Lack of ApoA-I Is Not Associated With Increased Susceptibility to Atherosclerosis in Mice

Hao Li, Robert L. Reddick, Nobuyo Maeda

The consequences of the lack of apolipoprotein A-I (apoA-I) were evaluated in mice made to lack apoA-I by gene targeting. Inbred strain 129 mice homozygous for the inactive Apoa1 gene and maintained on regular mouse chow had markedly reduced total cholesterol (26% normal) and high-density lipoprotein (HDL) cholesterol (25% normal) levels in their plasma. Their plasma lipoproteins lacked apoA-I and were reduced in all other apolipoproteins but apoE. ApoE comprises about one third of the protein of HDL particles in homozygotes, whereas it is present in only trace amounts in normal HDL. Despite the reduction of HDL cholesterol, no atherosclerotic lesions were observed in any of the homozygous mice evaluated (up to 15 months of age). After being maintained on an atherogenic diet for 4 weeks, total plasma cholesterol of the homozygous mutants increased by 20 mg/dL, while that of normals increased by 60 mg/dL. Mice with mixed 129 and C57BL/6J genetic backgrounds were fed the atherogenic diet for 20 weeks. A small number of foam cells were found attached to the aortic surface in some of the animals, but the extent and occurrence of these depositions were not related to the apoA-I genotype. Our results demonstrate that a lack of apoA-I does not by itself cause atherosclerosis in mice. (Arterioscler Thromb. 1993;13:1814-1821.)

KEY WORDS • gene targeting • HDL deficiency • inbred mice • atherosclerosis • atherogenic diet • apoA-I • apoE

Apolipoprotein A-I (apoA-I)* is the major protein component of high-density lipoprotein (HDL) particles and plays a crucial role in lipid transport and metabolism. In vivo, apoA-I activates lecithin: cholesterol acyltransferase and promotes cholesterol efflux from peripheral tissues.1 Several epidemiological studies have reported that in humans, the plasma HDL cholesterol (HDL-C) concentration and the plasma level of apoA-I are inversely related to the incidence and severity of coronary artery diseases.2,3 Clinically, decreased concentrations of HDL and apoA-I are associated with increased risk,4 and the majority of patients with severe HDL and apoA-I deficiencies suffer from premature atherosclerosis.5,6 These patients include those who carry mutations in the APOA1 gene that result in the failure of apoA-I synthesis. The first case, apoA-I/apoC-III deficiency, is caused by a DNA inversion with breakpoints in the fourth exon of the APOA1 gene and the first intron of the APOC3 gene, resulting in reciprocal fusion genes that do not produce any correct apoA-I or apoC-III mRNA.7 The second case is caused by a deletion of the whole APOA1/C3/A4 region from the genome.8 The third case is a nonsense mutation resulting from a single nucleotide insertion.9

The protective effects of HDL and apoA-I against atherosclerosis have been demonstrated experimentally in vivo by Badimon et al10 and She et al.11 Injection of HDL or apoA-I into rabbits fed a high-cholesterol diet not only reduced the total area and thickness of aortic fatty streak lesions but also induced the regression of preexisting aortic fatty streak lesions.10 Experiments with transgenic mice have also shown that overproduction of human apoA-I has a protective effect against atherosclerosis induced by a high-fat diet.12

The negative correlation between plasma HDL concentrations and atherosclerosis is not, however, observed in all disorders involving reduced HDL and apoA-I. There are reports of mutations in the APOA1 gene that cause severe reductions in HDL-C concentrations in plasma but that do not appear to increase coronary risk.13,14 A patient deficient in apoA-I synthesis resulting from a homozygous nonsense mutation at the codon for residue 84 of apoA-I had only moderately severe atherosclerosis,13 and an HDL-deficient patient whose condition resulted from a frameshift mutation in the APOA1 gene15 had no atherosclerosis. In animal models, Poernama et al16 have reported that mutant chickens having <10% of normal HDL-C and apoA-I concentrations are no more susceptible to diet-induced or spontaneous atherosclerosis than are normal chickens.

