Lipopolysaccharide-Dependent Prostaglandin E₂ Production Is Regulated by the Glutathione-Dependent Prostaglandin E₂ Synthase Gene Induced by the Toll-Like Receptor 4/MyD88/NF-IL6 Pathway

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Lipopolysaccharide-Dependent Prostaglandin E2 Production Is Regulated by the Glutathione-Dependent Prostaglandin E2 Synthase Gene Induced by the Toll-Like Receptor 4/MyD88/NF-IL6 Pathway

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Macrophages produce a large amount of PGE2 during inflammation. This lipid mediator modulates various immune responses. PGE2 acts on macrophages and inhibits production of cytokines such as TNF-α and IL-12. Membrane-bound glutathione-dependent PGE2 synthase (mPGES) has been shown to be a terminal enzyme of the cyclooxygenase-2-mediated PGE2 biosynthesis. Here we identified mPGES as a molecule that is induced by LPS in macrophages. The expression of mPGES was not induced by LPS in mice lacking Toll-like receptor 4 or MyD88. Furthermore, mice deficient in NF-IL6 showed neither induction of mPGES nor biosynthesis of PGE2 in response to LPS, indicating that mPGES expression in response to LPS is regulated by a Toll-like receptor 4/MyD88/NF-IL6-dependent signaling pathway. We generated mPGES-deficient mice and investigated the role of mPGES in vivo. The mice showed no augmentation of the PGE2 production in response to LPS. However, they were not impaired in the LPS-induced production of inflammatory cytokines and showed normal response to the LPS-induced shock. Thus, mPGES is critically involved in the biosynthesis of PGE2 induced by LPS, but is dispensable for the modulation of inflammatory responses.


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3 Abbreviations used in this paper: PLA2, phospholipase A2; PGE2, prostaglandin E2; PGHS, prostaglandin synthase; Cox, cyclooxygenase; cPGES, cytosolic PGE2 synthase; ePGES, embryonic stem; MAPEG, membrane-associated proteins involved in eicosanoid and glutathione metabolism; MGST1-L1, microsomal glutathione-S-transferase-1-like-1; mPGES, membrane-bound PGE2 synthase; TLR, Toll-like receptor.

Materials and Methods

Reagents

LPS from Salmonella minnesota Re-595 prepared by a phenol-chloroform-petroleum ether extraction procedure was purchased from Sigma-Aldrich (St. Louis, MO). Thioglycolate broth (Brewer’s formula) was purchased from Difco (Detroit, MI). IFN-γ was obtained from Genzyme (Cambridge, MA). Restriction and DNA modification enzymes were products of TOYOBO (Tsuruga, Japan).
RAW264.7 (1 × 10⁶) cells were stimulated with LPS (100 ng/ml) for 4 h. RNA was obtained from the cells with an RNA easy kit (Qiagen, Hilden, Germany) following poly(A)⁺ RNA selection using Oligotex-dT30 latex beads (Takara, Otsu, Japan). Then all procedures were performed according to the instructions of the PCR-select cDNA subtraction kit (Clontech Laboratories, Palo Alto, CA).

Preparation of peritoneal macrophages
Peritoneal macrophages from wild-type, TLR4-mutant, MyD88-mutant, NF-IL6-mutant, and mPGES-mutant mice were isolated as described previously (12–14).

Northern blot analysis
Total RNA was extracted from peritoneal macrophages (5 × 10⁶) using the TRIzol reagent (Invitrogen, Carlsbad, CA). Then total RNA (5 μg) was electrophoresed, transferred to a nylon membrane, and hybridized with ³²P-labeled cDNA probe specific for mPGES, Cox-1, Cox-2, and cPGES/p23 as described previously (14). The same membrane was rehybridized with cDNA specific for β-actin.

Western blot analysis
The cell lysates were separated on SDS-PAGE, transferred onto a nitrocellulose membrane, and incubated with the blocking buffer containing 5.0% skim milk. The membrane was incubated with the indicated Ab and then visualized with ECL system (NEN Life Science, Boston, MA).

RT-PCR
Total RNA was isolated from an adherent monolayer of peritoneal macrophages stimulated with LPS (100 ng/ml). cDNA synthesis was synthesized using Superscript II Moloney murine leukemia virus reverse transcriptase (Invitrogen). The cDNA product was amplified by primers for mPGES (5'-AGCAACTGCTGTGCATCAAGATGTAAC-3' and 5'-CCTGAGAGCAACGGAAATGTAC-3').

