Phospholipase A<sub>2</sub> Activity of Peroxiredoxin 6 Promotes Invasion and Metastasis of Lung Cancer Cells

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Abstract

Peroxiredoxins (PRDX) are a family of thiol-dependent peroxidases. Among the six mammalian members of this family, PRDX6 is the only protein that additionally exhibits phospholipase A<sub>2</sub> (PLA<sub>2</sub>) activity. The physiologic role of this interesting PRDX6 feature is largely unknown at present. In this study, we show that PRDX6 increases the metastatic potential of lung cancer cells. Functional analyses of the enzymatic activities of PRDX6, using specific pharmacologic inhibitors and mutagenesis studies, reveal that both peroxidase and PLA<sub>2</sub> activities are required for metastasis. Specifically, peroxidase activity facilitates the growth of cancer cells, and PLA<sub>2</sub> activity promotes invasiveness. Further investigation of the latter event discloses that PLA<sub>2</sub> activity promotes accumulation of arachidonic acid, which, in turn, induces the invasive pathway involving p38 kinase, phosphoinositide 3-kinase, Akt, and urokinase-type plasminogen activator. This study is the first to define the functions of the enzymatic activities of PRDX6 in metastasis and to show the involvement of arachidonic acid in PRDX6 action in intact cells. These novel findings provide a significant step toward elucidating the role of PRDX6 in cancer and the mechanism of its action.

Introduction

Metastasis of cancer cells is a major cause of therapy failure. Invasion by these cells through neighboring tissues requires the actions of matrix-degrading proteases, such as matrix metalloproteinases and urokinase-type plasminogen activator (uPA; refs. 1–3). These enzymes are upregulated in invasive cancer cells, which is caused by constitutive activation of signaling pathways that enhance the invasive potential of the cells (4–6). According to the oncogenic factors responsible for the constitutive activation of the invasive signals is essential for improving understanding of cancer biology and developing new treatment strategies.

Peroxiredoxins (PRDX) are a family of peroxidases that reduce peroxides using conserved cysteine residues in the catalytic center (7–10). Six members (PRDX1–PRDX6) of the family have been identified in mammalian tissues. These proteins contain either one (1-Cys PRDX) or two (2-Cys PRDX) such redox-active cysteine residues. The 2-Cys group includes PRDX1 to PRDX5, whereas PRDX6 is the sole member of the 1-Cys group. Despite this difference, peroxidase activities of both 1-Cys and 2-Cys groups commonly contribute to cellular protection against oxidative stress, as supported by analyses of PRDX6 knockout animals (13–15). Interestingly, PRDX6 has a unique property; it possesses phospholipase A<sub>2</sub> (PLA<sub>2</sub>) activity in addition to peroxidase. Thus, it is considered a bifunctional enzyme (16–18). PLA<sub>2</sub> catalyzes the hydrolysis of the sn-2 fatty acyl ester bond of glycerophospholipids to produce free fatty acids and lysophospholipids (19). PRDX6 prefers phosphatidylcholines as substrates, particularly those with arachidonic acid (AA) or palmitic acid at the sn-2 position (16–18). The ability of PRDX6 to release AA seems important, given the crucial role of AA in phospholipid metabolism and cell signaling (19). Nevertheless, most studies done thus far have focused on the peroxidase activity of PRDX6. Consequently, apart from the report that PRDX6 is expressed in rat (20) and human lungs (21) and possibly functions in lung surfactant turnover (18, 22), limited information is available on the physiologic role of its PLA<sub>2</sub> activity.

