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Lipopolysaccharide-Induced Up-Regulation of Triggering Receptor Expressed on Myeloid Cells-1 Expression on Macrophages Is Regulated by Endogenous Prostaglandin E₂

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Triggering receptor expressed on myeloid cells-1 (TREM-1) is a recently identified cell surface molecule that is expressed by neutrophils and monocytes. TREM-1 expression is modulated by various ligands for TLRs in vitro and in vivo. However, the influence of PGE₂, a potential mediator of inflammation, on TREM-1 expression has not been elucidated. In this study, we examined the effects of PGE₂ on LPS-induced TREM-1 expression by resident murine peritoneal macrophages (RPM) and human PBMC. PGE₂ significantly induced murine TREM-1 (mTREM-1) expression by RPM. Up-regulation of TREM-1 expression was specific to PGE₂ among arachidonic acid metabolites, while ligands for chemoattractant receptor-homologous molecule expressed on Th2 cells and the thromboxane-like prostanoid receptor failed to induce mTREM-1 expression. PGE₂ also increased expression of the soluble form of TREM-1 by PBMC. LPS-induced TREM-1 expression was regulated by endogenous PGE₂ especially in late phase (>2 h after stimulation), because cyclooxygenase-1 and -2 inhibitors abolished this effect at that points. A synthetic EP₄ agonist and 8-Br-cAMP also enhanced mTREM-1 expression by RPM. Furthermore, protein kinase A, PI3K, and p38 MAPK inhibitors prevented PGE₂-induced mTREM-1 expression by RPM. Activation of TREM-1 expressed on PGE₂-pretreated PBMC by an agonistic TREM-1 mAb significantly enhanced the production of IL-8 and TNF-α. These findings indicate that LPS-induced TREM-1 expression on macrophages is mediated, at least partly, by endogenous PGE₂ followed by EP₄ and cAMP, protein kinase A, p38 MAPK, and PI3K-mediated signaling. Regulation of TREM-1 and the soluble form of TREM-1 expression by PGE₂ may modulate the inflammatory response to microbial pathogens.

microbial inflammation. Therefore, we conducted this study to investigate the biological effects of PGE₂ on the expression and action of TREM-1.

Materials and Methods

Reagents

DI-004 (an EP1 agonist), AE1–259-01 (an EP2 agonist), AE-248 (an EP3 agonist), and AE1-329 (an EP4 agonist) were provided by Ono Pharmaceutica ls. A monoclonal rat anti-mouse TREM-1 Ab and a monoclonal mouse anti-TREM-1 Ab, as well as control mouse IgG1 and a polyclonal anti-actin Ab, were obtained from R&D Systems and Santa Cruz Biotechnology, respectively. HRP-conjugated rabbit anti-mouse IgG and HRP-conjugated rabbit anti-actin IgG were purchased from DakoCytomation. Specific ELISAs for human TNF-α and human IL-8 were obtained from BioSource International. 8-Bromoadenosine 3’, 5’ cyclic monophosphate (8-Br-cAMP), LPS, the MEK (MAPKK) inhibitor PD98059, the p38 MAPK inhibitor SB203580, and the PI3K inhibitor LY294002 were purchased from Sigma-Aldrich, while the protein kinase A (PKA) inhibitor H-89 was obtained from Seikagaku. PGD₂, PGE₂, 15-16, 2nM(16, 3,4,4)-7-[3-[3-hydroxy-4-(4-iodophenoxy)-1-butenyl]-7-oxabicyclo[2,2,1]hept-2-yl]-5-heptenoic acid (I-BOP), a COX-1 inhibitor

Western blot analysis

Culture medium or RPM (1 × 10⁶ cells) was dissolved in sample buffer (350 mM Tris (pH 6.8), 10% SDS, 30% glycerol, 600 mM DTT, and 0.05% bromophenol blue), loaded onto 10% SDS-PAGE gel, and run at 20 mA for 1.5 h. Proteins in the supernatant were transferred to a polyvinylidene difluoride membrane (Roche Diagnostics) for 1.5 h at 200 mA by semidy blotting. The membrane was then blocked with 5% skim milk in PBS containing 0.05% Tween 20 for 1 h at 37°C, washed with PBS containing 0.1% Tween 20, and incubated overnight at 4°C with a monoclonal anti-human TREM-1 Ab (1 µg/ml). The blots were washed four times with TBS and incubated for 30 min with HRP-conjugated rabbit anti-mouse IgG. Immunoreactive bands were developed using a chemiluminescent substrate (ECL plus; Amersham Biosciences).

