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Permalink
https://escholarship.org/uc/item/1hm378wj

Journal
The Journal of biological chemistry, 274(18)

ISSN
0021-9258

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Publication Date
1999-04-01

DOI
10.1074/jbc.274.18.12263

Peer reviewed
Regulation of Delayed Prostaglandin Production in Activated P388D1 Macrophages by Group IV Cytosolic and Group V Secretory Phospholipase A2s*

(Received for publication, May 21, 1998, and in revised form, February 26, 1999)

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Group V secretory phospholipase A2 (sPLA2) rather than Group IIA sPLA2 is involved in short term, immediate arachidonic acid mobilization and prostaglandin E2 (PGE2) production in the macrophage-like cell line P388D1. When a new clone of these cells, P388D1/MAB, selected on the basis of high responsivity to lipopolysaccharide plus platelet-activating factor, was studied, delayed PGE2 production (6–24 h) in response to lipopolysaccharide alone occurred in parallel with the induction of Group V sPLA2 and cyclooxygenase-2 (COX-2). No changes in the level of cytosolic phospholipase A2 (cPLA2) or COX-1 were observed, and Group IIA sPLA2 was not detectable. Use of a potent and selective sPLA2 inhibitor, 3-(3-acetamide 1-benzyl-2-ethylindolyl-5-oxy)-propanesulfonic acid (LY311727), and an antisense oligonucleotide specific for Group V sPLA2 revealed that delayed PGE2 was largely dependent on the induction of Group V sPLA2. Also, COX-2, not COX-1, was found to mediate delayed PGE2 production because the response was completely blocked by the specific COX-2 inhibitor NS-398. Delayed PGE2 production and Group V sPLA2 expression were also found to be blunted by the inhibitor methylarachidonyl fluorophosphonate. Because inhibition of Ca2+-independent PLA2 by an antisense technique did not have any effect on the arachidonic acid release, the data using methylarachidonyl fluorophosphonate suggest a key role for the cPLA2 in the response as well. Collectively, the results suggest a model whereby cPLA2 activation regulates Group V sPLA2 expression, which in turn is responsible for delayed PGE2 production via COX-2.

Arachidonic acid (AA)1 mobilization and the generation of prostaglandins by major immunoinflammatory cells such as macrophages and mast cells usually occur in two phases. The immediate phase, which takes minutes and is elicited by Ca2+-mobilizing agonists such as platelet-activating factor (PAF), is characterized by a burst of AA liberation. In some cells such as P388D1 macrophages (1, 2) and MMC-34 mast cells (3), this burst is mainly produced by a secretory phospholipase A2 (sPLA2) but is strikingly regulated by the cytosolic Group IV phospholipase A2 (cPLA2).

The delayed phase of prostaglandin production is accompanied by the continuous supply of AA over long incubation periods spanning several hours. There is some discrepancy about the identity of the PL2 isoform(s) involved in the delayed phase. Despite this phase being independent of a Ca2+ increase, the cPLA2 has often been suggested to be critically involved (3–5). However, other studies have suggested the quantitatively more important role of the sPLA2, an enzyme that is dramatically induced during long term incubation of the cells with a variety of stimuli (4–6). There is, however, agreement that COX-2, another enzyme whose expression is augmented dramatically after long term stimulation, is absolutely required for long term PGE2 production, irrespective of the constitutive presence of COX-1 (7–9).

Using a new clone of the P388D1 macrophage-like cells termed P388D1/MAB, we provide herein evidence for the involvement of Group V sPLA2 in delayed PGE2 production. Furthermore, our results suggest that Group V sPLA2 expression is dependent upon the activation of Group IV cPLA2.

