Cardiovascular diseases are the leading cause of morbidity and mortality in the Western world. The primary cause of cardiovascular diseases is atherosclerosis, which is characterized by lipid accumulation and inflammation in the vascular wall.1,2 Macrophages play a central role in the pathogenesis of atherosclerosis by internalizing modified low-density lipoprotein (LDL), production of cytokines and growth factors, and thus stimulate migration and proliferation of smooth muscle cells (SMCs), and plaque development and progression.13,14 Second, LRP regulates 2-integrin-mediated adhesion of monocytes to endothelial cells,15 allowing monocytes to migrate into the intima and to differentiate into macrophages. Third, macrophage LRP has also been demonstrated to play a role in the translocation of 12/15-lipoxygenase, which stimulates the formation of oxidized LDL.16,17 Finally, in concert with the LDLR, LRP can mediate the uptake of apoE-rich atherogenic lipoproteins into the macrophage.18–20

Key Words: atherosclerosis, collagen, genetically altered mice, LRP, macrophage

Objective—In vitro studies implicate that the low-density lipoprotein receptor (LDLR)-related protein (LRP) in macrophages has a pro-atherogenic potential. In the present study, we investigated the in vivo role of macrophage specific LRP in atherogenesis independent of its role in the uptake of lipoproteins.

Methods and Results—We generated macrophage-specific LRP-deficient mice on an apoE/LDLR double-deficient background. Macrophage LRP deletion did not affect plasma cholesterol and triglyceride levels, lipoprotein distribution, and blood monocyte counts. Nevertheless, macrophage LRP deficiency resulted in a 1.8-fold increase in total atherosclerotic lesion area in the aortic root of 18-week-old mice. Moreover, LRP deficiency also resulted in a relatively higher number of advanced lesions. Whereas macrophage and smooth muscle cell content did not differ between LRP-deficient mice and control littersmates, a 1.7-fold increase in collagen content and 2.3-fold decrease in relative number of CD3+T cells were observed in lesions from macrophage specific LRP-deficient mice.

Conclusions—Our data demonstrate that independent of its role in lipoprotein uptake, absence of LRP in macrophages resulted in more advanced atherosclerosis and in lesions that contained more collagen and less CD3+T cells. In contrast to previous in vitro studies, we conclude that macrophage LRP has an atheroprotective potential and may modulate the extracellular matrix in the atherosclerotic lesions. (Arterioscler Thromb Vasc Biol. 2006;26:2710-2715.)

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From the Vascular Medicine Unit (L.H., L.S.M.B., M.V.H., L.M.H., J.T.T.), Department of General Internal Medicine, LUMC, Leiden, The Netherlands; TNO-Quality of Life (L.S.M.B., L.M.H.), Gaubius Laboratory, Leiden, The Netherlands; Zentrum für Neurowissenschaften/Medizinische Klinik II (P.M.), Universität Freiburg, Freiburg, Germany; Department of Molecular Genetics (J.H.), UT Southwestern, Dallas, Tex; Department of Pathology (N.B.), UMCU, Utrecht, The Netherlands; Department of Endocrinology and Metabolic Diseases (J.F.P.B.), LUMC, Leiden, The Netherlands; Haemostasis and Thrombosis Research Center (B.J.M.v.V.), Department of Hematology, LUMC, Leiden, The Netherlands.

Correspondence to J.T. Tamsma, Vascular Medicine Unit, Department of General Internal Medicine, Leiden University Medical Center, C4-R, P.O. Box 9600, 2300 RC Leiden, The Netherlands. E-mail j.t.tamsma@lumc.nl

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Because all these processes promote the formation of foam cells, one would predict that LRP promotes the development of atherosclerosis at the level of macrophages.

