Group IB Secretory Phospholipase A₂ Promotes Matrix Metalloproteinase-2-mediated Cell Migration via the Phosphatidylinositol 3-Kinase and Akt Pathway*

Received for publication, December 29, 2003, and in revised form, June 18, 2004
Published, JBC Papers in Press, June 25, 2004, DOI 10.1074/jbc.M314235200

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Secretory phospholipase A₂ (sPLA₂), abundantly expressed in various cells including fibroblasts, is able to promote proliferation and migration. Degradation of collagenous extracellular matrix by matrix metalloproteinase (MMP) plays a role in the pathogenesis of various destructive disorders, such as rheumatoid arthritis, tumor invasion, and metastasis. Here we show that group IB PLA₂ increased pro-MMP-2 activation in NIH3T3 fibroblasts. MMP-2 activity was stimulated by group IB PLA₂ in a dose- and time-dependent manner. Consistent with MMP-2 activation, sPLA₂ decreased expression of type IV collagen. These effects are due to the reduction of tissue inhibitor of metalloproteinase-2 (TIMP-2) and the activation of the membrane type-1 MMP (MT1-MMP). The decrease of TIMP-2 levels in conditioned media and the increase of MT1-MMP levels in plasma membrane were observed. In addition, treatment of cells with decanoyl Arg-Val-Lys-Arg-chloromethyl ketone, an inhibitor of pro-MT1-MMP, suppressed sPLA₂-mediated MMP-2 activation, whereas treatment with bafilomycin A₁, an inhibitor of H⁺-ATPase, sustained MMP-2 activation by sPLA₂. The involvement of phosphatidylinositol 3-kinase (PI3K) and Akt in the regulation of MMP-2 activity was further suggested by the findings that PI3K and Akt were phosphorylated by sPLA₂. Expression of p85α and Akt mutants, or pretreatment of cells with LY294002, a PI3K inhibitor, attenuated sPLA₂-induced MMP-2 activation and migration. Taken together, these results suggest that sPLA₂ increases the pro-MMP-2 activation and migration of fibroblasts via the PI3K and Akt-dependent pathway. Because MMP-2 is an important factor directly involved in the control of cell migration and the turnover of extracellular matrix, our study may provide a mechanism for sPLA₂-promoted fibroblast migration.

Controlled degradation of extracellular matrix (ECM) is essential in physiologic situations involving connective tissue remodeling. Nevertheless, excessive breakdown of connective tissue plays an important role in pathogenesis, e.g. chronic inflammatory processes and malignancy (1, 2). The regulation of matrix metalloproteinases (MMPs) occurs on different levels, including gene expression, processing of the inactive proenzymes, and by inhibition of the active enzymes by their endogenous inhibitors delineated as tissue inhibitors of metalloproteinases (TIMPs). MMPs are important breakdown enzymes of ECM components such as collagen. These enzymes consist of gelatinases, collagenases, stromelysins, and membrane-type MMPs. MMPs are synthesized as preproenzymes, and most of them are secreted from the cells as proenzymes. Among them, MMP-2 is thought to be one of the key enzymes for degrading collagen, which is a major component of basement membranes (3, 4). MMP-2 is abundantly expressed in various tissues and cell types including fibroblasts (5). Transient fibroblast activation is probably regulated by a variety of mediators produced by infiltrating platelets, monocytes, and other inflammatory cells (6, 7). Numerous in vitro and in vivo studies have suggested that some cytokines and growth factors regulate fibroblast proliferation and ECM deposition (6–8).

