Deletion of the Fc receptors γ chain preserves endothelial function affected by hypercholesterolaemia in mice fed on a high-fat diet

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Aims To clarify the role of Fc receptors (FcR) for immunoglobulin in endothelial dysfunction induced by hypercholesterolaemia, we evaluated the effect of deletion of the FcR γ chain on endothelium-dependent relaxation and oxidative stress after 10 weeks on a high-fat diet in FcR γ²/² mice compared with that in wild-type mice.

Methods and results Plasma cholesterol levels of those on the high-fat diet were significantly increased compared with those on the normal chow diet in both groups of mice. Endothelium-dependent relaxation of the aortic ring with acetylcholine in wild-type mice was significantly reduced by the high-fat diet (ED50: 0.22 vs. 0.43 nM, P < 0.002), whereas the relaxation in FcR γ²/² mice was not inhibited (ED50: 0.22 vs. 0.23 nM, NS). Furthermore, superoxide detection by dihydroethidium-derived fluorescence and immunohistochemical staining of p22phox expression were significantly increased in wild-type mice fed on the high-fat diet, while these oxidative stresses in FcR γ²/² mice were not enhanced by the high-fat diet. Oil Red O-staining showed no significant lipid accumulation at the aortic sinus in both groups of mice.

Conclusion This study demonstrates that the deletion of the FcR γ chain preserves the endothelial function and attenuates oxidative stress affected by hypercholesterolaemia in FcR γ²/² mice. These results indicate that FcR may play the pivotal role in endothelial dysfunction through oxidative stress induced by hypercholesterolaemia.

1. Introduction

Vascular endothelium has multiple functions that protect against the development of atherosclerosis caused by risk factors that include hypertension, hypercholesterolaemia, diabetes mellitus, and smoking. At the initial stage of atherosclerosis, these risk factors induce endothelial dysfunction through the production of oxidant stress, which might reduce the bioactivity of endothelium-derived nitric oxide (NO), consequently impairing endothelium-dependent vasodilation.¹⁻³ In particular, hypercholesterolaemia is a major factor for oxidant stress-inducing endothelial dysfunction, which has been observed in patients with hypercholesterolaemia.⁴⁻⁵ and in animal models fed on hypercholesterolaemic diets.⁶⁻⁷ Further evidence has demonstrated that increased production of vascular superoxide and other reactive oxygen species (ROS) in hypercholesterolaemia contributes to the reduced bioactivity of NO in endothelial dysfunction.⁸⁻⁹

Recently, immune and inflammatory reactions have been demonstrated to be involved in the initiation and development of atherosclerosis.¹⁰ Fc receptors (FcR) for immunoglobulins play important roles in the activation and regulation of immune response and inflammatory reactions.¹¹⁻¹⁴ Vascular cells, such as endothelium, smooth muscle cell, monocyte, and neutrophils, express FcR and are crucially involved in atherosclerosis.¹⁵⁻¹⁶ The γ chain of the FcR is a membrane subunit and has important functions, specifically, to assemble the receptors for cell surface expression and to transmit the signal into the cell interior. Recent studies have reported that FcR activates the generation of superoxide and other ROS in mast cells.¹⁷⁻¹⁹ However, the role of FcR in endothelial dysfunction caused by the generation of superoxide and ROS in hypercholesterolaemia has not been elucidated.
The purpose of this study is to clarify the role of FcR in endothelial dysfunction and the oxidant stress-generating superoxide in hypercholesterolaemic mice. We used FcRγ chain knockout mice (FcRγ−/− mice), and compared the effect of deletion of the FcRγ chain on endothelium-dependent relaxation and superoxide production affected by a high-fat diet in the FcRγ−/− mice, and the wild-type mice.

