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Role of formyl peptide receptor 2 on the serum amyloid A-induced macrophage foam cell formation

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ABSTRACT

Recently we demonstrated that SAA induces macrophage foam cell formation. In this study we show that SAA-induced foam cell formation is inhibited by formyl peptide receptor 2 (FPR2) antagonist WRW[4], as well as by FPR2-targeted siRNA knockdown. SAA-stimulated LOX1 expression was also mediated by FPR2. We also found that SAA-stimulated foam cell formation and LOX1 expression was pertussis toxin-insensitive. In addition, FPR2 is upregulated in peripheral blood mononuclear cells from patients with atherosclerosis. Our findings therefore suggest that SAA stimulates foam cell formation via FPR2 signaling and LOX1 induction, and thus likely contributes to atherogenesis.

1. Introduction

During the pathogenesis of atherosclerosis, macrophages engulf modified low-density lipoprotein (LDL) and differentiate into foam cells [1]. Several scavenger receptors including lectin-like oxidized low-density lipoprotein receptor 1 (LOX1), SR-A, and CD36 play important roles in the uptake of modified LDL [2–4]. One of the scavenger receptors, LOX1 mediates oxidized LDL (oxLDL) uptake, and its expression is stimulated by many inflammatory stimuli [2,5]. Foam cells produce diverse growth factors and proinflammatory cytokines such as tumor necrosis factor (TNF)-α [6,7], and these inflammatory mediators stimulate proliferation of smooth muscle cells, resulting in plaque formation [8]. Since foam cell formation is critical step in the pathogenesis of atherosclerosis [7], it has been hot issue to identify molecules and their targets which regulate foam cell formation.

Serum amyloid A (SAA), which is a major acute-phase protein, is markedly produced in response to infection, injury, or many proinflammatory cytokines, such as interleukin (IL)-1β or tumor necrosis factor (TNF)-α [9]. SAA has been reported to induce inflammatory response by stimulating proinflammatory cytokines and chemokine production in several cell types such as monocytes/macrophages, rheumatoid synoviocytes, intestinal epithelial cells, and neutrophils [10–12]. Circulating SAA levels are markedly elevated in patients with atherosclerosis [13,14]. In case of patients with chronic vascular disease, SAA levels are reaching around 11–15 μg/ml [13]. Previously, we reported that SAA stimulates important atherogenic inflammatory markers, such as CCL2, matrix metalloproteinase (MMP)-9 in monocytes and endothelial cells [15–18]. Very recently we demonstrated that SAA stimulates macrophage foam cell formation via upregulation of an important scavenger receptor, LOX1 [19]. Although several different cell surface molecules recognize SAA including formyl peptide receptor 2 (FPR2), TLR2, TLR4, and P2X7 [20–23], it is unclear which receptor is involved in the SAA-induced foam cell formation. Here we show that SAA directly stimulates foamy macrophage formation via FPR2-dependent signaling, and thus implicate SAA and FPR2 as causal agents in atherogenesis.

2. Materials and methods

2.1. Materials

Recombinant human SAA (catalog number 300-13, produced in *Escherichia coli*, endotoxin level <0.1 ng/μg) was purchased from Peprotech (Rocky Hill, NJ, USA). Fetal bovine serum (FBS) and DMEM medium were purchased from Invitrogen (Carlsbad, CA, USA). Naïve LDL, LPS (from *E. coli 055:B5*, catalog number L2880), Pam3CSK4, and fMLF were purchased from Sigma–Aldrich (St. Louis, MO, USA). MMK-1 (13-residue peptide LESIFRSLLFRVM