Phospholipase A₂ (PLA₂) catalyzes the hydrolysis of the sn-2 ester bond in phospholipids as they generate free fatty acids, such as arachidonic acid (9, 10). Arachidonic acid is the key substrate for the synthesis of potent lipid mediators of inflammation. Several mammalian secretory PLA₂s (sPLA₂s) have been characterized and classified into different families (11). At present, 12 distinct sPLA₂s have been identified in mammals and classified into different groups, depending on their primary structures as characterized by the number and position of cysteine residues. Initially, sPLA₂s were thought to carry out digestive functions. However, the recent reports of a class of high affinity cell surface PLA₂ receptors and the delineation of novel receptor-mediated biological effects have changed this notion (12, 13). PLA₂ has been implicated in a wide range of cellular responses, including cell proliferation, signal transduction, host defense, chemokinesis, and membrane remodeling (14–16). In addition to an extensive understanding of its action in phospholipid hydrolysis, a role for sPLA₂ has been suggested in the remodeling of ECM, although little evidence for such involvement has yet been published (14). A previous study reported that porcine pancreatic PLA₂ promotes cell migration and ECM invasion via its high affinity receptor (14). Attiga et phospholipase A₂ receptor; MMP, matrix metalloproteinase; PI3K, phosphatidylinositol 3-kinase; TIMP-2, tissue inhibitor of metalloproteinase-2; MT1, membrane type 1; Ab, antibody; ELISA, enzyme-linked immunosorbent assay; FCS, fetal calf serum; dec, decanoyl; cmk, chloromethyl ketone; ERK, extracellular signal-regulated kinase; DN, dominant negative; MAPK, mitogen-activated protein kinase.

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al. (16) showed that the sPLA$_2$ inhibitor p-bromophenacyl bromide could reduce the pro-MMP-2 and active MMP-2 from prostate cancer cells. All these results support the possible role of sPLA$_2$ as a factor in MMP activation. However, the mechanism for this MMP-2 activation, including related TIMP in fibroblasts, is not clear. Moreover, the intracellular signaling pathway that regulates MMP-2 expression has not been characterized.

To investigate the role of group IB PLA$_2$ on MMP-2 activation in fibroblasts, we established an MMP-2 activation profile by using the mouse fibroblast cell line NIH3T3. In this study, we found that group IB PLA$_2$ increases the activity of MMP-2 in cell conditioned medium and that this increase is the result of a decreased level of TIMP-2 protein and an increased level of MT1-MMP activity. Moreover, the sPLA$_2$ regulation of MMP-2 seems to be mediated by PI3K and Akt. Because group IB PLA$_2$ is involved in promoting NIH3T3 migration, our results suggest that sPLA$_2$-promoted cell migration is mediated by MMP-2.

EXPERIMENTAL PROCEDURES

Materials—Group IB PLA$_2$ gelatin, and baflomycin A1 were purchased from Sigma. The ECL reagent was from PerkinElmer Life Sciences; RPMI 1640, LipofectAMINE 2000, and Opti-MEM were from Invitrogen; the MMP-2 ELISA kit was from R & D Systems (Minneapolis, MN); FCS was from Hyclone (Logan, UT); mouse polyclonal MMP-2, TIMP-2, type IV collagen, p58$_{sa}$ subunit antibodies, and the horseradish peroxidase-conjugated secondary antibodies were from Santa Cruz Bio-technology (Santa Cruz, CA); the MT1-MMP antibody was from Chemicon (Temecula, CA); the phospho-Akt antibody was from New England Bios (Beverly, MA); the furin inhibitor decaconly Arg-Val-Lys-Arg-chloromethyl ketone (dec-RVKR-cmk) was from Alexis Biochemicals (San Diego, CA); and LY294002 was from Biomol (Plymouth Meeting, PA). The latter was dissolved in Me$_2$SO prior to adding to the cell cultures. The final Me$_2$SO concentration were 0.1% or less, and these concentrations had no effect on cell viability.

Cell Culture—The NIH3T3 mouse fibroblast cell line was obtained from the American Type Culture Collection. Cells were cultured in Dulbecco's modified Eagle's medium supplemented with 2 mg l-glutamine, 100 units/ml penicillin, 100 µg/ml streptomycin, and 10% FCS. The cells were grown at 37°C in 5% CO$_2$, fully humidified air, and were subcultured twice weekly. They were then seeded in a 6-well plate at 3 × 10$^5$ cells/well and stimulated in the presence of group IB PLA$_2$, with or without inhibitors, for various times ranging from a few minutes to 24 h.

