Macrophage ATP-Binding Cassette Transporter 1 Overexpression Inhibits Atherosclerotic Lesion Progression in Low-Density Lipoprotein Receptor Knockout Mice

Miranda Van Eck, Roshni R. Singaraja, Dan Ye, Reeni B. Hildebrand, Erick R. James, Michael R. Hayden, Theo J.C. Van Berkel

Background—ATP-binding cassette transporter 1 (ABCA1) is a key regulator of cellular cholesterol and phospholipid transport. Previously, we have shown that inactivation of macrophage ABCA1 induces atherosclerosis in low-density lipoprotein receptor knockout (LDLr−/−) mice. Peritoneal macrophages isolated from the ABCA1 → LDLr−/− chimeras exhibited a 60% (P=0.0006) increase in cholesterol efflux to apolipoprotein AI. To induce atherosclerosis, the mice were fed a Western-type diet containing 0.25% cholesterol and 15% fat for 9, 12, and 15 weeks, allowing analysis of effects on initial lesion development as well as advanced lesions. No significant effect of macrophage ABCA1 overexpression was observed on atherosclerotic lesion size after 9 weeks on the Western-type diet (245±36×10^3 μm² in ABCA1 BAC → LDLr−/− mice versus 210±20×10^3 μm² in controls). However, after 12 weeks, the mean atherosclerotic lesion area in ABCA1 BAC → LDLr−/− mice remained only 164±15×10^3 μm² (P=0.0008) compared with 513±56×10^3 μm² in controls (3.1-fold lower). Also, after 15 weeks on the diet, lesions in mice transplanted with ABCA1 overexpressing bone marrow were still 1.6-fold smaller (393±27×10^3 μm² compared with 640±59×10^3 μm² in control transplanted mice; P=0.0015).

Conclusion—ABCA1 upregulation in macrophages inhibits the progression of atherosclerotic lesions. (Arterioscler Thromb Vasc Biol. 2006;26:000-000.)

Key Words: atherosclerosis □ leukocytes □ cholesterol □ transplantation

Atherosclerotic cardiovascular disease is the major cause of morbidity and mortality in Western societies. The genesis and progression of atherosclerotic lesions involves a complicated sequence of events in which various cell types in the arterial wall, including macrophages, play an important role.1 Deposition of excessive amounts of cholesterol in the arterial wall, including macrophages, play an important role.1 Deposition of excessive amounts of cholesterol in the arterial wall, including macrophages, play an important role.1 Deposition of excessive amounts of cholesterol in the arterial wall, including macrophages, play an important role.1 Deposition of excessive amounts of cholesterol in the arterial wall, including macrophages, play an important role.1 Deposition of excessive amounts of cholesterol in the arterial wall, including macrophages, play an important role.1 Deposition of excessive amounts of cholesterol in the arterial wall, including macrophages, play an important role.1 Deposition of excessive amounts of cholesterol in the arterial wall, including macrophages, play an 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Treatment of atherosclerotic lesions. Overexpression of ABCA1 in mice decreases atherosclerosis in apolipoprotein E (apoE) knockout and C57BL/6 mice. We have previously shown bone marrow transplantation to be a useful technique to study the role of macrophage ABCA1 in atherosclerosis. Specific disruption of ABCA1 in macrophages using bone marrow transplantation resulted in an increased susceptibility to atherosclerotic lesion development without altering plasma HDL levels, providing evidence that macrophage ABCA1 plays a critical role in the protection against atherosclerosis, independent of effects on HDL cholesterol. The expression of ABCA1 in macrophages is tightly controlled by intracellular cholesterol levels. Its activity is dramatically increased on cholesterol loading of macrophages and the subsequent transformation into foam cells. Therefore, it is conceivable that cholesterol efflux via ABCA1 is already maximally activated in macrophages in the atherosclerotic lesion. To study the therapeutic potential of upregulation of macrophage ABCA1 to prevent atherosclerosis, we determined atherosclerosis susceptibility of chimeras that specifically overexpress ABCA1 on macrophages, created by transplantation of bone marrow from human ABCA1 overexpressing bacterial artificial chromosome (BAC) transgenic mice into low-density lipoprotein (LDL) receptor knockout (LDLr−/−) mice. The findings from these studies revealed that specific upregulation of macrophage ABCA1 prevents progression of atherosclerosis and thus is an attractive therapeutic target for the prevention of atherosclerotic lesion development.