*The recommended notation for the human apoA-I gene is APOA1, for the mouse gene is Apoa1, and for their products is apoA-I.
To clarify the role of apoA-I and HDL in lipoprotein metabolism and their antiatherogenic properties, we have produced mice lacking apoA-I by using gene targeting in embryonic stem cells. To avoid other genetic factors that might have complicated the interpretation of our data, most of our studies compared mutant animals of an inbred 129 genetic background with their normal litter mates. These animals are genetically identical except for their ApoAI genes. We show in this article that homozygous mutants have markedly reduced total plasma cholesterol and HDL-C levels and that their plasma lipoprotein and apolipoprotein profile response to a high-fat/high-cholesterol diet is different from normal mice. Our results show that the HDL particles of the mutant mice contain no apoA-I but have higher amounts of apoE and apoA-IV than are present in HDL from normal mice. Evaluation of aortic segments from the mutants for the presence of atherosclerotic lesions shows that the lack of apoA-I alone does not cause development of atherosclerotic lesions in mice.

Methods

Animals

The mice used in this work had either the inbred strain 129 genetic background or various combinations between strains 129 and C57BL/6J. The embryonic stem cells used for introducing the modification into the ApoAI gene were derived from a mouse of strain C57BL/6J. For assessment of atherosclerosis, we used one embryonic stem cell that was unique for each particular animal; we refer to these animals as B6/129. Most of the B6/129 animals used in this work had either the inbred 129 or the C57BL/6J genetic background or various combinations between them.

Diet

The regular control diet was mouse chow, which contained 4.5% fat and 0.02% cholesterol (Prolab Formula 3000). The atherogenic diet contained 15.8% fat, primarily from cocoa butter, 1.25% cholesterol, and 0.5% sodium cholate and had a polyunsaturated/saturated fat ratio of 0.7 (TD88051; Teklad, Madison, Wis). The atherogenic diet was fed to groups of four to eight male and four to six female B6/129 mice and two to three strain 129 mice of each apoA-I genotype. Blood samples were collected from 8-week-old animals just before they were placed on the atherogenic diet and at every 2 or 4 weeks thereafter for up to 20 weeks.

Plasma Lipid and Lipoprotein Determinations

Blood from anesthetized animals that had been fasted for approximately 18 hours was collected into tubes containing anticoagulant and antimicrobial agents. Plasma was prepared by centrifugation of the whole blood for 15 minutes at 12 000 rpm at 4°C and was stored at 4°C for analysis within 1 week. Total plasma cholesterol and triglycerides were determined enzymatically (Sigma, St Louis, Mo). HDL-C was measured after selective precipitation of apoB-containing lipoproteins with polyethylene glycol. Esterified cholesterol was determined enzymatically without cholesterol ester hydrolase in the reaction. Protein concentrations were determined by the method of Lowry et al.

Lipoproteins were isolated by density gradient ultracentrifugation at 38 000 rpm at 20°C for 20 hours. Lipoprotein fractions were concentrated and desalted using Centricon 10 filters (Amicon, Beverly, Mass). Plasma lipoproteins were also fractionated by gel-filtration chromatography on Superose 6.

Apolipoprotein Analyses

Either individual lipoprotein fractions containing 20 µg protein or the total lipoprotein fraction isolated from 50 µl of plasma was denatured and separated in slab gels containing 0.1% sodium dodecyl sulfate (SDS) and 3% to 20% linear gradients of polyacrylamide. Electrophoresis was performed at room temperature in a Protean II system (Bio-Rad Laboratories, Richmond, Calif) at a constant voltage of 150 V for 6 hours. Gels were stained in 50% methanol and 10% acetic acid with 0.1% Coomassie Brilliant Blue R-250 and destained with 10% acetic acid. Protein compositions were estimated by planimetry after computer imaging of the stained gels (gel analysis system, National Institutes of Health). ApoA-I in plasma was identified by Western blot analysis with rabbit anti-mouse apoA-I antiserum kindly provided by Dr J. Lusis at the University of California, Los Angeles.

Statistical Analysis

The Student's t test of unpaired observations was used to determine statistical significance.