2. Methods

2.1 Mice and diets

FcRγ−/− mice were generated by a homologous recombination method, as described previously.20,21 The wild-type mice and FcRγ−/− mice in homozygous C57BL/6 background were bred and maintained in the SPF facility of Juntendo University. Mice used in all experiments were male. Two diets were used: (i) a normal chow diet: MF diet (from Oriental Yeast Co., Tokyo, Japan) containing 0.9% (w/w) cholesterol and 0.09% (w/w) cholesterol and 5.6% (w/w) fat; and (ii) a high-fat diet: MF diet (from Oriental Yeast Co., Tokyo, Japan) containing 1.5% (w/w) cholesterol and 6% (w/w) fat (essentially similar to Western style diet from Oriental Yeast Co., Tokyo, Japan). The wild-type mice and FcRγ−/− mice were fed on the high-fat diet for 10 weeks from the age of 8 weeks. Mice were provided with the diet and water ad libitum and were maintained on a 12 h light/dark cycle. After feeding them on the high-fat diet, both groups of mice were starved and euthanized for experiments. Plasma lipids including lipoproteins were measured by high-performance liquid chromatography analysis. All animal experiments were conducted and approved according to the Guidelines for Animal Experiments at Juntendo University, School of Medicine. The investigation conforms to 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 Examination of vascular relaxation with acetylcholine and sodium nitroprusside

After the mice were sacrificed under anaesthesia, the descending thoracic aorta was isolated and cut into transverse vascular rings (∼2 mm in length), and used to measure the changes in force. Care was taken not to touch the endothelial surface to preserve the functional endothelium. The techniques used for the measurement of changes in force in thermostated (37°C) and oxygenated Krebs bicarbonate buffer (pH 7.4), with the following content: 118 mM NaCl, 4.7 mM KCl, 1.5 mM CaCl₂, 25 mM NaHCO₃, 1.1 mM MgSO₄, 1.2 mM KH₂PO₄, and 5.6 mM glucose, were adapted from previously described methods.8 Optimal passive tension of 0.5 g was applied to vascular rings throughout the experiment. The vascular rings were precontracted with 30 mM KCl. After washing out, the vessels were submaximally contracted with 0.3 mM phenylephrine, and once a steady-state level of contraction was observed, endothelial-dependent relaxation was elicited by cumulative concentration of acetylcholine, and endothelial-independent relaxation was elicited by cumulative concentration of sodium nitroprusside, respectively. Relaxation was expressed as the percentage change of the steady-state level of contraction. R₉₅ was determined from the maximum relaxation of established tone, and ED₅₀ was calculated from a logit transformation of relaxation data.

2.3 Histological analysis of the atherosclerotic lesion at the aortic sinus

Atherosclerotic lesions at the aortic sinus were analysed by histological staining as described previously.12 Briefly, the upper portions of the heart and proximal aorta were embedded in OCT compound and stored at −70°C. Serial 10 μm thick cryosections of the aorta, beginning at the aortic root, were collected through 200 μm segments of the aortic sinus. These sections were stained with Oil Red O and haematoxylin. For each mouse, three different sections were examined and lipid lesions assessed as positive Oil Red O-staining were quantified for the comparison of atherosclerotic lesions.

2.4 Superoxide detection of the aorta with oxidative fluorescent dye dihydroethidium in vitro

Dihydroethidium (DHE) fluorescence is a widely used sensitive superoxide probe. Oxidation of membrane-permeable DHE by superoxide yields the fluorescent DNA-binding membrane-impermeable compound ethidium. Frozen, enzymatically intact, 10 μm thick cross-sections of aorta were incubated with DHE (10 μmol/L) in PBS for 30 min at 37°C in a humidified chamber protected from light.24,25 DHE is oxidized on reaction with superoxide to ethidium, which binds to DNA in the nucleus and fluoresces red. The images were obtained with a laser scanning confocal microscope (Carl Zeiss). DHE fluorescence from high-power (x200) images was quantified by automated image analysis using the J software (National Institutes of Health). For each vessel, mean fluorescent area and total vessel wall area (μm²) were determined from three separate cross-sections of the vessel to produce n = 1. The percentage of fluorescent area in the total vessel wall area was calculated for comparison.

2.5 Immunohistochemical analysis of the descending aorta with anti-p22phox

Cryosections of the descending aorta were incubated with goat anti-human p22phox antibodies (Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA). After washing with the medium, the sections were incubated with biotinylated rabbit anti-goat IgG (Chemicon, Temeculla, CA, USA) as secondary antibodies, and then treated with horseradish peroxidase-conjugated streptavidin using the LSAB2 kit (Dako). The counterstaining for the nucleus was performed with Mayer’s haematoxylin (Wako Co., Tokyo, Japan). Staining was completed using 3,3′-diaminobenzidine (Sigma, St Louis, MO, USA) as the chromogen. Samples were examined with a Zeiss Axioplan Microscope.26 For the quantification of chromogen, digitized images were captured and analysed with a KS400 version 3.0 image analysis system (KS400, Carl Zeiss Vision GmbH, Hallbergmoos, Germany). For each vessel, mean area (μm²) of p22phox-positive chromogen and total vessel wall area were determined from three separate cross-sections of the vessel to produce n = 1. The percentage of positive area in the total vessel wall area was calculated for comparison.