Recent evidence suggests that PRDX6 does specific functions in cancer cells. Firstly, PRDX6 is often upregulated in malignant tissues of various human organs, including lung (23, 24) and breast (25, 26). Moreover, functional studies using analyses of RNA interference and overexpression suggest that PRDX6 does not simply act as a cytoprotective antioxidant enzyme but also
supports the growth, invasiveness, and metastasis of breast cancer cells (27). The invasion-promoting action of PRDX6 has also been confirmed using lung cancer cells, in which upregulation of PRDX6 results in the activation of Akt via phosphoinositide 3-kinase (PI3K) and p38 kinase, which, in turn, promotes cell invasion by inducing uPA (28). Importantly, analyses of patient samples have revealed a significant association between PRDX6 expression in breast cancer cells and lymph node metastasis (26). It was similarly reported that PRDX6 expression in lung cancer cells was significantly associated with high-grade dysplasia and tumor progression (23, 29). Although these observations suggest that PRDX6 has the ability to support invasiveness and metastasis of the cancer cells analyzed, it is currently unclear whether such functions of PRDX6 depend on its enzymatic activities, although such information is essential for a better understanding of the mechanism of PRDX6 action in cancer cells.

This ability to support the growth and metastasis of cancer cells has also been reported for PRDX1 (30) and PRDX3 (31). Although this implies that the peroxidase activity shared by these PRDX members is involved in cancer cell growth and metastasis, we cannot discount the possibility that the PLA2 activity of PRDX6 is additionally required for metastasis. Therefore, in this study, we investigated the activity of PRDX6 that contributes to invasiveness and metastasis of cancer cells. Our particular focus was on determining the role and underlying mechanism of the PLA2 activity of PRDX6 in cancer cells. Human lung cancer cells were used as a model, as PRDX6-induced signaling is relatively well characterized in these cells (28).

Materials and Methods

Antibodies and materials
Anti–pan-cytokeratin and anti-cytokeratin 7 antibodies were obtained from Zymed and DAKO, respectively. All the other antibodies used in this study were purchased from the companies described previously (28). AA and all the synthetic inhibitors used were supplied by Calbiochem.

Cell culture and transfection
Human A549 and H460 lung cancer cells were obtained from the American Type Culture Collection and cultured in RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum and gentamicin (50 μg/mL). We routinely tested the cells for Mycoplasma and verified them via their morphology and growth curve analysis. The expression constructs for PRDX6, C47S-PRDX6, and S32A-PRDX6 were prepared using pCR3 vectors (generous gifts from Dr. Sang Won Kang, Ewha Womans University, Seoul, Korea). These expression vectors and small interfering RNAs of PRDX6 (Ambion) were introduced into cells using Lipofectamine 2000 (Invitrogen). Where necessary, transfected cells were selected using 1 mg/mL G418 sulfate.

Invasion assay
Cells were seeded onto the upper surfaces of Matrigel-coated polycarbonate filters (BD Biosciences) in modified Boyden chambers (Corning) and analyzed for their invasiveness as described previously (28).

Zymography
Conditioned media, prepared by incubating cells in serum-free medium for 24 h, were subjected to 10% SDS-PAGE on gels containing 2.5% casein and 10 μg/mL plasminogen. Gels were stained, and then uPA activity was visualized as clear bands (28).

Western blot analysis
Conditioned media or cell lysates prepared using a previously reported method (28) were subjected to SDS-PAGE. The proteins separated were then electro-transferred to Immobilon membranes (Millpore) and analyzed using the specified antibodies and the enhanced chemiluminescence detection system (Amer sham). Where indicated, proteins in Immobilon membranes were stained with Ponceau S to confirm equal loading of samples.

PI3K assay
Lysate proteins were immunoprecipitated with an antibody against the p85 subunit of PI3K. PI3K activity in the immune complexes was analyzed by an in vitro kinase assay using 1-α-phosphatidylinositol (Sigma-Aldrich) as a substrate and by TLC (32).

AA release assay
Cells were seeded on 12-well plates (1 × 10⁵ per well), allowed to grow overnight, and labeled with 5 μCi/mL [³H]AA (180–240 Ci/mmol; PerkinElmer Life Sciences). After a second overnight incubation, cells were washed with PBS and further incubated in the presence or absence of specified inhibitors for the indicated periods. Media were collected and centrifuged at 1,000 × g for 3 min. Radioactivity in the supernatant was measured as cpm on a scintillation counter (33).

