Human Phospholipase D1 Can Be Tyrosine-phosphorylated in HL-60 Granulocytes

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The human phospholipase D1 (hPLD1) has recently been cloned. Although recent data have implicated PLD in receptor-stimulated secretion, the regulation of the activity of PLD enzymes remains to be clarified. Purified hPLD1 is activated by several cytosolic cofactors among which are protein kinase Ca, ARF, and RhoA. In human granulocytes, a strong correlation between tyrosine phosphorylation of proteins and PLD activity has been established. In this study, the presence of hPLD1 in HL-60 granulocytes and its phosphorylation on tyrosine residues have been studied. We generated antipeptide antibodies (Abs) specific for hPLD1 but not PLD2 as shown by Western blotting (WB) of recombinant PLD1 and PLD2. These Abs identified the presence of hPLD1 in HL-60 cells with the bulk of it being detected in the membranes and only a minor fraction in the cytosol. The hPLD1 Abs detected a major band at 120 kDa (PLD1a) and a minor band at 115 kDa (PLD1b). The specificity of the Abs was confirmed using PLD antisera neutralized with the immunizing peptides. The two forms of hPLD1 were consistently detected by immunoprecipitation under non-denaturing and denaturing conditions following a WB analysis with hPLD1 Abs. Following exposure of HL-60 cells to peroxides of vanadate (V4+-OOH), an inhibitor of tyrosine phosphatases, hPLD1 was immunoprecipitated under non-denaturing conditions from HL-60 cell lysates and assayed for tyrosine phosphorylation by WB. hPLD1 comigrated with a 120-kDa tyrosine phosphorylated protein by gel electrophoresis. Other tyrosine-phosphorylated peptides of 160, 140, 135, 90, and 75–80 kDa were also detected in hPLD1 immune complexes. hPLD1 and the associated tyrosine-phosphorylated proteins were not immunoprecipitated by neutralized hPLD1 Abs. Using denaturing conditions, the PLD immunoprecipitates were sequenially immuno-blotted with anti-PLD1 and anti-phosphotyrosine Abs. PLD1a and PLD1b were detected, and the major PLD1a protein was superimposable with a major tyrosine-phosphorylated protein detected at 120 kDa. Conversely, PLD1a and PLD1b were recovered, at least in part, in the anti-phosphotyrosine immunoprecipitates. These results provide evidence that two PLD1 forms are expressed in human granulocytes. Furthermore, in response to stimulation by V4+-OOH, PLD1 was tyrosine-phosphorylated and associated with several, presently undefined, tyrosine-phosphorylated proteins.

Phospholipase D (PLD)1 plays an important role in signal transduction through the hydrolysis of phosphatidylcholine to choline and phosphatic acid (PA). The latter is a second messenger implicated in the regulation of many signaling proteins (1). PA can also be dephosphorylated by PA phosphatases to diacylglycerol, which is an activator of certain isoforms of protein kinase C (2). PLD activation following interaction of agonists with G protein-coupled receptors and receptor tyrosine kinases has been observed in many cells and tissues (1). Although the precise physiological function of PLD in cells is poorly understood, the receptor-stimulated PLD activity has been implicated in a broad range of human granulocyte cellular responses, including stimulated superoxide production and secretion (3).

Several studies have demonstrated in cell-free systems, or in permeabilized cells, the GTP/Y dependence of PLD activation (4–8). Reconstitution experiments using porated HL-60 cells or partially purified PLD from HL-60 cells or brain tissues led to the discovery of several regulatory proteins among which are the ADP-ribosylation factor (5, 6) and the small GTPase RhoA (7, 8). Rac1 and Cdc42 are also involved in the activation of PLD in liver and brain (8, 9). While the synergistic activation by RhoA and ARF suggests convergence of regulatory mechanisms on one single PLD isoform (8), additional biochemical studies indicate the presence of distinct RhoA- and ARF-regulated PLD isoforms in HL-60 cells and liver (10, 11). RhoA- and ARF-responsive PLD activities are observed in the plasma membrane, nuclei, Golgi, and endoplasmic reticulum (10, 12–15).