Assay of cytokine and chemokine production

Flat-bottom plates were precoated with 5 µg/ml of a monoclonal anti-human TREM-1 Ab or an isotype-matched control Ab (mouse IgG1) overnight at 4°C. After washing with PBS, PBMC (1 × 10⁶ cells) were preincubated with or without PGE₂ (1 µM) for 5 h. Then the PBMC were added to the Ab-coated wells, and briefly spun in a centrifuge at 1200 rpm to bind TREM-1. After incubation for 24 h, culture medium was obtained by centrifugation and stored at −80°C until use.

Assay of PGE₂ production

Concentration of PGE₂ in the supernatant was determined by using a PGE₂ ELISA kit according to the manufacturer’s instructions.
FIGURE 1. PGE₂ and LPS up-regulate mTREM-1 expression by RPM. RPM were incubated with or without PGE₂ (1 μM) for 1 h, and then were cultured in the presence or absence of LPS (100 ng/ml). The mTREM-1 mRNA level was determined by quantitative real-time PCR using murine GAPDH as the internal control. The relative level of mTREM-1 mRNA was evaluated by comparison with that in vehicle (EtOH)-treated RPM, which was defined as 1 arbitrary unit. Data are expressed as the mean ± SD of triplicate determinations.

Statistical analysis
Results are expressed as the mean ± SD. Statistical analysis was performed using the paired Student t test and p < 0.05 was considered to indicate significance.

Results
PGE₂ induces TREM-1 expression by RPM
PGE₂ is a mediator with a wide variety of biological effects in the process of microbial inflammation. To determine whether PGE₂ could influence the expression and action of TREM-1 in macrophages, RPM were pretreated with PGE₂ at a concentration of 1 μM for 1 h and then the cells were subsequently incubated in the presence or absence of LPS (100 ng/ml) for 1 h. Expression of mTREM-1 was determined by quantitative real-time PCR. LPS significantly increased expression of the TREM-1 gene (Fig. 1), as previously reported. PGE₂ also caused significant induction of TREM-1 expression and the magnitude of gene expression was significantly higher in PGE₂-treated cells than in LPS-treated cells. Furthermore, a combination of PGE₂ and LPS caused additive enhancement of mTREM-1 expression by RPM.

To investigate the time course of PGE₂-induced expression of mTREM-1, RPM were incubated with 1 μM PGE₂ for the indicated periods. Induction of gene expression occurred quite rapidly and was observed as early as 1 h after stimulation, following declined for 12 h (Fig. 2A). RPM were incubated with varying concentrations of PGE₂ for 1 h to determine whether physiological levels of PGE₂ enhanced mTREM-1 expression. It was shown that PGE₂ increased mTREM-1 expression in a concentration-dependent manner. PGE₂ at a concentration as low as 10⁻¹⁰ M significantly induced mTREM-1 expression and maximal expression occurred after stimulation with 10⁻⁶–10⁻⁷ M PGE₂ (Fig. 2B).

It has been demonstrated that monocytes and macrophages express various receptors for arachidonic acid metabolites, which are referred to EP, thromboxane-like prostanoid (TP), and CRTH₂ (20). Therefore, we investigated the effects of specific ligands for these receptors on mTREM-1 expression by RPM. The cells were incubated for 1 h with PGE₂ (an EP receptor ligand), I-BOP (a TP receptor ligand), or PGD₂ (a CRTH₂ ligand), and TREM-1 expression was evaluated by quantitative real-time PCR. PGE₂ induced TREM-1 expression, while neither I-BOP nor PGD₂ up-regulated mTREM-1 expression, indicating that PGE₂ was a specific inducer of mTREM-1 expression among these PGs (Fig. 2C).

Western blot analysis using a specific anti-mouse TREM-1 mAb was performed to evaluate mTREM-1 protein expression by RPM after incubation with or without PGE₂ for 5 h. mTREM-1 protein was detected faintly when RPM were incubated with the vehicle alone, whereas increased expression of mTREM-1 was clearly seen when RPM were incubated with PGE₂ (10⁻⁶ M) for 5 h (Fig. 2D).

