Volume 301, number 2, 190–194 FEBS 10943 April 1992

Transforming growth factors type-β and dexamethasone attenuate group II phospholipase A_2 gene expression by interleukin-1 and forskolin in rat mesangial cells

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Received 3 February 1992; revised version received 6 March 1992

Treatment of rat mesangial cells with interleukin-1β (IL-1β) and forskolin induced, in a synergistic fashion, the expression of group II phospholipase A_2 (PLA_2) mRNA, with subsequent increased synthesis and secretion of PLA_2. In contrast, interleukin-6 did not increase PLA_2 mRNA levels of PLA_2 activity. Transforming growth factor (TGF) β_1, TGFβ_2 and TGFβ_3 equipotently attenuated the IL-1β- and forskolin-induced elevation of PLA_2 mRNA, as well as PLA_2 synthesis and secretion. The glucocorticoid dexamethasone only partially suppressed the IL-1β- and forskolin-induced elevation of PLA_2 mRNA, but totally inhibited PLA_2 synthesis and secretion.

Phospholipase A_2; Interleukin-1; Transforming growth factor β; Dexamethasone; Phospholipase A_2 mRNA; Mesangial cell

1. INTRODUCTION

IL-1 is a polypeptide mediator that was originally reported as a secretory product of activated macrophages but later on was found to be produced by a variety of cell types [1], including mesangial cells [2,3]. IL-1 is a central factor in the pathogenesis of immune and inflammatory processes [1]. We and others have previously demonstrated that IL-1 induces prostaglandin E_2 [4–6] and group II PLA_2 [4,7] synthesis in mesangial cells. PLA_2 catalyses the release of arachidonic acid from the sn-2 position of phospholipids, thereby initiating the synthesis of eicosanoids which profoundly modulate inflammatory processes. Evidence to date suggests that PLA_2s are a heterogeneous family of enzymes that can be classified into two classes. A class of high molecular weight PLA_2s of 60–110 kDa, also referred to as cytosolic PLA_2s or cPLA_2s, and a class of low molecular weight PLA_2s of 14 kDa referred to as secretory PLA_2s or sPLA_2s. Members of both classes from human and rat sources have recently been cloned [8–13]. The sPLA_2s are further classified into two groups, based on their primary structure [14]. Mammalian group I PLA_2 comprises the pancreatic type of PLA_2 and mammalian group II PLA_2 is synthesized and secreted from many cell types and is believed to play a role in the initiation and propagation of inflammatory processes (see [15] for review). In addition to IL-1 and tumour necrosis factor α (TNFα), which have been shown to activate group II PLA_2 synthesis in a variety of cell types [15], Crowl and colleagues [16] observed a stimulating action of interleukin-6 on PLA_2 gene expression in human hepatoma cells. We were the first to report an increased secretion of PLA_2 from vascular smooth muscle cells [17] and mesangial cells [18,19] in response to agents that increase cellular levels of cAMP, such as forskolin. Furthermore, IL-1β and TNFα synergistically interact with forskolin to stimulate PLA_2 release from vascular smooth muscle [20] and glomerular mesangial cells [18,19]. Both forskolin-stimulated and cytokine-stimulated PLA_2 synthesis and secretion is dose-dependently prevented by pretreatment of cells with dexamethasone [21–23], TGFβ_2 [24,25] and platelet-derived growth factor [26].

In this report, we present evidence that IL-1β and forskolin synergistically increase group II PLA_2 mRNA levels in mesangial cells, whereas interleukin-6 shows no effect. Dexamethasone and the three members of the mammalian TGFβ family partially attenuate the stimulatory action of IL-1β and forskolin on PLA_2 mRNA levels.

Abbreviations: PLA_2, phospholipase A_2; IL-1, interleukin-1; TNF, tumour necrosis factor; TGF, transforming growth factor.