Zymogram Analysis—MMP-2 activity was determined by gelatin zymography using 0.1% gelatin as a substrate. The conditioned medium was mixed with SDS-PAGE sample buffer in the absence of reducing agent and electrophoresed in 10% polyacrylamide gel. After electrophoresis, the gels were washed three times with 2.5% Triton X-100 in water and then incubated overnight in a closed container at 37°C in 0.2% Brij 35, 5 mm CaCl$_2$, 1 mm NaCl, and 50 mm Tris, pH 7.4. The gels were stained for 30 min with 0.25% Comassie Blue R-250 in 10% acetic acid and 45% methanol and then destained for 30 min using an aqueous mix of 20% acetic acid, 20% methanol, and 17% ethanol. Areas of protease activity appeared as clear bands.

PI3K and Akt Activity Assay—NIH3T3 cells were seeded in 35-mm dishes and cultured overnight before they were serum-starved for 24 h. The cells were treated with or without group IB PLA$_2$ for the indicated times and doses. The cells were washed with cold phosphate-buffered saline, trypsinized, and pelleted at 700 × g at 4°C. Cell pellets were resuspended in lysis buffer (50 mm Tris-HCl, pH 8.0, 5 mm EDTA, 150 mm NaCl, 1% Triton X-100, 1 mm phenylmethylsulfonyl fluoride, and protease inhibitor mixture), and the preparation was cleared by centrifugation, and the supernatant was retained as a whole-cell lysate. The protein was separated by 8% reducing SDS-PAGE and transferred to nitrocellulose for subsequent immunoblot analysis by using Ab specific for the phosphorylated, activated forms of Akt.

Cell Migration—The effect of sPLA$_2$ on cell migration was assessed by using a modified cell dispersion assay (17). NIH3T3 cells were seeded and cultured in a 6-well plate containing a 6-mm glass ring. The cells were washed twice with serum-free media and serum-starved for an additional 12 h. After serum starvation, glass ring was removed, and the media were then switched to Dulbecco's modified Eagle's medium containing group IB PLA$_2$. In selected experiments, the sPLA$_2$ dependence of migration was determined by adding the PI3K inhibitor LY294002. To quantify the relative motility, the migratory front was photographed every 2 h for the indicated times, and the percentage of cells crossing a line designated “migration (%)” was enumerated.

RESULTS

Activation of MMP-2 by Group IB PLA$_2$ in NIH3T3 Fibroblast—Initially, we wanted to determine the effect of group IB PLA$_2$ on MMP induction and activation in fibroblasts. MMP activity was measured in the conditioned medium by using standard zymography. To investigate the effects of sPLA$_2$, we assayed the induction of MMP-2 release and activation, time kinetic analysis was performed with mouse fibroblast NIH3T3 cells. The results indicated a significant response to the treatment at 6, 12, and 24 h (Fig. 1A). sPLA$_2$ stimulated MMP-2 activity in a dose-dependent manner by zymography and Western blot analysis (Fig. 1B). Further, analysis was performed with supernatants at 24 h of culture. We further examined the total protein levels of MMP-2 and found that there was no dramatic change of MMP-2 protein by ELISA (Fig. 1C). An induction of the unknown band (85 kDa) was also detected by zymography in these experiments. However, MMP-9 was not detected under these experimental conditions, and therefore, no further studies on MMP-9 were conducted. To determine whether the induced MMP-2 activity was associated with collagen expression, Western blots were performed by using an antibody against type IV collagen. The collagen expression was carried out by treating the NIH3T3 cells with sPLA$_2$. Fig. 1B shows the dose response of collagen expression as a function of cell treatment with varying concentrations of sPLA$_2$. The de
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Fig. 1. Group IB PLA₂ stimulates NIH3T3 fibroblast MMP-2 activity. A, NIH3T3 cells were plated on 6-well plates in medium containing 10% FCS. Following overnight serum starvation, cells were treated with 100 nM sPLA₂. The conditioned media were collected at the indicated times and analyzed for MMP activity and type IV collagen by gelatin zymography (zymo) and Western blot (WB), respectively. B and C, the cells were starved overnight and treated with sPLA₂ at the indicated concentrations. The conditioned media were collected at 24 h and analyzed for MMP activity by gelatin zymography, for MMP-2 (2 μg/ml antibody) and collagen expression by Western blot, and for total MMP-2 amounts by ELISA. The values for the MMP-2 production are represented as average ± S.D. The Western blot and zymography data shown are representative of four independent experiments.