In the present study, we investigated the role of macrophage LRP in the development of atherosclerosis in vivo. To this end, macrophage LRP was constitutively deleted in macrophages, using the lysozyme M Cre/loxP system.21 Because apoE LDLR double-deficient mice develop spontaneously human-like atherosclerosis without the necessity of a cholesterol-rich diet, macrophage LRP was deleted on an apoE22 and LDLR23 double-deficient background. Moreover, this model allowed us to study the role of macrophage LRP independent of its classical role in the uptake of lipoproteins via the apoE-mediated and LDLR-mediated pathway. Our data demonstrate that the absence of macrophage LRP results in more advanced atherosclerosis, and in lesions that contain more collagen and less CD3+ T cells. In contrast to what in vitro studies would predict, we conclude that, like LRP on hepatocytes and SMCs, macrophage LRP has an atheroprotective potential.

**Materials and Methods**

**Mice**

Mice with or without Cre recombinase under the lysozyme M promoter (kindly provided by I. Förster, University of Munich, Germany) were bred with our previously generated LDLRflox/flox apoE-/- LDLR-/-1 to generate mice either with lysozymal M Cre21 (LysMCre RLPflox/loplox apoE-/- LDLR-/- further referred to as mLRP-/-) or without lysozymal M Cre (LysMCre RLPflox/loplox apoE-/- LDLR-/- further referred to as mLRP+/-).12 Mice were genotyped by polymerase chain reaction (PCR) for LysMCre, RLPflox/lox, apoE, and LDLR status.12 After 2 breeding rounds we obtained mice with the LysMCre RLPflox/loplox apoE-/- LDLR-/- genotype. LRP and lysozyme M are both localized on chromosome 10 in mice. Therefore, our third breeding (LysMCre RLPflox/loplox apoE-/- LDLR-/- × LRPflox/loplox apoE-/- LDLR-/-) generated only 2 out of 63 (3%) mice that were LysMCre RLPflox/loplox apoE-/- LDLR-/-, instead of 15 out of 63 (25%) as expected in case of a Mendelian inheritance. These 2 mice were subsequently used for generating LysMCre, RLPflox/loplox apoE-/- LDLR-/- mice in the consecutive breedings. The inheritance pattern of the offspring was Mendelian (19 female mice with the LysMCre RLPflox/loplox apoE-/- LDLR-/- genotype versus 18 female mice with the LRPflox/loplox apoE-/- LDLR-/- genotype). Subsequently, these mice were used for our experimental breeding yielding more female mice with the LRPflox/loplox apoE-/- LDLR-/- genotype (n=31) than the LysMCre RLPflox/loplox apoE-/- LDLR-/- genotype (n=17). A similar pattern was observed for male mice (18 mice with LysMCre RLPflox/loplox apoE-/- LDLR-/- genotype and 24 mice with LRPflox/loplox apoE-/- LDLR-/- genotype). Mice were fed a standard rodent chow diet (Technlab-BMI, Someren, The Netherlands) and water ad libitum. All animal experiments were approved by the institutional committee on animal welfare of TNO Quality of Life.

**Macrophage LRP Deletion**

Peritoneal macrophages were obtained from mLRP-/+ and mLRP-/- mice 4 days after in utero genetic injection of 1 ml thyroglobulin broth (3% wt/vol; Difco Grayson, Ga) by flushing the peritoneum with 10 ml ice-cold phosphate-buffered saline (PBS). Macrophages were washed twice with ice-old PBS and subsequently incubated in RPMI 1640 containing 10% fetal calf serum and streptomycin/penicillin in 12-cm culture plates at 37°C for 4 hours. After 3 washes with warm PBS, macrophages were lysed with 4 ml lysis buffer (0.1 mol/L Tris, 1 mol/L EDTA, 0.2 mol/L NaCl, 0.002% SDS, pH 8.6) containing 1 mg protease K at 55°C for 30 minutes. DNA was then isolated using the standard phenol/chloroform/iso-amylalcohol method.3 The LysMCre/loxP mediated recombination of the conditional LRP allele in the macrophages was established by PCR amplification of primer LRP postlox (5'-GTA GTT ATT CGG ATC ATC AGC TA-3', Invitrogen, The Netherlands) and mLRP12 (5'-GGT GTG ACA TAG AGT TTT AAA GAG G-3'), yielding a 400-bp recombination product.4

