Inhibition of arterial lesion progression in CD16-deficient mice: evidence for altered immunity and the role of IL-10

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Aims
Given the importance of IgG Fc receptors in immune regulation, we hypothesized that Fcg receptor type III (FcgRIII, CD16) plays an important role in atherogenesis. We therefore analysed the formation of arterial lesions in LDL receptor-deficient (LDLR−/−) and FcgRIII−/− × LDLR−/− double knockout mice at three different points up to 24 weeks of exposure to a high-fat diet.

Methods and results
Analysis of Oil Red-O-stained sections revealed no difference in lesion formation between strains after 6 weeks of a high-fat diet, and a modest decrease after 14 weeks in double knockouts relative to LDLR−/− controls. After 24 weeks, lesion formation was decreased in the aortic root (30%) and innominate artery (50%) in FcgRIII double knockouts relative to LDLR−/− controls. Analysis of peripheral CD4+ T-cells by intracellular flow cytometry from double knockouts after 24 weeks of a high-fat diet revealed statistically significant increases in the percentages of cells producing interferon-γ, interleukin (IL)-10, and IL-4 relative to controls, differences that were also observed by analyses of whole aortas for cytokine mRNA levels. As determined by flow cytometry, FcgRIII deficiency resulted in an expansion of CD4+ cells and an increase in the CD4 to CD8 ratio. Analysis of plasma anti-oxidized LDL (OxLDL) antibodies by chemiluminescent assay revealed that IgG1 and IgG2c titers to OxLDL were increased in FcgRIII−/− × LDLR−/− double knockouts relative to LDLR−/− controls, while total IgG levels were similar.

Conclusion
These results reveal altered immunity in FcgRIII−/− × LDLR−/− mice and a reduction in lesion formation associated with increased production of IL-10 by an expansion of CD4+ T-cells. The reduction in lesion formation was manifest well after evidence of an immune response to OxLDL, suggesting that FcgRIII contributes to lesion progression in murine atherosclerosis.

Keywords
Fc receptors • CD16 • Murine atherosclerosis • T-cells • Oxidized LDL • Lesions • IL-10 • Interferon • Lymphoid follicle

1. Introduction
Atherosclerosis is a complex disease with many contributing factors, including important roles for many elements of both innate and adaptive immunity.1–10 Several studies have highlighted the importance of T-cells in the atherogenic process11–15 and in addition there is now a well-documented humoral response to the various oxidation-specific neoepitopes triggered by LDL oxidation. For example, in hypercholesterolaemic murine models, a protective effect was associated with expansion of naturally occurring E06/T15 idiotypic IgM, which has the capacity to block uptake of oxidized LDL (OxLDL) by scavenger receptors.16,17 In the case

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of anti-OxLDL IgG, although the role of such antibodies remains to be clarified, many studies have demonstrated their presence in plasma or atherosclerotic lesions.\textsuperscript{19–22} Because the formation of arterial lesions was reduced in Fc receptor gamma chain knockout mice, it can be inferred that the triggering of activating-type FcγRs by IgG immune complexes is proatherogenic.\textsuperscript{23} However, gamma chain is also associated with the T-cell/CD3 receptor complex and the glycoprotein VI (GPVI) complex and as such plays an important role in T-cell signalling and platelet activation.\textsuperscript{24–27} This suggests that there may be multiple mechanisms by which the absence of gamma chain impacts lesion formation, some of which may function independently of activation by immune complexes. We therefore focused on murine FcγRIII (CD16), an activating-type FcγR expressed on macrophages, dendritic cells, and NK T-cells that binds immune complexes containing IgG1, IgG2c, and IgG2b.\textsuperscript{28–30} Depending on the model, signalling associated with FcγRIII can enhance either T helper cell 1 (Th1) or Th2 biased responses.\textsuperscript{31,32} FcγRIII is also unique among other activating-type FcγRs (FcγRI and FcγRIV) in that it may influence thymic B and T-cell development through interactions with non-immunoglobulin (Ig) ligands.\textsuperscript{33,34} In the present study, we tested the hypothesis that the formation of arterial lesions would be decreased in mice deficient in FcγRIII. We found that relative to LDLR\textsuperscript{−/−} controls, arterial lesion formation was dramatically decreased in FcγRIII-deficient mice on the LDLR receptor negative background, which was most apparent at a relatively later stage of atherogenesis. These data suggest that FcγRIII is important for lesion progression. In addition, analyses of cytokine production suggest that the decrease in arterial lesion formation in FcγRIII-deficient mice involves IL-10 produced by an expanded population of CD4+ T-cells. Signalling pathways associated with FcγRIII may represent targets for modulating the formation of atherosclerotic lesions.

