We demonstrated previously that oxidized 1-palmitoyl-2- arachidonoyl-sn-glycero-3-phosphorylcholine (ox-PAPC) and, specifically, the component lipid 1-palmitoyl-2-(5, 6-epoxyisoprostane E2)-sn-glycero-3-phosphorylcholine increase interleukin-8 (IL-8) synthesis in aortic endothelial cells. The goal of the current studies was to characterize the receptor complex mediating the increased transcription of IL-8. We demonstrate that scavenger receptor class A, types I and II, lectin-like ox-LDL receptor-1, macrophage receptor with collagenous structure, and CD36 are not responsible for the increase in IL-8. Using dominant-negative constructs and anti-sense oligonucleotides, we demonstrate a role for Toll-like receptor 4 (TLR4) as the ox-PAPC receptor mediating IL-8 transcription. We demonstrate that a glycosylphosphatidylinositol (GPI)-anchored protein is also necessary because phosphatidylsinositol-specific phospholipase C pretreatment inhibited the effect of ox-PAPC. CD14, a GPI-anchored protein that associates with TLR4 in mediating lipopolysaccharide action, did not appear to mediate ox-PAPC action because ox-PAPC-induced IL-8 transcription was not blocked by anti-CD14 neutralizing antibodies nor was it augmented by the addition of soluble CD14 or overexpression of membrane CD14. Instead, anti-TLR4 antibodies immunoprecipitated a 37-kDa protein that also bound ox-PAPC. A protein of this same size was found in aerolysin overlays used to detect GPI-anchored proteins. Therefore, these studies suggest that ox-PAPC may initially bind to a 37-kDa GPI-anchored protein, which interacts with TLR4 to induce IL-8 transcription.

Monocyte/endothelial interactions have been shown to play an important role in all stages of atherosclerosis (1). Our laboratory has demonstrated that phospholipid oxidation products of 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (PAPC)\(^1\) found in minimally modified low density lipoprotein (MM-LDL) activate this interaction (2, 3). These phospholipids have been shown to accumulate in atherosclerotic lesions of mice and rabbits. Antibodies that recognize these lipids demonstrate their presence in human lesions. Furthermore, PAPC oxidation products are increased in apoptotic cells (4) and cells exposed to oxidative stress (5). We have determined that treatment of human aortic endothelial cells (HAEC) and HeLa cells with oxidized PAPC (ox-PAPC) increased the synthesis of interleukin-8 (IL-8), a chemokine involved in monocyte transmigration and retention in the vessel wall. We have also determined that isomers of 1-palmitoyl-2-(5, 6-epoxyisoprostane E\(_2\))-sn-glycero-3-phosphorylcholine (PEIPC) and to a lesser extent 1-palmitoyl-2-oxovaleroylsn-glycero-3-phosphorylcholine (POVPC) are responsible for most of the effect of ox-PAPC to induce IL-8 (5). The increase in IL-8 was shown to be mediated by increased transcription; importantly, native PAPC was not found to have an effect (6).

The goal of these studies was to characterize the receptor responsible for the ability of ox-PAPC to increase IL-8 transcription. Several lines of evidence suggest that the induction of IL-8 by ox-PAPC is receptor-mediated. The increase in message is rapid with accumulation being observed as early as 15 min after treatment with ox-PAPC (6). PEIPC, the major bioactive lipid in ox-PAPC, is active at concentrations as low as 100 nM, and its effect is saturable and maximal at 1 \(\mu\)g/ml. We first examined the possibility that ox-PAPC and its derivatives act on a receptor belonging to the scavenger receptor family. Recent studies demonstrated that autoantibodies from apoE-deficient mice that bound to oxidized phospholipids (e.g. EO6 antibody) inhibited 60–80% of the binding of copper-oxidized LDL to scavenger receptors on mouse peritoneal macrophages (7). Although these particular studies were performed using macrophages, they suggested a possible role for scavenger receptors in endothelial cells mediating the effect of ox-PAPC. The expression of several known scavenger receptors was examined in the current study. Scavenger receptor class A, types I and II (SRA I/II), is a multifunctional receptor that binds to a broad variety of ligands including oxidized LDL (8). Another class A receptor, macrophage receptor with collagenous structure (MARCO), binds to modified LDL as well (9). CD36, a class MM-LDL, minimally modified low density lipoprotein; LPS, lipopolysaccharide; TNF-\(\alpha\), tumor necrosis factor-\(\alpha\); PMA, phorbol 12-myristate 13-acetate; IL-8, interleukin-8; TLR4, Toll-like receptor 4; GPI, glycosylphosphatidylinositol; HAEC, human aortic endothelial cells; MAEC, murine aortic endothelial cells; CHO, Chinese hamster ovary; MARCO, macrophage receptor with collagenous structure; SRA, scavenger receptor class A; ELISA, enzyme-linked immunosorbent assay; PI-PLC, phosphatidylinositol-specific phospholipase C; RT, reverse transcription; MCP-1, monocyte chemotactic protein-1; ANOVA, analysis of variance; LOX-1, lectin-like ox-LDL receptor-1.

