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Oxidized low-density lipoprotein-induced foam cell formation is mediated by formyl peptide receptor 2

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ABSTRACT

The increased level of LDL and its modification into oxLDL has been regarded as an important risk factor for the development of cardiovascular diseases such as atherosclerosis. Although some scavenger receptors including CD36 and RAGE have been considered as target receptors for oxLDL, involvement of other receptors should be investigated for oxLDL-induced pathological responses. In this study, we found that oxLDL-induced foam cell formation was inhibited by formyl peptide receptor 2 (FPR2) antagonist WRW^4. oxLDL also stimulated calcium signaling and chemotactic migration in FPR2-expressing RBL-2H3 cells but not in vector-expressing RBL-2H3 cells. Moreover, oxLDL stimulated TNF-α production, which was also almost completely inhibited by FPR2 antagonist. Our findings therefore suggest that oxLDL stimulates macrophages, resulting in chemotactic migration, TNF-α production, and foam cell formation via FPR2 signaling, and thus likely contributes to atherogenesis.

1. Introduction

Atherosclerosis is a serious chronic inflammatory disorder which is associated with upregulation of inflammatory chemokines, such as CCL2 [1]. Produced CCL2 recruits monocytes from blood vessels into the intima region, where macrophages engulf modified low-density lipoprotein (LDL) including oxidized LDL (oxLDL) [1]. During the process of uptake of oxLDL, macrophages use several different cell surface receptors, including some scavenger receptors such as lectin-like oxLDL receptor 1 (LOX1), CD36, and SR-A [2–4]. After uptaking oxLDL, macrophages can be differentiated into foam cells, which produce diverse growth factors and proinflammatory cytokines such as tumor necrosis factor (TNF)-α [1]. When upregulated, these factors stimulate proliferation of vascular smooth muscle cells, leading to plaque formation [1]. Since oxLDL is a crucial modified LDL, which induces foam cell formation, mediating the pathological process in atherosclerosis [5,6], the identification and characterization of target receptor(s) for oxLDL has been an important issue.

Although several cell surface receptors have been reported to act on the scavenger receptor, the possible involvement of different types of receptors has also been suggested [7–9]. Previously, it was demonstrated that oxLDL stimulates the activation of intracellular signaling molecules, which are inhibited by a pertussis toxin (PTX), such as p38 MAPK and ERK in smooth muscle cells [7]. Since PTX specifically blocks G_i-protein-mediated signaling, it has been suggested that oxLDL may stimulate a G_i-protein-induced signaling cascade. In a previous report we demonstrated that the stimulation of Raw264.7 cells with oxLDL induced foam cell formation, which was markedly inhibited by PTX, suggesting a putative role of PTX-sensitive G-protein or PTX-sensitive G-protein coupled receptor(s) [9]. Considering our previous reports and those by others, additional receptors should be considered as putative receptors for oxLDL, which may be associated with PTX-sensitive G-protein.

Formyl peptide receptor 2 (FPR2) is a classical chemoattractant receptor, which is mainly expressed on leukocytic cells including neutrophils, monocytes, macrophages, natural killer cells, and dendritic cells [10]. Unlike other chemoattractant receptors, FPR2 can recognize such diverse extracellular ligands as formyl peptides derived from Gram negative bacteria and host-derived agonists (serum amyloid A, lipoxin A4, annexin-1, LL-37, and humanin) [10]. The activation of FPR2 by its specific agonists induces a complex signaling cascade including intracellular calcium increase, mitogen-activated protein kinases, phospholipase A_2, C, D, and phosphoinositide 3-kinase and Akt activation [10–12]. In terms of functional activity, FPR2 mediates innate immunity against invading pathogens and polymicrobial sepsis by stimulating the production of reactive oxygen species and downregulating proinflammatory cytokines [13]. Recently we demonstrated that serum amyloid A, an acute reactant protein which acts on FPR2,

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stimulates macrophage foam cell formation [14]. We also showed that FPR2 is involved in the serum amyloid A-stimulated upregulation of scavenger receptor, LOX-1, resulting in foam cell formation [9]. However the functional role of FPR2 on the oxLDL-induced pathological process of atherosclerosis has not been investigated. In this study, we demonstrate that FPR2 is involved in the oxLDL-stimulated macrophage foam cell formation. We also showed that oxLDL-stimulated calcium increase, macrophage migration, and inflammatory cytokine production were mediated by FPR2. Collectively we suggest that FPR2 may be crucial for the oxLDL-induced pathological process of atherosclerosis.