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isolated from a random peptide library), LL37, WKYMVm, and F2L (acetylated amino-terminal peptide derived from heme-binding protein) were from Anygen (Gwangju, Korea). 5(*S*),6(*R*),15(*S*)-trihydroxyeicosa-7*E*,9*E*,11*Z*,13*E*-tetraenoic acid (lipoxin A4), was from BIOMOL Research Laboratories (Plymouth Meeting, PA, USA). Pertussis toxin (PTX), PD98059, SB203580, and SP600125 were purchased from Calbiochem (San Diego, CA, USA). All antibodies against the phospho-MAPKs were purchased from Cell Signaling Technology (Beverly, MA, USA), and the anti-LOX1 antibody (catalog number AF1564) was purchased from R&D Systems (Minneapolis, MN, USA). HRP-conjugated rabbit IgG and mouse IgG antibodies were purchased from Kirkegaard & Perry (Gaithersburg, MD, USA), and an HRP-conjugated antibody to goat IgG was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA).

2.2. Cell culture and isolation of bone marrow-derived macrophages

Raw264.7 cells were maintained in DMEM with 10% heat-inactivated fetal calf serum under standard incubator conditions (humidified atmosphere, 95% air, 5% CO_2, and 37 °C). Bone marrow cells were isolated by flushing the femurs and tibias of wild-type (WT C57BL/6), TLR2 KO (C57BL/6 background), TLR4 WT (C3H/HeN), or TLR4 mutant mice (C3H/HeJ) 5–8 weeks of age with ice-cold PBS. Red blood cells were lysed and bone marrow progenitor cells were plated in a 100 mm cell culture dish in α-MEM with 10% FBS. The next day suspended cells were collected and washed with PBS. Cells were cultured in 10% FBS containing α-MEM with 30 ng/ml M-CSF under standard incubator conditions for 3 days. The non-adherent cells were removed, and 10% FBS containing α-MEM with 30 ng/ml M-CSF was added, and the cells maintained for 2–3 days.

2.3. Foam cell formation and oil red O staining

Raw264.7 cells and bone marrow-derived macrophages (1×10^4) were seeded on 96-well plates and cultured overnight. oxLDL was prepared by exposing naive LDL to 5 μM $CuSO_4$ and 5 μM $CuCl_2$ for 18 h at 37 °C [24]. Cells were stimulated with oxLDL (50 μg/ml) alone or LDL (50 μg/ml) plus vehicle, SAA, or LPS for 24 h. After washing with PBS, the cells were fixed with 4% formaldehyde for 10 min at room temperature. After washing with distilled water 3 times, the fixed cells were stained with oil Red-O solution for 20 min. The stained cells were detected by light microscopy and total cells and foam cells were counted.

2.4. Western blot analysis

Raw264.7 cells were stimulated with SAA for various times. After stimulation, the cells were lysed in lysis buffer (20 mM HEPES [pH7.2], 10% glycerol, 150 mM NaCl, 1% Triton X-100, 50 mM NaF, 1 mM Na_3VO_4, 10 μg/ml leupeptin, 10 μg/ml aprotinin, and 1 mM PMSF). Detergent insoluble materials were pelleted by centrifugation (12,000*g* for 10 min at 4 °C), and the soluble supernatant fraction was removed and stored at either −80 °C or used immediately. Proteins were separated on 10% SDS–polyacrylamide gels and blotted onto a nitrocellulose membrane. Subsequently, the membranes were incubated with specific 1:5000 diluted goat anti-rabbit IgG antibody, combined with horseradish peroxidase, and antigen–antibody complexes were visualized by enhanced chemiluminescence.

2.5. Transfection of FPR2 siRNA

Raw264.7 cells were transfected with a final concentration of 1 μM mouse FPR2 siRNA (Invitrogen) or luciferase siRNA as a control, using Lipofectamine 2000 reagent (Invitrogen). The cells were incubated with the transfection mixture in serum free medium for 6 h and then the media was changed to 10% FBS containing DMEM and incubated for 48 h.