Generation of mPGES-mutant mice
Membrane-associated PGES genomic DNA was screened from a 129/SvJ mouse genomic library (Stratagene, La Jolla, CA), subcloned into pBlue-script vector (Stratagene), and characterized by restriction enzyme mapping and DNA sequencing. A targeting vector was constructed to replace the 1.2-kb genomic fragment containing the second exon with the neomycin resistance gene from pMC1-neo (Stratagene). The targeting vector was amplified by primers for mPGES (5'-AGCAACTGCTGTGCATCAAGATGTAAC-3' and 5'-CCTGAGAGCAACGGAAATGTAC-3').

Expression of mPGES mRNA in response to LPS in macrophages
To evaluate the production of cytokines by macrophages in vitro, thioglycolate-elicited peritoneal cells were seeded onto 96-well plates (2 × 10⁵ cells/well) and stimulated with the indicated reagents for 24 h. Concentrations of TNF-α, IL-12p40, and IL-6 were measured by ELISA according to the manufacturer’s instructions (Genzyme, Cambridge, MA). Production of PGE₂ was measured with a PGE₂ monoclonal enzyme immunoassay kit (Cayman Chemicals, Ann Arbor, MI). For the in vivo experiments wild-type and mPGES-mutant mice were i.p. injected with 0.1 ml PBS containing 1 mg LPS, and sera were taken at the indicated time points. Serum levels of TNF-α, IL-12p40, and PGE₂ were determined by ELISA.

Results
Membrane-associated PGES is induced by LPS in macrophages
To identify the LPS-inducible genes responsible for immune and inflammatory responses in activated macrophages we prepared a cDNA library from LPS-stimulated cells of the mouse macrophage line, RAW264.7, and screened the library by a suppression-subtracted hybridization technique. Using this technique we previously identified novel LPS-inducible genes such as the LPS-inducible CCR and inducible IκB kinase genes (15, 16). In addition we obtained a gene encoding membrane-bound glutathione-dependent PGE₂ synthase (mPGES). We examined the expression of mPGES in response to LPS in mouse peritoneal macrophages. Thioglycolate-elicited peritoneal macrophages were treated with 100 ng/ml LPS for 0.5, 2, 8, and 16 h, and the mRNA expression of mPGES was examined by Northern blot analysis. As shown in Fig. 1A, mRNA for mPGES was not detected in nonstimulated macrophages, but was markedly expressed in response to LPS. Four major transcripts were detected, and the shortest one matched the mouse mPGES cDNA (accession no. AB041997) in length. The mRNA expression of mPGES was induced at 2 h, reached a peak at 8 h, and lasted until 16 h.

We examined the LPS-induced expression of mPGES in macrophages from mice lacking TLR4 or MyD88, both of which mediate LPS signaling. LPS stimulation did not induce mPGES expression in TLR4- and MyD88-deficient mice, showing that mPGES is induced in response to LPS via a TLR4-MyD88-dependent pathway (Fig. 1B).

