Editorial

An A+ for Macrophages in Reducing Atherosclerosis?

Jonathan D. Smith

Epidemiological studies within developed populations have demonstrated that high levels of HDL cholesterol are associated with decreased risk of atherosclerotic cardiovascular disease, although the precise mechanism for this protective effect is not completely understood. Apolipoprotein (apo) A1 is the major protein constituent of HDL, and high-level hepatic production of human apoAI in transgenic mice leads not only to increased HDL cholesterol levels and a human-like polydisperse HDL profile, but also to a reduction of atherosclerosis in these mice, which is induced by feeding a high-cholesterol cholic acid–containing diet.1–3 Furthermore, breeding these apoAI transgenics onto the apoE-deficient background also substantially reduces spontaneous atherosclerosis in mice fed a low-fat chow diet.4,5 Similarly, recombinant adenovirus–mediated expression of apoAI also decreases lesion progression in apoE-deficient mice and has been found to lead to lesion regression in LDL receptor–deficient mice.6,7 Since the earliest cellular lesion of atherosclerosis consists of cholesterol-loaded macrophage–derived foam cells, much attention has been paid to the role of macrophages, and to macrophage cholesterol metabolism, in atherogenesis. A seminal role for macrophages in atherogenesis has been demonstrated by the marked reduction of atherosclerosis in several mouse models with disruptions of macrophage cytokines, chemokines, or their receptors,8–10 and of adhesion molecules responsible for macrophage binding to and across the arterial endothelium.11,12 Macrophages synthesize and secrete apoE, which can act as a cholesterol acceptor to remove cholesterol from cholesterol-loaded cells through the activity of the ABCA1 transporter.13–16

A macrophage-specific deficiency of apoE can be created in mice with the use of bone marrow transplantation, a method whose use in the study of murine atherosclerosis was pioneered in the laboratory of Sergio Fazio, MD, PhD, and MacRae Linton, MD (Vanderbilt University). Three labs have used this method to assess the role of macrophage apoE in diet-induced atherosclerosis. This can only be done in one direction, namely implantation of wild-type or apoE-deficient marrow cells into apoE-deficient bone marrow–irradiated hosts, which are then subjected to an atherogenic diet. Transplantation in the other direction, implantation of wild-type or apoE-deficient marrow into apoE-deficient hosts cannot be used to independently determine the effect of macrophage apoE expression on atherosclerosis, as wild-type bone marrow transplantation into apoE-deficient hosts leads to a sufficient amount of plasma apoE to alleviate the hypercholesterolemia, which is required for atherogenesis.17 Transplantation of wild-type or apoE-deficient bone marrow into wild-type irradiated hosts has no appreciable effect on the plasma lipoprotein profile, and two of the three labs that have performed this study have found increased lesion areas in the mice transplanted with apoE-deficient marrow.18–20 The increase in lesion area has been correlated with decreased cholesterol efflux from apoE-deficient macrophages,20 supporting the notion that apoE produced locally by macrophages leads to reduced lesion development via increased cholesterol efflux.

Reduced lesion development in mice that have an improved ability to get rid of macrophage cholesterol has been demonstrated once again in an article in this issue of the Journal from Fazio, Linton, and colleagues (Major et al21). In this study, transgenic mice were created in which human apoAI protein is found in the plasma of these mice associated with HDL, albeit at levels about 5000-fold lower than those found in human plasma and having no effect on the total plasma or HDL cholesterol levels. In the first bone marrow transplantation reported in this article, marrow cells from wild-type or macrophage specific apoAI transgenic were transplanted into apoAI-deficient hosts. After the mice were fed an atherogenic diet for 16 weeks, there was a nonsignificant 25% reduction in lesion area in the mice receiving the macrophage apoAI transgenic marrow cells. The authors surmised that macrophage apoE might be obscuring the effect of the macrophage apoAI, so they bred the macrophage apoAI transgenic onto the apoE deficient background. In the second bone marrow transplantation reported in this article, marrow cells from apoE-deficient, apoE-deficient/macrophage apoAI transgenic, and wild-type mice were transplanted into apoAI-deficient hosts. After the mice were fed an atherogenic diet for only 12 weeks, lesions in the aortic root were barely apparent in the mice that received the wild-type marrow (mean lesion area=200 μm², n=7). As previously observed, the lesions in the mice that received the apoE-deficient marrow were larger (mean lesion area=1100 μm², n=4). The lesions in the mice that received the apoE-deficient/macrophage apoAI transgenic marrow were smaller than those that received the apoE-deficient marrow (mean lesion area<100 μm², n=6). This is good preliminary data to support the hypothesis that macrophage apoAI expression in the absence of both systemic apoAI expression and macrophage apoE expression is antiatherogenic. However, further evidence is needed to strengthen this finding. This study was performed on a very small number of mice (only 4 were used as apoE-deficient marrow recipients), and only at

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one very early time point when lesions were just beginning to form. One wonders whether this effect would persist in larger fatty streak or fibroproliferative lesions, or if it is confined to this very early stage. Another issue not addressed by these studies is the whether systemic apoAI-deficiency is required to observe the antiatherogenic effect of macrophage apoAI expression. This could be addressed directly, without bone marrow transplantation, by comparing atherosclerosis in apoE-deficient and apoE-deficient/macrophase apoAI transgenic mice. Furthermore, could macrophase apoAI expression have an effect on preexisting lesions? This could be tested by transplanting macrophase apoAI transgenic or control bone marrow into atherosclerotic recipient mice such as wild-type mice that had been fed the atherogenic diet for several months or adult apoE-deficient mice on a chow diet.

Major et al. then examined cholesterol efflux in the absence of exogenous acceptors from AcLDL-loaded cultured peritoneal macrophages derived from apoE-deficient, apoE-deficient/macrophase apoAI transgenic, and wild-type mice. Efflux was mildly but significantly increased from the macrophages derived from the apoE-deficient/macrophase apoAI transgenic mice compared with those derived from the apoE-deficient mice, but was less than what was observed from macrophages from wild-type mice. This result supports the hypothesis that macrophase-produced apoAI can play an autocrine or paracrine role locally in the arterial wall giving rise to increased cholesterol efflux, and thus promoting reverse cholesterol transport from foam cells to nascent HDL, which can eventually be taken up by the liver.

Thus, the study by Major et al. provides further, yet preliminary, support that increasing macrophase cholesterol efflux in vivo, in the context of a hypercholesterolemic atherogenic lipoprotein profile, can lead to decreased foam cell deposition in the arterial wall. Therefore, the macrophase continues to be a prime target for therapeutic intervention to prevent or reverse atherosclerosis lesion progression. Increasing expression of endogenous macrophase apoE, adding exogenous apoAI expression to macrophages, or increasing macrophase cholesterol efflux to these acceptors by upregulating macrophase ABCA1, all appear to be sound strategies to promote reverse cholesterol transport and inhibit atherosclerosis.

References

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