Animals
Female BALB/c nude mice (6 wk old) were purchased from SLC, acclimatized for 1 wk before use, and maintained throughout at standard conditions (24 ± 2°C temperature and 50 ± 10% relative humidity). All animal experiments were done under the approved protocols of the Institutional Animal Care and Use Committee.

Tumor xenografts
A549 transfectants were s.c. implanted on the right hind legs of mice (1 × 10⁷ cells per mouse). When tumors became palpable, their dimensions were measured every 2 to 3 d. Tumor volumes were calculated using the following formula: tumor volume (mm³) = a × b²/2, where a is the largest and b is the smallest axis (34).
**Experimental lung metastasis assay**

A549 transfectants (2 × 10^6 cells/100 μL PBS) were injected into the lateral tail veins of nude mice (35). After 20 wk, animals were sacrificed, and the lungs and livers were harvested for weighing. Whole lungs were fixed in 10% neutral-buffered formalin, serially sliced into 1.5-mm-thick sections, and embedded in paraffin. Sections (4–6 μm) of these samples were used for standard H&E staining and microscopically analyzed for histopathological characteristics and metastatic involvement. Tumor nodules were identified as a collection of large plump tumor cells and further confirmed by immunohistochemistry using antibodies specific for the tumor markers: pan-cytokeratin and cytokeratin 7. Data are presented as the number of tumor nodules per lung.

**Statistical analysis**

Results were analyzed for statistical significance with one-way ANOVA using SPSS version 16.0 for Windows. Differences were considered significant at P < 0.05.

**Results**

**PRDX6 promotes lung cancer cell metastasis**

Earlier studies have shown that PRDX6 enhances the metastatic potential of breast cancer cells (27). To determine its activity in lung cancer, A549 cells were stably transfected with expression vectors for PRDX6 (Fig. 1A). Control and PRDX6 transfectants were injected into the lateral tail veins of nude mice. Lungs were harvested 20 weeks after injection and analyzed microscopically for metastatic tumor colonies based on histopathologic characteristics and immunoreactivity to antibodies against pan-cytokeratin or cytokeratin 7 (Fig. 1B). In the group receiving control transfectants, tumor nodules were observed at a frequency of 0.56 per lung (Fig. 1C). The frequency of tumor nodule formation increased >3-fold in the group receiving PRDX6 transfectants. The PRDX6 group consistently displayed increased weight of lungs, but not livers, compared with the control group (Table 1). Our data support the view that PRDX6 increases the metastatic potential of A549 cells.

**Both peroxidase and PLA2 activities of PRDX6 contribute to metastasis**

PRDX6 possesses not only peroxidase but also PLA2 activity (16–18). To determine which one contributes to metastasis, peroxidase and PLA2 activities were selectively abolished by mutating Cys^47^ to Ser (C47S) and Ser^32^ to Ala (S32A), respectively (17). PRDX6 mutants were stably expressed in A549 cells (Fig. 1A) and analyzed for metastatic potential. In contrast to wild-type (WT) PRDX6, injection of either mutant transfectant into mice failed to increase the incidence of pulmonary tumor nodules (Fig. 1C) and lung weight (Table 1). The results suggest that PRDX6 requires both peroxidase and PLA2 activities for promoting metastasis.

**Figure 1.** PRDX6 requires both peroxidase and PLA2 activities for the promotion of cancer cell metastasis. A, A549 cells were stably transfected with empty pCR3 vector control or vectors containing PRDX6, C47S-PRDX6, or S32A-PRDX6. Expression patterns of the introduced genes were analyzed by Western blotting using α-tubulin as a loading control. Supplementary Fig. S1 presents the uncropped original blots. B, transfectants (2 × 10^6 cells) were injected into the tail veins of nude mice. Animals were sacrificed 20 wk after injection. Lungs were fixed, stained with H&E, and analyzed under the microscope. The images depict tumor nodules. a, microscopic examination revealing a tumor nodule (arrow) in lung parenchyma. b, high magnification of the tumor nodule discloses cancer cell nests infiltrating the parenchyma. Cancer cells display typical cellular features of adenocarcinoma with prominent nuclei and abundant cytoplasm. c, immunohistochemical staining of the tumor nodule using a pan-cytokeratin antibody. d, staining of the tumor nodule with an anti-cytokeratin 7 antibody. Scale bars, 100 μm (a, c, and d) and 20 μm (b). C, data are presented as means and SDs of the number of tumor nodules per lung. n = 19 (vector), 18 (PRDX6), 22 (C47S-PRDX6), and 23 (S32A-PRDX6).
Peroxidase activity of PRDX6 supports cell growth