NF-IL6-deficient macrophages are defective in the LPS-induced expression of mPGES
When macrophages are activated by various inflammatory stimuli, NF-IL6 exhibits the augmented transcriptional activity and plays an important role in inflammatory responses of the macrophages (17). NF-IL6 binding motifs have been identified in the promoter regions of several LPS-inducible genes, including Cox-2 (18–20). Therefore, we analyzed the LPS-induced expression of mPGES in NF-IL6-deficient macrophages. Peritoneal macrophages from wild-type and NF-IL6-deficient mice were stimulated with LPS, and the expression of mPGES was examined by Northern blotting. In NF-IL6-deficient macrophages, LPS-induced expression of mPGES was almost completely abolished (Fig. 2A). We next examined the expression of Cox-1, Cox-2, and cPGES/p23 in NF-IL6-deficient macrophages. In wild-type macrophages Cox-1 mRNA was detected before stimulation with LPS and was downregulated after the stimulation (Fig. 2B). In contrast, Cox-2 mRNA was induced, reached a peak at 2 h, and then declined after 8 h in wild-type macrophages stimulated by LPS (Fig. 2C). The expression of cPGES/p23 mRNA was detected before and augmented after the stimulation (Fig. 2B). In NF-IL6-deficient macrophages, down-regulation of Cox-1 and up-regulation of cPGES/p23 were similarly observed (Fig. 2B). However, the LPS-induced expression of Cox-2 was compromised in NF-IL6-deficient cells. At 2 h the expression of Cox-2 mRNA was significantly reduced compared with that of wild-type cells, although the expression of Fig. 1. Expression of mPGES mRNA in response to LPS in macrophages. A, Thioglycolate-elicited peritoneal macrophages from wild-type mice were cultured with 100 ng/ml LPS for 0.5, 2, 8, and 16 h. Total RNA (5.0 μg) was electrophoresed, transferred, and hybridized with ³²P-labeled probe specific for mPGES. B, Thioglycolate-elicited peritoneal macrophages from wild-type, MyD88-deficient, and TLR4-deficient mice were cultured with 100 ng/ml LPS for 8 h and analyzed for mPGES expression by Northern blotting.
Cox-2 mRNA was increased at 8 h in NF-IL6-deficient cells (Fig. 2C). We further analyzed Cox-1 and Cox-2 protein expression in LPS-stimulated NF-IL6-deficient peritoneal macrophages. Despite reduced expression of Cox-1 mRNA after LPS stimulation, the protein level was not altered in wild-type or NF-IL6-deficient macrophages (Fig. 2D, upper panel). The expression of Cox-2 protein was induced at 12 h and declined at 24 h in wild-type macrophages, whereas the induction of Cox-2 protein in NF-IL6-deficient macrophages was observed with delayed kinetics compared with wild-type macrophages (Fig. 2D, lower panel). Thus, severe impairment in mPGES induction and delayed induction of Cox-2 was observed in LPS-stimulated NF-IL6-deficient macrophages.

We next analyzed the production of PGE2 in macrophages from NF-IL6-deficient mice. Thioglycolate-elicted peritoneal macrophages were cultured with various concentrations of LPS for 24 h. Nonstimulated cells secreted small amounts of PGE2, and stimulation with LPS induced the production of PGE2 in a dose-dependent manner in wild-type mice. In NF-IL6-deficient macrophages, LPS did not induce the production of PGE2, although nonstimulated cells produced small amounts. These results indicate that NF-IL6 is involved in the LPS-induced production of PGE2 by mediating the gene expression of mPGES.

**Generation of mPGES-deficient mice**

To elucidate the role of mPGES in vivo, we generated mPGES-mutant mice by gene targeting. The mouse mPGES gene was disrupted by introducing a targeted mutation into E14.1 ES cells. A targeting vector was designed to replace the second exon with the neomycin resistance gene (Fig. 3A). This region of the mPGES gene shows high homology with rat and human mPGES (15). Homologous recombination was achieved in seven of 120 ES cell clones resistant to neomycin and ganciclovir. Three ES cell lines...

**FIGURE 2.** Induction of mPGES mRNA and production of PGE2 in response to LPS in NF-IL6-deficient macrophages. A, Thioglycolate-elicited peritoneal macrophages from wild-type and NF-IL6-deficient mice were cultured with 100 ng/ml LPS for 0.5, 2, 8, and 16 h. Total RNA (5.0 μg) was electrophoresed, transferred, and hybridized with 32P-labeled probe specific for mPGES. B, Thioglycolate-elicited peritoneal macrophages from wild-type and NF-IL6-deficient mice were cultured with 100 ng/ml LPS for 8 h and analyzed for expression of Cox-1 and cPGES/p23 by Northern blotting. Two representatives are shown from four independent experiments. C, Thioglycolate-elicited peritoneal macrophages from wild-type and NF-IL6-deficient mice were cultured with 100 ng/ml LPS for the indicated period and analyzed for the expression of Cox-2 by Northern blotting. D, Thioglycolate-elicited peritoneal macrophages from wild-type and NF-IL6-deficient mice were cultured with 100 ng/ml LPS for the indicated period, followed by Western blot analysis with anti-Cox-1 or anti-Cox-2-specific Ab. E, Thioglycolate-elicited peritoneal macrophages from wild-type and NF-IL6-deficient mice were cultured with various concentrations of LPS for 24 h. The concentrations of PGE2 in the culture supernatants were measured by ELISA. Experiments were independently performed three times with similar results.