2. Methods

2.1 Mice and study protocol

Expanded methods are provided as Supplemental material online. Male and female LDLR\textsuperscript{−/−} and LDLR\textsuperscript{−/−} × FcγRIII\textsuperscript{−/−} mice, 4–7 weeks of age, were placed on high-fat western diet (Harlan-Teklad no. 88137) and analysed as indicated after 6, 14, or 24 weeks. All procedures and manipulations were approved by the local Institutional Animal Care and Use Committee (IACUC) and conform to guidelines listed in the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.2 Analysis of lesions

Oil Red-O-stained sections of the aortic root and innominate artery were analysed according to Plump et al.\textsuperscript{35} For immunohistochemical analyses for macrophages, acetone-fixed cryosections were stained with anti-CD68. Antibody binding was detected with goat anti-rat Fab\textsubscript{2} conjugated to alkaline phosphatase. To detect the presence of T-cells, serial transverse 10 μm sections of the aortic root, aortic arch, or innominate artery were stained with APC-anti-CD3 (or APC-anti-CD3 plus FITC-conjugated anti-B220) after 14 weeks (5 LDLR\textsuperscript{−/−} and 5 double knockouts) or 24 weeks of high-fat diet (4 LDLR\textsuperscript{−/−} and 4 double knockouts) and analysed with a Nikon Eclipse 80i immunofluorescence microscope with NIS Elements software.

2.3 Analyses of plasma for lipids and antibody levels

Total plasma cholesterol and triglycerides were determined enzymatically (Raichem, Columbia, MD, USA). Antibody titers to OxLDLs were determined by chemiluminescent immunoassay.\textsuperscript{36}

2.4 Flow cytometry

To determine the CD4–CD8 ratio, splenocytes were counted by haemacytometer then stained with FITC-anti-mouse CD4 plus PE-anti-mouse CD8 and analysed by flow cytometry. For intracellular staining of cytokines, peripheral mononuclear cells or purified CD4+ splenocytes were restimulated for 6 h at 37 °C with a leukocyte activation cocktail (eBiosciences). Cells were stained first with PE-Cy5-anti-mouse CD4 followed by fixation in methanol-free paraformaldehyde. The cells were then washed in a permeabilization buffer containing saponin then stained with FITC-anti-mouse IL-10 (rat IgG2b), FITC-anti-mouse IL-4 (rat IgG1), or PE-anti-mouse interferon-γ (rat IgG1) prepared in permeabilization buffer (eBiosciences). Isotype-matched controls were included to determine background fluorescence in each experiment and cells were analysed with a FacScan or Facs Canto flow cytometer.

2.5 Real-time RT–PCR

For the analysis of mRNA levels, aortas were homogenized on ice in Trizol and total RNA immediately isolated and stored at −80°C. Total RNA was subsequently reverse transcribed and the cDNA was used to measure IL-10 and interferon-γ (IFN-γ). The data were normalized to GAPDH and are presented as fold-increase relative to mRNA levels obtained from an aorta from a chow-fed C57BL/6 control.

2.6 Statistical methods

All data were analysed using Prism software. Unpaired Student’s t-test was used to compare groups of data that were normally distributed and of similar variance; otherwise the non-parametric Mann–Whitney test was used. In each case, $P < 0.05$ was taken to indicate statistical significance.