Histological Methods

The animals were killed with an overdose of tribromoethanol (Avertin) after an overnight fast. Portions of the liver, intestines, and spleen were quickly frozen in liquid nitrogen and stored at −70°C. Necropsy observations of the heart, liver, kidney, intestines, stomach, gallbladder, and subcutaneous tissues were recorded. The heart and aorta were perfused with 4% paraformaldehyde in 0.12 mol/L phosphate buffer, pH 7.4. For histological evaluation, sections of the aorta and other tissues were processed according to the method described by Zhang et al. At least 20 sections, beginning with the ascending aorta and proceeding through the entire aortic sinus to the ventricular chamber, were evaluated. Sizes of lesions were scored in four to five evenly spaced sections by using the scanning program IMAGE-PROII (Media Cybernetics).
Results

Plasma Lipid Levels of Mice on the Normal Diet

Plasma lipid levels in strain 129 mice with and without the disrupted apoA-I gene are summarized in Table 1. A highly significant reduction of total plasma cholesterol was observed in the homozygous mutants; their levels are approximately one third of normal. HDL-C and triglyceride levels were also decreased in homozygotes to about one fourth and one half of normal levels, respectively. About 60% of total cholesterol in normal mice is cholesterol ester, while in the homozygous mutants the fraction of cholesterol ester is reduced to 38%. The various plasma lipid levels in heterozygous mutants are close to midway between the values for the normals and homozygotes. Plasma lipid levels did not change significantly with age, sex, or body weight (data not shown).

Plasma Lipid Levels of Mice on the Atherogenic Diet

Two normal, three heterozygous, and three mutant homozygous mice with the strain 129 genetic background were fed a high-fat/high-cholesterol diet. After 4 weeks of the atherogenic diet, plasma cholesterol levels in normal mice, heterozygous mutants, and homozygous mutants increased by about 60, 50, and 20 mg/dL, respectively. The plasma lipid levels in heterozygous mutants remained at the origin after agarose gel electrophoresis. Only a small amount of cholesterol ester was observed in the homozygous mutants, while in the normals and homozygotes plasma lipid levels did not change significantly with age, sex, or body weight (data not shown).

When fed for longer than about 8 weeks, the atherogenic diet appeared to be toxic in our strain 129 mice regardless of their apoA-I genotype. Thus, after 10 weeks of the atherogenic diet, the plasma lipid levels increased continuously in all mice to the extent that some animals had a total plasma cholesterol level >1000 mg/dL. The HDL-C levels in the mice did not increase. Major lipoproteins in the plasma of these mice remained at the origin after agarose gel electrophoresis (data not shown), indicating the accumulation of chylomicrons. Because the mice with high plasma cholesterol levels began to die after 10 weeks on this diet, the remaining mice were killed between 10 to 12 weeks. Autopsy showed that all animals had severely fatty livers.

The unexpected toxicity of the atherogenic diet was not seen in B6/129 animals having a mixed genetic background. These mice tolerated the atherogenic diet without obvious distress. Their plasma cholesterol levels increased only during the first 4 weeks on the diet, and at that time they were essentially the same as in the strain 129 mice. Thereafter, the levels in the B6/129 animals stayed steady for as long as 20 weeks while the levels in the strain 129 mice began to increase continuously. Both female and male B6/129 mice responded to the atherogenic diet similarly.

Plasma Lipoprotein Profiles

We pooled plasma samples from several mice of each apoA-I genotype and applied equal volumes to a Superose 6 column to fractionate the lipoproteins by their size (Fig 1). In normal and heterozygous mice fed regular chow, the major lipoprotein eluted in the region corresponding to HDL. Only a small amount of cholesterol was found in the regions corresponding to very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL). Homozygous mutants had a reduced amount of cholesterol in the HDL fraction, which eluted slightly earlier than the major HDL particles in normal plasma.

A 4-week atherogenic diet resulted in an increase in the lipoprotein fractions eluting in the IDL and LDL region, with more of an increase in the LDL than the VLDL region. In the homozygous mutants, the peaks of the major lipoproteins shifted toward the LDL fraction.

