Interplay Between Apolipoprotein E and Scavenger Receptor Class B Type I Controls Coronary Atherosclerosis and Lifespan in the Mouse

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The mouse has become a standard model for the study of atherosclerosis induced by extreme dyslipidemia in genetically modified strains such as the apolipoprotein E (apoE)-deficient or the LDL-receptor–deficient mouse. Although the process of plaque formation appears to repeat the fundamental steps of the human disease, it has been notoriously difficult to reproduce in the mouse the clinical consequences of atherosclerosis, such as myocardial infarction and stroke, that so commonly in patients signal plaque rupture or total lumen occlusion.1 The apoE-deficient mouse is a particularly interesting model because of its susceptibility to atherosclerotic lesions spanning from the aortic sinus to the abdominal aorta and involving the brachiocephalic and carotid arteries as well.2,3 It has recently been reported that the brachiocephalic plaque in the apoE-deficient mouse is prone to rupture on feeding a high-fat diet for periods as short as 8 weeks,4 but even in this setting of exaggerated hypercholesterolemia, the aortic sinus and coronary tree do not appear to be susceptible to plaque rupture. Scavenger receptor class B type I (SR-BI) is a scavenger-type receptor expressed by many tissues and accepted by consensus to represent the type I (SR-BI) is a scavenger-type receptor expressed by the macrophage may regulate cholesterol homeostasis in arterial foam cells. Although apoE and SR-BI play crucial roles in lipoprotein metabolism and have been demonstrated to have an impact on atherosclerosis through their expression by macrophages in the artery wall, it would have been difficult to theorize more than a loose connection between these 2 proteins until the discovery that their combined interaction could produce significant effects.
it is perhaps not surprising that the low level of apoE produced by the hypomorphic mice on chow was sufficient to correct the abnormal lipoprotein profile of SR-BI/apoE double-KO mice to resemble the profile typical of SR-BI+/− mice. Why then does the liver produce so much apoE if <5% of the amount produced is adequate to normalize the plasma lipoprotein profile? Interestingly, Zhang et al demonstrate that under the stress of a high-fat–high-cholesterol diet, the small amount of apoE is not adequate to prevent the accumulation of very-low-density lipoprotein–size lipoproteins of abnormal conformation and enriched in unesterified cholesterol, similar to those seen in the plasma of SR-BI/apoE double-KO mice fed a chow diet. These results suggest that hepatic apoE becomes limiting in the face of a dietary fat challenge, perhaps because of the role of hepatic apoE in the secretion-capture of dietary remnant lipoproteins.11 Recently, we reported studies in the hypomorphic apoE mice (with normal SR-BI expression) demonstrating that hepatocyte apoE is more efficient than extrahepatic apoE in promoting clearance of remnant lipoproteins.12 We have previously demonstrated a critical role for hepatic expression of apoE in the clearance of remnant lipoproteins when the low-density lipoprotein receptor (LDLR) is absent.13 Macrophage apoE introduced by bone marrow transplantation is not able to promote lipoprotein clearance in apoE/LDLR double-KO mice.14 The LDLR and low-density lipoprotein receptor–related protein (LRP) have long been implicated in remnant lipoprotein clearance,15–18 and recent studies have suggested a role for SR-BI in remnant lipoprotein clearance.19,20 The physiological relevance of SR-BI as a remnant receptor remains unclear, however, given the fact that mice deficient for SR-BI do not significantly accumulate remnant lipoproteins.21 Because SR-BI has been proposed to participate in remnant lipoprotein clearance,19,20 it would be important to determine whether extrahepatic apoE is adequate to promote remnant lipoprotein clearance in the apoE/SR-BI double-KO mice.

Zhang et al4 suggest that the accumulation of the abnormal unesterified cholesterol–rich very-low-density lipoprotein–size lipoproteins in response to the high-fat–high-cholesterol diet probably contributes to the rapid development of occlusive coronary atherosclerosis in the hypomorphic mice. Although this suggestion seems plausible, it is not clear why this pattern of dyslipidemia is so toxic. When we look into the details of the dyslipidemia, it appears obvious that a more severe hypercholesterolemia with accumulation of similar absolute amounts of unesterified cholesterol in the fat-fed apoE-deficient mouse does not produce any clinical consequences for the heart or lifespan. Perhaps there is a “double whammy” on lipoprotein metabolism in the SR-BI/apoE double-KO mice because apoE and SR-BI play crucial roles in the metabolism of both remnant lipoproteins and HDL cholesterol. The lack of both apoE and SR-BI may essentially shut down reverse cholesterol transport, leading to rapid accumulation of cholesterol in the artery wall. Because fat feeding results in an overall increase in plasma apoE levels in the hypomorphic model (Karl H. Weisgraber, PhD, oral communication, March, 2005), it is plausible that the cause of aggressive coronary atherogenesis in this model is not linked to systemic apoE availability but rather to the lack of local SR-BI and apoE production in the vessel wall. This would implicate a structural and/or functional connection between these 2 proteins in cells of the atheroma. An obvious choice is the macrophage, considering that in the hypomorphic model there is little apoE made by this cell type.

In addition to the apparently toxic dyslipidemia, it is likely that the macrophage deficiency of both apoE and SR-BI also contributes significantly to the dramatically accelerated occlusive coronary atherosclerosis. Macrophage expression of apoE22 and SR-BI23 both have been implicated in promoting cholesterol efflux. In macrophages expressing apoE, however, increased expression of SR-BI has been reported to reduce expression of apoE and cholesterol efflux,24 suggesting a connection between these 2 pathways. Furthermore, the deficiency of macrophage apoE has been shown to increase atherosclerosis in a number of murine models.14,25–28 Similarly, macrophage SR-BI deficiency promotes atherosclerosis in LDLR−/− and apoE−/− mice.27,28 It seems unlikely that the low levels of apoE expressed by macrophages in the hypomorphic mice12 would be adequate to fulfill the normal role played by this protein in macrophage cholesterol efflux. In this scenario, the SR-BI-deficient hypomorphic mouse would not have coronary atherosclerosis on a chow diet because there is no plaque without dyslipidemia, whereas the development of malignant coronary disease on fat feeding would be the result of the inability of vascular macrophages to deal with the increased lipid burden.

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References


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