PRDX6 may promote metastasis formation by accelerating cancer cell growth. Indeed, reduction of PRDX6 levels using its small interfering RNAs resulted in a decrease in the growth rate of cells in culture (Fig. 2A) without a significant influence on cellular viability (data not shown). This confirms the growth-promoting action of PRDX6 in A549 cells. To determine whether this action of PRDX6 depends on its enzymatic activities, cells were incubated in the presence or absence of mercaptosuccinate (M-succinate) and MJ33, which inhibit the peroxidase and PLA2 activities of PRDX6, respectively (16, 17). Although treatments with these compounds did not significantly alter cell viability (data not shown), cell growth was retarded in the presence of M-succinate but not MJ33 (Fig. 2B). This suggests that cell growth selectively requires the peroxidase activity of PRDX6. To further confirm this, the growth rates of established transfectants were compared. No significant differences were evident between the control and PRDX6 transfectants (Fig. 2C), suggesting that endogenous PRDX6 levels in A549 cells are sufficient for growth and that the growth rate of these cells is not further increased by an additional supply of exogenous PRDX6. Similar results were reported when the function of PRDX3 was analyzed in breast cancer cells (31). The growth rate of A549 cells was not affected by S32A-PRDX6 but was significantly reduced by C47S-PRDX6.

Table 1. Body and organ weight of mice received indicated transfections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Body weight (g)</th>
<th>Lung (g/100 g body weight)</th>
<th>Liver (g/100 g body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vector (n = 19)</td>
<td>24.40 ± 1.74</td>
<td>1.06 ± 0.08</td>
<td>6.23 ± 0.57</td>
</tr>
<tr>
<td>PRDX6 (n = 18)</td>
<td>23.53 ± 1.99 (P &gt; 0.05)</td>
<td>1.20 ± 0.14 (P &lt; 0.05)</td>
<td>6.06 ± 0.29 (P &gt; 0.05)</td>
</tr>
<tr>
<td>C47S (n = 22)</td>
<td>23.81 ± 1.50 (P &gt; 0.05)</td>
<td>1.05 ± 0.10 (P &gt; 0.05)</td>
<td>6.32 ± 0.36 (P &gt; 0.05)</td>
</tr>
<tr>
<td>S32A (n = 23)</td>
<td>24.70 ± 1.34 (P &gt; 0.05)</td>
<td>1.05 ± 0.18 (P &gt; 0.05)</td>
<td>6.18 ± 0.46 (P &gt; 0.05)</td>
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NOTE: Results are means ± SDs for n indicated. P values were obtained versus vector controls.

Figure 2. Peroxidase activity of PRDX6 promotes growth of A549 cells. A, top, control and PRDX6 small interfering RNAs (siRNA) were introduced into A549 cells. After 36 h of incubation, cellular levels of PRDX6 were compared via Western blotting using α-tubulin as a loading control. Supplementary Fig. S2 shows the uncropped original blots. Bottom, growth rates of the treated cells were compared by counting the number of viable cells via trypan exclusion. B, A549 cells (1 × 10⁵) were seeded in medium containing M-succinate (20 μmol/L), MJ33 (10 μmol/L), or left untreated. At the indicated periods of incubation, the number of viable cells was determined. C, growth rates of A549 transfectants were compared. D, A549 transfectants (1 × 10⁷ cells) were s.c. implanted on the right hind legs of mice. At the indicated days after implantation, tumor diameters were measured and volumes were calculated.