Endogenous PGE₂ induces TREM-1 expression by RPM
It has been demonstrated that LPS induces TREM-1 expression as well as the release of PGE₂ by macrophages (7–9, 21). To evaluate the possible influence of endogenous PGE₂ on LPS-induced mTREM-1 expression, RPM were stimulated with LPS (100 ng/ml) for the indicated periods, after which PGE₂ production and mTREM-1 gene expression were determined by EIA and quantitative real-time PCR, respectively. PGE₂ synthesis gradually increased up to 4 h, and then the maximum level was maintained.

FIGURE 2. PGE₂ induces mTREM-1 expression in a time- or concentration-dependent manner. A. RPM were incubated with PGE₂ (1 μM) for the indicated periods and the mTREM-1 mRNA level was determined by quantitative real-time PCR. B. RPM were cultured with or without various concentrations of PGE₂ for 1 h and the mTREM-1 mRNA level was determined by quantitative real-time PCR. C. RPM were incubated with PGE₂ (1 μM), PGD₂ (1 μM), or I-BOP (0.2 μM) for 1 h and the mTREM-1 mRNA level was determined by quantitative real-time PCR. D. RPM were cultured with or without PGE₂ (1 μM) for 5 h, and expression of mTREM-1 protein and actin was determined by Western blot analysis. Data are expressed as the mean ± SD of triplicate determinations.

FIGURE 3. LPS-induced PGE₂ production up-regulates mTREM-1 expression by RPM. RPM were stimulated with LPS (100 ng/ml) for the indicated periods. Then the mTREM-1 mRNA level was determined by quantitative real-time PCR, and PGE₂ synthesis was determined by using a PGE₂ EIA kit. Data are expressed as the mean ± SD of triplicate determinations.
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FIGURE 4. Effect of COX inhibitors on LPS-induced mTREM-1 expression by RPM. RPM were pretreated with or without SC560 and/or NS398 for 1 h, and were subsequently incubated in the presence or absence of LPS (100 ng/ml) for the indicated periods. A, The mTREM-1 mRNA level at 2 h after LPS stimulation was determined by quantitative real-time PCR. B, PGE2 synthesis at 2 h after LPS stimulation was determined by a PGE2 EIA kit. C, Time course of mTREM-1 mRNA expression was determined by quantitative real-time PCR. D, mTREM-1 protein and actin were determined by Western blot analysis. Data are expressed as the mean ± SD of triplicate determinations. *, p < 0.01, vs LPS-stimulated RPM by Student’s unpaired t test.

mTREM-1 expression was significantly induced by a physiological concentration of PGE2. Therefore, the regulatory roles of PGE2 on TREM-1 expression was investigated. Because PGE2 synthesis is regulated by COX-1 and COX-2, RPM were incubated for 1 h in the presence or absence of SC560 (a selective COX-1 inhibitor) or NS398 (a selective COX-2 inhibitor), and then the cells were stimulated with LPS for 2 h. mTREM-1 expression and PGE2 synthesis was determined by quantitative real-time PCR and EIA, respectively. Both inhibitors for COX-1 and COX-2 partially, but significantly, inhibited LPS-induced expression of mTREM-1 (Fig. 4A). When the effects of COX inhibitors on PGE2 synthesis by LPS-stimulated RPM were investigated, these inhibitors also suppressed PGE2 synthesis (Fig. 4B). Vehicle (DMSO) did not affect on LPS-induced PGE2 synthesis and mTREM-1 expression (data not shown).

To investigate the effect of PGE2 on LPS-induced mTREM-1 mRNA expression at early time points, RPM were stimulated with LPS in the presence or absence of COX inhibitors for the indicated periods. Both COX-1 and COX-2 inhibitors failed to inhibit mTREM-1 expression at 0.5 h after LPS stimulation, whereas mTREM-1 expression at 1 h was partially inhibited, and that at 2 and 4 h was significantly abolished by COX inhibitors (Fig. 4C). These findings indicated that the effect of PGE2 on LPS-induced mTREM-1 expression was predominant at late time points (>2 h after stimulation) but not at early time points (0.5 and 1 h after stimulation).