Methods

Mice

ABCA1 BAC transgenic mice hemizygous for the human ABCA1 gene were described previously. Nontransgenic littermates were used as controls. LDLr−/− mice were obtained from the Jackson Laboratory (Bar Harbor, Me). Mice were maintained on stabilized regular chow containing 4.3% (w/w) fat and no cholesterol (RM3; Special Diet Services) or fed a Western-type diet containing 15% (w/w) fat and 0.25% (w/w) cholesterol (Diet W; Hope Farms). Drinking water was supplied with antibiotics (83 mg/L ciprofloxacin and 67 mg/L polymyxin B sulfate) and 6.5 g/L sucrose. Animal experiments were approved by the ethics committee for animal experiments of Leiden University.

Bone Marrow Transplantation

To induce bone marrow aplasia, male LDLr−/− recipient mice were exposed to a single dose of 9 Gy (0.19 Gy/min, 200 kV, 4 mA) total body irradiation using an Andrex Smart 225 Röntgen source (YX-LON International) with a 6-mm aluminum filter 1 day before the transplantation. Bone marrow was isolated by flushing the femurs and tibias from male ABCA1 BAC or wild-type (WT) littermates. Irradiated recipients received 0.5×107 bone marrow cells by tail vein injection.

Assessment of Chimerism

The hematologic chimerism of the LDLr−/− mice was determined using genomic DNA from bone marrow by polymerase chain reaction (PCR) at 20 weeks after transplant. The forward and reverse primers 5′GGCTGGATTACGATCTCTCA3′ and 5′ATCCCAACTCTAAACCACA3′ for human ABCA1 and 5′TGGAAGCTCTCTTTAT3′ and 5′CCATGTGTTTGTAGACAA3′ for mouse ABCA1 gene were used. Murine and human ABCA1 mRNA expression relative to 18S rRNA in peritoneal macrophages was quantitatively determined on an ABI Prism 7700 Sequence Detection system (Applied Biosystems) using the following primers and probes for human ABCA1: forward, 5′CCTGACGGGTGTTCC3′; reverse, 5′TCCTGGGGATGGTCTC3′; probe, 5′ACATCTGGGAAGAAAGCATCTGCTGTA3′ and for murine ABCA1: forward, 5′TCGAGGCGGTGCCTTC3′; reverse, 5′CGCTCAACTTATCAGAAGGCC3′; probe, 5′CCACACTCTGGCACGCGCTCATCT3′. For analyses of ABCA1 protein expression, 100 to 150 µg of protein was separated on 7.5% polyacrylamide gels and was transferred to polyvinylidene difluoride membranes (Millipore) and probed with ABCA1EP antibody or anti-GAPDH (Chemicon) as a control. Immunolabeling was detected by enhanced chemiluminescence (Amersham Pharmacia Biotech), and protein levels were quantitated using NIH Image software.

Macrophage Cholesterol Efflux Studies

Thioglycollate-elicited peritoneal macrophages were incubated with 0.5 µCi/mL 3H-cholesterol in DMEM/0.2% BSA for 24 hours at 37°C. To determine cholesterol loading, cells were washed 3 times with washing buffer (50 mmol/L Tris containing 0.9% NaCl, 1 mmol/L EDTA, and 5 mmol/L CaCl2, pH 7.4), lysed in 0.1 mol/L NaOH, and the radioactivity was determined by liquid scintillation counting. Cholesterol efflux was studied by incubation of the cells with DMEM/0.2% BSA alone or supplemented with either 10 µg/mL apoAI (Calbiochem) or 50 µg/mL human HDL. Radioactivity in the medium was determined by scintillation counting after 24 hours of incubation.