2. Materials and methods

2.1. Materials

WRWWWW (WRW^4), WKYMVm, and MMK-1 were synthesized from Anygen (Gwangju, Korea). fMLF and cyclosporine H (CsH) were purchased from Enzo Life Sciences, Inc. (Farmingdale, NY, USA). Lyso-phosphatidylserine (Lyso-PS) was obtained from Avanti Polar Lipids, Inc. (Alabaster, AL, USA). Fura-2 pentaacetoxymethylester (fura-2/AM) was purchased from Molecular Probes (Eugene, OR, USA).

2.2. Oxidation of LDL

Naïve LDL was purchased from Sigma–Aldrich (St. Louis, MO, USA). Oxidized LDL was generated according to a previous report [15]. Briefly, naïve LDL (0.5 mg/ml in PBS) was co-incubated with 5 μM copper sulfate for 24 h at 37 °C.

2.3. Foam cell formation and Oil Red O staining

Raw264.7 cells were differentiated to foam cells according to a previous report [14,15]. Briefly, Raw264.7 cells (1×10^4) were stimulated with oxLDL (50 μg/ml) for 24 h. Foam cell formation was measured by detected under light microscopy and total cells and foam cells after staining with Oil Red-O solution as previously described [14,15].

2.4. Measurement of intracellular Ca^{2+} increase

Intracellular calcium concentration was measured using Grynkiewicz's method with fura-2/AM [16,17]. Briefly, fura-2/AM loaded vector- or FPR2-expressing RBL-2H3 cells were stimulated with fMLF, MMK-1, oxLDL or lyso-PS. Intracellular calcium levels were determined by monitoring fluorescence changes at dual excitation wavelengths of 340 and 380 nm and at an emission wavelength of 500 nm as previously described [16,17].

2.5. Chemotaxis assay

Chemotaxis assays were performed according to a previous report using a multiwell chamber (Neuroprobe Inc., Gaithersburg, MD [17]. Briefly, Raw264.7 cells, vector- or FPR2-expressing RBL-2H3 cells were applied to the polycarbonate filters (8 μm pore size) for 4 h at 37 °C. Migrated cells were stained with hematoxylin (Sigma, St. Louis, MO, USA), and counted under a light microscope as previously described [17].

2.6. Measurement of TNF-α

TNF-α levels were measured according to a previous report [18]. Raw264.7 cells (5×10^5 cells/ml) were stimulated by the vehicle, oxLDL or LDL for 24 h. To observe the role of FPR2 on the oxLDL-induced TNF-α production, Raw264.7 cells were preincubated with several (0, 10 and 60 μM) concentrations of WRW^4 for 30 min, and subsequently oxLDL was added for 24 h. Culture supernatants were collected and analyzed by ELSIA for the measurement of TNF-α according to a previous report [18].

2.7. Data analysis

Results are expressed as mean ± S.E. The Student's *t*-test was used to compare individual treatments with their respective control values. Statistical significance was set at $p < 0.05$.

3. Results

3.1. oxLDL promotes foam cell formation via FPR2

To investigate the putative role of the FPR family (which are well-characterized G_i-protein coupled receptors), on the oxLDL-induced foam cell formation, we tested the effect of an FPR1 antagonist (CsH) [19] or an FPR2 antagonist (WRW^4) [20] on the process. An FPR1 antagonist CsH failed to affect oxLDL-induced foam cell formation (Fig. 1A). However, oxLDL-stimulated foam cell formation was inhibited by WRW^4, showing concentration-dependency (Fig. 1A and B). We also tested the effects of agonists for FPR1 or FPR2 on the oxLDL-stimulated foam cell formation. Not all of the tested FPR family agonists (fMLF, MMK-1, and WKYMVm) affected foam cell formation induced by oxLDL (Fig. 1A). The results indicate that oxLDL promotes foam cell formation via FPR2.