**EXPERIMENTAL PROCEDURES**

**Materials**—Mouse P388D1 macrophage-like cells were obtained from the American Type Culture Collection (Rockville, MD). Iscove’s modified Dulbecco’s medium (endotoxin <0.05 ng/ml) was from Whittaker Bioproducts (Walkersville, MD). Fetal bovine serum was from HyClone Laboratories (Logan, UT). Nonessential amino acids were from Irvine Scientific (Santa Ana, CA). [5,6,8,9,11,12,14,15-3H]Arachidonic acid (specific activity, 100 Ci/mmol) was from NEN Life Science Products, and 1-palmitoyl-2-[14C]palmitoyl-sn-glycero-3-phosphocholine (specific activity, 54 mCi/mmol) was from Amersham Pharmacia Biotech. PAF, LPS (Escherichia coli 0111:B4), and actinomycin D were from Sigma. Methylarachidonyl fluorophosphonate (MAFP) and NS-398 were from Biomol (Plymouth Meeting, PA). Antibodies against murine COX isoforms were generously provided by Dr. W. L. Smith (Department of Biochemistry, Michigan State University, East Lansing, MI). The antibody against Group IV cPLA2 was generously provided by Dr. Ruth Kramer (Lilly). The sPLA2 inhibitor, 3-(3-acetamide 1-benzyl-2-ethylindolyl-5-oxy)propanesulfonic acid (LY311727), was generously provided by Dr. Edward Mihelich (Lilly). cDNA probes for Groups V and IIA sPLA2 were synthesized as described previously (11). cDNA probes for murine glyceraldehyde-3-phosphate dehydrogenase were from Cayman (Ann Arbor, MI).

**Cell Culture and Labeling Conditions**—P388D1 cells were maintained at 37 °C in a humidified atmosphere at 90% air and 10% CO2 in Iscove’s modified Dulbecco’s medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin, and nonessential amino acids. P388D1 cells were plated at 106/well, allowed to adhere overnight, and used for experiments the following day. All experiments were conducted in serum-free Iscove’s...
modified Dulbecco’s medium. When required, radiolabeling of the P388D1 cells with [3H]AA was achieved by including 0.5 μCi/ml [3H]AA during the overnight adherence period (20 h). Labeled AA that had not been incorporated into cellular lipids was removed by washing the cells four times with serum-free medium containing 1 mg/ml albumin.

**Measurement of PGE2 Production and Extracellular [3H]AA Release**—The cells were placed in serum-free medium for 30 min before the addition of LPS for different periods of time. Afterward, the supernatants were removed and cleared of detached cells by centrifugation, and PGE2 was quantitated using a specific radioimmunoassay (PerSpective Biosystems, Framingham, MA). For [3H]AA release experiments, cells labeled with [3H]AA were used, and the incubations were performed in the presence of 0.5 mg/ml bovine serum albumin. The supernatants were removed, cleared of detached cells by centrifugation, and assayed for radioactivity by liquid scintillation counting. The standard LPS/PAF stimulation protocol for immediate responses has been described previously (1). Briefly, the cells were incubated in a 10 mM solution of PIIA, 0.5% Triton X-100, 1 mM sodium vanadate, 1 mM phenylmethylsulfonyl fluoride, 20 μM leupeptin, 20 μM aprotinin, pH 7.5. Samples from cell extracts (10 μg for GPLA1, 200 μg for COX) were separated by SDS-polyacrylamide gel electrophoresis (10% acrylamide gel) and transferred to Immobilon (Millipore). For GPLA2 mobility shift studies, 24-cm acrylamide gels were run. Nonspecific binding was blocked by incubating the membranes with 5% nonfat milk in phosphate-buffered saline for 1 h. Membranes were then incubated with anti-GPLA1, anti-COX-1, or anti-COX-2 antisera and treated with horseradish peroxidase-conjugated protein A (Amersham Pharmacia Biotech). Bands were detected by enhanced chemiluminescence (ECL, Amersham Pharmacia Biotech).

**Northern Blot Analyses**—Total RNA was isolated from unstimulated or LPS-stimulated cells by the TriZOL reagent method (Life Technologies, Inc.) as indicated by the manufacturer. Fifteen μg of RNA were electrophoresed in a 1% formaldehyde/agarose gel and transferred to nylon membranes (Hybond, Amersham Pharmacia Biotech) in 10× SSC buffer. Hybridizations were performed in QuickHyb solution (Stratagene) following the manufacturer’s instructions. 32P-Labeled probes for Group IIA or glyceraldehyde-3-phosphate dehydrogenase were co-incubated with the filters for 1 h at 66 °C followed by three washes with 2× SSC containing 0.1% SDS at room temperature for 30 min. A final wash was carried out at 60 °C for 30 min with 1× SSC containing 0.1% SDS. For Group V sPLA2, hybridizations were performed in ExpressHyb solution (CLONTECH) following the manufacturer’s instructions. 32P-Labeled probes were co-incubated with the filters for 1 h at 66 °C followed by two washes with 2× SSC containing 0.05% SDS for 15 min: the first at room temperature and the second at 40 °C. Afterward the filters were washed twice more with 0.1× SSC containing 0.1% SDS for 15 min at room temperature. Bands were visualized by autoradiography.