**FIGURE 3.** Targeted disruption of the mPGES gene. A, Schematic drawing of the targeting procedure. The mPGES wild-type genome, the targeting vector, and the predicted disrupted gene are shown. A solid bar denotes the second exon. The neo box represents the MC-1 neo poly(A)+ gene. The HSV-thymidine kinase box represents the HSV-thymidine kinase gene. Restriction enzymes: B, BamHI; E, EcoRI; S, SalI. B, Southern blotting of genomic DNA from offspring of the heterozygous intercrosses. Genomic DNA was extracted from mouse tails, digested with BamHI, and hybridized with the radiolabeled probe indicated in A. Southern blotting gave a single 2.4-kb band for wild-type mice (+/+), a 1.8-kb band for homozygotes (−/−), and both bands for heterozygotes (+/−). C, Northern blot analysis of peritoneal macrophages. Wild-type (+/+), homozygous (−/−), and both bands for heterozygotes (+/−) were injected with 2 ml 4% thioglycolate. Three days later, peritoneal exudate cells were harvested and cultured with or without 100 ng/ml LPS for 8 h. Total RNA was extracted from adherent cells, electrophoresed, transferred to a nylon membrane, and hybridized with the mouse mPGES cDNA probe. The same membrane was rehybridized with the radiolabeled probe indicated in A. The neo box represents the MC-1 neo poly(A)+ gene. The HSV-thymidine kinase box represents the HSV-thymidine kinase gene. Restriction enzymes: B, BamHI; E, EcoRI; S, SalI. B, Southern blotting of genomic DNA from offspring of the heterozyzous intercrosses. Genomic DNA was extracted from mouse tails, digested with BamHI, and hybridized with the radiolabeled probe indicated in A. Southern blotting gave a single 2.4-kb band for wild-type mice (+/+), a 1.8-kb band for homozygotes (−/−), and both bands for heterozygotes (+/−). C, Northern blot analysis of peritoneal macrophages. 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containing a mutant mPGES allele were microinjected into C57BL/6 blastocysts. One line of these chimeric mice successfully transmitted the disrupted mPGES gene through the germline. Homozygous mice carrying the mutant allele were born at the expected Mendelian ratio (Fig. 3B). They were healthy and did not show any obvious abnormalities until 20 wk. We investigated the expression of mPGES mRNA in peritoneal macrophages stimulated with 100 ng/ml LPS for 8 h by Northern blot analysis (Fig. 3C). We detected in the mutant mice transcripts of almost the same size. We next conducted RT-PCR using mRNA of LPS-stimulated macrophages from the mutant mice (Fig. 3D). RT-PCR with primers that flank the cDNA coded by the second exon resulted in the production of a 270-bp band in wild-type mice and a 190-bp band in the mutant mice. Sequence analysis of these products showed that second exon was completely deleted in mRNA from the mutant mice, indicating that normal mPGES protein was not produced in these animals (Fig. 3E).

Membrane-associated PGES is indispensable for PGE\(_2\) production in response to LPS

We first examined the production of PGE\(_2\) in response to LPS in macrophages from mPGES-mutant mice. Thioglycolate-elicited peritoneal macrophages were cultured with various concentrations of LPS. Macrophages from mPGES-mutant mice produced small amounts of PGE\(_2\), similar to wild-type cells in the unstimulated condition (Fig. 4A). However, no LPS-induced augmentation of PGE\(_2\) production was observed in mPGES-mutant macrophages. This indicates that the targeted deletion of the mPGES gene leads to a loss of functional protein production, and that mPGES is essential for LPS-induced PGE\(_2\) production in macrophages.

We further analyzed the LPS-induced PGE\(_2\) production in vivo. Wild-type mice (\(n = 10\)) and mPGES-mutant mice (\(n = 9\)) were i.p. injected with 0.1 ml PBS containing 1 mg LPS (Fig. 4B). The serum level of PGE\(_2\) was measured 6 h after injection. In wild-type mice, the serum level of PGE\(_2\) increased by 3-fold in response to LPS, whereas it remained at the basal level after administration in mPGES-mutant mice. Taken together these results demonstrate that mPGES is an indispensable enzyme for the production of PGE\(_2\) in response to LPS.