Serum Lipid Analyses

After an overnight fast, blood was drawn from each mouse by tail bleeding. Total cholesterol, triglycerides, and phospholipids in serum were determined using enzymatic colorimetric assays (Roche Diagnostics). The distribution of lipids over the different lipoproteins was determined by fractionation using a Supersose 6 column (3.2×30 mm; Smart-system; Pharmacia). Total cholesterol, triglyceride, and phospholipid contents in the effluent were determined as above.

Histological Analysis of the Aortic Root

To analyze the effect of macrophage ABCA1 overexpression on atherosclerosis, transplanted mice were euthanized after 9, 12, and 15 weeks on the Western-type diet. The atherosclerotic lesion areas in oil red O-stained cryostat sections of the aortic root were quantified using the Leica image analysis system, consisting of a Leica DMRE microscope coupled to a video camera and Leica Qwin Imaging software (Leica Ltd.). Mean lesion area (in µm2) was calculated from 10 oil red O-stained sections, starting at the appearance of the tricuspid valves. For the assessment of macrophage infiltration, sections were immunolabeled with MOMA-2 (generous gift of Dr. G. Kraal, Vrije Universiteit, Amsterdam, The Netherlands). The amount of collagen in the lesions was determined using Masson’s Trichrome Accustain according to manufacturer instructions (Sigma Diagnostics). TUNEL of lesions was performed using the In Situ Cell Death Detection kit (Roche). TUNEL-positive nuclei were visualized with Nova Red (Vector), and sections were counterstained with 0.3% methylgreen. Sections treated with DNase I (2U per section) served as positive control. All quantifications were done blinded by computer-aided morphometric analysis using the Leica image analysis system.

Statistical Analyses

Statistical analyses were performed using the unpaired Student t test (Instat GraphPad software).

Results

Generation of LDLr−/− Mice Overexpressing Macrophage ABCA1

To assess the therapeutic potential of increasing macrophage ABCA1 to prevent atherosclerotic lesion development, we
used bone marrow transplantation to selectively upregulate ABCA1 in hematopoietic cells. Bone marrow from ABCA1 overexpressing BAC transgenic mice was transplanted into LDLr−/− mice, which represent an established model for the development of atherosclerosis. Genomic DNA isolated from the LDLr−/− mice transplanted with bone marrow from ABCA1 BAC transgenic mice contained both the human and the mouse ABCA1 transcript, whereas the control transplanted group contained only mouse ABCA1, indicating that the bone marrow transfer was successful (Figure 1A). No effect was observed of human ABCA1 overexpression on murine ABCA1 mRNA levels (0.27 ± 0.06 and 0.24 ± 0.03 for human ABCA1 overexpressing macrophages and WT macrophages, respectively). Overexpression of ABCA1 in macrophages resulted in a 2.5-fold increase in ABCA1 protein expression (Figure 1B) and a 60% (n = 3; P = 0.0006) increase in cholesterol efflux to apoA1 (Figure 1C) of ABCA1 in macrophages affected lesion formation. Lesion development was analyzed in the aortic root of WT → LDLr−/− mice and in ABCA1 BAC → LDLr−/− chimeras after 9, 12, and 15 weeks of Western-type diet feeding (Figure 3). After 9 weeks on the Western diet, no significant effect of macrophage ABCA1 overexpression on the atherosclerotic lesion size was observed (245 ± 36 × 10^3 μm^2 in ABCA1 BAC → LDLr−/− mice [n = 11] versus 210 ± 20 × 10^3 μm^2 in controls [n = 11]). Lesions in both groups of mice were primarily composed of macrophage-derived foam cells (94 ± 2.3% and 94 ± 2.1% for WT and ABCA1 transplanted mice, respectively), indicating that macrophage ABCA1 overexpression does not prevent foam cell formation and thus the initiation of atherosclerosis. Between 9 and 12 weeks of

Effect of Macrophage ABCA1 Overexpression on Plasma Lipid Levels

On regular chow diet, the majority of the cholesterol in LDLr−/− mice is transported by LDL and HDL, phospholipids by HDL, and triglycerides by very low–density lipoprotein (VLDL) and LDL (Figure 2). In contrast to the ABCA1 BAC transgenic mice that displayed mildly increased HDL cholesterol levels,20 no significant effect on HDL cholesterol, triglyceride, or phospholipid levels was observed when ABCA1 was overexpressed solely in macrophages.