2.6 Flow cytometric measurement of superoxide production in neutrophils

Intracellular generation of superoxide and the other ROS was indirectly measured using 2′,7′-dichlorofluorescein diacetate (DCFH-DA) oxidation as described previously.27 An aliquot (100 μL) of cell suspension of whole blood at a density of 1 × 10⁸ cells/mL was preloaded with 100 μM DCFH-DA at 37°C in a shaking water bath for 15 min. Cell stimulation was then initiated with the addition of phorbol myristate acetate (PMA) (10 μg/mL). The non-fluorescent deacetylated product dichlorofluorescein (DCF) is rapidly oxidized to a fluorescent compound dichlorofluorescein (DCF) in the presence of superoxide. After red blood cells in whole blood were lysed and white blood cells were suspended with PBS, the intracellular fluorescence of DCF was immediately measured using a Coulter flow cytometer.28 Spontaneous oxidation of DCFH by resting cells without PMA stimulation was evaluated with saline-treated preparations. At least 10,000 cells were examined per sample. The data were analysed using Cell Quest software.
(Becton–Dickinson), and the mean fluorescence intensity (MFI) was used to quantify the response.

2.7 Statistical analysis

The data were presented as mean ± SE. Statistical differences between the two groups were analysed by unpaired t-test. The differences between the four groups were analysed by one-way ANOVA, followed by an appropriate post hoc analysis with Bonferroni correction for multiple comparisons. Data analysed with P < 0.05 were considered statistically significant.

3. Results

3.1 Plasma lipids in mice on the normal chow diet and on the high-fat diet

Plasma levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in the wild-type mouse and in the FcRγ⁻/⁻ mouse are shown in Table 1. For the basal reference, TC and LDL-C levels in the mice fed on the normal chow diet did not differ between the wild-type mouse and the FcRγ⁻/⁻ mouse (n = 9, TC: 107 ± 4 vs. 96 ± 4 mg/dL, NS; LDL-C: 14 ± 2 vs. 12 ± 1 mg/dL, NS). After 10 weeks on the high-fat diet, the levels of TC and LDL-C were significantly increased compared with those on the normal chow diet in both wild-type (n = 9, TC: 69% increased, P < 0.01; LDL-C: 86%, P < 0.005) and FcRγ⁻/⁻ mice (n = 7, TC: 57% increased, P < 0.01; LDL-C: 83%, P < 0.005). On the high-fat diet, the levels of TC and LDL-C in the FcRγ⁻/⁻ mice were not different compared with those in the wild-type mice.

<table>
<thead>
<tr>
<th>Diet</th>
<th>Cholesterol (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
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<tr>
<td></td>
<td>Normal chow</td>
<td>High-fat</td>
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<tr>
<td>Wild-type mice</td>
<td>107 ± 4</td>
<td>181 ± 10⁺</td>
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<td>(n = 9)</td>
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<tr>
<td>FcRγ⁻/⁻ mice</td>
<td>96 ± 4</td>
<td>151 ± 12⁺</td>
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<td>(n = 9)</td>
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Table 1 Plasma levels of TC and LDL-C in wild-type mice and in FcRγ⁻/⁻ mice on normal chow diet and high-fat diet

All values are mean ± SE. *P < 0.0005.

3.2 Effect of a high-fat diet on endothelium-dependent relaxation of the aortic ring with acetylcholine

Relaxations with acetylcholine of aortic rings from mice fed on the normal chow diet and of those fed on the high-fat diet are shown in Figure 1A and B. In the wild-type mice, relaxation in the mice fed on the normal chow diet had ED₅₀ = 0.22 ± 0.03 nM and Rmax = 75.7 ± 4.3% (n = 6), and relaxation in the mice fed on the high-fat diet had ED₅₀ = 0.43 ± 0.04 nM and Rmax = 60.3 ± 3.8% (n = 6). These results show endothelium-dependent relaxation was significantly reduced in the wild-type mice fed on the high-fat diet compared with the response on the normal chow diet (P < 0.002). In contrast, the relaxation response in FcRγ⁻/⁻ mice was not inhibited by feeding on the high-fat diet (normal chow diet: ED₅₀ = 0.22 ± 0.03 nM, Rmax = 77.5 ± 2.7%, vs. high-fat diet: ED₅₀ = 0.23 ± 0.04 nM, Rmax = 72.6 ± 7.3%, NS). Furthermore, endothelium-independent relaxation with sodium nitroprusside is shown in Figure 1C and D. In both groups of mice, relaxation with sodium nitroprusside was not changed by feeding on the high-fat diet compared with the response on the normal chow diet.