Normal production of proinflammatory cytokines in response to LPS in mPGES-mutant mice

PGE\(_2\) has been shown to modulate the production of proinflammatory cytokines (21). Therefore, we analyzed the LPS-induced production of proinflammatory cytokines in mPGES-mutant mice. Thioglycolate-elicited peritoneal macrophages were cultured with 100 ng/ml LPS in the presence or the absence of IFN-\(\gamma\) (50 U/ml) for 24 h, and the production of TNF-\(\alpha\)-IL-12p40 and IL-6 was examined by ELISA (Fig. 5A). The production of these cytokines in mPGES-mutant macrophages was comparable to that observed in wild-type macrophages. We further examined in vivo the response to LPS in wild-type and mPGES-deficient mice. Wild-type

![FIGURE 4](http://www.jimmunol.org/)

**FIGURE 4.** Impaired PGE\(_2\) production in response to LPS in mPGES-mutant mice. A. Thioglycolate-elicited peritoneal macrophages from wild-type and mPGES-mutant mice were cultured with 100 ng/ml LPS for 24 h. Concentrations of PGE\(_2\) in the culture supernatants were measured by ELISA. Experiments were independently performed three times with similar results. B. Wild-type (\(n = 10\)) and mPGES-mutant (\(n = 9\)) mice were i.p. injected with 0.1 ml PBS containing 1 mg LPS. Serum levels of PGE\(_2\) were measured by ELISA. Data are represented as the mean serum level ± SD.

![FIGURE 5](http://www.jimmunol.org/)

**FIGURE 5.** Normal responsiveness of mPGES-mutant mice to LPS. A. Thioglycolate-elicited peritoneal macrophages from wild-type and mPGES-mutant mice were cultured with 100 ng/ml LPS in the presence or the absence of IFN-\(\gamma\) (50 U/ml) for 24 h. Concentrations of TNF-\(\alpha\)-IL-12p40 and IL-6 in the culture supernatants were measured by ELISA. ND, not detected. B. Wild-type (\(n = 3\)) or mPGES-mutant (\(n = 3\)) mice were i.p. injected with 1.0 mg LPS. Serum levels of TNF-\(\alpha\) and IL-12p40 were measured at the indicated time points by ELISA. Experiments were independently performed three times with similar results. C. Age-matched wild-type (\(n = 10\)) and mPGES-deficient (\(n = 10\)) mice were i.p. injected with 1.0 mg LPS. Mortality was assessed daily for 6 days.
(n = 3) or mPGES-mutant (n = 3) mice were i.p. injected with 1 mg LPS. Sera were taken at the indicated time points, and concentrations of TNF-α and IL-12p40 were determined by ELISA (Fig. 5B). Both mice had significantly elevated serum concentrations of these cytokines, and there was no difference in the level of cytokine production between wild-type and mPGES-mutant mice. We monitored the survival rate of mice after LPS administration. Almost all wild-type and mPGES-mutant mice died within 5 days of the LPS challenge (Fig. 5C). Thus, mPGES-mutant mice succumbed to endotoxin shock despite showing no elevation of PGE₂.

Discussion

A previous study demonstrated that the expression of mPGES is increased by LPS in macrophages (11). We also identified mPGES from the screening of an LPS-stimulated macrophage cDNA library. LPS-stimulated expression of mPGES was not observed in TLR4-deficient macrophages. TLR4 triggers intracytoplasmic signaling by recruiting the adaptor molecule MyD88 to the membrane (13, 14). Recent studies indicated the existence of MyD88-dependent and -independent pathways in TLR4-mediated signaling (22, 23). LPS-induced Cox-2 expression has been shown to be mediated by a MyD88-dependent pathway (23). Similarly, LPS induction of mPGES completely depends on MyD88. Furthermore, LPS-induced mPGES expression was abolished in NF-IL6-deficient macrophages. NF-IL6 is a member of the C/EBP family of transcription factors involved in the expression of various genes induced by inflammatory stimuli (24). We tried to identify NF-IL6 binding sites in the promoter region of the mPGES gene, but could not find a cis-acting element responsible for LPS-induced transcriptional activation within the 2.5-kb fragment upstream of the transcription start site (data not shown). This may indicate that NF-IL6 regulates mPGES gene expression via the cis-acting element present outside the proximal promoter.