Increase of collagen expression by sPLA₂ is clearly dose-dependent and almost completely disappeared at an sPLA₂ concentration of 50 nM.

Involvement of TIMP-2 and MT1-MMP in the sPLA₂-induced MMP-2 Activity—We speculated that the sPLA₂-mediated MMP-2 activation in cells may be through the regulation of TIMP and MT-MMP. The latter was initially considered, because it has been demonstrated that TIMP-2 can form a complex with pro-MMP-2 through their carboxyl terminus (18). To test this hypothesis, we measured sPLA₂-stimulated TIMP-2 expression. The conditioned medium from NIH3T3 cells stimulated by sPLA₂ was resolved by Western blot with monoclonal antibody against TIMP-2. As expected, TIMP-2 protein was strongly expressed at basal states, but this protein level was dramatically decreased by sPLA₂ in a dose-dependent manner (Fig. 2A). We confirmed the effect of TIMP-2 on the activation of pro-MMP-2 by sPLA₂. Cells were incubated with sPLA₂ and recombinant TIMP-2 protein. Activation of pro-MMP-2 by sPLA₂ was not enhanced in the presence of TIMP-2 at concentrations greater than 5 nM (Fig. 2B). MT1-MMP is a transmembrane MMP known to bind and activate pro-MMP-2 at the cell surface (19). To determine the change of MT1-MMP stimulation, we prepared plasma membrane fractions after treatment of sPLA₂, and we performed Western blot analysis. The active form of MT1-MMP protein was increased by sPLA₂ treatment in a dose-dependent manner (Fig. 3A). To investigate the involvement of MT1-MMP in sPLA₂-dependent pro-MMP-2 activation, cells were treated with a furin inhibitor dec-RVKR-cmk, which has been shown to block activation of pro-MT1-MMP (19–21). Treatment of cells with dec-RVKR-cmk inhibited sPLA₂-mediated MMP-2 activation, implicating MT1-MMP in the sPLA₂-induced pro-MMP-2 activation (Fig. 3B). A previous report (22) showed that the catalytic activity of MT1-MMP on the cell surface is regulated through a vacuolar H⁻-ATPase-dependent degradation process. To confirm whether or not the sPLA₂-induced MMP-2 activation reflected enhanced MT1-MMP activation, the vacuolar H⁻-ATPase inhibitor bafilomycin A1 was utilized. Cells were cultured in sPLA₂ for 24 h in various concentrations of bafilomycin A1, and the conditioned media were collected, concentrated, and evaluated for MMP-2 activity by zymography and Western blot. As shown in Fig. 3C, bafilomycin A1 potentiated the sPLA₂-induced pro-MMP-2 activation.