**Phospholipase A2 Assay**—Aliquots (50–100 μl) of supernatants from LPS-treated cells were assayed for GPLA activity as follows. The assay mixture (500 μl) consisted of 100 μM 1-palmitoyl-2-[14C]palmitoyl-sn-glycero-3-phosphocholine substrate (2000 cpm/nmol), 10 mM CaCl2, 100 mM KCl, 25 mM Tris-Cl, pH 8.5. Reactions proceeded at 40 °C for 30 min, after which [14C]palmitate release was determined by a modified Dole procedure (10).

**Antisense Inhibition Studies in P388D1 Cells**—Transient transfection of P388D1 cells with antisense oligonucleotide, ASGV-2, or its sense counterpart, SGV-2, or its sense counterpart, SGV-2, or its sense counterpart, SGV-2, was carried out as described (11). Briefly, P388D1 cells were transfected with oligonucleotide (125 nM) in the presence of 5 μg/ml LipofectAMINE (Life Technologies, Inc.) under serum-free conditions for 8 h prior to treating the cells with or without 100 ng/ml LPS for 10 h after transfection (11). Anti-Group IIA oligonucleotide ASGV-2 (5′-GGA CUU GAG UUC TAC GAA GCC-3′) is complementary to nucleotides 64–84 of the mouse Group V PLA2 gene. SGV-2 (5′-GGC UUG CUA GAA CUC UCC-3′) is the sense complement of SGV-2.

For Group VI iPLA2, antisense experiments, a protocol identical to that reported elsewhere was followed (12).

**Data Presentation**—Assays were carried out in duplicate or triplicate. Each set of experiments was repeated three times with similar results. Unless otherwise indicated, the data presented are from representative experiments.
could be possible that part of the MAFP effects reported herein resulted from inhibition of the iPLA₂ in addition to any effect on the cPLA₂. We have recently described the inhibition of iPLA₂ expression in P388D₁ cells by antisense RNA oligonucleotides (12). Using this technique, we have been able to significantly inhibit iPLA₂ expression, assayed both by protein content by immunoblot and activity by a specific in vitro assay (12). Antisense RNA inhibition of the iPLA₂ under identical conditions as those shown previously (12) showed no reduction in AA release in response to LPS (not shown). Therefore these data make it likely that the above reported effects of MAFP on the response are because of the inhibition of the cPLA₂.

Role of sPLA₂—LPS-induced long term [³H]AA release was also noticeably blocked by the selective sPLA₂ inhibitor LY311727 (17), indicating that in addition to the cPLA₂, a sPLA₂ is also involved in the process (Fig. 4). PGE₂ production by LPS was also inhibited by LY311727 by about 90%. Although originally described as a selective Group II sPLA₂ inhibitor (17), we have recently shown that this compound is also a potent Group V sPLA₂ inhibitor (18).

Our previous work (11) has demonstrated that P388D₁ cells express measurable message levels for Group V sPLA₂, both under unstimulated and LPS/PAF-stimulated conditions. However, message levels for Groups IIA sPLA₂ or IIC sPLA₂ were undetectable even by reverse transcriptase-polymerase chain reaction (11). As shown in Fig. 5A, an antisense oligonucleotide specific for Group V sPLA₂ (ASGV-2) strongly blocked PGE₂...
production in LPS-treated cells, whereas its sense control (SGV-2) had no effect. Moreover, mRNA analyses by Northern blot at long times of stimulation with LPS confirmed the presence of mRNA for Group V sPLA2 (Fig. 5, B and C) but not for Group IIA sPLA2 (data not shown). The signal for Group V sPLA2 markedly increased after LPS stimulation, reaching a peak at approximately 10 h.

PLA2 activity measurements in the supernatants of LPS-stimulated cells revealed a time-dependent increase in activity (Fig. 6), which correlated well with the time course of Group V sPLA2 mRNA induction (cf. Figs. 5B and 6). Extracellular PLA2 activity was decreased if the experiments were conducted in the presence of the RNA synthesis inhibitor actinomycin D (Fig. 7A). This increased extracellular activity was found to correspond to that of Group V sPLA2 by the following criteria:

(i) it was completely inhibited by the sPLA2 inhibitor LY311727 (Fig. 7B) and (ii) it was decreased in supernatants from cells treated with an antisense RNA oligonucleotide specific for Group V sPLA2, ASGV-2 (11) (Fig. 7C).