3. Results

3.1 Effects of FcγR deficiency on lesion formation

Lesion area in LDLR\textsuperscript{−/−} and LDLR\textsuperscript{−/−} × FcγRIII\textsuperscript{−/−} mice was analysed in the aortic root after 6, 14, or 24 weeks of high-fat diet. By Oil Red-O staining, no differences in lesion formation were found between LDLR\textsuperscript{−/−} and LDLR\textsuperscript{−/−} × FcγRIII\textsuperscript{−/−} mice after 6 weeks (not shown). After 14 weeks, FcγRIII deficiency was associated with a modest but statistically significant decrease in lesion area in the aortic root for males and females relative to LDLR\textsuperscript{−/−} controls (Figure 1A). After 24 weeks of high-fat diet (Figures 1B and C, and 2), lesion formation relative to LDLR\textsuperscript{−/−} controls had decreased 30% in the aortic root and 50% in the innominate artery ($P < 0.0001$ and 0.0008, respectively). No effect of gender was evident at any time point (not shown).

As shown in Figure 2, the smaller lesions of FcγRIII\textsuperscript{−/−} double knockouts delineated by Oil Red-O staining contained...
correspondingly less CD68+ macrophages. Analyses of CD3 immunofluorescence established the presence of numerous clusters of T-cells in the aortic root, aortic arch, and innominate artery from each strain of mice after 14 weeks of high-fat diet (data not shown). Results were similar after 24 weeks of high-fat diet. Representative examples of clusters of T-cells in the aortic root of an FcγRII−/− double knockout after 24 weeks of high-fat diet are shown in Figure 3. A difference between the controls and double knockouts was the presence of areas adjacent to the aorta in the double knockouts that stained densely for both CD3+ T-cells and B-cells after 24 weeks of high-fat diet (Figure 3). These regions resembled adventitial ectopic lymphoid follicles that were reported for the apolipoprotein E knockout mouse where clusters of T-cells and clusters of B-cells appeared together after a year or more in mice on standard chow. The implications of this are addressed below but the important point is that these data demonstrate the presence of significant numbers of T-cells in the double knockouts at a point (24 weeks of high-fat diet) when differences in cytokine mRNA levels in whole aortas were noted (see what follows).

### 3.2 Effects of FcγR deficiency on plasma lipids

FcγRII−/− deficiency was associated with increased total plasma cholesterol for both males and females (Tables 1 and 2) and the differences were statistically significant after 24 weeks of high-fat diet. Plasma triglyceride levels in FcγRII−/− double knockouts also tended to be greater relative to LDLR−/− controls and the differences were statistically significant for females after 14 weeks of high-fat diet. FcγRII−/−-deficient mice appeared to thrive on high-fat diet and at the time of sacrifice exhibited increased body weight relative to controls (Tables 1 and 2). These data suggest that the reduction in lesion formation in FcγRII−/− double knockouts was not due to changes in plasma lipid levels.

### 3.3 Effects of FcγR deficiency on plasma anti-OxLDL antibodies

Analysis of plasma anti-OxLDL antibodies revealed increased IgG1 and IgG2c titers in FcγRII−/− double knockouts relative to LDLR−/− controls. Statistically significant increases were obtained for each isotype at 14 and 24 weeks of high-fat diet when malondialdehyde-LDL was used for antigen (see Supplementary material online, Figure S1), and the difference was greatest in the case of IgG2c. Similar results were obtained with copper OxLDL (see Supplementary material online, Figure S1). Total plasma IgG was also not different at any point between LDLR−/− mice and FcγRII−/− double knockouts (data not shown). Surprisingly, the levels of anti-OxLDL IgG titers for both strains, which were greatest at 14 weeks of high-fat diet, had fallen by 24 weeks, while anti-OxLDL IgM titers were greatest at 24 weeks. Similar to IgG1 and IgG2c titers, IgM titers in FcγRII−/− double knockouts were significantly increased relative to LDLR−/− controls (see Supplementary material online, Figure S2). These data suggested that there was a dysregulation of antibody production to OxLDLs raising the possibility of altered cytokine production in FcγRII−/− double knockouts after weeks of high-fat diet.