3.2. oxLDL stimulates intracellular calcium increase via FPR2

Since oxLDL-induced foam cell formation and oxLDL1 expression was blocked by the FPR2 antagonist, we asked whether oxLDL stimulated FPR2-mediated signaling in vector- or FPR2-expressing RBL-2H3 cells. Stimulation of FPR2-expressing RBL-2H3 cells by MMK-1 (an FPR2-selective agonist) selectively increased intracellular calcium concentration (Fig. 2A). However, MMK-1 did not induce calcium increase in vector-expressing RBL-2H3 cells (Fig. 2B). Lyso-PS induced calcium increased in vector-expressing RBL-2H3 cells (Fig. 2B). Stimulation of FPR2-expresssing RBL-2H3 cells with oxLDL markedly increased intracellular calcium concentration (Fig. 2A). However, oxLDL failed to stimulate calcium increase in vector-expressing RBL-2H3 cells (Fig. 2B). The results indicate that oxLDL stimulates intracellular calcium concentration via FPR2. To test whether heat-sensitive component is involved in the oxLDL-induced calcium increase in FPR2-expressing RBL-2H3 cells, we examined the effect of boiled oxLDL on calcium signaling. As shown in Fig. 2A, not only intact oxLDL but also boiled oxLDL stimulated calcium increase in FPR2-expressing RBL-2H3 cells. The result indicates that the heat stable component of oxLDL induces calcium increase by acting FPR2.

3.3. oxLDL stimulates macrophage chemotactic migration via FPR2

In this study, we also found that the stimulation of Raw264.7 cells with oxLDL caused cheomotactic migration of the cells (Fig. 3A). Since oxLDL-induced foam cell formation was blocked by an FPR2 antagonist, WRW^4 (Fig. 1), here we also tested the role of FPR2 on the oxLDL-induced macrophage chemotaxis. Preincubation of Raw264.7 cells with WRW^4 prior to chemotaxis assay strongly inhibited oxLDL-induced chemotaxis (Fig. 3A). However, another important monocyte/macrophage chemoattractant, CCL2-induced Raw264.7 cell chemotaxis, was not affected by WRW^4 (Fig. 3A). We also investigated the effect of oxLDL on chemotaxis in vector- or FPR2-expressing RBL-2H3 cells. As shown

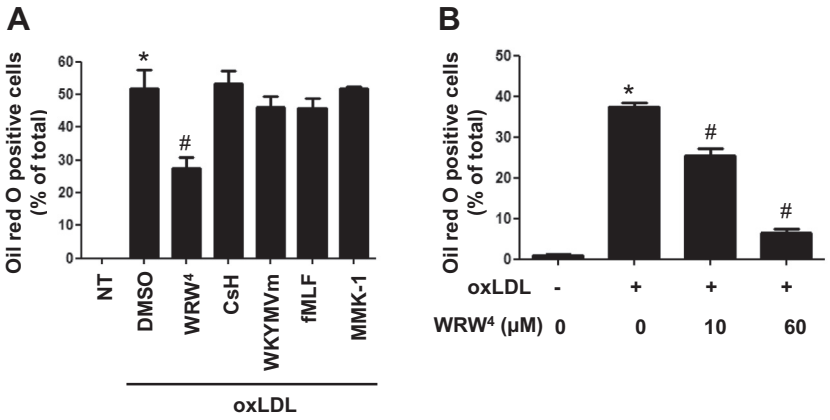

Fig. 1. oxLDL stimulates foam cell formation via FPR2. (A) Raw264.7 cells were stimulated with 50 μg/ml oxLDL in the presence of DMSO, WRW^4, CsH, WKYMVm, fMLF, or MMK-1 for 24 h. (B) Raw264.7 cells were preincubated at several concentrations (0, 10, and 60 μM) of WRW^4 prior to addition of 50 μg/ml oxLDL. The cells were stained with Oil-Red O, and the stained cells were detected by microscopy. Total cells and foam cells were counted. The results are presented as mean ± S.E. $^*p < 0.05$ compared to the NT (not treated) control, $^\#p < 0.05$ compared to oxLDL alone treated.