To induce atherosclerotic lesion development, the transplanted mice were fed Western-type diet starting at 8 weeks after transplantation. On diet feeding, serum cholesterol levels increased ≈3-fold in both groups of mice because of an increase in VLDL and LDL cholesterol (Table 1). The increase in VLDL and LDL cholesterol coincided with an increase in phospholipids. No significant effect of macrophage ABCA1 overexpression on serum lipid levels or lipid distribution among the different lipoproteins was observed (Figure 2).

Figure 1. Verification of success of bone marrow transplantation. A, Verification of successful reconstitution with donor hematopoietic cells by PCR amplification of the human ABCA1 and murine ABCA1 gene at 20 weeks after transplant using genomic DNA isolated from bone marrow. B, Analyses of the effect of ABCA1 overexpression on macrophage ABCA1 protein levels by Western blotting. C, ApoA1 and HDL induced cellular cholesterol efflux from [3H]-cholesterol-labeled peritoneal macrophages isolated from LDLr−/− mice transplanted with either ABCA1 BAC (n = 3) or control (n = 3) bone marrow at 20 weeks after transplant. Statistically significant differences from WT are shown *P < 0.05; **P < 0.01; ***P < 0.001 compared with WT → LDLr−/− mice.

Effect of Macrophage ABCA1 Overexpression on Atherosclerotic Lesion Initiation and Progression

To investigate the therapeutic potential of increasing macrophage ABCA1 expression as a means of preventing atherosclerosis, we assessed whether and to what degree upregulatio
diet feeding, atherosclerosis in the mice transplanted with control bone marrow progressed further in size to 513±56×10^3 μm² (n=14). However, in the ABCA1 BAC → LDLr−/− mice, no time-dependent increase in lesion size was observed. The mean atherosclerotic lesion area was thus 3.1-fold smaller (164±15×10^3 μm²; n=14, P=0.0008) compared with control transplanted animals. Interestingly, at this time point, lesions were still primarily composed of macrophage-derived foam cells (88±3.0% and 91±4.0% for WT and ABCA1 transplanted mice, respectively). Thus, although macrophage ABCA1 overexpression did not inhibit the initiation of foam cell formation, the progression of lesions was markedly inhibited by upregulation of ABCA1 in macrophages. Between 12 and 15 weeks of diet feeding, lesions in control transplanted mice had progressed only slightly in size to 640±59×10^3 μm² (n=9), whereas lesion development in mice transplanted with ABCA1 overexpressing bone marrow had increased to 393±27×10^3 μm² (n=9; P=0.0015). At this time point, the lesion composition was markedly different. The macrophage content of the lesions of mice transplanted with WT bone marrow was 40±4.0%, whereas the collagen content was 15±2.2%. In contrast, mice transplanted with ABCA1 overexpressing bone marrow contained more macrophages and less collagen (53±3.9% [P=0.026] and 8.9±1.1% [P=0.029], respectively), indicative of less advanced lesions. Also, a predominant part of the lesions consisted of acellular necrotic areas. However, the acellular area of the lesions of mice reconstituted with ABCA1 overexpressing bone marrow was 2-fold smaller compared with control transplanted animals (53±17×10^3 μm² in ABCA1 and 108±20×10^3 μm², respectively; P=0.057). Thus, although lesion progression was not completely halted by overexpression of ABCA1 in macrophages, the progression was still largely reduced.