### 3.4 Analyses of cytokine production

To address potential mechanisms by which the absence of FcγRII resulted in decreased lesion formation, CD4+ T-cells isolated from peripheral blood (Figure 4), and spleen (Figure 5), were analysed for the presence of cytokines by intracellular flow cytometry after 24 weeks of high-fat diet. The results indicated similar increases in the numbers of CD4+ T-cells expressing interleukin-4 (IL-4), IL-10, or IFN-γ obtained from FcγRII−/− double knockouts relative to LDLR−/− controls, each difference being statistically significant (Figure 4). Cytokine expression was barely detectable in cells obtained from age-matched controls.
Figure 2 Decreased lesion formation in FcγRIII−/− × LDLR−/− double knockout mice. Representative illustrations of the distribution of neutral lipid (A and B) or of CD68+ macrophages (C and D) in the aortic root of the indicated strains after 24 weeks of high-fat diet. Sections taken through the valve leaflets are shown in each case. All of the material extending into the lumen stained with Oil Red-O, but gaps indicative of cholesterol clefts are present in regions largely devoid of cells in each case.

Figure 3 T-cell content of arterial lesions in the aortic root of FcγRIII double knockouts after 6 months of high-fat diet. Sections were fixed in acetone and stained with APC-anti-CD3 (A) or APC-anti-CD3 plus FITC-anti-B220 (B) as described in Methods. (A) A typical example of clusters of T-cells (red) is shown in the plaque from a section taken through the aortic root; (B) an ectopic follicle with a core of T-cells surrounded by numerous B-cells (green) in a section adjacent to the aortic root. The upper arrow denotes the aorta while the lower arrow is opposite a layer of heart muscle.
of each strain on chow diet (data not shown), consistent with a response to the inflammatory effects of high-fat diet. More dramatic results were obtained with CD4+ T-cells purified from spleens. In the example shown in Figure 5, there was a 5.2-fold increase in the number of CD4+ T-cells expressing IL-10 in FcRRII−/− double knockouts after 24 weeks of high-fat diet and a two-fold increase in the number of cells expressing IFN-γ. These data suggest an alteration in T-cell development and/or function in FcRRII−/− double knockouts dependent in part on high-fat diet. This was supported further by measuring the number of CD4+ and CD8+ T-cells in spleens taken from each strain after 24 weeks of high-fat or chow diet. FcRRII−/− double knockouts on high-fat diet exhibited a dramatic increase in the total number of splenocytes (Figure 6B), a significant increase in the total number of CD4+ cells, and as a result, a significant increase in the CD4 to CD8 ratio (for 14 double knockouts and 10 LDLR−/− controls, the mean CD4 to CD8 ratios were 3.0 ± 0.3 vs. 1.7 ± 0.1, respectively, P = 0.003). Thus, relative to the situation for controls, there was an expansion of the numbers of CD4+ T-cells in FcRRII−/− double knockouts that was dependent on high-fat diet.

Data supporting that the changes in cytokine production noted above may have contributed to the reduction in lesion formation in the absence of FcRRII was obtained by analysing mRNA levels of IL-10 and IFN-γ in aortas taken after 24 weeks of high-fat diet. Using an aorta from a chow-fed C57BL/6 mouse for baseline, we determined that the levels of mRNA for each cytokine in LDLR−/− mice and FcRRII−/− double knockouts were statistically significant in each case. For IL-4, P = 0.002; for IL-10, P = 0.02, and for IFN-γ, P = 0.009. Shown are the means ± SD.