**Blood Sampling and Analysis**

Blood samples were obtained via tail bleeding. Samples were collected in EDTA-coated vials (Sarstedt, Nümbrecht, Germany). Plasma cholesterol levels were measured by a commercially available enzymatic kit (Roche Diagnostics GmbH, Mannheim, Germany). Plasma triglyceride levels were measured by a commercially available 1-step enzymatic kit that detects free and triglyceride-derived glycerol levels (Roche Diagnostics GmbH, Mannheim, Germany). Plasma lipoproteins were size-fractionated by fast protein liquid followed by the determination of the cholesterol levels in the individual fractions. Total blood leukocyte (CD45+), T cell (CD3+), B cell (CD19+), and monocyte/granulocyte (CD11b+) numbers were determined by fluorescence activated cell sorting (fluorescence-activated-cell sorter [FACS]) analysis (TruCOUNT; FACSalibur, BD Biosciences, Calif), as described previously.23

**Atherosclerosis Analysis**

Female mLRP-/- mice and control mLRP+/- littermates were euthanized at 18 weeks of age (n=17 and n=31 for mLRP-/- and mLRP+/-, respectively). Heart and aorta were perfused with PBS and were subsequently fixed in phosphate-buffered 4% formaldehyde (pH 7.4), dehydrated overnight, and embedded in paraffin. Hearts were cross-sectioned (5 μm) with 40-μm intervals throughout the entire aortic root. Sections of the aortic valve area were routinely stained with hematoxylin-phloxine-saffron for morphometric analysis and characterization of the lesions. For each mouse, 3 lesions at the aortic root were analyzed. Per mouse, 4 cross-sections were used for quantification of atherosclerotic lesion area.26 Areas were determined using Leica Qwin image software (EIS, Ashbury, NJ). Atherosclerotic lesions were classified according to severity (ie, early, moderate or advanced lesions), as described previously.23 The numbers observed in each category were expressed as percentage of the total number of lesions observed within one group of mice.27

**Lesion Composition Analysis**

Serial sections of the aortic valve area were stained with rabbit anti-mouse macrophage antibody (AIA-312040, 1/1500; Accurate Chemical and Scientific, Westbury, NY) and a monoclonal mouse anti-smooth muscle cell α-actin antibody (clone 1A4, M-851, 1/1600; DakoCytomation, Belgium), as described previously.12 Serial sections of the aortic valve area were stained with goat α-human matrix metalloproteinase (MMP-9) antibody (C-20, Santa Cruz) or with rat α-human CD3 (Serotec). Sections were deparaffinized. Endogenous peroxidase was quenched with 0.3% H2O2 in 100% methanol, and nonspecific binding was blocked with 5% bovine serum albumin in PBS. Antigen was retrieved by 0.1% trypsin (wt/vol) in PBS at 37°C for 30 minutes before MMP-9 staining or heat treatment in 1 mol/L EDTA, pH 8.0, for 20 minutes before CD3 staining. The primary MMP-9 (1:200) or CD3 antibody (1:1000) in 5% bovine serum albumin in PBS was incubated overnight at 4°C followed by a 1-hour incubation with biotinylated secondary rabbit anti-goat (1:300) or goat α-rabbit antibody in 1% bovine serum albumin in PBS. After incubation with hors eradish peroxidase-labeled avidin-biotin complex (Dako), peroxidase activity was visualized using NovaRED (Vector). Sections were counterstained with Mayer hematoxylin.

Collagen was stained using Sirius red (Chroma-Gesellschaft, Stuttgart, Germany). Lesion macrophage (AIA-31240-positive area), smooth muscle cell (α-actin-positive area), MMP-9, and collagen (Sirius red-positive area) areas were quantified using EIS. Number of CD3+ cells was counted in 4 cross-sections per valve. All analyses were performed double blindly without previous knowledge of the genotype.
Likewise, the CD11b+ monocyte and CD11b+ granulocyte populations were also similar between the mo LRP− mice and control mo LRP+ littermates (supplemental Table I).

