Macrophage Liver X Receptor Is Required for Antiatherogenic Activity of LXR Agons


Objective—Complications of atherosclerotic cardiovascular disease due to elevated blood cholesterol levels are the major cause of death in the Western world. The liver X receptors, LXRα and LXRβ (LXRs), are ligand-dependent transcription factors that act as cholesterol sensors and coordinately control transcription of genes involved in cholesterol and lipid homeostasis as well as macrophage inflammatory gene expression. LXRs regulate cholesterol balance through activation of ATP-binding cassette transporters that promote cholesterol transport and excretion from the liver, intestine, and macrophage. Although LXR agonists are known to delay progression of atherosclerosis in mouse models, their ability to abrogate preexisting cardiovascular disease by inducing regression and stabilization of established atherosclerotic lesions has not been addressed.

Methods and Results—We demonstrate that LXR agonist treatment increases ATP-binding cassette transporter expression within preexisting atherosclerotic lesions, resulting in regression of these lesions as well as remodeling from vulnerable to stable lesions and a reduction in macrophage content. Further, using macrophage-selective LXR-deficient mice created by bone marrow transplantation, we provide the first evidence that macrophage LXR expression is necessary for the atheroprotective actions of an LXR agonist.


Key Words: atherosclerosis ■ LXRs ■ nuclear receptors ■ reverse cholesterol transport

Elevated plasma non–high-density lipoprotein cholesterol (non–HDL cholesterol) levels, a major risk factor in the development of cardiovascular disease, increase macrophage cholesterol accumulation and foam cell formation in the underlying epithelium of large arteries. Progressive recruitment of macrophages to this site, combined with their uptake of oxidized low-density lipoprotein (LDL) particles, leads to the development of atherosclerotic lesions. In addition to lipid loading, progression of early lesions to complex lesions (plaques) is a chronic inflammatory process in which monococyte-derived macrophages play a key role. The liver X receptors LXRα and LXRβ (LXRs) are members of the nuclear receptor family that control transcription of genes that coordinately regulate cholesterol transport and lipid metabolism in 3 major sites (macrophage, liver, and intestine) and play a critical role in the maintenance of cholesterol homeostasis. Recently, we demonstrated that reconstitution of macrophages from mice deficient in LXRα and β (LXRaβ−/−) by bone marrow transplantation increased atherosclerosis in apolipoprotein E−/− (apoE−/−) and LDL receptor−null (LDLR−/−) mice fed a high-fat cholesterol-containing ("Western") diet, signifying that macrophage LXR expression plays a critical role in the inhibition of atherogenesis.

LXRs modify the atherogenic program in the macrophage through regulation of genes involved in both inflammation and cholesterol elimination pathways. LXR agonists negatively regulate macrophage inflammatory gene expression, and recent data indicate that pathogens that contribute to the initiation and progression of atherosclerosis interfere with macrophage cholesterol metabolism by inhibition of the LXR signaling pathway. Further, LXRs directly regulate the expression of ATP-binding cassette transporters ABCA1 and ABCG1 and apoE, which mediate cellular cholesterol efflux in the presence of acceptors, such as HDL. This process of reverse cholesterol transport is necessary for the maintenance of normal cellular cholesterol balance. Mutations in the ABCA1 gene produce dysregulation of cellular cholesterol efflux, resulting in Tangier disease, characterized by low HDL levels and cholesterol accumulation in macrophages. Similarly, sterol/agonist–inducible cholesterol efflux is defective in LXRaβ−/− macrophages and results in cellular cholesterol accumulation. These observations confirm the central importance for macrophage LXRs as cellular cholesterol sensors in the context of the atherogenic response to elevated plasma cholesterol.
In the liver, LXRs regulate genes involved in cholesterol homeostasis, including cholesterol 7α-hydroxylase (Cyp7a1), the rate-limiting enzyme that promotes conversion of cholesterol to bile acids in the liver for excretion into bile, and ABCG5 and ABCG8, which regulate cholesterol trafficking.13–15 LXRs also regulate fatty acid metabolism in the liver through control of sterol regulatory element–binding protein (SREBP)-1c, a key factor involved in regulating the expression of several hepatic lipogenic enzymes, including acetyl coenzyme A carboxylase, fatty acid synthase, and stearoyl coenzyme A desaturase-1.16–18 Synthetic LXR agonists increase plasma triglyceride levels17,19 and reduce dietary cholesterol absorption.8 Thus, hepatic LXR activity can influence atherosclerosis by modifying processes that directly impact plasma lipid levels.