LPS-induced Cox-2 expression was observed with delayed kinetics in NF-IL6-deficient macrophages. Transcriptional activation of the Cox-2 gene induced by LPS has been shown to partly depend on NF-IL6 in macrophages. Indeed, NF-IL6 binding sites have been identified in the promoter region of the Cox-2 gene (4, 25–28). A recent study showed that Cox-2 mRNA induction and promoter activity were defective in NF-IL6-deficient macrophages, and the defect could be rescued by the expression of NF-IL6 (26). Furthermore, it has been demonstrated that Cox-2 mRNA induction is biphasic. The initial phase of Cox-2 induction depends on NF-IL6, and the second phase requires coordination of NF-IL6 and NF-IL6β in activated macrophages (29). NF-κB and cAMP response element CRE have also been shown to regulate the expression of the Cox-2 gene (25–28). From these findings we speculate that the reduced expression of Cox-2 during the early time period is due to the absence of NF-IL6, but enhanced Cox-2 expression in the late period may be due to compensation by other transcription factors. Although Cox-2 protein was significantly induced at the late time period of LPS stimulation, PGE₂ production was severely reduced in NF-IL6-deficient macrophages. Thus, NF-IL6 is critically involved in LPS-induced production of PGE₂ through modulating the expression of mPGES. In contrast, Cox-1 and cPGES/p23 induction was not altered in NF-IL6-deficient macrophages. After LPS stimulation, down-regulation of Cox-1 mRNA and up-regulation of cPGES/p23 mRNA were observed. However, the protein level of Cox-1 was not changed after LPS stimulation. At present, it remains unknown how LPS stimulation down-regulates the expression of Cox-1 mRNA.

Generation of mPGES-mutant mice revealed an essential role for mPGES in the LPS-induced production of PGE₂. A recent study showed that the kinetic change in PGE₂ production correlated well with that in mPGES mRNA and protein expression and that dexamethasone reduced both PGE₂ synthesis and mPGES expression in LPS-stimulated macrophages. This implies that the PGE₂ production activity detected in LPS-stimulated macrophages is largely dependent on mPGES. PGE₂ production in response to LPS was completely abolished in mPGES-mutant mice, demonstrating that mPGES is essential for LPS-induced biosynthesis of PGE₂. Although LPS-induced PGE₂ production was abolished in mPGES-mutant mice, the basal PGE₂ level in mPGES-mutant mice was comparable to that in wild-type mice. This indicates that production of PGE₂ at the basal level occurs independent of mPGES and mainly depends on Cox-1 and cPGES/p23, which are constitutively expressed. Indeed, mice lacking Cox-1 reduced PGE₂ levels in the stomach (30). Thus, the present study also established that the Cox-2/mPGES pathway is indispensable for PGE₂ production induced by proinflammatory stimuli, whereas Cox-1/cPGES is required for the basal PGE₂ production responsible for maintenance of homeostasis.

There are several reports that PGE₂ contributes to immune suppression and that PGE₂ secreted from activated macrophages in response to proinflammatory stimuli acts on the macrophages themselves and exhibits an inhibitory function in a negative feedback loop (21). Addition of exogenous PGE₂ has been shown to reduce LPS-induced IL-6 and TNF-α production, but not IL-1β production, in macrophages (31). Another study showed that PGE₂ induces the production of IL-6 (32). Thus, it remains unclear how PGE₂ regulates the production of inflammatory cytokines. Membrane-associated PGES-mutant mice showed no LPS-induced elevation of PGE₂, providing a good model to analyze the involvement of PGE₂ in the production of inflammatory cytokines. The LPS-induced production of TNF-α and IL-12 was not altered at various time points, even 24 h after LPS injection in mPGES-mutant mice, indicating that endogenous PGE₂ expressed in response to LPS is not essential for the regulation of inflammatory cytokine production.

To date, four PGE₂ receptors, designated EP₁, EP₂, EP₃, and EP₄, have been identified, and their physiological roles demonstrated (1). Mice deficient in EP₄ show an increased incidence of patent ductus arteriosus with high neonatal mortality. EP₂-deficient female mice consistently deliver fewer pups than their wild-type counterparts due to slightly impaired ovulation and a marked reduction in fertilization. EP₄-deficient mice show an impaired fertilization response (1). However, mPGES-deficient mice do not show these abnormalities. This may be due to the basally produced PGE₂, probably through the Cox-1/EP₄ pathway.

In this study we have demonstrated that LPS-induced mPGES expression is essential for LPS-dependent PGE₂ production, but not for inflammatory cytokine production. It should be analyzed whether cPGES/p23 is involved in the basal PGE₂ production. The generation of mice lacking both mPGES and cPGES should provide new insight into the role of PGE₂.

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References

IN VIVO ROLE OF mPGES