\(^1\) The abbreviations used are: PAPC, 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine; ox-PAPC, oxidized PAPC; PEIPC, 1-palmitoyl-2-(5, 6-epoxyisoprostane E\(_2\))-sn-glycero-3-phosphorylcholine; POVPC, 1-palmitoyl-2-oxovaleroylsn-glycero-3-phosphorylcholine; MM-LDL, minimally modified low density lipoprotein; LPS, lipopolysaccharide; TNF-\(\alpha\), tumor necrosis factor-\(\alpha\); PMA, phorbol 12-myristate 13-acetate; IL-8, interleukin-8; TLR4, Toll-like receptor 4; GPI, glycosylphosphatidylinositol; HAEC, human aortic endothelial cells; MAEC, murine aortic endothelial cells; CHO, Chinese hamster ovary; MARCO, macrophage receptor with collagenous structure; SRA, scavenger receptor class A; ELISA, enzyme-linked immunosorbent assay; PI-PLC, phosphatidylinositol-specific phospholipase C; RT, reverse transcription; MCP-1, monocyte chemotactic protein-1; ANOVA, analysis of variance; LOX-1, lectin-like ox-LDL receptor-1.
B scavenger receptor, binds to the lipid moiety of oxidized LDL (10). LOX-1, an oxidized LDL receptor belonging structurally to the C-type lectin family, was initially identified in vascular endothelial cells (11). We present evidence that these receptors are not responsible for ox-PAPC-induced IL-8 synthesis.

We also examined the role of Toll-like receptor 4 (TLR4) and associated proteins in mediating the action of ox-PAPC. C3H/HeJ mice have a missense mutation in the Tlr4 gene resulting in nonfunctional TLR4 (12). These mice are resistant to atherosclerosis, attenuated in their chemotaxis to these lipid molecules, and unresponsive to MM-LDL (13). We hypothesized a role for TLR4 additionally because of the epitope similarity of bacterial lipids, known regulators of TLR4 (14), and oxidized phospholipids (recognized by the antibody EO6) (7). We further hypothesized that, like lipopolysaccharide (LPS), the interaction of ox-PAPC with TLR4 may be enhanced by binding to a glycosylphosphatidylinositol (GPI)-anchored protein. These studies present evidence for a role of both TLR4 and a GPI-anchored protein in mediating ox-PAPC induction of IL-8 synthesis in endothelial cells.

**EXPERIMENTAL PROCEDURES**

**Reagents—**Tissue culture media and reagents were obtained from Irvine Scientific, Inc. unless otherwise stated. Fetal bovine serum was obtained from Hyclone. PAPC was obtained from Avanti Polar Lipids, Inc. (Alabaster, AL) or Sigma. PAPC was oxidized as described previously (12). PVPV was prepared as described previously (2, 15). LPS from Escherichia coli O111:B4 (a natural, smooth strain) was obtained from List Biological Laboratories, Inc. Phorbol 12-myristate 13-acetate (PMA) and anti-TLR4 monoclonal antibodies were obtained from BD Transduction Laboratories (catalog number 610844). Anti-histone monoclonal antibodies (catalog number G6160) were obtained from Sigma. Tumor necrosis factor-alpha (TNF-alpha), anti-human CD14 polyclonal antibodies (catalog number AB383), anti-human CD14 monoclonal antibodies (catalog number MAB3831), and a human IL-8 enzyme-linked immunosorbent assay (ELISA) kit were obtained from R & D Systems. Anti-CD36 monoclonal antibodies (clone FA6-152) were obtained from Immunotech. A murine monocyte chemotactic protein-1/JE (MCP-1/JE) and IL-8 ELISA kit were obtained from R & D Systems. Anti-CD36 polyclonal antibodies (catalog number sc-2004) were obtained from Santa Cruz Biotechnology (San Diego, CA) or from Hyclone. PAPC was obtained from Avanti Polar Lipids, Irvine Scientific, Inc. unless otherwise stated. Fetal bovine serum was obtained from Hyclone. PMA (500 ng/ml), or PMA (500 pg/ml) for 4 h. After the treatment period, supernatants were collected and analyzed for luciferase activity.