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2. MATERIALS AND METHODS

2.1. *Cell cultures and incubation*

Rat mesangial cells were cultured, cloned and characterized as described previously [26,27]. The cells were grown in RPMI 1640 supple-

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mented with 10% fetal calf serum, penicillin (100 U/ml), streptomycin (100 μg/ml) and bovine insulin at 0.66 U/ml. For the experiments passages 15–37 of mesangial cells were used. Confluent mesangial cells cultured in 16 mm diameter wells were washed twice with PBS and incubated with 1 ml of RPMI 1640, containing 0.1 mg/ml of fatty acid-free bovine serum albumin (Sigma) with or without agents for the indicated time periods. Thereafter, the medium was withdrawn and centrifuged for 10 min at 1000 rpm in an IEC Centra-7R lab centrifuge. The supernatant was removed and frozen in liquid nitrogen and stored until assayed for protein content and PLA_2 activity.

2.2. *Phospholipase A_2 assay*

PLA_2 activity was determined using [1-^{14}C]oleate-labelled *E. coli* as substrate as described [28]. Assay mixtures (1.0 ml) contained 100 mM Tris-HCl (pH 7.4), 1.0 mM $CaCl_2$, 5 nM *E. coli* phospholipid (3000–5000 cpm) and the enzyme to be tested at a dilution producing approximately 5% substrate hydrolysis. Reactions were stopped after 1 h and the liberated [^{14}C]oleate was extracted by a modified Dole extraction procedure [28].

2.3. *Northern blot analysis*

Confluent mesangial cells were harvested from 60 mm diameter culture dishes with a rubber policeman. Total RNA was extracted from the cells using the guanidinium thiocyanate/phenol/chloroform method [29]. The RNA was precipitated and samples of 15 μg RNA were separated on 1% agarose gels containing 6.6% formaldehyde, prior to transfer to Gene Screen membranes (New England Nuclear) [30]. After baking the filters at 80°C for 2 h and prehybridization for 6 h, the filters were hybridized with a 39-mer antisense oligonucleotide for rat group II PLA_2 (nucleotide 58–96, [10]), that had been labelled with T4-polynucleotide kinase and [γ-^{32}P]ATP [30]. To correct for variations in RNA amount a parallel filter was hybridized with a genomic clone for rat 28 S ribosomal RNA [31], labelled with the random primer technique described by Feinberg and Vogelstein [32]. After hybridization, the membrane was washed 3 times in 4 × SSPE, 0.1% sodium dodecyl sulfate at 50°C for 20 min (20 × SSPE: 3.6 M sodium chloride, 0.2 M sodium phosphate, 0.02 M EDTA, pH 7.4). The signal was detected by autoradiography.

2.4. *Chemicals*

[1-^{14}C]Oleic acid and nylon membranes (Gene Screen) were purchased from DuPont de Nemours International (Regensdorf, Switzerland); adenosine 5'-[γ-^{32}P]triphosphate (specific activity >110 TBq/mM) was purchased from Amersham International (UK); forskolin was from Calbiochem (Lucerne, Switzerland); recombinant human IL-1β, recombinant human TGFβ_2 and TGFβ_3 were prepared by the Biotechnology Department of Ciba-Geigy Ltd (Basel, Switzerland), recombinant human interleukin-6 and human TGFβ_1 were from British Bio-technology, Oxford, UK; T4-polynucleotide kinase and all cell culture nutrients were from Boehringer-Mannheim (Germany), and all other chemicals used were from either Merck (Darmstadt, Germany) or Fluka (Buchs, Switzerland).