Apolipoprotein Compositions

To characterize their apolipoprotein compositions, total plasma lipoproteins were isolated from an equal amount of plasma from normal mice and heterozygous and homozygous mutant mice fed regular chow and were then subjected to SDS-polyacrylamide gel electrophoresis. The relative amounts of apolipoproteins were
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Mice Lacking ApoA-I 1817

"5
6
100
28
Elution Volume (ml)

Fig 1. Fractionation of plasma lipoproteins by Superose 6 column chromatography. Aliquots (200 µL) of pooled plasma from (A) normal mice, (B) heterozygous mutants, and (C) homozygous mutants were applied to Superose 6 columns (1 × 50 cm). Fractions (420 µL) were collected at 230 µL/min and 100 µL of each fraction was used to measure cholesterol content. Open circles indicate plasma from animals fed regular chow, and filled circles indicate that from animals fed an atherogenic diet. Areas where various lipoprotein particles in humans normally elute are indicated by brackets. OD 500 indicates optical density at 500 nm; VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

Table 3 summarizes the apolipoprotein compositions of HDL particles in strain 129 mice fed regular chow and the atherogenic diet. On the regular diet, the HDL particles of the mutant mice were composed of 34% apoE, 31% apoA-II, 25% apoC-III, 10% apoA-IV, and 0% apoA-I. These compositions were markedly different from those seen in normal mice, in which about 70% of the apolipoprotein was apoA-I, with apoE and apoA-IV being present in only trace amounts. In the HDL of normal mice maintained on the atherogenic diet, apoE increased to 25% of the total apolipoproteins and to 42% in the HDL of homozygotes. No significant changes in the amounts of other proteins were observed in response to the atherogenic diet.

In animals of mixed B6/129 genetic background, the apoE content was also high (26% of the total proteins) in the HDL of the homozygous mutants (Table 3). However, in B6/129 mice unlike the strain 129 mice, the apoE content remained the same after consumption of

As expected, apoA-I protein was absent in the plasma of homozygotes; this finding was confirmed by Western blot analysis (not shown). There was a 25% reduction in total apoA-I in heterozygotes compared with normal animals.

An unexpected finding was that the level of apoE in the mutant homozygotes was about twofold higher than in normal and heterozygous mice. The amounts of all other major apolipoproteins were reduced in the homozygous mutants compared with normal mice. The increase of apoE in homozygotes occurred in the HDL particles, as illustrated in Fig 3. The HDL particles of the homozygous mutants fed regular chow contained substantial amounts of apoE (lane 5), while HDL particles in heterozygotes had only a trace (lane 3) and those from normal animals had undetectable amounts (lane 1) of apoE. The amount of apoE in HDL increased significantly in response to the atherogenic diet in all mice, regardless of their genotype (lanes 2, 4, and 6).
A-I-Deficient Mice

TABLE 3. Apolipoprotein Composition of High-Density Lipoprotein Particles in Apolipoprotein A-I-Deficient Mice

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Regular Chow</th>
<th>Atherogenic Diet</th>
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<td></td>
<td>+/+</td>
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<tr>
<td>ApoA-IV</td>
<td>t</td>
<td>5</td>
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<tr>
<td>ApoE</td>
<td>t</td>
<td>4</td>
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<tr>
<td>ApoA-I</td>
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<tr>
<td>ApoA-II</td>
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<td>16</td>
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<tr>
<td>ApoC</td>
<td>15</td>
<td>25</td>
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Strain B6/129

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<tr>
<th>Apolipoprotein</th>
<th>Regular Chow</th>
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<tr>
<td>ApoC</td>
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+/+ indicates high-density lipoprotein (HDL) from normal animals; –/+; HDL from homozygous mutants; +/–, HDL from homozygous mutants; Apo, apolipoprotein; and t, trace amount. Values given are percents.

Morphological Findings

In evaluating the development of atherosclerotic lesions in the aortas of the mutant mice, two factors led us to use mutant mice with the mixed B6/129 genetic background. First, strain 129 mice have smaller litters and are more susceptible to infections than B6/129, so it is difficult to obtain a large number of older strain 129 mice. Second, C57BL/6J mice are more susceptible than strain 129 mice to diet-induced atherosclerosis,25 so any effects of the lack of apoA-I on atherogenesis are likely to be enhanced in mice with the B6/129 genetic background compared with those with the strictly inbred 129 background.

No atherosclerotic lesions were observed in B6/129 mice maintained on regular chow that were homozygous mutants lacking apoA-I (n=14), heterozygotes (n=10), or normal animals (n=8). These mice were older than 8 months of age, and the oldest mice that we evaluated were four homozygotes and five heterozygotes of 15 months' age. No gross or histopathological differences from normal animals were found in other tissues of mutant animals, such as the liver, spleen, kidney, and lung.