Intracellular cAMP is a major regulator of PKA (22) and cAMP also activates the PI3K-, p38 MAPK-, and ERK-signaling pathways (23–25). Therefore, we investigated the signaling pathways involved in PGE2-induced expression of TREM-1 by using synthetic inhibitors of these kinases. A PKA inhibitor (H89), a p38 MAPK inhibitor (SB203580), and a PI3K inhibitor (LY294002) significantly suppressed PGE2-induced TREM-1 expression, whereas a MAPKK inhibitor (PD98059) failed to influence TREM-1 expression (Fig. 6). Inhibitory effects of these inhibitors were observed in a dose- or time-dependent manner (data not shown). These results suggested that PGE2-induced TREM-1 expression was mediated via the PKA, PI3K, and p38 MAPK pathways.
Activation of TREM-1 significantly enhances cytokine production by PGE₂-treated PBMC

An agonistic anti-TREM-1 mAb has been shown to stimulate the production of proinflammatory cytokines by monocytes (1, 7, 9). It was difficult to transfer PGE₂-treated RPM to Ab-coated wells, because the cells tightly adhere to the culture dishes. Therefore, PBMC were used to determine whether TREM-1 could enhance cytokine production by PGE₂-treated monocytes. Cells were incubated in the presence or absence of PGE₂ (10⁻⁶ M) for 5 h, and then harvested for incubation in agonistic anti-TREM-1 mAb-coated wells for 24 h. Then the levels of TNF-α and IL-8 in the culture supernatant were determined by specific ELISAs. The agonistic anti-TREM-1 mAb caused a significant increase of TNF-α production by PGE₂-treated PBMC (Fig. 7A). Production of TNF-α by PGE₂-treated cells was 6-fold higher than that by untreated cells. The agonistic anti-TREM-1 mAb also increased IL-8 production by PGE₂-treated PBMC and the magnitude of this enhancement was 4.6-fold (Fig. 7B). These results indicated that TREM-1 induced by PGE₂ was functional and enhanced the production of proinflammatory cytokines by PBMC.

PGE₂ induces hTREM-1 and hsTREM-1 expression by PBMC

It has been demonstrated that human monocytes are capable of expressing sTREM-1 as well as the cell surface form (3–5). Although stTREM-1 has also been identified in mice, the precise structure and function of soluble mTREM-1 are not yet known. Therefore, we investigated the expression of hTREM-1 and hsTREM-1 by PBMC to evaluate which type was predominantly expressed. After PBMC were incubated with PGE₂, hTREM-1 and hsTREM-1 gene expression were separately determined by quantitative real-time PCR.

Induction of both hTREM-1 and hsTREM-1 gene expression occurred quite rapidly and was seen as early as 1 h after stimulation, a subsequent declined until 9 h (Fig. 8A). To determine whether physiological concentrations of PGE₂ could induce the expression of hTREM-1 and hsTREM-1, PBMC were incubated with various concentrations of PGE₂ for 1 h and gene expression was determined. It was found that PGE₂ promoted both hTREM-1 and hsTREM-1 expression in a concentration-dependent manner, with maximal expression occurring at 10⁻⁶ or 10⁻⁷ M (Fig. 8B).

Western blot analysis using a specific anti-human TREM-1 mAb was performed to detect stTREM-1 protein. PBMC were incubated with or without PGE₂ for 5 h, and then the stTREM-1 protein level in the culture supernatant was determined by Western blotting. stTREM-1 was detected at very low levels when PBMC were incubated with the vehicle alone, whereas stTREM-1 expression was increased when PBMC were incubated with PGE₂ for 5 h (Fig. 8C). Taken together, these findings showed that PGE₂ up-regulated the expression of hTREM-1 as well as hsTREM-1 by monocytes.

Discussion

The present study provided evidence that PGE₂ up-regulates mTREM-1 expression by RPM, as well as hTREM-1 and hsTREM-1 expression by human PBMC. LPS-induced TREM-1 expression is at least partly regulated by endogenous PGE₂, because COX inhibitors significantly reduced TREM-1 expression. PGE₂-induced TREM-1 expression was mediated by EP-4, cAMP, and various kinases such as PKA, PI3K, and p38 MAPK. PGE₂-induced TREM-1 was functional,
because agonistic anti-TREM-1 mAb promoted a significant increase in the production of TNF-α and IL-8.