2.6. Reverse transcription polymerase chain reaction (RT-PCR) analysis

Total RNA was isolated by using Trizol reagent (Invitrogen, Carlsbad, CA, USA) and 1 μg of total RNA was used as a template for cDNA using the Bioneer Reverse Transcriptase System. The primers used for the RT-PCR analyses have been reported previously. The sequences of the primers were as follows: hFPR1: sense, 5′-CTCCAGTTGGACTAGCCACA-3′; antisense, 5′-CCATCACCCAGGGCCCAATG-3′. hFPR2: sense, 5′-CTGCTGGTGCTGCTGGCAAG-3′, antisense, 5′-AATATCCCTGACCCCATCCTCA-3′. hFPR3: sense, 5′-GCCAAGGTCTTTCTGATCC-3′, antisense, 5′-GGTCTGGGCTGAGTCAGGGA-3′. cDNA was subjected to 35 PCR cycles at 94 °C (denaturation, 30 s), 55–65 °C (annealing, 30 s), and 72 °C (extension, 30 s). PCR products were electrophoresed on a 1.5% agarose gel and visualized by ethidium bromide staining.

2.7. Data analysis

Results are expressed as mean ± SE. 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. SAA-induced foam cell formation is FPR2-mediated

Very recently we demonstrated that SAA stimulates macrophage foam cell formation [19]. As SAA acts on several cell surface receptors including TLR2 [21], TLR4 [22], and FPR2 [20], we investigated which receptor is involved in SAA-induced foam cell formation. To test the role of TLR2 or TLR4 on SAA-induced foam cell formation, bone marrow-derived macrophages were generated from WT, TLR2 KO, TLR4 WT (C3H/HeN), or TLR4 mutant (C3H/HeJ) mice and stimulated with vehicle, LPS (TLR4 agonists), Pam3CSK4 (TLR2 agonist), or SAA in the presence of LDL for 24 h. As anticipated, foam cell formation induced by LPS and Pam3CSK4 was reduced in macrophages derived from TLR4 mutant mice or TLR2 KO mice-derived macrophages, respectively, compared with WT mice (Figs. 1A and 1B). In contrast, SAA-induced foam cell formation was not affected in TLR2 KO or TLR4 mutant mouse-derived macrophages (Figs. 1A and 1B). We therefore hypothesized that FPR2 is involved in SAA-induced foam cell formation. Indeed, FPR2 antagonist WRW^4 inhibited SAA-induced Raw264.7 foam cell formation in a concentration dependent manner (Fig. 1C). We further investigated the role of FPR2 on SAA-induced foam cell formation using siRNA against FPR2. Transfection of mFPR2 siRNA dramatically decreased FPR2 protein levels in Raw264.7 cells (Fig. 1D). mFPR2 knockdown inhibited SAA-mediated foam cell formation (Fig. 1D). In contrast, however, LPS-induced foam cell formation was not affected by mFPR2 knockdown, indicating that SAA acts specifically on FPR2 to generate foamy macrophages. We also tested the effects of other FPR2 ligands on foam cell formation. Unlike SAA, other FPR2 ligands such as MMK-1, LL37, lipoxin A4, WKYMVm, and F2L failed to stimulate foam cell formation (Fig. 1E). An FPR1 ligand fMLF also did not stimulate foam cell formation (Fig. 1E).

3.2. SAA-induced foam cell formation is mediated by a PTX-independent pathway

FPR2 ligands such as WKYMVm and MMK-1 induced signaling via $G\alpha_i$ heterotrimeric G proteins. Furthermore, PTX-sensitive G-proteins play a role in SAA receptor-mediated cellular responses