*P < 0.05, statistically different from controls. n = 3 (A–C) and 4 (D).
This suggests that C47S-PRDX6 masks the growth-promoting action of endogenous PRDX6 in a dominant-negative manner. In view of the consistent growth-inhibitory effects of M-succinate and C47S-PRDX6, it seems that PRDX6 supports cell growth via its peroxidase activity.

To confirm the results in vivo, transfectants were s.c. implanted in nude mice, and subsequent growth was analyzed by measuring tumor size. Mice implanted with control transfectants efficiently formed tumors. Whereas the rate and extent of this process was not significantly altered by PRDX6 or S32A transfectants, C47S transfectants induced a marked delay in tumor formation (Fig. 2D). This finding supports the view that the peroxidase activity of PRDX6 is required for tumor growth in vivo. On considering the results of these studies collectively, we propose that the peroxidase activity of PRDX6 contributes to metastatic colony formation by facilitating cancer cell growth.

**PRDX6 promotes invasion via PLA2 activity**

We recently reported that PRDX6 promotes lung cancer cell invasion by stimulating cellular pathways that sequentially involve p38 kinase/PI3K, Akt, and uPA (28). In contrast to cell growth, PRDX6-induced cell invasiveness was abolished on addition of MJ33 but not M-succinate (Fig. 3A). Consistently, the S32A, but not C47S, mutation of PRDX6 abrogated the ability of PRDX6 to promote the activity of PI3K, phosphorylation of Akt and p38 kinase, uPA protein levels and activity (Fig. 3B), and, consequently, cell invasiveness (Fig. 3C). These results suggest that PRDX6 requires PLA2 activity, but not peroxidase activity, to stimulate invasion signals.

**PLA2 activity of PRDX6 promotes AA release in A549 cells**

Previous enzymatic assays show that PRDX6 cleaves phosphatidylcholines to generate AA (16, 17, 19). To confirm this in intact cells, a [3H]AA release assay was done. PRDX6 transfection enhanced the ability of A549 cells to release AA, which was attenuated by the addition of MJ33 but not by M-succinate (Fig. 4A). The data suggest that PRDX6 induces AA release in intact cells via PLA2 activity, which is further supported by the observation that whereas C47S-PRDX6 enhances AA release to a comparable extent as WT PRDX6, S32A-PRDX6 is much less effective (Fig. 4B).

**AA promotes cell invasion**

To determine the specific function of AA in this system, A549 cells were exposed to exogenous AA. This treatment resulted in increased cell invasiveness (Fig. 4C). In contrast, the same concentrations of arachidic or palmitic acid failed to produce similar enhancement (data not shown), suggesting a specific requirement of AA for invasion. Treatment with AA additionally enhanced the phosphorylation levels of p38 kinase and Akt as well as enhancing uPA protein levels and activity (Fig. 4D). Moreover, inhibitors for PI3K (LY294002), p38 kinase (PD169316), or uPA (amiloride) prevented AA-induced invasion (Fig. 4C). Overall, it seems that AA mediates the ability of PRDX6 to stimulate the invasion pathway that involves p38 kinase, PI3K, Akt, and uPA.

**Role of PLA2 activity of PRDX6 in other lung cancer cell types**

To investigate the cell type specificity of PLA2 activity, an alternative lung cancer cell line, H460, was analyzed.
Similar to data obtained with A549 cells, PRDX6 or C47S-PRDX6 transfection promoted the release of AA (Fig. 5A), phosphorylation of Akt and p38 kinase, uPA expression (Fig. 5B), and, consequently, cell invasiveness (Fig. 5C). These events were not, or were poorly, stimulated by S32A-PRDX6. Furthermore, the invasiveness of H460 cells was enhanced by exposure to exogenous AA (Fig. 5D). This event was efficiently attenuated by inhibitors for PI3K, p38 kinase, and uPA. The data collectively suggest that PRDX6 stimulates the previously defined invasion pathway (28), via AA generated by its PLA2 activity, in multiple types of lung cancer cells.