MMP-2 Activation by sPLA₂ Is Mediated through the PI3K and Akt Pathway but Not the MAPK Pathway—It has been suggested that PI3K plays a role in pro-MMP activation and cell migration in various cells (23). To investigate the role of PI3K/Akt in MMP-2 regulation, sPLA₂-treated cells were analyzed for activation of PI3K and Akt. Quiescent cells were exposed to 100 nM sPLA₂ for different periods (0–30 min), and protein extracts were analyzed either by immunoprecipitation with phosphotyrosine Ab for PI3K activity or by Western blot with phosphospecific Ab for Akt activity. Phosphorylation of PI3K by sPLA₂ peaked at 5 min, whereas that of Akt began to occur within 3 min, peaked between 5 and 10 min, and then progressively declined to the basal level (Fig. 4, A and B). To gain insight into the mechanism of PI3K/Akt leading to pro-MMP-2 activation, cells were exposed to sPLA₂ alone or in combination with the specific PI3K inhibitor LY294002. As shown in Fig. 5A, LY294002 dose-dependently suppressed the sPLA₂-induced pro-MMP-2 activation. To confirm whether the sPLA₂ signal was dependent on PI3K, cells were transfected with wild type p85α or the deletion mutant of p85α (Δp85α). NIH3T3 cells transfected with wild type p85α or Δp85α cDNA were exposed to sPLA₂, and conditioned medium from these cells was assayed in order to measure MMP-2 activity. Overexpression of wild type p85α and Δp85α was checked by Western blot analysis. Overexpression of Δp85α resulted in signifi-
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Because the activation of extracellular signal-regulated kinase (ERK) is also central to sPLA₂-induced cell proliferation, we were interested in defining the role of ERK in the stimulation of pro-MMP-2 activity. Quiescent cells were exposed to 100 nM sPLA₂ for different times (3–30 min), and protein extracts were analyzed by Western blotting with phosphospecific antibody. sPLA₂-stimulated phosphorylation of ERK1/2 occurred within 5 min, peaked between 10 and 20 min, and then progressively declined. In addition, sPLA₂ stimulated phosphorylation of p38 over a similar period to the time kinetics of the ERK activation (Fig. 6A). To gain insight into the mechanism of sPLA₂ signaling leading to pro-MMP-2 activation, cells were exposed to sPLA₂ alone or in combination with each specific inhibitor. The results of zymography demonstrated that none of them had any effect on the sPLA₂-induced MMP activation (Fig. 6B). These results suggested that sPLA₂ acts through the PI3K/Akt pathway, rather than the MAPK pathway, to activate pro-MMP-2.

sPLA₂ Stimulates Cell Migration via a PI3K- and Akt-dependent Pathway—A critical response of skin fibroblasts during wound healing is their migration into regions of repair and remodeling. For migration, fibroblasts must degrade the surrounding basement membrane, rich in type IV collagen (24, 25), which is the principal substrate for MMP-2. To evaluate the functional consequences of sPLA₂-induced MMP-2 activation, the effect of sPLA₂ on NIH3T3 cell migration was examined. Migration was quantified by using an in vitro cell dispersion assay, in which cells are plated at high density in a hole made in the middle of a 6-well plate and allowed to migrate...
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PLA$_2$-induced pro-MMP-2 activation was associated with an MT1-MMP and TIMP-2 combination. Our data showed that sPLA2 induced a decline of TIMP-2 levels in culture media. A similar phenomenon has been reported recently in other model systems. For example, phorbol 12-myristate 13-acetate or calcium-induced MMP-2 activation in HT1080 or SCC25 cells is coupled with TIMP-2 expression (29). We also found that MT1-MMP is required to trigger the activation of pro-MMP-2 by showing direct MT1-MMP activation or dec-RVKR-cmk and bafilomycin A1 effects. MT1-MMP activity is regulated by several mechanisms. Pro-MT1-MMP is activated by furin (30). Mature MT1-MMP can be inhibited by all the TIMPs except TIMP-1. Although TIMP-2 is the major inhibitor of MT1-MMP (30), it also participates in the activation of MMP-2 by mediating the binding of pro-MMP-2 to MT1-MMP through the formation of a ternary complex (32, 33). It is well established that acidification of intracellular vacuolar compartments plays an important role in membrane trafficking, protein sorting, and degradation (34). This acidification is caused by vacuolar H$^+$-ATPase, which can be selectively inhibited by bafilomycin A1 (35). Bafilomycin A1 effectively promotes the sPLA2-induced pro-MMP-2 activation, suggesting that inhibition of vacuolar H$^+$-ATPase prevents the degradation of MT1-MMP and increases its activity at the cell surface.

Discussion

Group IB PLA$_2$ has been identified as a mitogen for fibroblasts, smooth muscle cells, chondrocytes, and synovial cells (26). The growth-promoting effects of sPLA$_2$ are observed at relatively low concentrations (1–20 nM) in a variety of cells, including NIH3T3 cells (27). In addition, a previous study showed that fibroblast cell proliferation and migration were stimulated by group IB PLA$_2$ treatment (14, 28), and the authors suggested the role of sPLA$_2$ in MMP regulation. However, the detailed biological significance of sPLA$_2$ is not clear. In the present study, we demonstrated first that the enhanced production of the active form of MMP-2 after group IB PLA$_2$ treatment is in agreement with the continued reduction of TIMP-2 protein, and second, we demonstrated that selective elevation of only the MMP-2 activity elevated zymogen secretion but not the increased pro-form of the enzyme. The observed lack of elevation in the MMP-2 total protein suggests that these molecules did not contribute to the synthetic processing of pro-MMP-2 during sPLA$_2$ stimulation.