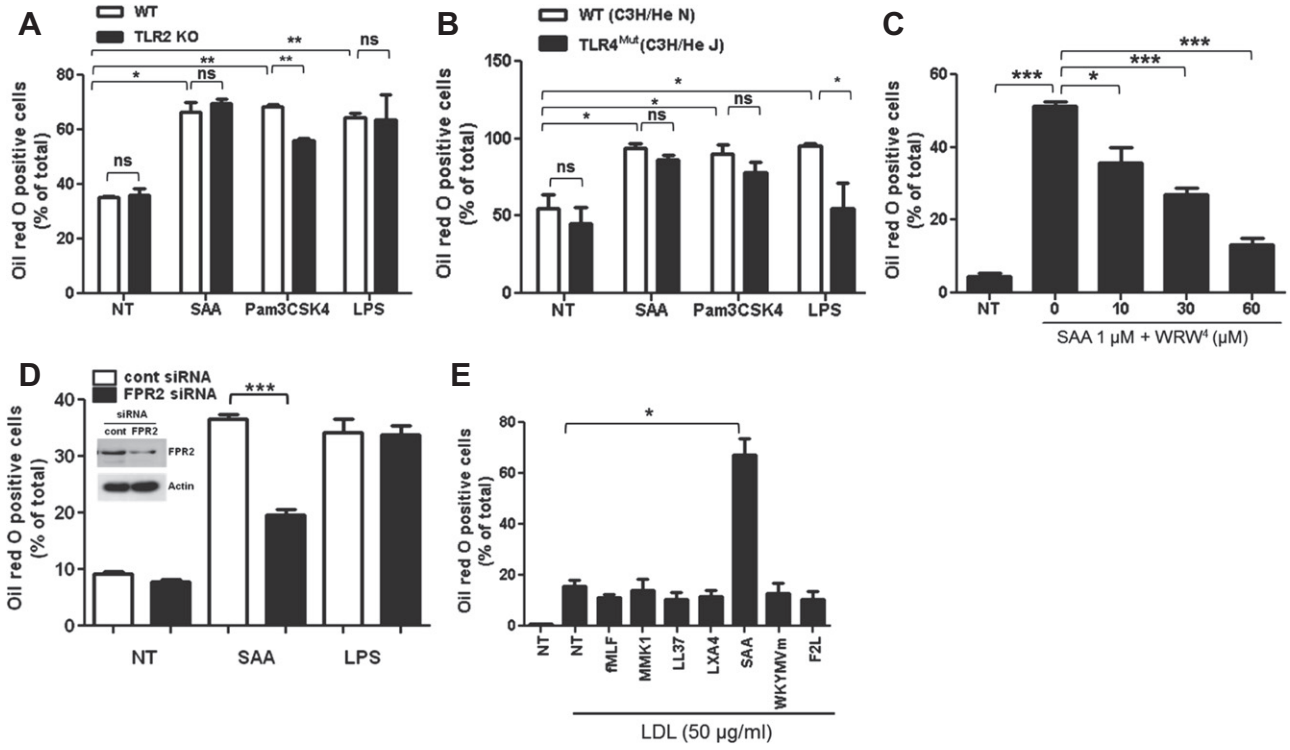

Fig. 1. SAA-stimulated foam cell formation is FPR2-dependent. (A, B) Bone marrow-derived macrophages were isolated from WT, TLR2 KO, TLR4 WT (C3H/HeN), and TLR4 mutant (C3H/HeJ) mice. The cells were stimulated with vehicle, TLR4 agonist LPS (1 μg/ml), TLR2 agonist Pam3CSK4 (1 μg/ml), and SAA (1 μM) in the presence of LDL (50 μg/ml) for 24 h. (C) Raw264.7 cells were pre-incubated with various concentrations of WRW^4 (0, 10, 30, and 60 μM) prior to SAA treatment in the presence of LDL (50 μg/ml) for 24 h. (D) Raw264.7 cells were transfected with a final concentration of 1 μM mFPR2 siRNA or control siRNA using the Lipofectamine 2000 reagent. Knockdown of mFPR2 by siRNA was confirmed by Western blot analysis using anti-FPR2 antibody (D, insert). The transfected cells were stimulated with SAA (1 μM) and LPS (1 μg/ml) in the presence of LDL (50 μg/ml) for 24 h. (E) Raw264.7 cells were stimulated with fMLF (1 μM), MMK-1 (1 μM), LL37 (1 μM), lipoxin A4 (1 μM), SAA (1 μM), WKYMVm (1 μM), or F2L (1 μM) in the presence of 50 μg/ml LDL for 24 h. (A–E) All cells were stained with Oil-Red O, and total cells and foam cells were counted. Data are mean ± SE of two independent experiments performed in duplicate. ns: not significant, $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