Recent atherosclerosis prevention studies have demonstrated that synthetic LXR agonists inhibit the initiation and development of atherosclerosis,19,20 even in the absence of major changes in plasma lipid levels. Although these protective effects of LXR agonist treatment on atherosclerosis are clear, there is no information regarding the potential benefit of LXR agonist therapy in the more clinically relevant setting of preexisting hypercholesterolemia and atherosclerotic lesions. Also, although the preventative effect of LXR agonist treatment was largely attributed to increases in ABCA1 and ABCG1 expression in the intestine and artery wall,6 the relative importance of macrophage LXR expression in mediating LXR agonist beneficial actions has not been determined. In view of these questions, we investigated the ability of LXR agonist administration to induce regression and stabilization of preexisting atherosclerotic lesions and determined whether macrophage LXR expression is essential for the atheroprotective effects of the LXR agonist.

Methods

Animals and Diets

Homozygous male LDLR−/− mice (C57BL/6 genetic background) purchased from The Jackson Laboratory (Bar Harbor, Me) were bred at X-Ceptor Therapeutics Inc. Male C57BL/6 mice were purchased from the Harlan Laboratory Inc (San Diego, Calif). Homozygous male LXRsβ−/− double knockout mice (LXRsβ−/−) on the C57BL/6 genetic background were from a colony established and maintained at X-Ceptor Therapeutics Inc.13 Mice were fed standard chow ad libitum until study, at which time LDLR−/− mice were fed a Western-type diet (21% fat wt/wt, 0.15% cholesterol wt/wt; Purina 5001). Male LXR−/− mice (C57BL/6 genetic background) were bred at X-Ceptor Therapeutics Inc.13 Mice were fed standard chow ad libitum until study, at which time LDLR−/− mice were fed a Western-type diet (21% fat wt/wt, 0.15% cholesterol wt/wt; Purina Test Diets #21551) beginning at 8 weeks of age to induce hypercholesterolemia and atherosclerosis.

In lesion regression studies, mice were subsequently treated with either vehicle (PEG400: Tween 80, 4:1) or LXR agonist (T0901317, 10 mg/kg body weight/day) daily by oral gavage (0.1 mL per mouse) either vehicle (PEG400: Tween 80, 4:1) or LXR agonist (T0901317, 10 mg/kg body weight/day) daily by oral gavage (0.1 mL per mouse). Mice were subsequently fed the Western-type diet during the 6-week treatment phase. Eight additional LDLR−/− mice were similarly fed the Western diet for 8 weeks, beginning at 8 weeks of age, but were euthanized at the end of the 8-week dietary lead-in, and tissues were collected for selected baseline measurements (plasma total and HDL cholesterol and triglyceride concentrations and aortic en face atherosclerosis evaluation as described below).

In bone marrow studies, LDLR−/− mice were fed chow diet for the first 4 weeks after irradiation and bone marrow transplantation and were subsequently fed the Western diet during an 8-week treatment period when mice received either vehicle or the LXR agonist (n=12 per group) as described above.

Bone Marrow Transplantation

Recipient male LDLR−/− mice (8 weeks of age) housed in microisolation cages were lethally irradiated with 900 rads (9 Gy) from a cobalt source. Bone marrow cells were harvested from 6- to 8-week-old LXRαβ−/−, LDLR−/−, and C57BL/6 donor mice by flushing tibia and femurs with RPMI medium 1640 supplemented with 2% FBS and heparin (5 U/mL). Cells were washed, suspended in fresh medium, and counted. Recipient LDLR−/− mice were transplanted with 3×106 bone marrow cells through tail vein injection within 6 hours after irradiation.

Lipid and Lipoprotein Analyses

Nonfasting mice were anesthetized with isoflurane, and blood samples were obtained from the retro-orbital plexus. Plasma total cholesterol and triglyceride levels were determined by colorimetric enzymatic assays that were adapted to 96-well plate formats (Infinity Total Cholesterol Reagent or Infinity Triglyceride Reagent, Sigma), using a Multiskan plate reader. Plasma HDL cholesterol was determined by precipitating non–HDL cholesterol (Wako Diagnostic 278-67409) and then assaying the remaining HDL cholesterol by means of the Infinity Total Cholesterol Reagent. Terminal plasma samples from mice treated with vehicle or LXR agonist in the lesion regression study were pooled (6 to 12 mice in each group) and fractionated by fast protein liquid chromatography (FPLC) gel filtration (Amersham Pharmacia Biotech) on Superose 6 columns, and cholesterol concentration of each fraction was determined as above.