It is known that TREM-1 is specifically up-regulated by microbial products such as LPS, lipoteichoic acid (LTA), or zymosan (1, 7, 9, 26). However, the present study provided the first demonstration that PGE2 could induce TREM-1 expression by both RPM and PBMC. Induction of TREM-1 expression by PGE2 was also observed in a human monocyte cell line (U937) and a murine macrophage cell line (J774.1) (data not shown), indicating that PGE2 is an inducer of TREM-1 expression by both monocytes and macrophages. PGE2 was a specific regulator of mTREM-1 expression, because specific ligands for the CRTH2 and TP receptors (which are expressed on macrophages) failed to induce mTREM-1 expression. Biological effect of endogenous PGE2 on TREM-1 expression was predominant in the late phase of LPS-induced TREM-1 expression. This is based on the findings that COX inhibitors abrogated mTREM-1 expression after 2 h and also reduced mTREM-1 protein expression after 4–8 h following LPS stimulation.

In the present study, both COX-1 and COX-2 inhibitors suppressed PGE2 synthesis and TREM-1 induction. It has been documented that LPS promoted PGE2 production through the induction and activation of the COX-2, but not COX-1 (21, 27). However, Rouser et al. (21) also reported that SC560 (COX-1 inhibitor) inhibits PG synthesis through inhibition of COX-2 as well as COX-1 in LPS-stimulated RPM. Because this cross-inhibition was not observed in other cells, it appeared to be specific in RPM. TNF-α is also an inducer of PGE2 synthesis, but a previous study demonstrated that TNF-α had a limited effect on TREM-1 expression (7, 28). The reasons for this difference are not known, but it might be related to different mechanisms of action on monocytes and macrophages.

EP4, one of the receptors for PGE2, increases intracellular cAMP levels via activation of adenylate cyclase and promotes activation of the PKA, PI3K, p38 MAPK, and MAPK pathways (22–25). The present study demonstrated that a specific EP4 agonist and 8-Br-cAMP both enhanced mTREM-1 gene expression, while inhibitors of PKA, p38 MAPK, and PI3K blocked the PGE2-induced increase of mTREM-1 expression. These findings suggested that PGE2-induced up-regulation of mTREM-1 expression was mediated by the binding of PGE2 to EP4, which was followed by accumulation of cAMP and activation of various kinases, including PKA, p38 MAPK, and PI3K. This is consistent with the findings of previous studies demonstrating that PGE2 potentially activate various kinases such as PKA, PI3K, and p38 MAPK independently (29, 30). COX inhibitors failed to completely suppress LPS-induced up-regulation of mTREM-1 expression by RPM, and these inhibitors abolished TREM-1 expression only in the late phase, but not early phase of LPS stimulation. These indicate that other pathways might also be involved in the induction of TREM-1 expression by LPS. Knapp et al. (28) recently demonstrated that PI3K-dependent pathway played a central role, while MAPK also played a limited role, in LPS-induced up-regulation of TREM-1 expression by monocytes. Several signaling pathways might be involved in LPS-induced TREM-1 expression, and the endogenous PGE2-mediated pathway seems to be one of the mechanisms of LPS-induced TREM-1 expression on monocytes and macrophages.

TLR and TREM-1 cooperate to induce an inflammatory response, because activation of TREM-1 causes a marked increment in the production of proinflammatory cytokines by macrophages when LPS is used as the costimulus (1, 8, 9). TREM-1 activates a downstream signaling pathway through DAP12, which involves tyrosine phosphorylation, activation of mitogen-activated protein kinases, and mobilization of Ca2+. In contrast, TLRs directly recognize certain microbial products and components, such as LPS, LTA, and bacterial DNA. MyD88, IRAK, TRAF6, and IKK are essentially involved in the TLR-signaling pathway. These kinases can potentially induce the production of proinflammatory cytokines via the activation of NF-κB (31). Natural ligands for TREM-1 remain to be identified. If specific ligands for TREM-1 are located at the foci of microbe-induced inflammation, interactions between TREM-1 and TLRs can synergistically induce inflammatory responses. In this case, cooperation between TLRs and TREM-1 could occur at several levels during the process of LPS-induced inflammation. The present study showed that an LPS-induced increase in the production of PGE2 promoted TREM-1 expression, and activation of TREM-1 on PGE2-treated PBMC enhanced the production of proinflammatory cytokines. Based on these findings, we hypothesized that PGE2-induced up-regulation of TREM-1 expression may play an important role in enhancing the TLR-mediated response of macrophages to LPS stimulation.