3. RESULTS

Northern blot analysis using an oligonucleotide probe for group II PLA_2 revealed that IL-1β dose-dependently increased the amount of group II PLA_2 mRNA (Fig. 1) which was accompanied by an enhanced secretion of PLA_2 into the culture supernatant, as monitored by PLA_2 activity measurements (Table I). Fig. 2 shows that while IL-1β (lane 2) and forskolin (lane 4) alone induced only a modest increase in PLA_2 mRNA, when given together they evoked a strong synergistic response on PLA_2 mRNA levels (lane 3) and PLA_2 activity (Table I). In contrast, interleukin-6 had no effect on either PLA_2 mRNA levels (Fig. 2, lane 5) or PLA_2 activity (Table I). Next we examined the effects of dexamethasone and TGFβ_2 on IL-1β- and forskolin-stimulated PLA_2 gene expression. As shown in Fig. 3, dexamethasone and TGFβ_2 dose-dependently antagonized IL-1β plus forskolin-induced PLA_2 mRNA accumulation. All three of the human TGFβ isoforms displayed a comparable potent inhibitory action on cytokine- and forskolin-stimulated PLA_2 mRNA accumulation (Fig. 4). Whereas the inhibitory effects of TGFβ_1, TGFβ_2 and TGFβ_3 on mRNA levels (Figs. 3 and 4) were closely paralleled by the PLA_2 activity measure-

Table I

Effects of TGFs type-β and interleukin-6 on IL-1β and forskolin-stimulated PLA_2 secretion from mesangial cells

Addition					PLA_2 secretion (cpm/100 μl)
Control					260 ± 14
IL-1β	(1 nM)				1464 ± 41
Forskolin	(10 μM)				1515 ± 92
IL-1β	(1 nM)	+ Forskolin (10 μM)			6834 ± 201
Interleukin-6	(18 ng/ml)				285 ± 21
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ TGFβ_1	(1 ng/ml)	6136 ± 254
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ TGFβ_1	(10 ng/ml)	3754 ± 184
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ TGFβ_1	(30 ng/ml)	2454 ± 122
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ TGFβ_2	(1 ng/ml)	6015 ± 193
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ TGFβ_2	(10 ng/ml)	3598 ± 144
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ TGFβ_2	(30 ng/ml)	2198 ± 135
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ TGFβ_3	(1 ng/ml)	5981 ± 239
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ TGFβ_3	(10 ng/ml)	3618 ± 204
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ TGFβ_3	(30 ng/ml)	2085 ± 95
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ Dexamethasone	(10 nM)	3441 ± 118
IL-1β	(1 nM)	+ Forskolin (10 μM)	+ Dexamethasone	(10 μM)	190 ± 12

Control mesangial cells were incubated with the indicated concentrations of IL-1β, Forskolin, TGFβ_1, TGFβ_2, TGFβ_3 or Dexamethasone for 24 h. Thereafter, the medium was withdrawn and PLA_2 activity determined as described in section 2. Results are means ± SE (n = 4).

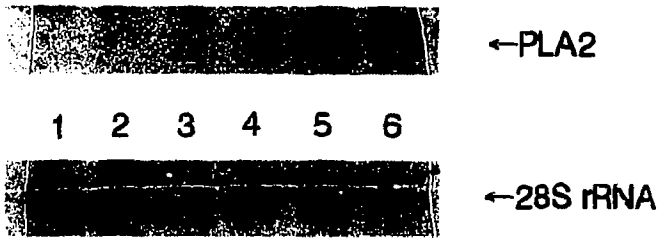

Fig. 1. Dose-dependent accumulation of group II PLA_2 mRNA in IL-1β-stimulated mesangial cells. Mesangial cells were incubated with vehicle (control) (1), or IL-1β 100 pM (2), 500 pM (3), 1 nM (4), 5 nM (5) and 10 nM (6) for 20 h. Cellular RNA (15 μg) was analyzed by Northern blotting as described in section 2.

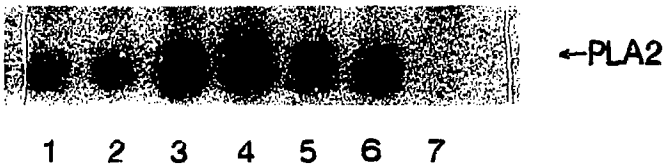

Fig. 3. Effect of TGFβ_2 and dexamethasone on group II PLA_2 mRNA levels in stimulated mesangial cells. Mesangial cells were incubated with vehicle (control) (7), IL-1β (10 nM) plus forskolin (10 μM) alone (3) or in combination with TGFβ_2 1 ng/ml (4), 10 ng/ml (5), 30 ng/ml (6), or in combination with dexamethasone 10 nM (1) or 10 μM (2) for 20 h. Cellular RNA (15 μg) was analyzed by Northern blotting as described in section 2.

ments (Table I), showing a 60–70% suppression at the highest concentrations used, the inhibitory action of dexamethasone was strikingly more pronounced at the PLA_2 activity values (Table I) as compared to the PLA_2 mRNA levels (Fig. 3). At the highest concentration of dexamethasone used (10 μM), PLA_2 mRNA was reduced by approximately 70%, whereas a 100% inhibition of secreted PLA_2 activity was determined.