**PI-PLC Treatment—**HAE cells were pretreated with medium alone or PI-PLC (0.5 units/ml). Cells were rinsed then incubated with medium, ox-PAPC (30 μg/ml), LPS (1 ng/ml), TNF-alpha (5 ng/ml), or PMA (500 pg/ml) for 4 h. After the treatment period, supernatants were collected and assayed for IL-8.

**Immunoprecipitation—**Cells were grown to confluency, washed once with phosphate-buffered saline, and then scraped twice with phosphate-buffered saline. Cells were pelleted and resuspended in a small amount of Buffer A (25 mM Tris, pH 7.5, 150 mM NaCl, 5 mM EDTA). This suspension was transferred to a 2-ml tube, spun briefly at 800 × g for 30 s, and resuspended in Buffer A containing Sigma protease inhibitors. This suspension was sonicated (5 times for 5 s each, maximum power), transferred to a 2-ml Eppendorf tube, and centrifuged at 800 × g for 10 min. The post-nuclear supernatants were then used for immunoprecipitations with anti-human TLR4 polyclonal antibodies using the Seize® Primary Mammalian Immunoprecipitation Kit (Pierce).

**Western Blot Analysis—**The protein content of cell lysates was determined by Bio-Rad assay, and equal amounts of protein were denatured by boiling and reduced in β-mercaptoethanol followed by electrophoresis in SDS-polyacrylamide gel. The protein was transferred to Immobilon-P (Millipore) and immunoblotted. Secondary anti-mouse antibodies conjugated to horseradish peroxidase were used for detection using chemiluminescence (SuperSignal, Pierce) and x-ray film exposure. TLR4 and anti-GPI-linked proteins were obtained visualized using the peroxo-aryl overlay assay as described previously (22).
RESULTS

Role of Scavenger Receptors in Ox-PAPC Induction of IL-8—Although many studies have been performed regarding scavenger receptors in macrophages, less has been done to elucidate scavenger receptor expression in human aortic endothelial cells. Therefore, to better understand the role of endothelial scavenger receptors in ox-PAPC action, we determined which of the known scavenger receptors are present in HAEC and whether oxidized phospholipids affect their expression. RT-PCR was performed to determine the presence of CD36, LOX-1, SRA I/II, and MARCO on HAEC. HAEC were found to express low levels of CD36 mRNA and no detectable levels of SRA I/II or MARCO mRNA (data not shown). RT-PCR showed LOX-1 to be extremely low or not present with three primer sets being utilized along with modifications of the PCR protocol (varying MgCl2, annealing temperature, cycle length). Our results were confirmed by a study demonstrating that LOX-1 expression was negligible by RT-PCR in aortae without atherosclerosis (23). Treatment of HAEC with ox-PAPC was found to increase the mRNA levels for CD36, whereas levels for SRA I/II, MARCO, and LOX-1 remained undetectable (data not shown).

Next, we sought to determine whether CD36 is necessary for MCP-1/JE production. MAEC from CD36 knockout mice (courtesy of Dr. Maria Feggraio, Cornell University) and parental C57Bl/6 mice were treated with medium alone, LPS (1 ng/ml), MM-LDL (250 μg/ml), or native LDL (250 μg/ml) (Fig. 1). MAEC produced MCP-1/JE in response to both LPS and MM-LDL but not in response to native LDL. MAEC from CD36 knockout mice produced MCP-1/JE in response to MM-LDL at levels comparable with those from cells treated with LPS. In addition, CD36-blocking antibodies and CD36 peptides had no effect on HAEC treated with ox-PAPC and PEIPC (data not shown). These results indicate that CD36 is not required for MM-LDL- and ox-PAPC-induced signaling.

Presence and Function of Toll-like Receptor 4—Previous studies by Zhang et al. (24) demonstrated that human dermal microvascular endothelial cells express significant levels of TLR4 mRNA, as determined by RT-PCR, and protein, as determined by immunohistochemistry and immunoblotting. Similarly, Frantz et al. (25) found that rat coronary microvascular endothelial cells express high levels of TLR4 mRNA as determined by Northern blot analysis. However, no studies have been performed that examine large vessel endothelial cell expression of TLR4. To determine whether HAEC express TLR4 mRNA, two methods were used: RT-PCR to detect mRNA levels and cell-surface ELISAs to detect protein levels. It was determined by RT-PCR from RNA isolated from HAEC that they express TLR4 mRNA (Fig. 2A). Two other ox-PAPC-responsive cell types, HeLa cells and human microvascular endothelial cells, were also found to express TLR4 mRNA (Fig. 2B). Results from cell-surface ELISAs parallel the RT-PCR results (Fig. 2C), indicating that HAEC express TLR4 protein on the cell surface.