Discussion

In this study, we have shown that PRDX6 enhances the metastatic potential of lung cancer cells. This function of PRDX6 may be clinically relevant, given the significant association between PRDX6 expression in lung cancer cells and tumor progression (23, 29). Moreover, considering the recent similar findings reported using breast cancer cells (27), PRDX6 may exert this function in cancer cells from multiple organs. A novel finding of this study is that PRDX6 requires both its peroxidase and PLA2 activities for promoting metastasis. This conclusion is based on the observation that PRDX6 fails to enhance metastasis formation of A549 cells in a mouse model when either of its enzymatic activities is abrogated via point mutations. To clarify the specific mechanisms by which these activities contribute to metastasis, we investigated their possible influence on the growth and invasiveness of A549 cells.

Our data suggest that the peroxidase activity of PRDX6 promotes the formation of metastatic colonies by stimulating cancer cell proliferation. This latter action was supported by the ability of M-succinate and C47S-PRDX6 to retard the growth of cells in either culture or a xenograft model. In contrast, cell growth was not significantly influenced by MJ33 at concentrations that effectively suppressed PRDX6-induced AA release and invasion. This finding suggests that the PLA2 activity of PRDX6 is dispensable for cell growth, consistent with reports that cancer cell growth is facilitated by PRDX1 (30) and PRDX3 (31), which lack PLA2 activity.

A key finding of this study is that PRDX6 promotes invasion via PLA2 activity, which is supported by the ability of MJ33 to prevent PRDX6-induced invasion, and is further confirmed by the finding that, in contrast to PRDX6, S32A-PRDX6 fails to stimulate invasion components (p38 activity).
kinase, PI3K, Akt, and uPA) and, thus, fails to increase cell invasiveness. Therefore, it seems that the PLA₂ activity of PRDX6 contributes to metastasis by enhancing the invasiveness of cancer cells. Given that these effects of MJ33 and S32A-PRDX6 are not mimicked by M-succinate and C47S-PRDX6, the peroxidase activity of PRDX6 seems to be irrelevant for invasion.

Another important finding of this study is that AA, a bioactive lipid implicated in carcinogenesis (36, 37), acts as a proximal mediator of PRDX6-induced invasion. Initially, we showed that PRDX6 induces AA release in intact cells. Importantly, this action of PRDX6 was mimicked by C47S-PRDX6, but not by S32A-PRDX6, suggesting that AA release selectively reflects the PLA₂ activity, but not the peroxidase activity, of PRDX6. This was further confirmed by the observation that PRDX6-induced AA release was prevented by MJ33 but not by M-succinate. In addition to the PLA₂ activity-dependent production of AA, we analyzed the function of AA by directly exposing cells to the compound exogenously.

Our results show that AA enhances cellular invasiveness by stimulating the signaling pathway involving p38 kinase, PI3K, Akt, and uPA. This ability of AA may be mediated by biologically active eicosanoids that are produced as a result of the metabolism of AA through lipoxygenase pathways and stimulate various signaling components, such as p38 kinase, PI3K, and Akt (38). Based on the collective data, we propose that PRDX6 induces the invasion-promoting signaling pathways by generating AA via its PLA₂ activity. To our knowledge, this is the first report to provide direct evidence of the biological role and underlying mechanism of the PLA₂ activity of PRDX6. Given that these effects of PLA₂ activity were found in both A549 and H460 cells, the role of PLA₂ activity of PRDX6 defined in this study may be applicable in multiple cancer cell types.

In summary, we have shown that both peroxidase and PLA₂ activities of PRDX6 contribute to the metastatic ability of lung cancer cells. Whereas peroxidase activity facilitates the growth of cancer cells, PLA₂ activity...
promotes invasion via AA generation. These findings significantly advance our understanding of the mechanism of action of PRDX6 and its role in cancer metastasis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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