**Effect of mo-Specific LRP Deficiency on Atherosclerotic Lesion Size**

We investigated the role of LRP in macrophages in the development of atherosclerosis on an apoE and LDLR double-deficient background. The total atherosclerotic lesion area was significantly increased in mo LRP− mice as compared to control mo LRP+ littermates at 18 weeks of age [geometric mean (68% CI): 24.2 (20.8–28.2) × 10^3 μm^2 and 11.3 (9.6–13.3) × 10^3 μm^2 for mo LRP− and mo LRP+, respectively, P<0.001; Figure 2A]. In addition, mo LRP− mice showed a significant increase in lesion severity as compared to control mo LRP+ littermates (Figure 2B). Mo LRP− mice had a significant lower incidence of early lesions (4.0% versus 18.7%; P<0.05), an equal percentage of moderate lesions (18.0% versus 18.7%) and a significant higher incidence of advanced lesions (78.0% versus 62.7%, P<0.05) as compared to the control mo LRP+ littermates. These data indicate that LRP deficiency in macrophages results in increased atherosclerotic lesions in mice.

**Effect of mo-Specific LRP Deficiency on Atherosclerotic Lesion Composition**

To investigate whether the LRP in the macrophages also affects the composition of the atherosclerotic lesions, we determined the percentage of macrophages (AIA-31240–positive area), SMC (α-actin–positive area), and collagen (Sirius red-positive area) content in the individual atherosclerotic lesions of 18-week-old mo LRP− mice and control mo LRP+ littermates. As expected from the increased total lesion area in the mo LRP− mice, the total macrophage and collagen lesion contents were increased in the mo LRP− mice as compared to control mo LRP+ littermates (Table). The total SMC lesion content was also higher in the mo LRP− mice as compared to control mo LRP+ littermates, although this was not statistically significant. To analyze the macrophage, SMC and collagen content independent of the total lesion area, we corrected the lesion content for the total lesion area at the level of individual lesions. The percentages of macrophage and SMC in the lesions were similar between the mo LRP− and control mo LRP+ littermates (Table). However, the mean percentage of collagen in the lesions per mouse was

**Statistical Analysis**

All data are presented as geometric mean with 68% confidence interval (CI), which represents 1 standard deviation from the geometric mean if a log-normal distribution is assumed. Data are analyzed by means of the Mann-Whitney U test (Graphpad Software version 4.02; San Diego, Calif). Frequency data for lesion classification were compared by means of the χ^2 test. P<0.05 was regarded as statistically significant.

**Results**

**General Characteristics of mo-Specific LRP-Deficient Mice on an ApoE^−/− and LDLR^−/− Background**

DNA isolated from peritoneal macrophages from LysMCre^−/− LRPlox/lox apoE^−/− LDLR^−/− (mo LRP−) mice and control LRP^lox/lox apoE^−/− LDLR^−/− (mo LRP+) littermates was subjected to PCR analysis to detect the presence of LysMCre/loxP-mediated recombination of LRP (ΔLRP). A 400-bp ΔLRP PCR product of DNA from these isolated peritoneal macrophages was present in the mo LRP− mice (Figure 1, lane 1 and 2), whereas no PCR product was detected in peritoneal macrophages from mo LRP+ mice (lane 3 and 4), indicating successful recombination of LRP in macrophages in the mo LRP− mice only. All mice appeared healthy and displayed no signs of abnormalities. Mean body weight, plasma cholesterol, and triglyceride levels, and plasma lipoprotein distribution were similar between mo LRP− mice and control mo LRP+ littermates (supplemental Table I and Figure I, available online at http://atvb.ahajournals.org). The circulating CD45+ (total blood leukocytes), CD3+ (T cells), and CD19+ (B cells) cells were similar between the mo LRP− mice and control mo LRP+ littermates (supplemental Table I).
Collagen Accumulation in Atherosclerotic Lesions

Potential Mechanism Contributing to Increased Collagen Accumulation in Atherosclerotic Lesions of mφ-Specific LRP-Deficient Mice