Next, we determined whether TLR4 is involved in ox-PAPC-induced signaling. We previously demonstrated that ox-PAPC increases IL-8 transcription in HeLa cells and activates an IL-8 promoter/luciferase construct (6). We used this system to examine the role of TLR4 in the ox-PAPC induction of IL-8. HeLa cells were transfected with a dominant-negative construct of TLR4; an IL-8 promoter/luciferase construct was utilized to examine the role of TLR4 in the ox-PAPC induction of IL-8. HeLa cells were transfected with a dominant-negative construct of TLR4; an IL-8 promoter/luciferase construct was utilized to examine the role of TLR4 in the ox-PAPC induction of IL-8. HeLa cells were transfected with antisense oligonucleotides targeting TLR4 along with the pIL-8/luciferase construct. There was a significant decrease in the luciferase levels of cells transfected with the antisense oligonucleotides compared with those transfected

Fig. 1. Expression and function of CD36 in AECs. MAEC were treated with medium alone (C), 1 ng/ml LPS (L), 250 μg/ml MM-LDL (M), or 250 μg/ml N-LDL (N) for 4 h. *, * p < 0.05 compared with control as calculated by one-way ANOVA.

Fig. 2. Expression of TLR4. A, RT-PCR was performed using RNA isolated from HAEC treated for 4 h with medium alone (C), 10 μg/ml POXPC (P), or 50 μg/ml ox-PAPC (Ox). GAPDH was used as a control. B, RT-PCR was performed using RNA isolated from HeLa cells and human microvascular endothelial cells. GAPDH was used as a control. C, cell-surface ELISAs were performed on HAEC using anti-TLR4 antibodies. *, * p < 0.05 compared with irrelevant antibody (irr. Ab) and secondary antibody alone (2° alone) as calculated by one-way ANOVA.
with the sense oligonucleotides (Fig. 3B). No effect on TNF-α-induced IL-8 synthesis was observed.

Role of GPI-anchored Proteins in Ox-PAPC-induced Signaling—Following the paradigm of the LPS receptor complex (containing GPI-anchored CD14 and TLR4), we hypothesized that ox-PAPC may also bind to a GPI-anchored protein interacting with TLR4. To address this hypothesis, we treated HAEC with bacterial PI-PLC, which releases GPI-anchored proteins from the cell-surface, and then incubated the cells with ox-PAPC. Supernatants were then collected and assayed for IL-8. Pretreatment with PI-PLC was found to decrease IL-8 production in response to ox-PAPC and LPS (Fig. 4), suggesting that a GPI-anchored protein plays a key role in ox-PAPC-induced signaling. PI-PLC did not alter the induction of IL-8 by TNF-α or PMA.

We next investigated the role of CD14 in ox-PAPC action because CD14 is known to complex with TLR4 (26). HAEC were found to express CD14 mRNA (Fig. 5A). Results from cell-surface ELISAs paralleled the RT-PCR results (Fig. 5B), indicating that HAEC express CD14 on the cell surface. We confirmed that CD14 staining was localized to the cell surface because the staining for the intracellular markers (histones, Rab8, β-coatomer protein, and IcB-α) increased with permeabilization, whereas the staining for CD14 did not (data not shown).

To assess the role of CD14 in ox-PAPC-induced IL-8 synthesis, neutralizing anti-CD14 antibodies were used. Although these antibodies effectively blocked LPS-induced IL-8 synthesis in HAEC, they did not block the effect of ox-PAPC (Fig. 5C).

Our previous studies demonstrated that ox-PAPC increases IL-8 transcription in HAEC and HeLa cells (6). The current studies characterize the receptor responsible for this effect of ox-PAPC. Scavenger receptors have been studied extensively in macrophages in the context of atherosclerosis (28–30), but their role in endothelial cells is less clear. We demonstrate that HAEC do not express SRA III, MARCO, or LOX-1; expression of these genes did not increase.