Preatherosclerotic lesions, defined as small, intimal, foam-cell deposits, were present in some of the mice fed the atherogenic diet for 12 to 32 weeks. These lesions were limited to small numbers of foam cells usually near

the atherogenic diet. Another difference between mouse strains was seen in the amounts of apoA-IV. The amount of apoA-IV in the HDL of B6/129 homozygous mutants increased from 24% of total apolipoproteins when on the normal diet to 44% on the atherogenic diet. In contrast, there were only trace amounts of apoA-IV in the HDL from the inbred strain 129 normal homozygous mutants.

The amount of cholesterol in the tissues, and on catabolism. The low plasma cholesterol level in mutant mice is not likely to be caused by low cholesterol synthesis, judging from our preliminary data, which indicate that the 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in the liver of these mice is not influenced by the apoA-I genotype (J.F. Goodrum, H. Li, and N. Maeda, unpublished observations). An increased fractional catabolic rate of VLDL apoB has been demonstrated in human patients with apoA-I/C-III deficiency,26 and it is possible that a similar increase in cholesterol catabolism contributes to the low plasma cholesterol levels in the homozygous mutants.

Triglyceride levels in the plasma of the mutants were also reduced compared with the normal animals. This contradicts the situation in comparable human patients. Thus, in general, humans with HDL deficiencies have elevated levels of triglyceride, except when the HDL deficiencies are accompanied by apoC-III deficiencies. It has been suggested that the decreased triglyceride levels in these cases may be a consequence of the lack of apoC-III, which acts as an inhibitor of lipoprotein lipase.6 Our mutants have about half as much apoC associated with plasma lipoproteins as do normal animals, but whether this reduction alters lipoprotein

Discussion

In contrast to human plasma lipoproteins in which the most abundant class is LDL, the predominant class of mouse plasma lipoprotein is HDL. Thus, although the mouse low-density fractions contain a high percentage of cholesterol, mouse HDL appears to be the quantitatively major carrier of cholesterol because of its high plasma concentration. We have shown in this study that mice lacking apoA-I have a marked reduction in total plasma cholesterol compared with their normal littermates and that most of the reduction is in the HDL-C fraction. Cholesterol carried by apoB-containing particles in the homozygous animals is not increased compared with normal mice.

Total plasma cholesterol levels are dependent on the absorption of cholesterol in the intestine, on the synthesis of cholesterol in the tissues, and on catabolism. The low plasma cholesterol level in mutant mice is not likely to be caused by low cholesterol synthesis, judging from our preliminary data, which indicate that the 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in the liver of these mice is not influenced by the apoA-I genotype (J.F. Goodrum, H. Li, and N. Maeda, unpublished observations). An increased fractional catabolic rate of VLDL apoB has been demonstrated in human patients with apoA-I/C-III deficiency,26 and it is possible that a similar increase in cholesterol catabolism contributes to the low plasma cholesterol levels in the homozygous mutants.
We found that the plasma cholesterol levels in the mice lacking apoA-I responded to the atherogenic diet to a lesser extent than normal animals. While cholesterol levels in normal mice increased by almost 60 mg/dL, mostly in VLDL, IDL, and LDL fractions, these levels in mice lacking apoA-I increased by only ~20 mg/dL. One possible explanation for the lesser increase in larger-size lipoproteins in the mutants fed the atherogenic diet is that mice lacking apoA-I could have poorer intestinal absorption of fat compared with normal mice. Support for the possible involvement of apoA-I in the intestinal absorption of fat comes from the observation that some humans with apoA-I deficiency also have a deficiency of plasma vitamin E and linoleic acid.27

The HDL particles in mutants completely lack apoA-I. Surprisingly, the fraction of apoE associated with plasma lipoproteins was considerably increased in the mutants. Normally, apoA-I is more than 70% of the protein component of HDL, while the apoC, apoA-II, apoA-IV, and apoE are minor components. We find that in the absence of apoA-I, the homozygous mutants have HDL particles that contain apoA-IV and apoE as the major protein constituents. Elevation of these two proteins in plasma lipoproteins has not been described in humans with HDL deficiencies.