Several line of evidence indicated that decoy receptors can modulate inflammatory responses by blocking the action by agonists (32, 33). sTREM-1 is a natural decoy receptor that could potentially inhibit TREM-1-mediated activation of cells through competition with natural ligand(s) for receptor binding. Synthetic sTREM-1 has been shown to inhibit LPS-induced cytokine production by monocytes in vitro (6). Furthermore, a recombinant sTREM-1 fusion protein and synthetic soluble TREM-1 have been shown to protect mice against lethal LPS challenge or bacterial sepsis by suppressing inflammatory cytokine production (6, 9). In contrast, it has been demonstrated that PGE2 can suppress the production of various cytokines (such as TNF-α, IL-8, MCP-1, IFN-γ-inducible protein-10, and MIP-1β) by LPS-stimulated macrophages through EP2- and/or EP4-mediated pathways (34, 35). PGE2 also induces the production of IL-10, which can have an anti-inflammatory effect (36). Present study demonstrated that PGE2 induced the release of sTREM-1 by PBMC. Therefore, PGE2 might suppress inflammation not only by inhibiting the production of proinflammatory cytokines, but also by inducing expression of the decoy receptor sTREM-1 and increasing the production of IL-10. However, activation of TREM-1 on PGE2-treated PBMC enhanced the production of proinflammatory cytokines, indicating that PGE2 may exert bidirectional effects on monocytes and macrophages to modulate inflammation through altering the expression of TREM-1 and sTREM-1.

Blocking of PGs has been shown to increase LPS-induced cytokine production both in vitro and in vivo (36–39). This is consistent with the previous finding that PGE2 and EP4 agonists attenuated LPS-induced cytokine production in mice (40). However, a number of studies have provided evidence that COX inhibitors can improve survival after the onset of endotoxic shock and COX-deficient mice are resistant to endotoxin-induced inflammation and death (17, 19, 41). Thus, the precise pathophysiological role of PGE2 in microbe infection still remains undefined. Further investigations should be directed toward the in vivo effects of PGE2-induced TREM-1 and sTREM-1 in sepsis models.

Increased expression of TREM-1 has been observed at sites of inflammation caused by microbial pathogens (9). However, we recently demonstrated that monosodium urate monohydrate (MSU) crystals induced mTREM-1 expression in monocytes and macrophages in vitro and in vivo (42), indicating that TREM-1 might be involved in the development of acute gouty arthritis. We also observed that MSU crystal-induced mTREM-1 expression is regulated, at least in part, by endogenous produced PGE2 (our unpublished data). These findings suggest the possibility that PGE2 might enhance TREM-1 expression in nonmicrobial inflammatory diseases including acute gouty arthritis. If a natural TREM-1 ligand is also induced in nonmicrobial inflammation, it could enhance inflammatory responses by activating PGE2-induced...
TREM-1. Furthermore, nonmicrobial products such as heat shock protein 60, which are induced in various inflammatory diseases, have been shown to stimulate TLRs (43). Thus, it is presumed that activation of PGE2-induced TREM-1 and TLRs by specific ligands might cooperatively increase the inflammatory responses in patients with nonmicrobial inflammatory diseases.

The present study provided a first evidence that PGE2 induces the expression of both TREM-1 and sTREM-1 by macrophages. This finding sheds new light on the role of PGE2 as a regulator of the inflammatory response to microbial infection. Further investigations should be directed toward the assessment of pathophysiological roles of TREM-1 and sTREM-1 in various inflammatory diseases. Such studies may help to elucidate the precise role of PGE2-induced TREM-1 expression in inflammation and could possibly provide evidence leading to new strategies for the treatment of inflammatory diseases.

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Disclosures

The authors have no financial interest of conflict.

References