RNA Isolation and Analysis of Gene Expression by Quantitative RT-PCR

Atherosclerotic lesions were fresh hand dissected from the length of the aorta at the termination of the regression study, starting from aortic arch and finishing at the terminal abdominal aorta. Lesions were visualized using a stereo-microscope (Leica MZ12) and harvested using a sterile scalpel to ensure the material collected contained only atherosclerotic lesion and not underlying aortic tissue. Bone marrow was collected at the termination of the bone marrow transplant study. Total RNA from tissues was isolated from these tissues using RNeasy kits (QIAGEN Inc) according to the supplier’s total RNA isolation procedure. Because of the low recovery of total RNA from the microdissected atherosclerotic lesions, samples were pooled (5 mice per pool) to create 2 independent samples (n=10 mice total) for each treatment condition. Quantitative RT-PCR was performed using a Perkin-Elmer/ABI 7700 Prism. DNase-treated RNA samples were reverse transcribed, followed by quantitative polymerase chain reactions following standard protocols and conditions as recommended by the manufacturer (RNase-free DNase, Roche; Superscript II Reverse Transcriptase and Taq Polymerase, Life Technologies). Levels of cyclophilin were measured in all samples, and results are presented as number of target mRNA transcripts per cyclophilin mRNA transcript.

Analysis of Atherosclerosis and Lesion Composition

The extent of atherosclerosis in en face mouse aortic preparations was quantified by computer-assisted image analysis of Sudan IV stained aortas using Image-Pro Plus image analysis software (Media Cybernetics).21,22 Immunohistochemical analysis of frozen aortic root sections was performed as described previously.23 The total lesion area in oil red O–stained aortic root sections was determined on digitized root images from 5 equally spaced sections per mouse. For detection of macrophages, aortic sections were incubated with macrophage-specific antibody to mouse macrophages (MOMA-2, Accurate Chemicals). Collagen in lesion was detected using trichrome stain (Sigma). The macrophage- and collagen-positive areas in digitized color images of stained aortic root sections (3 equally spaced sections per mouse; n=5 per group) were quantified.
using Image-Pro Plus image analysis software (Media Cybernetics), and the data are expressed as percent of total lesion area.

Statistical Analyses
Results were analyzed by 1- or 2-way ANOVA with Newman–Keuls Multiple Comparisons (for 1-way ANOVA) or Bonferroni (for 2-way ANOVA) posttests, or Student unpaired t-test, using GraphPad Prism (GraphPad Software Inc).

Results
LXR Agonist Induced Regression of Established Atherosclerotic Lesions
To examine effects of LXR activation on regression of atherosclerosis in a model with preexisting atherosclerotic lesions, male LDLR−/− mice were fed a Western diet and then treated with the LXR agonist or vehicle for 6 weeks, while they continued to consume the Western diet ad libitum (Figure 1A). En face analysis of lesion area at baseline, before the initiation of LXR agonist treatment, revealed that LDLR−/− mice developed advanced lesions throughout the aortic arch and distal portions of thoracic and abdominal aortic regions, which continued to progress in the vehicle-treated group during the 6-week treatment period (Figure 1B and 1C). LXR agonist treatment resulted in a 70% reduction of lesion area in comparison to vehicle-treated controls (Figure 1B, middle versus bottom, and 1C), demonstrating a preventive effect of the LXR agonist on lesion development. More importantly, LXR agonist treatment resulted in significant 62% reduction in lesion areas compared with mice assessed at baseline (Figure 1B, top versus middle and bottom, and 1C), demonstrating that the LXR agonist induced regression of preexisting atherosclerotic lesions. When atherosclerosis was measured by quantitation of aortic root sections, once again a significant delay in disease progression was observed in LXR agonist–treated mice (vehicle=1.9×10^6 μm², n=8; T0901317=1.5×10^6 μm², n=8, P<0.01); however, lesion area in both agonist- and vehicle-treated mice was significantly greater than that of the baseline control (7.4×10^7 μm², n=8, P<0.01 versus vehicle- and agonist-treated groups). The ability to selectively observe regression in the en face analysis most likely arises from the difference in the type of information provided by the 2 methods. The root section quantitation provides cross-sectional informational from a single area and also includes the necrotic core of the lesion which is not a target for reverse cholesterol transport. In contrast, the en face analysis provides an aggregate measure of the length of the aorta covered by lesions.