4. Discussion

There are two important findings of this study. The first is a significant reduction in the formation of arterial lesions in FcγRIII-deficient mice after 24 weeks of high-fat diet but not earlier, suggesting that FcγRIII plays an important role in lesion progression (Figure 1). The second is that this reduction was associated with the

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### Table 1 Selected endpoints from LDLR−/− and FcγRIII−/− double knockouts after 14 weeks of high-fat diet

<table>
<thead>
<tr>
<th>Strain</th>
<th>N</th>
<th>TC</th>
<th>TG</th>
<th>BW</th>
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<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLR−/−</td>
<td>25</td>
<td>742 ± 37</td>
<td>679 ± 48</td>
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<tr>
<td>DKO</td>
<td>14</td>
<td>812 ± 34</td>
<td>785 ± 59</td>
<td>42.7 ± 1.9†</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLR−/−</td>
<td>21</td>
<td>578 ± 23</td>
<td>281 ± 18</td>
<td>24.2 ± 3.7</td>
</tr>
<tr>
<td>DKO</td>
<td>18</td>
<td>682 ± 51</td>
<td>373 ± 30‡</td>
<td>32.2 ± 4.7*</td>
</tr>
</tbody>
</table>

TC, total plasma cholesterol; TG, plasma triglycerides, each in mg/dL; DKO, double knockout; BW, body weight, in grams. For comparisons between strains: †, P = 0.03; ‡, P = 0.009; *, P > 0.0001.

### Table 2 Selected endpoints from LDLR−/− and FcγRIII−/− double knockouts after 24 weeks of high-fat diet

<table>
<thead>
<tr>
<th>Strain</th>
<th>N</th>
<th>TC</th>
<th>TG</th>
<th>BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLR−/−</td>
<td>6</td>
<td>788 ± 96</td>
<td>424 ± 75</td>
<td>37.4 ± 7.1</td>
</tr>
<tr>
<td>DKO</td>
<td>5</td>
<td>934 ± 86†</td>
<td>620 ± 229</td>
<td>42.2 ± 7.2†</td>
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<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLR−/−</td>
<td>6</td>
<td>660 ± 145</td>
<td>449 ± 186</td>
<td>26.3 ± 4.0</td>
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<tr>
<td>DKO</td>
<td>5</td>
<td>867 ± 134‡</td>
<td>550 ± 62</td>
<td>29.7 ± 5.1</td>
</tr>
</tbody>
</table>

TC, total plasma cholesterol; TG, plasma triglycerides, each in mg/dL; DKO, double knockout; BW, body weight, in grams. For comparisons between strains: †, P = 0.02; ‡, P = 0.047.

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Figure 4 Increased cytokine expression in peripheral blood CD4+ T-cells from FcγRIII−/− × LDLR−/− double knockout mice. CD4+ T-cells were obtained from four LDLR−/− mice and four FcγRIII−/− double knockouts after 24-weeks of high-fat diet. Levels of the indicated cytokines were determined by intracellular staining and flow cytometry. The differences in cytokine levels between LDLR−/− mice and FcγRIII−/− double knockouts were statistically significant in each case. For IL-4, P = 0.002; for IL-10, P = 0.02, and for IFN-γ, P = 0.009. Shown are the means ± SD.
development of an expanded population of CD4+ T-cells producing the anti-atherogenic cytokine IL-10.48–43 (Figures 4–6). The presence of T-cells in lesions from double knockouts together with decreased numbers of macrophages (Figures 2 and 3) suggests that T-cells may have been an important source of cytokines in the lesions (Figure 7). Contributions from macrophages or dendritic cells, however, cannot be excluded. While an exhaustive analysis of leukocyte content in lesions was not undertaken, the data suggest that the absence of FcγRIII was associated with differences in leukocyte content after 6 months of high-fat diet. It was interesting and surprising to note the presence of numerous clusters of T-cells and B-cells that resembled adventitial ectopic lymphoid follicles first reported for atherosclerosis in the apolipoprotein E knockout mouse.27 In the present study, we noted these structures at the level of the aortic root (Figure 3) and ascending arch (not shown) in the double knockouts, but not LDLR<sup>−/−</sup> controls. The role that these structures serve has not been defined, but it is interesting to speculate that the absence of FcγRIII signalling, which was associated with increased numbers of peripheral T-cells (Figures 5 and 6), may have played a role in enhancing the formation of these ectopic lymphoid structures.

