lines. Therefore, we must consider the idea that apoE may block atherogenesis by mechanism(s) that are independent of its ability to normalize plasma cholesterol concentrations.

Although this study by Thorngate et al suggests that the amount of plasma apoE generated by the low-expressor lines was insufficient to alter plasma cholesterol levels, additional studies are needed. Could the adrenal apoE have an effect on only a small population of plasma atherogenic lipoproteins that was not detected by the methods used? In fact, can any characterization of static lipoprotein levels (no matter how sensitive) provide sufficient data to conclude that even small amounts of systemic apoE cannot alter lipoprotein metabolism? Another concern is that only 1 parameter of atherosclerosis was measured in this study, as in many studies. Are all measurements of atherosclerosis in mice, including measurements of cholesteryl ester mass within aortas, percent of intimal involvement in aortas, or lesion areas in aortic valve lesions, comparable measures of the extent of disease? Ultimately, these questions will need to be answered by additional studies. Nevertheless, these data on adrenal expression of apoE strongly suggest that apoE can wear multiple hats with respect to its ability to protect against atherosclerosis.

Other studies have implicated multiple roles for apoE as well. Transduced apoE–deficient bone marrow (created with apoE–expressing retroviral constructs) was used to reconstitute apoE–deficient mice. In these studies, only low levels of apoE expression were observed that had no effect on plasma cholesterol levels, yet they significantly reduced the lesion areas. Moreover, Shimano et al established transgenic mice that expressed human apoE in the vessel wall and identified reduction of atherosclerotic lesions in the absence of any change in plasma cholesterol. Each of these observations forces us to speculate on mechanisms whereby small amounts of apoE could protect against atherosclerosis in the absence of a direct effect on plasma cholesterol. At least 3 mechanisms come to mind. First, apoE in concert with apoA–I could facilitate cellular cholesterol efflux from macrophage foam...
cells within the intima of the lesion. Second, apoE could directly modify T lymphocyte– and smooth muscle cell (SMC)–mediated inflammatory responses of atherosclerosis. Third, apoE possesses antioxidant activity, suggesting that apoE could protect by limiting oxidation.

Direct evidence for the cooperative participation of both apoE and apoA-I in efficient cholesterol efflux in vivo has been provided by Boisvert et al. Zhu et al compared the cholesterol efflux capacities of plasmas from apoE-deficient mice and human E3 transgenic mice and determined that the reduced atherosclerosis was a reflection of the ability of the transgenic apoE to associate with α-migrating HDL and to increase its capacity to accept cholesterol. Macrophages can efflux cholesterol in the absence of an exogenously added cholesterol acceptor, but this efflux appears to be influenced by apoE. Thus, it is likely that if adrenal cell–produced apoE in the transgenic animals is present in lesions, it could facilitate cellular cholesterol efflux.

ApoE regulates chronic inflammatory responses and could be protective via direct regulation of inflammation. The importance of intimal T lymphocytes and SMCs in inflammation is well documented. ApoE-deficient mice crossed with mice defective in both T and B lymphocyte function show a 42% reduction in atherosclerosis when they are fed a chow diet, which indicates that atherosclerosis-prone mice can display a prominent immune system component within their lesions. Importantly, apoE inhibits the proliferation of T lymphocytes and can suppress mitogen-activated proliferation of both CD4 and CD8 T cells. Importantly, this antiproliferative effect of apoE is not a direct cytotoxic effect, and other outcomes of mitogen stimulation are comparably affected, including T lymphocyte interleukin 2 production and interferon (IFN)-γ production. Analysis of immune components of atherosclerosis has demonstrated that IFN-γ can accelerate atherosclerosis. Thus, apoE in the intima of a vessel wall could regulate T-lymphocyte responses represented by either T cell–mediated cytokine production, cellular cytotoxicity, or help of B-cell antibody production. SMCs also participate in inflammatory responses within the intima, and it was recently reported that apoE inhibits SMC migration and proliferation induced by the inflammatory agonists platelet-derived growth factor and oxidized LDL.

Therefore, the report by Thorngate et al that small amounts of adrenal cell–produced apoE can safeguard against atherosclerosis via mechanisms that need not be related to direct changes in plasma cholesterol concentrations should stimulate further studies. We need detailed information about the antioxidative properties of apoE. We must understand how apoE facilitates cellular cholesterol efflux (particularly from lesion macrophage foam cells within the intima) and how apoE works in concert with apoA-I or other proteins to mediate this protective effect. We must examine how apoE regulates chronic inflammatory responses, how it modifies lymphocyte and SMC proliferation, and how regulated cytokine expression influences chronic inflammatory components of atherosclerosis.

References


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