4. DISCUSSION

IL-1α, IL-1β, and TNFα as well as cAMP-elevating compounds have been shown to induce the synthesis and release of group II PLA_2 into the medium of cultured rat glomerular mesangial cells [4,7,17–19]. The lag period of several hours before the onset of PLA_2 secretion and the inhibition by actinomycin D and cycloheximide indicated the involvement of RNA synthesis and protein synthesis in these processes. Recently we and others have shown that IL-1 and forskolin indeed stimulate group II PLA_2 gene expression in mesangial cells [26,33]. In the present report we have extended our studies and demonstrate that IL-1β dose-dependently increases PLA_2 mRNA levels in mesangial cells. Furthermore, we show that forskolin synergistically interacts with IL-1β to increase group II PLA_2 mRNA accumulation, thus confirming our previous data based on activity measurements [18,19]. These data suggest that there exist at least two distinct activation mechanisms for the induction of $sPLA_2$, one is activated by cAMP and the other is triggered by IL-1, and uses a signalling pathway different from the adenylate cyclase system. In contrast, interleukin-6 which has been shown to induce group II PLA_2 gene expression in human hepatoma cells [16], has no effect on PLA_2 gene expression in mesangial cells, thus displaying a more restricted cell and tissue selectivity than IL-1 or TNFα.

TGFβ is a 25 kDa dimeric peptide, which exerts diverse actions on many cells, ranging from growth promotion to growth inhibition and immunomodulation (for review see [34,35]). TGFβ has been purified from normal kidney [36], and the presence of high-affinity receptors for TGFβ on mesangial cells has been reported [37]. It is now known that TGFβ belongs to a family of closely homologous dimeric proteins. Three distinct forms of TGFβ have been described in mammals and were designated as TGFβ_1, TGFβ_2 and TGFβ_3 [34,35]. We have previously shown that TGFβ_2 strongly inhibits PLA_2 secretion from mesangial cells induced by IL-1 or tumour necrosis factor [24,25]. In the present report, we demonstrate for the first time the potent inhibition of IL-1β- and forskolin-induced PLA_2 gene expression by all three human TGFβ isoforms (Figs. 3 and 4). This inhibitory action of TGFβ_1, TGFβ_2 and TGFβ_3 is also evident from the marked reduction of PLA_2 activity (Table I) in the culture supernatant of stimulated mesangial cells. In this respect all three isotypes of TGFβ displayed an equally potent inhib-

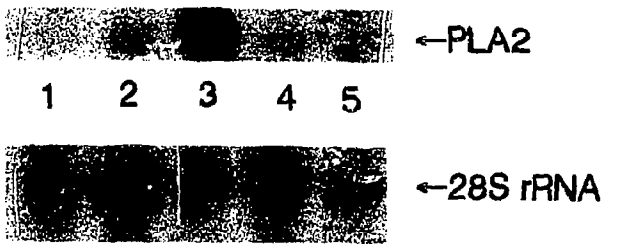

Fig. 2. Synergistic stimulation of group II PLA_2 mRNA levels in mesangial cells treated with IL-1β and forskolin. Mesangial cells were incubated with vehicle (control) (1), IL-1β (5 nM) (2), forskolin (10 μM) (4); IL-1β (5 nM) plus forskolin (10 μM) (3) or interleukin-6, (18 ng/ml) (5) for 20 h. Cellular RNA (15 μg) was analyzed by Northern blotting as described in section 2.