LXR Activation Alters Composition of Atherosclerotic Lesions
Immunostaining of aortic root lesions with the macrophage-specific antibody MOMA-2 showed a significant 48% reduction of macrophage-positive areas in LXR agonist–treated mice (Figure 2A versus 2B and Table 1). This effect was accompanied by a 34% increase in collagen content of lesions in LXR agonist–treated mice (Figure 2C versus 2D and Table 1). Interestingly, the increases in collagen were observed above necrotic core and in fibrous cap regions of atherosclerotic lesions (Figure 2C versus 2D). The reduction of macrophage content and an increase in collagen content of lesions is consistent with stabilization of vulnerable lesions that may protect advanced necrotic lesions from plaque rupture and thrombosis.24

LXR Regulation of Gene Expression in Atherosclerotic Lesions
To further evaluate the effects of LXR agonist treatment within atherosclerotic lesions, gene expression was assessed in RNA isolated from micro-dissected aortic lesions from LDLR−/− mice on Western diet for 8 weeks, after treatment with vehicle or LXR agonist (10 mg/kg per day for 6 weeks). These aortas were separate from those examined by en face atherosclerosis analysis. Expression of the macrophage marker CD6825 in these aortic lesions was significantly reduced by 45% in LXR agonist–treated mice compared with vehicle-treated controls (Figure 3A) and consistent with the reduction in macrophage-positive immunostaining (Figure 2A and 2B). In addition, LXR agonist treatment significantly increased ABCA1 mRNA levels in atherosclerotic lesions by 67% (Figure 3A). There was also a slight (≈10%) increase in ABCG1 mRNA levels in the atherosclerotic lesions, which did not attain statistical significance (data not shown). Consistent with the immunohistochemical data presented earlier, these results demonstrate that LXR agonist treatment reduces the inflammatory tone of atherosclerotic lesions while inducing expression of genes that promote reverse cholesterol transport from macrophages.

LXR Agonist Treatment Ameliorates Hypercholesterolemia in LDLR−/− Mice
Plasma FPLC analysis revealed a substantial effect of LXR agonist treatment across the lipoprotein cholesterol profile (Figure 3B). LXR agonist treatment significantly reduced plasma total cholesterol levels by ≈28% (Figure 3C), along with a nonsignificant reduction of HDL cholesterol after 6 weeks of treatment (Figure 3D). As expected, the LXR agonist increased plasma triglyceride concentrations (Figure 3E).17,19

Critical Role of Macrophage LXR in Antiatherogenic Activity of LXR Agonist
In previous studies, we demonstrated that macrophage LXRαβ deficiency leads to increased atherosclerosis in apoE−/− and LDLR−/− mice.3 Because LXRs are expressed in multiple tissues and coordinately regulate several target genes involved in cholesterol homeostasis and inflammatory signaling, it is not clear which site(s) of LXR activity is critical to the inhibitory effects of LXR agonists on atherosclerosis. To address whether macrophage LXR activity contributes to the atheroprotective effects of LXR agonists, we created LDLR−/− mice with bone marrow macrophage LXR deficiency using bone marrow transplantation (BMT). Irradiated LDLR−/− mice were transplanted with C57Bl/6, LXRαβ−/−, or LDLR−/− bone marrow (C57Bl/6→LDLR−/−, LXRαβ−/−→LDLR−/−, and LDLR−/−→LDLR−/−, respectively). The C57Bl/6→LDLR−/− and LDLR−/−→LDLR−/− groups represent controls in which macrophages are positive for LXR expression while being either positive (C57Bl/6→
LDLR−/− mice (treatments as described in Figure 1) were immunostained for macrophages with the macrophage-specific antibody, MOMA-2. Arrows indicate macrophage-positive areas within total aortic root lesions. C and D, Adjacent aortic root sections were analyzed for collagen content after trichrome staining. Arrows indicate collagen staining (blue), which was increased in fibrous cap regions of lesions in the LXR agonist–treated mice (D) compared with vehicle-treated controls (C). See Table 1 for quantification.