The overall effects of a lack of apoA-I on plasma lipid and lipoprotein profiles were essentially the same in inbred strain 129 mice and B6/129 mice. We did, however, observe some differences in the response to the atherogenic diet of the strain 129 and B6/129 animals, but these differences between strains were unrelated to the apoA-I genotypes. The HDL-C levels in normal and heterozygous strain 129 mice did not change before and after the atherogenic diet, while in B6/129 mice the HDL-C levels were reduced by half (data not shown). This observation is consistent with similar findings reported by Ishida et al.28 who have found that various inbred strains of mice respond differently in their HDL-C levels to a high-fat/high-cholesterol diet.

We also observed differences between strains in the apolipoprotein composition of HDL in response to the atherogenic diet. The HDL particles of the homozygous 129 mice have more apoE and less apoA-IV protein than do the HDL particles in B6/129 mice. This difference is present in the plasma of animals fed regular chow but becomes far more apparent in the plasma of mice fed the atherogenic diet (Table 3). Thus, the major apolipoprotein of HDL in the 129 genetic background mutants fed the atherogenic diet is apoE, while the major apolipoprotein of HDL in B6/129 mutants fed the atherogenic diet is apoA-IV.

Because of the close genetic linkage of the Apoa1 and Apoa4 genes, mutants in the 129 and B6/129 genetic backgrounds carry the same Apoa4 gene (derived from the strain 129 genome). Consequently, the difference in the amounts of apoA-IV in the 129 and B6/129 genetic background mutants cannot be explained by (known) structural differences between the Apoa4 genes of 129 and 129/B6 genetic background mutants. We suggest that the differences in the apolipoprotein compositions observed in the HDL particles of strain 129 versus
B6/129 animals may be related to the fact that the apoE content in strain 129 mice increases in response to the atherogenic diet while in B6/129 mice does not. This feature, which is strain dependent and not related to the apoA-I genotype, is of considerable interest in relation to previous work showing that C57BL mice are susceptible to diet-induced atherosclerosis while mice of strain 129 are moderately resistant. A 1.5-fold to twofold increase in the plasma apoE concentration in mice in response to a high-fat diet has previously been reported.20 It is therefore possible that there is a genetic factor or factors that determine the levels of apoE induction in response to the atherogenic diet and thereby affect atherosclerosis susceptibility and HDL levels in mice. Some of the genes affecting HDL levels and atherosclerosis susceptibility have been identified and mapped by Paigen et al.31,32

We expected, as a result of the human clinical-association studies, that the absence of apoA-I would make the mutant animals susceptible to atherosclerosis. However, we found no atherosclerotic lesions in the mice lacking apoA-I after 15 months of a regular chow diet, nor were any lesions found in normal animals or heterozygous mutants. Thus, our results clearly show that a reduction of plasma HDL levels caused by the elimination of apoA-I does not cause spontaneous atherosclerosis in mice. After about 20 weeks on the atherosclerotic diet, we observed small preatherosclerotic lesions near the aortic valve attachment sites in some of the mice. However, the extent and frequency of the lesions were not related to the Apoal locus to the C57BL/6J genetic background, whereas Paigen et al used inbred C57BL/6J mice. We are currently transferring the mutation in the Apoal locus to the C57BL/6J genetic background to further evaluate the effects of genetic background on responses to an atherogenic diet.

In our current study, however, it is important to note that the extent and occurrence of the preatherosclerotic lesions in the animals fed a high-fat diet appear to be unrelated to the Apoal genotype. These results imply that a simple reduction of apoA-I alone does not cause atherosclerosis, even in mice on a high-fat diet. As in some of the Apoal mutations in humans and in the Wisconsin hypo-alpha mutant chicken, our results suggest that the inverse correlation observed in humans between plasma apoA-I concentrations and the risk of coronary heart disease should be reevaluated. The increased risk may not be a direct consequence of a reduction of apoA-I function; rather, it may be that the reduction in apoA-I level and the increased risk both result from some other metabolic disturbance.24 Questions remain as to whether a lack of apoA-I accelerates the development of atherosclerosis when other problems, such as an increase in atherogenic lipoprotein particles, are present at the same time. Some resolution of these different possibilities should be obtained by determining whether the reduction of HDL caused by an apoA-I deficiency will influence the atherogenic process that develops in mice lacking apoE.22,35 Experiments combining these two mutations are currently in progress.

Acknowledgments

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