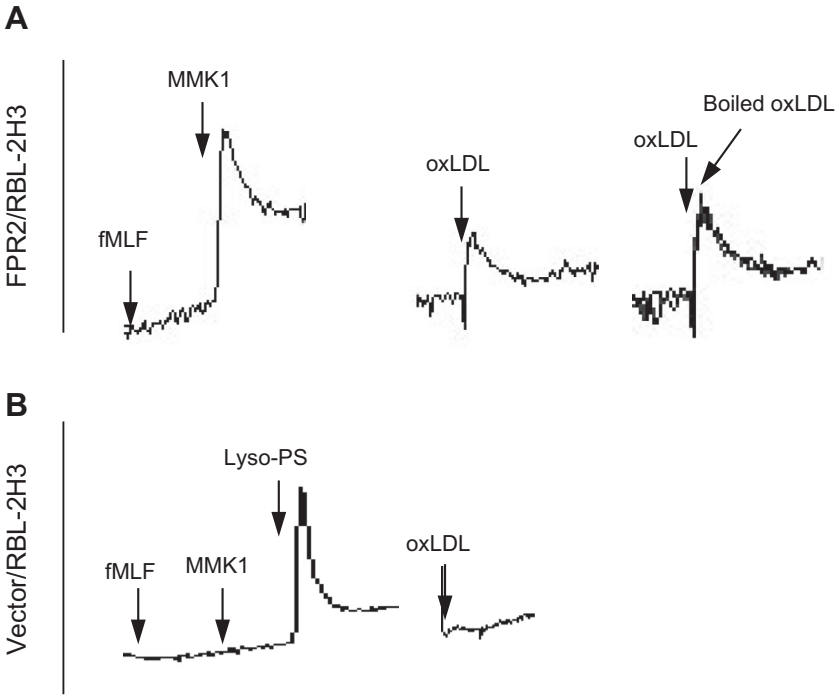

Fig. 2. oxLDL stimulates intracellular calcium increase via FPR2. Fura-2 loaded (A) FPR2- or (B) vector-expressing RBL-2H3 cells were stimulated with fMLF (1 μM), MMK-1 (1 μM), naïve oxLDL (50 μg/ml), boiled oxLDL (50 μg/ml), or lyso-PS (10 μM). Fluorescence changes at dual excitation wavelengths of 340 and 380 nm and at an emission wavelength of 500 nm were monitored. Data are representative of three independent experiments.

in Fig. 3B, oxLDL caused chemotactic migration in FPR2-expressing RBL-2H3 cells. However, oxLDL failed to stimulate chemotactic migration in vector-expressing RBL-23 cells (Fig. 3B). The results support our notion that oxLDL stimulates FPR2, resulting in the chemotactic migration of macrophages.

3.4. oxLDL enhances TNF-α production via FPR2

Modified LDL such as oxLDL can induce inflammation by producing proinflammatory cytokines such as TNF-α [1,21]. Here, we also observed that the stimulation of Raw264.7 cells by oxLDL augmented the production of TNF-α (Fig. 4A). Unlike oxLDL, LDL did not stimulate TNF-α production in Raw264.7 cells (Fig. 4A). To observe the role of FPR2 on the oxLDL-induced TNF-α production in macrophages, we investigated the effect of WRW^4 on the process. Preincubation of Raw264.7 cells with several concentrations of WRW^4 prior to the addition of oxLDL markedly inhibited the oxLDL-induced TNF-α production (Fig. 4B).

4. Discussion

During the pathological process of atherosclerosis, foam cell formation is a very important step. Previously, it has been demonstrated that foam cell formation is mediated by produced modified LDL such as oxLDL [1,9,5]. Although oxLDL has been reported to act on several scavenger receptors, its effect on other types of receptors has also been studied. Previously, Chen et al. demonstrated that oxLDL downregulates endothelial basic fibroblast growth

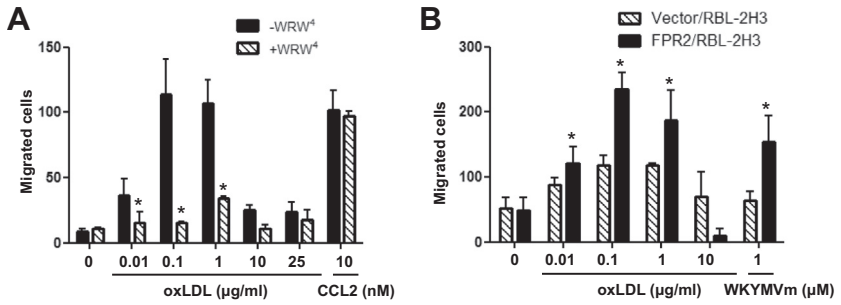

Fig. 3. oxLDL stimulates FPR2, resulting in chemotactic migration. (A) Raw264.7 cells which were preincubated in the presence or absence of WRW^4 (10 μM) for 30 min were applied to the upper well of the multiwall chamber containing several concentrations (0, 0.01, 0.1, 1, 10 and 25 μg/ml) of oxLDL, or 10 nM of CCL2 for 4 h. (B) Vector- or FPR2-expressing RBL-2H3 cells were applied to the upper well of a multiwell chamber containing several concentrations (0, 0.01, 0.1, 1 and 10 μg/ml) of oxLDL or 1 μM of WKYMVm. The number of migrated cells was determined by counting under light microscope. Data are presented as means ± S.E. $^*p < 0.05$ compared to the $-WRW^4$ control (A) or compared to the vector/RBL-2H3 control (B).