The effects of BMT and LXR agonist treatment on atherosclerosis were determined by en face quantification of aortic lesion areas. As previously reported,3 vehicle-treated LDLR−/− → LDLR−/− mice developed significantly more atherosclerosis than did vehicle-treated C57Bl/6 → LDLR−/− mice (Figure 4B), reflecting the antiatherogenic activity of macrophage LXR expression. LDLR−/− → LDLR−/− mice in this study appeared to develop more atherosclerosis than C57Bl/6 → LDLR−/− mice after 8 weeks of vehicle treatment; however, this difference did not attain statistical significance (Figure 4B), and may reflect the higher plasma total cholesterol levels in vehicle-treated LDLR−/− → LDLR−/− mice compared with C57Bl/6 → LDLR−/− mice, as mentioned above (Table 2). LXR agonist treatment for 6 weeks significantly reduced atherosclerosis in mice with macrophages that express LXR (57% reduction in C57Bl/6 → LDLR−/− and 68% reduction in LDLR−/− → LDLR−/−, Figure 4B). In contrast, LXR agonist treatment had no inhibitory effect on atherosclerosis in mice with macrophages devoid of LXRs (LXRαβ−/− → LDLR−/−, Figure 4B). These results demonstrate that LXR activity in the macrophage is obligatory for the LXR agonist–dependent inhibition of atherosclerosis.
To determine the impact of macrophage LXR deficiency on LXR agonist–induced gene expression, RNA was isolated from bone marrow cells harvested from each group of mice at the end of the study. In bone marrow cells from C57Bl/6→LDLR−/− and LDLR−/−→LDLR−/− mice, LXRβ mRNA levels were ∼3-fold higher than those of LXRα mRNA, and LXR agonist treatment did not significantly affect mRNA levels of either receptor isotype (data not shown). ABCA1 and ABCG1 mRNA levels were significantly increased by LXR agonist treatment in bone marrow cells from C57Bl/6→LDLR−/− and LDLR−/−→LDLR−/− mice, whereas bone marrow cells from LXRαβ−/−→LDLR−/− mice showed no induction of these mRNA transcripts (Figure 4C and 4D). Taken together with the atherosclerosis data, these findings suggest that LXR agonist treatment may delay the progression of atherosclerosis through induction of genes that promote reverse cholesterol transport from the macrophage.

**Discussion**

These data demonstrate that an LXR agonist induces the regression of preexisting atherosclerotic lesions. Regression was accompanied by remodeling of the lesions in a manner consistent with their stabilization. Our data suggest that the ability of the LXR agonist to induce regression of atherosclerotic lesions may also be linked mechanistically to increased cholesterol efflux from macrophages in the artery wall, specifically through induction of expression of the ABC transporters, including ABCA1 and ABCG1. The recent reports that LXR agonists have antiinflammatory activity and inhibit expression of several proinflammatory genes in macrophages and in the artery wall,4 combined with their ability to reduce macrophage content of atherosclerotic lesions observed here, suggest a beneficial clinical impact of LXR agonist treatment in preexisting atherosclerosis.

Although a number of pharmacological intervention studies with statins, bile acid-binding resins, fibrates, and ACAT inhibitors have been reported to inhibit atherosclerosis pro-
gression in animal models, regression achieved with pharmacological agents has generally been associated with significantly decreased plasma cholesterol concentrations. Notably, the dramatic effect of LXR agonist treatment on atherosclerotic lesion progression reported here occurred in the presence of only a modest reduction in plasma total cholesterol levels and elevated plasma triglyceride levels. Rapid and substantial lesion regression has been induced in animal models treated with either native or a naturally occurring mutant of apoA-1 in the absence of significant lowering of plasma cholesterol. Recently, a similarly rapid regression of coronary atherosclerosis was demonstrated in humans treated with the apoA-1 Milano variant, the mechanism of which is presumably related to an increase in reverse cholesterol transport out of the atherosclerotic lesion. Although possibly affecting the same reverse cholesterol transport process, the LXR agonist and the apoA-I variant represent distinct therapeutic strategies, with the LXR agonist acting directly on the atherosclerotic lesion after oral administration whereas the injected apoA-I molecule acts by drawing cholesterol into the vascular space.