such as chemotactic migration [25]. To determine if PTX-sensitive $G\alpha_i$ proteins are involved in SAA-induced foam cell formation, Raw264.7 cells were pre-incubated with PTX and then stimulated with SAA and LPS in the presence of LDL or oxLDL. PTX had no effect on SAA-induced foam cell formation (Fig. 2A). These data indicate that a $G\alpha_i$-protein-independent pathway is involved in SAA-induced foam cell formation via FPR2. We next investigated the role of PTX-sensitive G-proteins on SAA-induced MAPK phosphorylation. PTX completely blocked SAA-induced ERK and p38 MAPK phosphorylation. However, SAA-induced JNK phosphorylation was not affected by PTX (Fig. 2B). Recently we demonstrated that JNK phosphorylation is important for SAA-induced foam cell formation [19]. These data indicate that JNK phosphorylation, which is important for SAA-induced foam cell formation, is regulated by a PTX-insensitive G protein.

3.3. SAA induces LOX1 expression via FPR2-mediated, resulting in foam cell formation

Since SAA-induced foam cell formation proceeds via a FPR2-dependent, JNK mediated PTX-insensitive signaling pathway, we next asked if SAA-induced LOX1 expression has similar require-

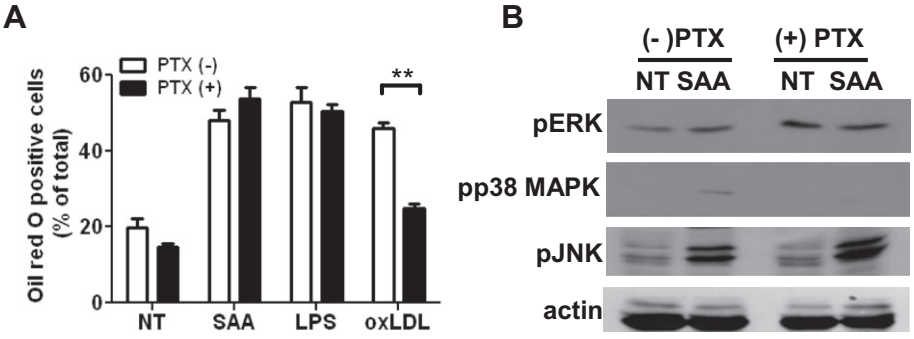

Fig. 2. SAA-induced foam cell formation is mediated by independent of $G\alpha_i$-protein. (A) Raw264.7 cells were pre-incubated in the absence or presence of 100 ng/ml PTX for 24 h. Then, the cells were stimulated with LDL (50 μg/ml) plus SAA (1 μM), LDL (50 μg/ml) plus LPS (1 μg/ml) or 50 μg/ml oxLDL for 24 h. (A) The cells were stained with Oil-Red O, and total cells and foam cells were counted. (B) Raw264.7 cells were pre-incubated in the absence or presence of 100 ng/ml PTX for 24 h and then stimulated with 1 μM SAA for 24 h. (B) Anti-phospho-ERK, -p38 MAPK, and -JNK antibodies were used to detect kinase phosphorylation by Western blot. All experiments were repeated three times independently, and the results are presented as mean ± SE. $^{**}p < 0.01$.

ments. As shown in Fig. 3A, pre-incubation of Raw264.7 cells with FPR2 antagonist WRW^4 dramatically inhibited SAA-induced LOX1 expression. Knock-down of mFPR2 using mFPR2 siRNA also strongly blocked SAA-induced LOX1 expression (Fig. 3B). These results indicate that FPR2 mediates SAA-induced LOX1 expression in macrophages. Pre-incubation of Raw264.7 cells with PTX did not affect SAA-induced LOX1 expression (Fig. 3C). It is clear that SAA induces foam cell formation and LOX1 expression independently of PTX-sensitive G-protein-mediated signaling. Taken together, FPR2-mediated but PTX-insensitive signaling pathway is necessary for both SAA-induced LOX1 expression and foam cell formation.