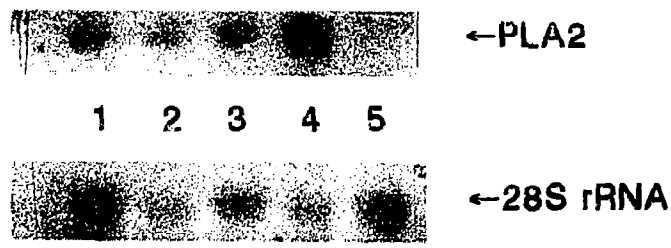

Fig. 4. Effect of the different TGFβ isotypes on group II PLA_2 mRNA levels in stimulated mesangial cells. Mesangial cells were incubated with vehicle (control) (5), IL-1β (10 nM) plus forskolin (10 μM) alone (4) or in combination with 30 ng/ml TGFβ_1 (3), 30 ng/ml TGFβ_2 (2) or 30 ng/ml TGFβ_3 (1) for 20 h. Cellular RNA (15 μg) was analyzed by Northern blotting as described in section 2.

itory profile on PLA_2 mRNA levels and PLA_2 activity (Fig. 4 and Table I).

The glucocorticoid inhibition of PLA_2 was initially attributed to the production of the PLA_2 inhibitor protein lipocortin [38]. However, recent reports have questioned the role of lipocortin as a biologically relevant PLA_2 inhibitor, in that inhibition of PLA_2 by lipocortin in vitro was only observed at very low substrate concentrations and was due to substrate sequestration, rather than to direct PLA_2–lipocortin interaction [39,40]. Furthermore, several reports described lipocortin-independent inhibition of PLA_2 activities and eicosanoid synthesis [41–44]. We and others have shown that dexamethasone treatment inhibits the cytokine- and forskolin-stimulated synthesis and secretion of group II PLA_2 from mesangial cells [21,23] and smooth muscle cells [22], thus providing an alternative explanation for the potent inhibition of eicosanoid mediator synthesis by glucocorticoids. In the present report we describe that dexamethasone partially suppresses IL-1β- and forskolin-stimulated elevation of group II PLA_2 mRNA levels (Fig. 3). At the highest concentration of dexamethasone used (10 μM), there was only a 70% reduction of PLA_2 mRNA levels. In contrast, PLA_2 synthesis and secretion were completely prevented by treatment of the cells with such a high concentration of dexamethasone (Table I and [23]). We have observed that the inhibition of PLA_2 activity in both culture media and cells is paralleled by decreases in PLA_2 mass [23]. This indicates that dexamethasone inhibits not only secretion of induced PLA_2, with accumulation of PLA_2 protein in the cells, but inhibits PLA_2 protein synthesis. Furthermore, this also excludes an increased reuptake of secreted PLA_2 back into the cells. These data observed in rat mesangial cells confirm a recent report [22] describing the action of dexamethasone on group II PLA_2 expression in vascular smooth muscle cells. TNFα-induced PLA_2 mRNA accumulation was less affected compared to the severe suppression of PLA_2 protein and activity, suggesting that glucocorticoids can also inhibit PLA_2 expression at a posttranscriptional level [22]. Measurement of PLA_2 mRNA stability and in vitro translation of PLA_2 mRNA would be an important next step in elucidating the effect of dexamethasone on IL-1β- and forskolin-induced group II PLA_2 expression.

There is substantial evidence that extracellular group II PLA_2 plays an important role in the pathogenesis of diverse inflammatory processes [15]. The selective inhibition of cytokine induction of group II PLA_2 may become a useful therapeutic approach to the treatment of these diseases. Glucocorticoids have already proven to exert beneficial effects on inflammatory reaction in a variety of organs, including the kidney [45]. The inhibition of IL-1 and TFNα induction of group II PLA_2 in mesangial cells may be one aspect of this curative glucocorticoid action seen in certain renal diseases. Anti-inflammatory steroids may act in line with TGFβ [24,46] and platelet-derived growth factor [26] to protect the kidney from damage resulting from IL-1- and TNFα-induced mediator secretion and subsequent inflammatory reactions.

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