In a previous study with the synthetic LXR agonist T0901317 was administered orally (10 mg/kg per day) for 8 weeks, beginning 4 weeks after irradiation and bone marrow transplantation. Despite the significant decrease in plasma cholesterol concentrations, the mechanism of this effect is not well understood. The LDL cholesterol reduction observed in the LDLR−/− mice in the regression study suggests that LDL receptor–independent mechanisms, potentially including upregulation of ABCG5 and ABCG8 and enhanced excretion of cholesterol into bile, are responsible for LXR agonist–mediated plasma cholesterol lowering. However, a similar effect of LXR agonist treatment was not observed in the bone marrow transplant study. The reason for this difference is not known. The design of the 2 studies may contribute to this differential response, because LDLR−/− mice in the regression study were fed the Western diet for a total of 14 weeks, whereas mice in the bone marrow transplant study were fed the Western diet only during the 8-week treatment period. Similar to the plasma cholesterol lowering observed in the lesion regression, there was a significant ≈32% decrease in plasma cholesterol in LDLR−/−→LDLR−/− mice in the bone marrow transplant study, which was not observed in the C57Bl/6→LDLR−/− mice. This finding, which appears to stem from the 50% higher plasma cholesterol level in vehicle-treated LDLR−/−→LDLR−/− mice compared with the other bone marrow transplant conditions, has been observed previously and suggests a role for LDLR expression in cells of hematopoietic origin in regulating plasma cholesterol concentrations. This elevated plasma cholesterol level may also contribute to the increased atherosclerotic lesion area observed in the vehicle-treated LDLR−/−→LDLR−/− mice, in comparison to the C57Bl/6→LDLR−/− controls. It is clear from the literature that the bone marrow–transplanted LDLR−/− model is not equivalent to its nontransplanted counterpart, at least with respect to atherosclerotic disease progression. Further studies are required to elucidate precise LXR-dependent mechanism(s) contributing to lowering of plasma cholesterol and the interaction between...
experimental manipulations and LXR agonist induced reductions in circulating cholesterol concentrations.

In addition to reductions in lesion area, our studies demonstrate a decrease in CD68 mRNA expression and macrophage-positive immunostaining in atherosclerotic lesions in mice treated with an LXR agonist. The ability of LXR agonist treatment to reduce macrophage content and increase collagen content of advanced lesions, coupled with the reported antiinflammatory role of LXR agonists in the artery wall, strongly suggests that LXR agonists can be effective agents to reverse existing atherosclerosis. It should be noted that changes in CD68 expression in aortas of mice were not detected by Joseph et al; however, these investigators used a different strain of atherosclerotic mice and LXR agonist than those used here. We have shown that the regressed lesions from LXR agonist–treated mice contain fewer macrophages and are more fibrous than lesions from vehicle-treated controls, suggesting that LXR agonist intervention can reduce the inflammatory nature and increase the stability of atherosclerotic lesions. 

In conclusion, the data presented here demonstrate the obligatory role of macrophage LXR expression and to promote reverse cholesterol transport. Because LXR activation in the liver contributes to cholesterol efflux in liver cells in LXR receptor-deficient mice. Circulation. 2002;106:1147–1153. Further, the data argue that this effect does not result from activation of LXR-dependent effects in tissues such as liver and intestine (where LXR agonists regulate target genes that control lipid homeostasis) and that the effect can be appreciated in the absence of significant plasma lipid lowering. Because LXR activation in the liver contributes to plasma triglyceride elevation, LXR agonists that selectively target macrophages can be effective agents to induce ABC transporter expression and to promote reverse cholesterol transport in the artery wall without undesirable liver effects. In conclusion, the data presented here demonstrate the obligate role of macrophage LXR expression for the antiatherogenic activity of LXR agonists and suggest that selectively targeting macrophage LXR activity may provide novel promising therapeutic agents for the treatment of atherosclerosis.

Acknowledgments

We thank Dr B. Wagner, M. Petrowski, and J. Morimitsu for quantitative polymerase chain reaction analyses; Dr A. Johnson for providing T0901317, Dr J. Witztum for FPLC plasma fractionation; Dr D.J. Mangelsdorf for the provision of the LXRα and LXRβ founder mice; and Drs P. Willy and B. Wagner for critical review of the manuscript.

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Arterioscler Thromb Vasc Biol. 2005;25:135-142; originally published online November 11, 2004;
doi: 10.1161/01.ATV.0000150044.84012.68
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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