**DISCUSSION**

Our previous studies demonstrated that ox-PAPC increases IL-8 transcription in HAEC and HeLa cells (6). The current studies characterize the receptor responsible for this effect of ox-PAPC. We first examined the hypothesis that scavenger receptors mediate the effect of ox-PAPC. Scavenger receptors have been studied extensively in macrophages in the context of atherosclerosis (28–30), but their role in endothelial cells is less clear. We demonstrate that HAEC do not express SRA III, MARCO, or LOX-1; expression of these genes did not increase...
upon ox-PAPC treatment. HAEC express low levels of CD36 mRNA, which is up-regulated by ox-PAPC treatment (data not shown), similar to what was observed in macrophages. However, we present evidence that MAEC lacking CD36 are still responsive to MM-LDL, of which ox-PAPC is a major bioactive component (2) (Fig. 1), and that HAEC treated with CD36-blocking antibodies or CD36 peptides are still responsive to ox-PAPC (data not shown). This suggests that CD36, although important in macrophage activation (31), is not necessary for endothelial cell activation by MM-LDL or ox-PAPC.

Next we examined the presence and function of TLR4, the signaling component of the LPS receptor complex, in ox-PAPC-induced IL-8 expression. HAEC, HeLa cells, and human microvascular endothelial cells, all of which respond to ox-PAPC, express TLR4 (Fig. 2, A and B). Furthermore, ox-PAPC induced TLR4 synthesis (Fig. 2 A). Both dominant-negative constructs (Fig. 3A) and antisense oligonucleotides (Fig. 3B) specific for TLR4 significantly inhibited IL-8 promoter activation by ox-PAPC, indicating that TLR4 plays an important role in ox-PAPC-induced IL-8 synthesis. Previous studies demonstrate that TLR4 is expressed by endothelial cells in atherosclerotic plaques (32) and an D299G TLR4 polymorphism, which attenuates receptor signaling, is associated with a decreased risk of atherosclerosis (33).

We also present evidence that GPI-anchored proteins are necessary for ox-PAPC-induced IL-8 synthesis. PI-PLC pretreatment significantly decreased ox-PAPC-induced IL-8 synthesis (Fig. 4). This inhibition could not be explained by the destruction of the bioactive lipids in ox-PAPC because the enzyme and the lipids were not present together. RT-PCR and cell-surface ELISAs demonstrate the presence of CD14 in HAEC (Fig. 5, A and B). Similarly, early passages of human umbilical vein endothelial cells (but not later passages) were previously shown to express CD14 (34). However, we demonstrate that CD14 is not involved in ox-PAPC-induced IL-8 synthesis (Fig. 5, C–E). Furthermore, we demonstrate that MD-2 is not necessary for ox-PAPC induction of IL-8 transcription in HeLa cells, as these cells do not express this molecule (Fig. 6). The role of MD-2 in ox-PAPC induction of IL-8 in endothelial cells is not known. Anti-TLR4 antibodies immuno-
precipitate a 37-kDa protein that also binds ox-PAPC (Fig. 7A); a 37-kDa protein was also found in aerolysin overlays used to detect GPI-anchored proteins (Fig. 7B). This band may represent the GPI-anchored protein interacting with TLR4 that is responsible for ox-PAPC-induced IL-8 expression (it is not CD14, which has a molecular mass of 54 kDa).

Previous studies by Miller et al. (35) have concluded that MM-LDL induces actin polymerization and spreading of macrophages by binding to CD14 and signaling through the LPS receptor complex composed of TLR4 and MD-2. Miller et al. found that MM-LDL binding was significantly higher in macrophages of the J774 cell line and induced a greater F-actin response than in CD14-deficient LR-9 cells. Similar results were seen in CHO cells transfected with human CD14. They also demonstrated that CHO cells transfected with human TLR4 and MD-2 showed a higher F-actin response than cells transfected with TLR4 alone, suggesting that MD-2 is required for ox-PAPC-induced IL-8 synthesis (it is not CD14, which has a molecular mass of 54 kDa).

TLR4 and a GPI-anchored Protein Mediate Ox-PAPC-induced IL-8

There are several important similarities between the findings of the Miller studies (35) and our studies. Both studies suggest an important role for TLR4 in the actions of MM-LDL and ox-PAPC (a major bioactive component of MM-LDL) in macrophages and endothelial cells. Additionally, like our previous findings on ox-PAPC induction of IL-8 (6), Miller et al. determined that activation of NF-κB, the most well studied downstream target of TLR4, is not required because an inhibitor of NF-κB nuclear translocation did not affect the F-actin response to MM-LDL. Thus, both studies suggest a novel pathway of TLR4 signaling that may be important in chronic inflammatory processes.

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