**Role of cPLA2 in sPLA2 Activation**—Our previous studies have indicated that the immediate AA release triggered by LPS/PAF in these cells involves the sequential action of both cPLA2 and sPLA2, with the activity of the latter being dependent on previous activation of the former (1, 2). Thus we sought to investigate if a similar cross-talk exists between the two enzymes during long term stimulation conditions. We found that no increased PLA2 activity beyond what was observed in the basal state could be found in supernatants from cells treated with MAFP (Fig. 6). In addition, the cPLA2 inhibitor markedly decreased the LPS-induced expression of Group V sPLA2 mRNA (Fig. 8).

**DISCUSSION**

A striking hallmark of the immunoinflammatory response is the generation of oxygenated derivatives of AA such as the prostaglandins. The response of major prostaglandin-secreting cells such as macrophages and mast cells to proinflammatory stimuli is generally biphasic (4). The first phase is completed within minutes after the addition of the stimulus, whereas the second phase usually takes several hours (4). Using the murine macrophage-like cell line P388D1, we have been studying the molecular mechanisms responsible for AA mobilization and prostaglandin production in response to LPS/PAF. When primed by LPS, these cells will respond to Ca\(^{2+}\)-mobilizing stimuli such as PAF by generating a rapid burst of free AA, part of which is converted to prostaglandins such as PGE2. Strikingly, this process is completed within minutes after the addition of PAF (19). No free AA or prostaglandins are produced after the immediate phase is completed, not even after several hours of cell exposure to LPS/PAF (13). Such a behavior, which is abnormal for a macrophage cell, has prevented us from studying the molecular mechanisms responsible for delayed prostaglandin production in macrophages. In an attempt to overcome this problem, we subcloned the P388D1 cells by limit dilution, and selecting on the basis of high responsiveness to LPS/PAF, we obtained a clone termed MAB.
which shows enhanced sensitivity to LPS/PAF in the immediate phase (min) and exhibits a delayed response (h) to LPS alone.

Using the MAB clone, we have characterized the LPS-induced delayed prostaglandin production in terms of the role played by distinct PLA2 enzymes and their coupling with downstream COX enzymes during LPS signaling. Our previous work on the immediate response of the cells to LPS/PAF highlighted the very important role played by the novel Group V sPLA2 as the provider of most of the free AA directed to PGE2 biosynthesis (11). Herein, several lines of evidence suggest that Group V sPLA2 also behaves as a major provider of AA for the delayed phase of PGE2 production in LPS-treated cells. First, delayed [3H]AA release and PGE2 production correspond with the induction of Group V sPLA2 mRNA and enhanced secretion of a sPLA2-like activity to the supernatants, with no change in the constitutive levels of cPLA2 and no detectable induction of Group IIA sPLA2. Second, delayed PGE2 production is strongly blunted by LY311727, a selective sPLA2 inhibitor. Third, an antisense oligonucleotide specific for Group V sPLA2 (11) suppresses Group V sPLA2 activity and inhibits delayed PGE2 production. Our conclusions in this regard fully agree with recent works by Kudo and co-workers (20, 21) that were published while this manuscript was under review. By using transfection techniques, Kudo and co-workers (20, 21) have also documented the importance of Group V sPLA2 in delayed AA release and PGE2 production.

Our data have also implicated the cPLA2 as an important step in LPS signaling by enabling the subsequent action of the sPLA2. Thus the cPLA2 inhibitor MAFP (1) markedly blocked both long term [3H]AA release and Group V sPLA2 mRNA induction. Collectively, these results suggest an intriguing cross-talk between the cPLA2 and the Group V sPLA2 for the delayed phase of prostaglandin production in macrophages. This is a very interesting concept because cross-talk appears to exist as well between these two enzymes during the immediate phase of prostaglandin production (1, 2). In the immediate phase, cPLA2 activation generates a rapid and early burst of free AA inside the cell that enables sPLA2 activation by an as yet unidentified mechanism (1, 2). In the delayed phase, cPLA2 activation influences sPLA2 apparently by regulating sPLA2 mRNA levels.