3.4. FPR2 is overexpressed in atherosclerosis patient-derived peripheral blood mononuclear cells (PBMCs)

Our finding that SAA induces foam cell formation via FPR2 led us to investigate whether FPR2 is overexpressed in atherosclerosis patient-derived blood mononuclear cells. We collected 42 atherosclerosis patient-derived and 24 healthy donor-derived PBMC samples. FPR2 mRNA levels were significantly increased in PBMC from atherosclerosis patients compared with healthy donors (Fig. 4). The level of FPR1 mRNA was not different between the two groups, and there was a slight but significant increase in FPR3 mRNA level in atherosclerosis samples (Fig. 4).

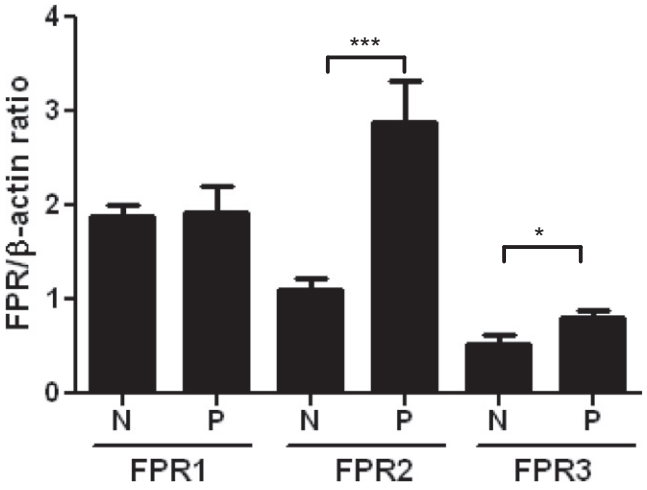

Fig. 4. Overexpression of FPR2 in patients with atherosclerosis. PBMCs were isolated from 42 patients with atherosclerosis and 24 healthy donors. Cells were harvested for RNA preparation and RT-PCR was performed with specific primers for FPR1, FPR2, FPR3, and actin. The mRNA expression levels of FPRs were normalized to actin. N, normal PBMC, P: atherosclerosis patient PBMC. Data are shown as mean ± SE of 42 atherosclerosis patients or 24 healthy normal individuals. $^*p < 0.05$ and $^{***}p < 0.001$.

4. Discussion

In this study, we demonstrated that FPR2 was upregulated in blood mononuclear cells (Fig. 4), implicating FPR2 in the pathogenesis of atherosclerosis. In addition to our data demonstrating FPR2 upregulation in blood mononuclear cells from atherosclerosis patients (Fig. 4), FPR2 is also upregulated in fibroblast-like synoviocytes from rheumatoid arthritis (RA) patients [26,27]. FPR2 is upregulated by proinflammatory stimuli such as TNF-α [28], which is abundant in atherosclerotic lesions as well as RA synovial fluid. Interestingly, RA synovial fluid also contains elevated levels of SAA [26]. While we can only speculate on the role of FPR2 and SAA in RA, our current work indicates a more defined role for FPR2 and SAA in atherogenesis. We hypothesize that TNF-α, concentrated in atherosclerotic plaques, upregulates SAA receptor FPR2 on newly recruited monocytes, and that elevated circulating levels of SAA in atherosclerosis patients binds to FPR2, induces LOX1 upregulation, LDL uptake, and the formation of atherogenic foamy macrophages.