3.3 Superoxide detection with oxidative fluorescent dye dihydroethidium in the aortic wall

The presence and distribution of superoxide induced by the high-fat diet in the descending aortic wall were detected using the fluorescent dye DHE. Representative images of DHE-derived fluorescence microscopy in the cross-sections of the descending aortic wall are shown in Figure 2A, and quantitative analysis of DHE-derived fluorescent-positive areas is shown in Figure 2B. Total vessel wall areas from the cross-sections were not significantly different between the four groups of mice, and the percentage of fluorescent-positive area in the total vessel wall area was compared. Wild-type mice showed significantly increased positive areas of DHE-derived fluorescence in the aortic wall on the high-fat diet compared with the positive areas on the normal chow diet (n = 6, normal chow diet: 4154 ± 666 μm², 3.9 ± 0.7%, vs. high-fat diet: 5673 ± 2015 μm², 5.1 ± 2.0%, NS). Furthermore, positive areas of DHE-derived fluorescence in the wild-type mice were significantly greater than those in FcRγ⁻/⁻ mice on the high-fat diet (P < 0.0005).

3.4 Immunohistochemical staining with anti-p22phox in the aortic wall

Immunohistochemical detection of p22phox, which is a membrane-integrated protein for a subunit of the NADPH oxidase, was performed. Representative images of immunohistochemical staining with anti-p22phox in the cross-sections of the descending aortic wall are shown in Figure 3A, and a quantitative analysis of p22phox-positive areas is shown in Figure 3B. Total vessel wall areas from cross-sections were not significantly different between the four groups of mice, and the percentage of p22phox-positive areas in the total vessel wall area was compared. Wild-type mice showed significantly increased expression of p22phox in the aortic wall on the high-fat diet compared with the expression of those on the normal chow diet (n = 6, normal chow diet: 1379 m², 72.6%, vs. high-fat diet: 2015 m², 72.6%, P < 0.0001). In FcRγ⁻/⁻ mice, however, there was no change of p22phox expression on the high-fat diet (n = 6, normal chow diet: 1379 m², 72.6%, vs. high-fat diet: 2015 m², 72.6%, P < 0.0001). In FcRγ⁻/⁻ mice, however, there was no change of p22phox expression on the high-fat diet (n = 6, normal chow diet: 1379 m², 72.6%, vs. high-fat diet: 2015 m², 72.6%, P < 0.0001). In contrast, FcRγ⁻/⁻ mice did not show significant change of DHE-derived fluorescent-positive areas by feeding on the high-fat diet (n = 6, normal chow diet: 4154 ± 666 μm², 3.9 ± 0.7%, vs. high-fat diet: 5673 ± 2015 μm², 5.1 ± 2.0%, NS). Furthermore, positive areas of DHE-derived fluorescence in the wild-type mice were significantly greater than those in FcRγ⁻/⁻ mice on the high-fat diet (P < 0.0005).

3.5 Measurement of superoxide production by flow cytometric analysis

Figure 4 presents measurement of the production of superoxide in neutrophils by flow cytometric analysis. As shown...
Figure 1  Comparison of vascular relaxation of aortic ring to acetylcholine and sodium nitroprusside between high-fat and normal chow diets. (A and B) Endothelium-dependent relaxation response was elicited by cumulative concentration of acetylcholine (1 nM –1 μM) in wild-type mice (n = 6) and FcRγ−/− mice (n = 6). (C and D) Endothelium-independent relaxation response was elicited by cumulative concentration of sodium nitroprusside (0.5 nM –1 μM) in wild-type mice (n = 6) and FcRγ−/− mice (n = 6). The results of relaxation were expressed as the percentage changes of steady-state level of contraction with 0.3 μM phenylephrine. Open and closed circles represent normal chow diet and high-fat diet, respectively. Error bars represent SE. *P < 0.05 when compared with normal chow diet.