Collagen content in the extracellular matrix can be controlled among others by the MMP/tissue inhibitor metalloproteinase (TIMP) system and interferon-γ (INF-γ). MMP-9 is an important representative of the MMP/TIMP system that may be involved in collagen degradation in the extracellular matrix of atherosclerotic lesions. However, T cells can produce IFN-γ, a modulator of collagen synthesis. Therefore, we explored the MMP-9 content and T cells in the atherosclerotic lesions. The total MMP-9 area was significantly increased in the mφ LRP− mice as compared with control LRP+ littermates [geometric mean (68% CI): 18.5 (14.5–23.8) × 103 μm2 and 11.6 × 103 (10.0–13.6) × 103 μm2 for mφ LRP− and mφ LRP+ mice, respectively, P<0.05, Figure 4A]. When corrected for the total lesion area at the level of individual lesions, the percentage of MMP-9 content was similar in mφ LRP− and mφ LRP+ mice (geometric mean (68% CI): 0.21 (0.17–0.25)% and 0.29 (0.26–0.32) % for mφ LRP− and mφ LRP+ mice, respectively, P=0.12, Figure 4B). The total number of CD3+ T cells in the lesions of the mφ LRP− and mφ LRP+ littermates was similar (Figure 4C). However, the number of CD3+ T cells corrected for lesion size was significantly decreased in the mφ LRP−
Furthermore, macrophage LRP is demonstrated to mediate at the level of the liver and SMCs.7,12 However, to date, the role of LRP in macrophages, the key mediators in the pathogenesis of atherosclerosis, has not been elucidated in vivo. In the present study, we investigated the role of LRP in macrophages in the development of atherosclerosis in vivo independent of its classical role in the uptake of lipoproteins via the apoE- and LDLR-mediated pathways. We demonstrated that macrophage specific LRP deficiency leads to a significant increase in atherosclerosis. In addition, macrophage specific LRP-deficient mice exhibit an increase in relative collagen content, whereas the macrophage and SMC contents of the plaques were not affected. Furthermore, the plaques of the macrophage-specific LRP-deficient mice contain less relative numbers of CD3+ T cells, whereas the MMP-9 content was not different. We conclude that, like LRP from the liver and SMCs, macrophage LRP has an atheroprotective potential in apoE LDLR double-knockout mice.

Our results are in apparent contradiction with previous in vitro studies, showing that macrophage LRP has pro-atherogenic properties. LRP has a well-established role in the apoE-mediated uptake of remnant lipoproteins and has thereby pro-atherogenic potentials in the macrophages.4,6,30 Furthermore, macrophage LRP is demonstrated to mediate the adhesion and migration of leukocytes,15 formation of atherogenic oxidized low-density lipoprotein (LDL),16,17 and the clearance of pro-atherogenic ligands, such as tissue-type plasminogen activator (t-PA),12,31 and plasminogen activator inhibitor-1 (PAI-1).32 All these processes promote the formation of foam cell in vitro, which point to less atherosclerosis in the absence of macrophage LRP. However, we observed increased atherosclerosis macrophage specific LRP-deficient mice, despite the exclusion of possible apoE- and LDLR-mediated uptake of pro-atherogenic remnant lipoproteins (Table, Figure 2). The difference between the previous studies15–17 and our current study may be caused by the differences in the study designs. In vitro isolated macrophage systems were used in the previous studies, whereas an in vivo mouse model was used in the present study. In our in vivo model LRP exhibits both pro-atherogenic and anti-atherogenic properties. Our results demonstrate that the anti-atherogenic properties of LRP in the macrophages dominate the pro-atherogenic properties in the apoE and LDLR double-deficient mice.