Because ABCA1 has been implicated in the removal of apoptotic cells, the effect of macrophage ABCA1 overexpression on the number of TUNEL-positive cells was determined at the different stages of lesion development (Figure 4). After 9 weeks on Western-type diet, no effect of macrophage ABCA1 overexpression on the absolute number of TUNEL-positive cells in the lesions was observed. However, after 12 and 15 weeks, the number of TUNEL-positive cells was significantly lower in the ABCA1 BAC transplanted animals. In addition, the percentage of apoptotic nuclei to the total number of nuclei was decreased in lesions of mice transplanted with ABCA1 BAC overexpressing bone marrow. However, this effect was also observed at 9 weeks on Western-type diet and was independent of the extent of lesion development.

**Discussion**

Insights into the role of ABCA1 in atherogenesis have been gained from both patients affected with Tangier disease and...
recently developed animal models. Patients with mutations in ABCA1 are significantly at risk for coronary artery disease. The cardioprotective effects of ABCA1 have been confirmed recently in animal models. Overexpression of ABCA1 resulted in decreased susceptibility to spontaneous atherosclerosis in apoE knockout mice and in C57BL/6 mice with diet-induced atherosclerosis. In addition to its expression in macrophages, ABCA1 is also highly expressed by hepatocytes in the liver, where it is important for HDL lipidation. In agreement, the reduction in atherosclerosis susceptibility as a result of ABCA1 overexpression coincided with an increase in HDL cholesterol levels. Using bone marrow transplantation, we have shown that selective inactivation of ABCA1 in macrophages results in markedly increased atherosclerosis in different animal models without affecting HDL cholesterol levels. ABCA1-dependent cholesterol efflux is thus a crucial factor in the prevention of excessive cholesterol accumulation in macrophages of the arterial wall and their transformation into foam cells.

To study the therapeutic potential of upregulation of macrophage ABCA1 to prevent atherosclerosis, we determined atherosclerosis susceptibility of chimeras that specifically overexpress ABCA1 on macrophages, created by transplantation of bone marrow from human ABCA1 BAC transgenic mice into LDLr−/− mice. In this study, we show that overexpression of ABCA1 in macrophages did not influence initial lesion development in LDLr−/− mice. However, specific deletion of macrophage ABCA1 in LDLr−/− mice did induce initial lesion development (unpublished data). The expression of ABCA1 in macrophages is tightly controlled by intracellular cholesterol levels. Its activity is dramatically increased on cholesterol loading of macrophages and the subsequent transformation into foam cells. It is therefore conceivable that cholesterol efflux via ABCA1 is already maximally activated in macrophages in the atherosclerotic lesion. As a result, further upregulation of ABCA1 expression does not inhibit initial lesion development. However, ABCA1 overexpression did inhibit the progression of the size of these fatty streak lesions. During the progression of atherosclerosis, macrophage foam cells accumulate large amounts of unesterified cholesterol, a process that is thought to contribute to macrophage death. Increased levels of intracellular free cholesterol accelerate the degradation of ABCA1 in macrophages. In agreement, Albrecht et al recently showed that the microenvironment of the atherosclerotic plaque induces ABCA1 protein degradation. This might provide a possible explanation for the fact that overexpression of ABCA1 did not inhibit initial lesion formation, whereas the progression of these lesions was inhibited. Progression of atherosclerotic lesions is also characterized by an ongoing chronic inflammatory reaction and extensive cellular necrosis and apoptosis. Several lines of evidence have suggested a role for ABCA1 in the engulfment of apoptotic cells. In agreement, we demonstrate that the percentage of apoptotic nuclei to the total number of nuclei was decreased in lesions of mice transplanted with ABCA1 BAC overexpressing bone marrow. However, this effect was independent of the extent of lesion development. It is thus unlikely that the protective effects of macrophage ABCA1 overexpression in later stages of lesion development are solely the result of accelerated clearance of apoptotic cells.

In conclusion, the important effect of macrophage ABCA1 overexpression in later stages of lesion development are solely the result of accelerated clearance of apoptotic cells.

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References


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