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. 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. 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, 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 other cells, by the hepatocyte and the macrophage. ApoE is an efficient ligand for receptor-mediated lipoprotein removal by the liver, but it is also a strong acceptor of cellular cholesterol. As such, it may control the rate of foam cell formation in the vessel wall. Similarly, SR-BI channels cholesterol in and out of the cell, and its abundant expression 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 deficiency induces malignant lesion formation, with coronary involvement progressing to complete luminal occlusion, myocardial ischemia, and early demise.

The apoE/SR-BI double-knockout (KO) model represents a significant advance in terms of reproducing the lethal cardiovascular consequences of human atherosclerosis, but the rapid lethality of the model also presents a potential limitation. To address this limitation, Krieger and colleagues have found intriguing approaches to prolong the life of apoE/SR-BI double-KO mice. The first was the use of probucol, a lipid-lowering agent with antioxidant properties. Now in an article in this issue of Circulation, they report that SR-BI-deficient mice with hepatic apoE expression reduced to <5% of normal (hypomorphic mice) have no evidence of severe coronary atherosclerosis unless they are challenged with a high-fat diet. Because the hypomorphic mice have near-normal cholesterol concentrations in plasma, it can be hypothesized that the presence of dyslipidemia is a mandatory component of the aggressive vascular degeneration seen in apoE/SR-BI double-KO mice. The authors placed the hypomorphic mice on a high-fat diet, with the intent to overwhelm the cholesterol-clearing ability of the low amounts of apoE produced by the liver. As a result, plasma cholesterol concentrations quickly reached 1500 mg/dL, with the accumulation of large amounts of unesterified cholesterol; the mice developed a phenotype similar to that seen in the apoE/SR-BI double-KO model, with coronary atherosclerosis, myocardial ischemia, and early mortality. Of importance was the fact that age did not appear to play a role in the susceptibility of the animal to coronary disease development and to early death because the initiation of the atherogenic diet at different ages (25, 60, or 172 days) resulted in a remarkably consistent induction of death in an average of ≈31 days. In addition to representing an interesting experimental model of coronary heart disease, the SR-BI/apoE double-KO mice and the high-fat diet fed hypomorphic mice highlight a number of important questions about the roles of apoE and SR-BI in lipoprotein metabolism and macrophage cholesterol homeostasis that remain to be answered.

The mechanism for hepatic clearance of dietary remnant lipoproteins involves the complex interplay of apoE, lipoprotein receptors, and heparin sulfate proteoglycans. The vast majority of apoE in plasma is derived from the liver, yet we previously reported that the small amount of apoE produced by macrophages is adequate to correct dyslipidemia and prevent atherosclerosis in apoE-deficient mice. Therefore,
apoE is more efficient than extrahepatic apoE in promoting normal SR-BI expression) demonstrating that hepatocyte apoE is more efficient than extrahepatic apoE in promoting clearance of remnant lipoproteins.14 The LDLR and low-density lipoprotein receptor–related protein (LRP) have long been implicated in remnant lipoprotein receptor class B type I–deficient, hypomorphic apolipoprotein ER61 knockin mouse.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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