Figure 2  Superoxide detection with oxidative fluorescent dye DHE in the descending aortic wall. (A) Cross-sections of descending aorta were labelled with the fluorescent dye DHE. (a–d) Upper (a and b) and lower (c and d) panels are representative fluorescent photomicrographs in wild-type mice and FcRγ−/− mice, respectively. Left (a and c) and right (b and d) panels are those on normal chow diet and high-fat diet, respectively. Scale bars = 50 μm. (B) Positive area of fluorescent dye DHE was determined by quantitative method in wild-type mice (n = 12) and FcRγ−/− mice (n = 12). Each group consisted of normal chow diet (n = 6) and high-fat diet (n = 6). The percentage of fluorescent-positive area in the total vessel wall area was compared. The fluorescent-positive area and total vessel wall area (μm²) were also presented. Horizontal bars represent mean ± SE.

in Figure 4A, the histogram of the wild-type mice fed on the high-fat diet is shifted to the right compared with the histogram of the normal chow diet, and also with the histogram in the FcRγ−/− mice fed on the high-fat diet. Comparison of MFI representing the production of superoxide calculated from the histogram in neutrophils is shown in Figure 4B. Superoxide production in the wild-type mice was significantly increased by feeding on the high-fat diet compared with the production in the mice fed on the normal chow diet (n = 6, 60 ± 14 vs. 118 ± 42 MFI, P < 0.005), whereas superoxide production in the FcRγ−/− mice was not changed by feeding on the high-fat diet (n = 6, 47 ± 33 vs. 40 ± 18 MFI, NS).
3.6 Histological analysis for lipid-staining area at the aortic sinus

Figure 5 shows representative images of Oil Red O-stained aortic sinus in the wild-type mice (n = 6) and FcRγ2/2 mice (n = 6) fed on the high-fat diet. Histological analysis of three sections in each mouse showed no significant finding of lipid accumulation at the aortic sinus both in wild-type mice and in FcRγ2/2 mice fed on a high-fat diet.

4. Discussion

This study demonstrates that endothelium-dependent vascular relaxation was not reduced in FcRγ2/2 mice fed on the high-fat diet, suggesting that the deletion of the FcRγ chain preserves the endothelial function in hypercholesterolaemia. Furthermore, superoxide production of oxidant stress was not enhanced in the FcRγ2/2 mice by the high-fat diet compared with that in the wild-type mice. These results indicate that FcR is involved in endothelial dysfunction induced by the oxidant stress of hypercholesterolaemia.

Hypercholesterolaemia is thought to be one of the causal factors for endothelial dysfunction by its oxidant stress producing ROS and decreasing NO bioactivity in the endothelium. Many clinical studies have demonstrated that endothelial function is impaired in patients with hypercholesterolaemia and that lipid-lowering therapy, especially with statins, improves endothelial function impaired by hypercholesterolaemia.29,30 However, the precise mechanism of hypercholesterolaemia-inducing endothelial dysfunction has not been fully elucidated. In this study, we show...
that the wild-type mice fed on a high-fat diet significantly reduced endothelium-dependent relaxation of the aortic ring with acetylcholine and did not alter endothelium-independent relaxation with sodium nitroprusside. In contrast, FcRγ−/− mice did not alter either endothelium-dependent or independent relaxation through the high-fat diet. These results indicate that endothelial function is preserved by the deletion of the FcRγ chain even in hypercholesterolaemia. Although, to our knowledge, the functional role of FcR in endothelial dysfunction induced by hypercholesterolaemia has not been proposed, the present study clearly showed for the first time that FcR contributes to endothelial dysfunction in hypercholesterolaemic mice.

Evaluating the oxidative stress in both types of mice, the high-fat diet significantly increased superoxide detection by DHE-derived fluorescence and the expression of p22phox by immunohistochemical analysis in the wild-type mice, but not in the FcRγ−/− mice. These findings are consistent with the results of superoxide production measured by flow cytometric analysis of fluorescent DCF and are also linked to the vascular relaxation response. Consequently, oxidant stress of hypercholesterolaemia induces superoxide production and endothelial dysfunction in the wild-type mice, but not in FcRγ−/− mice, suggesting that FcR may play a pivotal role in generating superoxide and ROS through activating NADPH oxidase. Recent immunological studies have reported that signalling of FcR activates the intracellular generation of ROS in mast cells. Based on this association between FcR and superoxide production upon oxidant stress, we speculate that immunoreceptor tyrosine-based activation motif of the FcR subunit, activated by the γ chain, is linked to tyrosine phosphorylation for the activation of NADPH oxidase. Therefore, deletion of the FcRγ chain might not activate NADPH oxidase through the same pathway of tyrosine phosphorylation and attenuate the superoxide production and endothelial dysfunction induced by oxidant stress of hypercholesterolaemia in FcRγ−/− mice.