The mechanism by which macrophage LRP modulates atherosclerosis is not clear. First, because LRP recognizes >50 distinct pro-atherogenic and anti-atherogenic ligands, it can be postulated that the increased atherosclerosis in macrophage LRP-deficient mice might be caused by accumulation of pro-atherogenic LRP ligands locally in the vascular wall or in the plasma. Pro-atherogenic LRP ligands include coagulation factor VIII,33 von Willebrand factor,34 and t-PA.31,35 We have previously shown that disruption of the hepatic LRP gene results in increased plasma levels of these LRP ligands. Second, recent work has implicated LRP in several signal transduction pathways including the regulation of cell migration and the remodeling of the extracellular matrix. In the present study, we show that deletion of the LRP gene in macrophages leads to increased collagen content of atherosclerotic lesion independent total area, whereas no differences were observed in SMC content (Figure 3, Table). The collagen content in the extracellular matrix can be controlled by the MMP/TIMP system and activated T cells.28,29 Whereas we observed no differences in MMP-9 content in the lesions, the relative number of T cells is significantly lower in the atherosclerotic lesions of macrophage specific LRP-deficient mice (Figure 4). Possibly, the regulation of lesional collagen as modulated by T cells.28,29 Whereas we observed no differences in MMP-9 content in the lesions, the relative number of T cells is significantly lower in the atherosclerotic lesions of macrophage specific LRP-deficient mice (Figure 4). Possibly, the regulation of lesional collagen as modulated by T cells is impaired in the absence of LRP in the macrophages. Obviously, further detailed studies are required to gain additional insight into the underlying mechanisms how LRP affects T cell number and collagen content, and their possible interaction.

Our data provide evidence that LRP has an atheroprotective potential in the apoE LDLR double-knockout mice at the level of macrophages in addition to the previously shown anti-atherogenic characteristics of LRP in the liver and SMCs, and may modulate the extracellular matrix in the atherosclerotic lesions.

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Disclosures
None.

References
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Macrophage Low-density Lipoprotein Receptor-related Protein Deficiency Enhances Atherosclerosis in ApoE/LDLR Double Knockout Mice
Hu, L. et al
### Table I

Body weight, plasma lipid levels and blood leukocytes of 18-weeks old of mφ LRP- mice and mφ LRP+ littermates.

<table>
<thead>
<tr>
<th></th>
<th>mφ LRP+</th>
<th>mφ LRP-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>21.1 (20.7-21.4)</td>
<td>20.9 (20.5-21.3)</td>
</tr>
<tr>
<td>Plasma cholesterol (mM)</td>
<td>23.2 (22.3-24.2)</td>
<td>21.9 (21.0-22.9)</td>
</tr>
<tr>
<td>Plasma triglyceride (mM)*</td>
<td>1.8 (1.7-1.9)</td>
<td>1.6 (1.5-1.8)</td>
</tr>
<tr>
<td>CD45+ (10⁶ cells/mL)</td>
<td>13.4 (12.5-14.4)</td>
<td>13.3 (11.9-14.9)</td>
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<tr>
<td>CD19+ (10⁶ cells/mL)</td>
<td>6.8 (6.3-7.4)</td>
<td>6.5 (5.9-7.3)</td>
</tr>
<tr>
<td>CD3+ (10⁶ cells/mL)</td>
<td>4.6 (4.1-5.0)</td>
<td>4.1 (3.6-4.7)</td>
</tr>
<tr>
<td>CD11b+ monocytes (10⁶ cells/mL)</td>
<td>1.0 (0.9-1.0)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>CD11b+ granulocytes (10⁶ cells/mL)</td>
<td>1.7 (1.6-1.9)</td>
<td>1.6 (1.5-1.7)</td>
</tr>
</tbody>
</table>

Data represent geometric mean and 68% CI. *Sum of free and triglyceride-derived glycerol.
Figure I

The graph shows the distribution of cholesterol (mM) across fraction number. Two conditions are compared:
- "mφ LRP+" represented by white circles with error bars.
- "mφ LRP-" represented by black circles with error bars.

The x-axis represents the fraction number, ranging from 0 to 25, and the y-axis represents cholesterol concentration in mM, ranging from 0.0 to 4.5.
**Figure I. Plasma lipoprotein distribution.** Plasma lipoprotein profiles of mφ LRP- mice (■) and control mφ LRP+ (○) littermates were size-fractionated by FPLC followed by the determination of the individual fractions. Identical lipoprotein distribution is observed between mφ LRP- mice and control mφ LRP+ littermates. VLDL: very-low density lipoprotein, LDL: low density lipoprotein, HDL: high density lipoprotein.