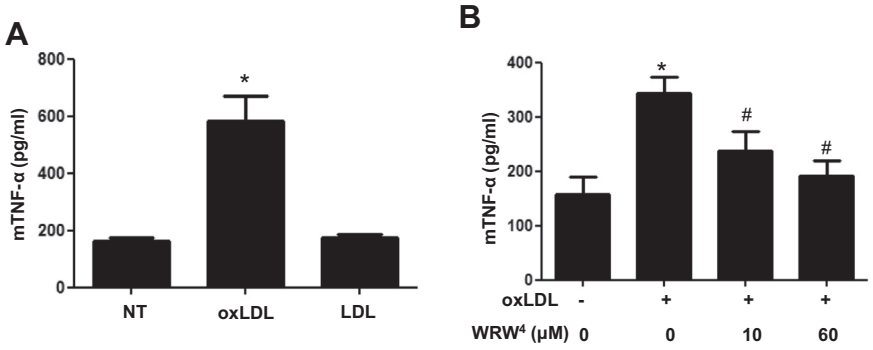

Fig. 4. oxLDL stimulates TNF-α production via FPR2. (A) Raw264.7 cells were stimulated with oxLDL (50 μg/ml) or LDL (50 μg/ml) for 24 h. (B) Raw264.7 cells were preincubated at several concentrations (0, 10 and 60 μM) prior to the addition of oxLDL (50 μg/ml) for 24 h. Supernatants were collected from cultures, and evaluated for TNF-α production by ELISA. Data are presented as mean ± S.E. $^*p < 0.05$ compared to the NT (not treated) control, $^\#p < 0.05$ compared to oxLDL alone treated.

factor, which is mediated by PTX-sensitive G-protein-dependent signaling [8,22]. By demonstrating that a platelet activating factor (PAF) receptor antagonist (WEB 2086) blocked the action of oxLDL, Chen et al. suggested that oxLDL shows its stimulatory activity by targeting the PAF receptor [8,22]. Moreover, previous reports demonstrated that oxLDL stimulates mitogen-activated protein kinase and the phosphoinositide-3-kinase pathway via PTX-sensitive signaling in vascular smooth muscle cells [7,23]. It has commonly been regarded that oxLDL may stimulate aortic endothelial cells or vascular smooth muscle cells, resulting in downstream signaling and cellular response, which is PTX-sensitive. In a previous report, we demonstrated that oxLDL stimulates foam cell formation, which is inhibited by PTX [9]. The results suggest that oxLDL may act on PTX-sensitive G-protein coupled receptor(s). Here we report that one of the important chemoattractant receptors, FPR2, which is a PTX-sensitive G-protein coupled receptor, mediates oxLDL-induced foam cell formation.

oxLDL stimulated an intracellular calcium increase and chemotactic migration in the FPR2-expressing RBL-2H3 cells but not in the vector-expressing RBL-2H3 cells (Figs. 2 and 3). The oxLDL-stimulated intracellular calcium increase was not affected by the boiling of oxLDL (Fig. 2). The result indicates that the heat stable component may induce an intracellular calcium increase by stimulating FPR2. Since LDL did not induce calcium increase and foam cell formation (data not shown), the oxidized component of LDL may be involved in the intracellular calcium increase and foam cell formation. The addition of copper sulfate causes oxidation of LDL components, especially lipid components. Consequently, it will be reasonable to assume that certain oxidized heat stable lipid components may act on FPR2, resulting in calcium increase, foam cell formation, and chemotactic migration.

Several scavenger receptors for oxLDL including LOX1, CD36, and SR-A have been reported to be upregulated in atherosclerotic samples and the upregulation of these scavenger receptors is associated with the pathological progress of atherosclerosis [24–26]. In a previous report, we demonstrated that PBMCs derived from atherosclerosis patients express an upregulated level of FPR2 compared to normal healthy PBMCs [9]. Since oxLDL acts on FPR2, the produced oxLDL may induce strong signaling leading to foam cell formation via upregulated FPR2 during the progress of atherosclerosis in atherosclerosis patients. Taken together, we suggest that a novel oxLDL receptor, FPR2, may be importantly considered as a new target receptor to treat atherosclerosis.

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