Chen et al. reported that mFPR2-deficient mice were protected against allergic airway inflammation in an ovalbumin sensitization/challenge model [29], while Dufton et al. reported that ischemia/reperfusion injury and atherogenesis were exacerbated in mFPR2-deficient mice [30]. Thus, based on the knockout mouse models, it is there difficult to assign a definitive pro- or anti-inflammatory action to FPR2. The contribution of mFPR2 to inflammation may depend on the experimental model; it may also depend on the agonist signal. We and others have previously reported that FPR2 can be differentially activated by two different agonists, resulting in different cellular responses [31,32]. For example, SAA induces proinflammatory cytokines by activating FPR2 [15], whereas WKYMVm shows anti-inflammatory activity against polymicrobial sepsis [33]. In this study we demonstrated that SAA strongly induced foam cell formation, which may result in atherosclerosis, which correlates with our previous results and is generally consistent with the pro-inflammatory action of FPR2 in airway inflammation in the FPR2-deficient mice. Alternate FPR2 ligands WKYMVm, MMK-1, and lipoxin A4 signal via PTX-sensitive Gα_i-protein(s) to increase intracellular calcium levels, activate MAPKs, and trigger chemotactic migration of leukocytes and superoxide anion production [34,35]. In contrast, in this study we showed that FPR2 ligand SAA stimulated foam cell formation, JNK activation, and LOX1 upregulation via a PTX-insensitive signaling pathway (Figs. 2A, B and 3C). Unlike other FPR2 ligands such as WKYMVm, MMK-1, and F2L, only SAA stimulated foam cell formation (Fig. 1D) and CCL2 production from monocytes [15], and only SAA but no other short FPR2 peptide ligands (WKYMVm and

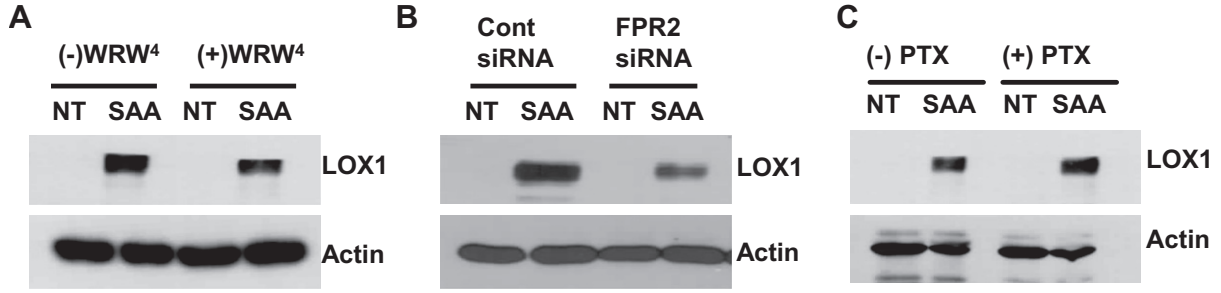

Fig. 3. SAA-induced LOX1 expression requires FPR2 and JNK activity independently of Gα_i. (A) Raw264.7 cells were pre-incubated with 60 μM WRW^4 for 15 min prior to SAA treatment. (B) Raw264.7 cells were transfected with mFPR2 siRNA and control siRNA. The transfected cells were stimulated with SAA for 6 h. (C) Raw264.7 cells were pre-incubated in the absence or presence of 100 ng/ml PTX for 24 h and then stimulated with 1 μM SAA for 6 h. NT: no treatment, Cont: control scramble siRNA for FPR2 (A–C). The LOX1 expression level was determined by Western blot. The experiment was repeated three times independently.

MMK-1) induce downstream signaling of FPR2 independently of PTX-sensitive $G\alpha_i$-protein(s), we may assume that this is why SAA but not other short peptide ligands induce a proinflammatory response by modulating FPR2. Inhibitors that specifically target SAA-mediated FPR2 signaling may therefore provide a selective approach to treating or preventing atherosclerosis. Taken together, we suggest that SAA and its cognate receptor FPR2 may be important new targets for the development of therapeutic agents against atherosclerosis.

Acknowledgments

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