Immune reactions linked to inflammatory response are now thought to contribute to the development of atherosclerosis. The FcR for immunoglobulins binds the immune-complex of antigen–antibody to mediate signals that induce immune and inflammatory reactions. Growing evidence indicates that the FcγR-dependent pathway is involved in the pathogenesis of atherosclerosis. Several experimental studies have implicated that FcR plays an important role in the phagocytosis of monocyte-macrophage against the immune complex composed of native or oxidized LDL binding to antibodies or C-reactive protein. Furthermore, some clinical studies have shown an association between the polymorphism of FcR genes and atherosclerotic coronary artery disease as well as peripheral atherosclerotic disease. Although a direct association of FcR with the development of atherosclerosis has not been investigated, a recent study indicates the contribution of FcR to the development and progression of atherosclerosis using double-knockout mice by crossing apolipoprotein E-deficient mice with FcRγ chain-deficient mice, which they generated. They demonstrated that FcRγ chain deficiency prevents against the development of atherosclerosis and regulates chemokine expression and leukocyte invasion of the vessel wall. In our study, histological analysis of the aortic sinus did not reveal lipid accumulation after feeding the high-fat diet to both groups of mice. Moreover, lipid rich atherosclerotic lesions were not recognized at the surface wall of the dissected aorta stained with Oil Red O in both groups of mice fed on the high-fat diet (data not shown). These results indicate that FcR contributes to the immune mechanisms underlying the development of atherosclerosis, in addition to endothelial dysfunction in which atherosclerosis is initiated without lipid accumulation at the vessel wall.

Besides oxidant stress on the vascular wall, the effect of deletion of the FcRγ chain on systemic immune and inflammatory reactions should be considered. In general, the activating-type FcR comprises the γ chain and the inhibitory-type FcR lacks the γ chain. The activating-type FcR does not function efficiently in the FcRγ−/− mice, whereas the inhibitory-type FcR is predominant in vivo. This imbalance between the two types of FcR induces suppression of systemic immune and inflammatory reactions, which might protect endothelial function from systemic effect of hypercholesterolaemia. Moreover, we previously demonstrated that neointimal formation after mechanical injury by spring wire is inhibited in the FcRγ−/− mice in vivo. This protective effect against injury such as endothelial denudation was considered as resulting from suppressed platelets and neutrophil activation, consequently...
leading to downregulation of cytokines, chemokines, and adhesion factors. Several studies have shown that these molecules are related to the endothelial function and the development of atherosclerosis.

Interestingly, the effect of FcR on lipid metabolism has not been examined. The present study clarified whether plasma lipids were increased by the high-fat diet in the FcR γc−/− mice as well as the wild-type mice. The levels of TC and LDL-C were not different between each group of mice fed on the normal chow diet. After feeding on the high-fat diet, the levels of TC and LDL-C in each group of mice were significantly increased by 1.6- and 1.8-fold, respectively, compared with those on the normal chow diet (TC, P < 0.01, LDL-C, P < 0.005). These levels were not significantly different between the wild-type mice and the FcR γc−/− mice. These results indicate that FcR does not contribute to the increased plasma levels of LDL-C induced by the high-fat diet. However, the levels of TC and LDL-C in the FcR γc−/− mice were not significantly different, but consistently and slightly, lower than those in the wild-type mice on the high-fat diet. The potential effect of FcR on lipid metabolism should be further investigated in the FcR γc−/− mice.

In conclusion, this is the first study demonstrating that the deletion of the γ chain of the FcR subunit preserves the endothelial function affected by hypercholesterolaemia in the FcR γc−/− mice compared with the wild-type mice, and that superoxide production of oxidative stress was not enhanced by hypercholesterolaemia in the FcR γc−/− mice. These results imply that FcR plays a pivotal role in endothelial dysfunction by enhancing NADPH oxidase and oxidative stress induced by hypercholesterolaemia, contributing to the elucidation of immune systems associated with the initiation of atherosclerosis. Further investigation of FcR functions involved in the endothelial dysfunction and oxidative stress is expected.

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Conflict of interest: none declared.

References