Cross-talk between cPLA2 and sPLA2 in the immediate phase of prostaglandin production was also found to take place in mast cells (3) when the same protocol originally used in macrophages (1) was employed. Furthermore, a recent study by Kuwata et al. (22) about fibroblasts suggests that cross-talk between cPLA2 and sPLA2 in the delayed phase could also constitute a general mechanism of activation. Using a different cPLA2 inhibitor, arachidonyl trifluoromethyl ketone, Kuwata et al. (22) found that cPLA2 inhibition blocked sPLA2 expression in fibroblasts, leading to reduced PGE2 generation. The
study by Kuwata et al. (22) is interesting not only because it supports the possible universality of cross-talk between cPLA₂ and sPLA₂ but because the sPLA₂ expressed by rat fibroblasts is a Group IIA enzyme, not Group V. This lends further support to the emerging notion that Group IIA and Group V sPLA₂ may be functionally redundant (23). In addition, Kuwata et al. (22) were able to show that overcoming cPLA₂ inhibition by exogenous AA partially restored the Group IIA sPLA₂ expression. These results suggest that the AA mobilized by cPLA₂ is responsible for cross-talk between cPLA₂ and sPLA₂ (22). This is again reminiscent of what happens in the immediate phase of activation, wherein the cPLA₂-derived AA is also responsible for cross-talk between cPLA₂ and sPLA₂, albeit by different mechanisms (1, 2). Unfortunately, inhibition by MAFP of Group V sPLA₂ expression and activity could not be reversed in our macrophage studies with LPS alone by supplementing the medium with exogenous AA (up to 100 μM). This was not unexpected because P388D₁ cells manifest an extraordinarily high capacity to import free AA from exogenous sources and incorporate it into membranes (19, 24, 25), which is much higher than that of most other cells (26). Thus, the half-life of the free AA in the cell would be too short to adequately mimic the low but continued production of AA-derived cPLA₂ upon long term LPS exposure.

A model has recently emerged suggesting differential actions of COX-1 and COX-2 by virtue of differential coupling to distinct PLA₂s (2, 3, 6, 8, 20, 21, 27). Thus, depending on whether cPLA₂ or sPLA₂ is the provider of free AA, either COX-1 or COX-2 would be responsible for PGE₂ release. However, which PLA₂ form couples to which COX isoform appears to depend strongly on cell type. We have recently demonstrated that the immediate, PAF receptor-mediated phase of PGE₂ production in LPS-primed macrophages involves sPLA₂ coupling to COX-2 (2). The current results support a similar kind of coupling for the delayed phase of PGE₂ production in LPS-treated cells. Identical coupling has been suggested by Arm and co-workers (6) for the delayed phase of PGE₂ generation in mast cells. These results raise another interesting concept regarding the regulation of PGE₂ during both phases of activation. As is the case for AA release (Fig. 2A), we have observed that the amount of PGE₂ generated during the Ca²⁺-dependent short term stimulation is comparable to the amount produced in the late phase. It follows from this comparison that although the effector enzymes involved in the response are the same (i.e. cPLA₂, sPLA₂, COX-2), the regulatory mechanisms differ. Thus, in the short phase at low levels of COX-2, it appears that the dramatic burst in AA release is what determines the amount of PGE₂ produced. In contrast, in the delayed phase at comparatively lower AA availability, it appears that both the induction of large amounts of COX-2 protein and of the AA provider, Group V sPLA₂, determine the amount of PGE₂ produced.

It is important to note, however, that our results have not excluded that a minor fraction of the long term PGE₂ produced in response to LPS could arise from the AA generated by the cPLA₂. Should this be the case, some cPLA₂/COX-2 coupling may exist as well, similar to what has been suggested by Reddy and Herschman (3) for delayed PGE₂ production in mast cells and by Murakami et al. (5) in cells derived from Group IIA-deficient mice. The striking feature of the current work is that although COX-1 is present in active form in the P388D₁ cells (2), it appears to be spared from the process of long term PGE₂ production. This finding remains unexplained but has recently been recognized in other cell types as well (6, 8, 22). Recent work by Spencer et al. (16) showed no differences in the distribution of COX-1 versus COX-2 among subcellular fractions in a variety of cells. Thus subcellular compartmentalization may not be the cause for COX-1 not being utilized during LPS signaling. Other putative explanations may include the existence of COX-selective regulatory components, selective coupling to terminal PG synthases, or kinetic differences in AA utilization by the two isoforms.

In summary, we have established a subclone of P388D₁ cells, MAB, that displays long term responsiveness to LPS in terms of PGE₂ generation. We have confirmed (11) that these cells express Group V sPLA₂, not Group IIA sPLA₂, and found that (i) Group V sPLA₂ is a key enzyme in long AA mobilization as well and (ii) Group V sPLA₂ is functionally coupled to COX-2. Furthermore, our results have suggested that cPLA₂ plays a key role in long term AA mobilization, at least partly by regulating the expression of Group V sPLA₂.

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J. Biol. Chem. 1999, 274:12263-12268.
doi: 10.1074/jbc.274.18.12263

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