The decreased accumulation of lipids and macrophages seen in lesions of FcγRIII<sup>−/−</sup> double knockouts was also observed in studies of IL-10 hyperexpression in murine atherosclerosis.41 Remarkably, the reduction in lesion formation was lower in the absence of FcγRIII despite the fact that total plasma cholesterol levels in FcγRIII<sup>−/−</sup> double knockouts tended to be greater relative to LDLR<sup>−/−</sup> controls (Tables 1 and 2). That the reduction in lesion formation was more evident after 24 weeks of high-fat diet rather than 14 weeks suggests that FcγRIII activity is important for lesion progression. These results contrast with the study of Hernandez-Vargas et al.23 who found that lesion formation was significantly decreased in gamma chain-deficient mice on the apoE-deficient background by 16 weeks of high-fat diet. Although results of later time points were not reported in that study, the differences between their findings at 16 weeks and ours at a similar time point suggest that the mechanisms underlying lesion formation are unique in each model. This is not surprising given the differences noted between the two models. As stated earlier, reports suggest that both T-cell signalling and platelet activation mediated by GPVI are altered by the absence of the Fc receptor gamma chain.24,25

Of the three activating-type FcγRs in mice, FcγRIII is unique in its IgG ligand binding properties and in its ability to bind non-Ig ligands, each of which could have played a role in the present study. The increase in both anti-OxLDL IgG<sub>2c</sub> (Th1 dependent) and IgG1 (Th2 dependent) in the absence of FcγRIII is consistent with increases in both Th1-dependent (IFN-γ) and Th2-dependent cytokines (IL-10) seen in this study (see Supplementary material).
online, Figure S1) and may have occurred as a result of the effects on B-cells of altered cytokine production. These results add to the complexity of FcγRIII activity in the regulation of immune phenomena in these models. Indeed, in combination with TLR-4 ligands such as lipopolysaccharide (LPS), FcγRIII cross-linking on dendritic cells regulates Th2 cytokine production independently of its ability to process immune complexes, a characteristic that was not shared by the high-affinity FcγRI.

In mice, FcγRIII mediated signalling is important for thymic T-cell development and includes the involvement of non-immunoglobulin ligands. The effects of FcγRIII activity on lesion formation could therefore depend on the interaction with immune complexes and/or with non-immunoglobulin ligands. In support of this, a recent report demonstrated that FcγRIII is a receptor for E. coli.

The finding of increased production of both IL-10 and IFN-γ was surprising in that IFN-γ is a Th1 cytokine with well-documented pro-atherogenic activity. On the other hand, IL-10 is a Th2-like cytokine with a well-documented anti-atherogenic role. Similar to the present study, hyperexpression of IL-10 in LDLR−/− mice resulted in a 50% reduction in aortic lesion formation after 20 weeks of high-fat diet, but in contrast, production of IFN-γ by T-cells was reduced and the ratio of anti-OxLDL IgG1 to IgG2c was increased. The increase in production of IFN-γ in the present study may have been at least in part responsible for the lack of a change in the ratio of anti-OxLDL IgG2c to IgG1 (see Supplementary material online, Figure S1). IFN-γ is important for priming T-cells for production of Th2 cytokines such as IL-4 and could have played such a role in the absence of FcγRIII.

These findings are consistent with the changes in cytokines and the decrease in arterial lesion formation seen in the present study. Thus, while decreased lesion formation observed in the present study is consistent with the inhibitory role of IL-10, it does not exclude the importance of IFN-γ.

In summary, the data support that the activity of FcγRIII, a structurally and functionally unique activating-type FcγR, contributes to arterial lesion progression in LDL receptor-deficient mice and that IL-10 may play an important role in this phenomenon. In the absence of FcγRIII, there was an expansion of CD4+ T-cells producing IL-10 and IFN-γ and a reduction in the size and lipid content of arterial lesions that was more apparent after 24 weeks of high-fat diet. Signalling pathways regulating these phenomena may represent targets that could be exploited therapeutically to regulate the progression of atherosclerotic diseases.

Supplementary material

Supplementary Material is available at Cardiovascular Research online.

Conflict of interest: none declared.

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