Diagram

Fig. 6. sPLA$_2$-induced MMP-2 activation mediated independently of the MAPKs pathway. A, cells were treated with 100 nM sPLA$_2$ for the indicated times. Cell lysates were analyzed by immunoblotting with anti-phospho-ERK1/2, anti-phospho-p38, or anti-phospho-c-Jun NH$_2$-terminal kinase (pJNK) Ab to recognize specifically the phosphorylated of ERK1/2, p38, and c-Jun NH$_2$-terminal kinase, respectively. B, the cells were serum-starved overnight and incubated for an additional 24 h with sPLA$_2$ in the presence of PD98059 (25 μM), SB203580 (5 μM), or SP600125 (2.5 μM). The conditioned media were collected at 24 h and analyzed for MMP activity by gelatin zymography. The data shown are representative of three independent experiments.
effect is thought to involve binding of sPLA₂ to the M-type sPLA₂R (43). The nature of the group IB PLA₂ cellular target involved in these biological effects remains, however, to be clearly identified. NIH3T3 cells expressed M-type sPLA₂R, suggesting that these cells could also be targets of sPLA₂ (13). To determine whether MMP-2 activity is required to induce a signal through sPLA₂R, we examined the effect of M-type sPLA₂R overexpression on sPLA₂-induced activation of pro-MMP-2. Cells were transfected either by vector (pClneo) alone as a control or by the full length of the mouse M-type sPLA₂R construct. Reverse transcriptase-PCR detection by using specific primers against the M-type sPLA₂R increased the specific band of ~300 bp in the sPLA₂R-transfected cells. However, gelatin zymography of conditioned medium showed that overexpression of M-type sPLA₂R did not affect pro-MMP-2 activation by sPLA₂ (data not shown). These results suggest that this receptor may not be involved and that other surface molecules may therefore play a major role.

The purpose of this study was also to analyze the role of cell migration in the activation of pro-MMP-2 by exogenous sPLA₂ in NIH3T3 cells. Our data demonstrated that migration is enhanced in sPLA₂-stimulated cells and under conditions that down-regulate TIMP-2 expression. The effect of cell migration, which we observed, was both dose- and time-dependent. Secreted PLA₂ from Indian cobra (Naja naja) venom induced migration of a gastric epithelial cell line (46), whereas pancreatic PLA₂ induced migration of rat embryonic thoracic aorta smooth muscle cells (47). Moreover, N. naja and pancreatic PLA₂ induced migration of vascular endothelial cells (48). Although previous studies have demonstrated a role for group IB PLA₂ as a positive regulator of cell motility, there is no direct evidence regarding the effect of sPLA₂-induced MMP-2 activation on cell migration. Our data additionally link PI3K and Akt activities with MMP-2 activity and cell migration by demonstrating that inhibition of PI3K results in decreased cell migration. We hypothesize that the decrease in cell migration is a result of the diminution of MMP-2 activity.

In summary, our findings implicate a physiologic role for sPLA₂ as a mediator of fibroblast migration. The mechanisms by which sPLA₂ influences cell migration appear to depend on MMP-2 activity. In addition, we identified the PI3K and Akt pathway as a key regulator of pro-MMP-2 activation, collagen cleavage, and ultimately cell migration. These results provide important clues into the regulatory mechanisms underlying fibroblast migration and specifically identify sPLA₂ as a potential new target in a novel signaling cascade.

Acknowledgment—We thank Dr. Wataru Ogawa for providing plasmids p85α and mutant.

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J. Biol. Chem. 2004, 279:36579-36585.
doi: 10.1074/jbc.M314235200 originally published online June 25, 2004

Access the most updated version of this article at doi: 10.1074/jbc.M314235200

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