An ARF-regulated PLD enzyme (hPLD1) has recently been cloned (16). The gene contains several consensus sequences highly conserved in PLDs from yeast and plants (16–20). The recombinant enzyme is regulated by ARF1 and Rho proteins (21). Protein kinase Ca can also activate hPLD1 in a kinase-independent mechanism independently of and synergistically with the ARF and the Rho families of small GTPases (21, 22). In granulocytes, receptor-stimulated PLD activity is regulated by tyrosine phosphorylation of proteins (23). Protein kinase activities regulate, at least in part, the recruitment and the membrane association of ARF and RhoA, thereby potentiating the response to GTP/Y in HL-60 cell membranes (24). Furthermore, inhibitors of tyrosine phosphatases such as peroxides of

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1 The abbreviations used are: PL, phospholipase; hPL, human phospholipase; rPL, recombinant phospholipase; Abs, antibodies; ARF, ADP-ribosylation factor; GTP/Y, guanosine 5’-3’-O(bio)triphosphate; PA, phosphatic acid; Tyr(P), phosphorysine; V4+-OOH, peroxides of vanadate; WB, Western blotting; PAGE, polyacrylamide gel electrophoresis; PVDF, polyvinylidene difluoride.

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vanadate (V\textsuperscript{3+}-OH), stimulate PLD activity by G protein-independent (25) and -dependent mechanisms (26). The present study was undertaken to examine the presence and distribution as well as the potential tyrosine phosphorylation status of hPLD1 in HL-60 granulocytes. We provide evidence that V\textsuperscript{3+}-OH induces the tyrosine phosphorylation of hPLD1 and stimulates its association with several tyrosine-phosphorylated proteins.

**EXPERIMENTAL PROCEDURES**

**Materials**—HL-60 cells were purchased from the American Type Culture Collection (Rockville, MD). Fetal bovine serum was from HyClone (Logan, UT). t-GLutamine, penicillin/streptomycin, and bicarbonate-free medium RPMI 1640 were from Life Technologies, Inc. (Burlington, Ontario, Canada). Sephadex G-10 and protein A were purchased from Pharmacia Biotech (Dorval, Quebec, Canada). Nonidet P-40, sodium orthovanadate (Na\textsubscript{2}VO\textsubscript{4}), and all other reagents were from Sigma. Catalase was purchased from Boehringer Mannheim (Laval, Quebec, Canada). Molecular weight standards were purchased from Bio-Rad (Mississauga, Ontario, Canada). V\textsuperscript{3+}-OH was prepared essentially as described by Bourquin and Grinstein (25). The monoclonal anti-phospho-tyrosine 4G10 (UB-05–521) antibody was obtained from UBI (Lake Placid, NY). Human PLD1 peptides (1–16, MLKKEPRVNTSALK; 144–162, RRQNVREEPREMPS; 967–981, DDPSEDPIQDPVSDK; and 1027–1040, KEDPIRAEEELKKI) were synthesized by HUKABEL (Ville St Laurent, Quebec, Canada). Horseradish peroxidase-conjugated anti-mouse IgG, anti-rabbit IgG, and the enhanced chemiluminescence (ECL) Western blotting system were obtained from Amersham Corp. (Oakville, Ontario, Canada). Recombinant human PLD1 (rPLD1) and mouse PLD2 (rPLD2) were generous gifts from Drs. M. Frohman and A. Morris.

**Antipeptide Antisera**—PLD1 antisera were raised against a mixture of the PLD1 peptides coupled to keyhole limpet hemocyanin with glutaraldehyde. Two rabbits were immunized each with 250 μg of the four peptides.

**HL-60 Cell Culture**—HL-60 cells were grown in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum, t-glutamine (2 mM), streptomycin (100 units/ml), and penicillin (100 μg/ml), and differentiation to granulocytes was induced with 1.25% (v/v) Me\textsubscript{2}SO\textsubscript{4} as described (25). Differentiated cells were harvested by centrifugation and resuspended in bicarbonate-free, Hepes-buffered RPMI 1640 to be used for experiments.

**Cell Stimulation, Lysis, and Immunoprecipitation**—HL-60 cell suspensions (6 × 10\textsuperscript{6} cells/ml) were either stimulated with 100 μM V\textsuperscript{3+}–OH or treated with the same volume of appropriate diluents. After selected times, cell suspensions were mixed to an equal volume of non-denaturing lysis buffer (2×) containing 50 mM Tris-HCl buffered to pH 7.4, 150 mM NaCl, 1.5 mM MgCl\textsubscript{2}, 5 mM EGTA, 10% glycerol, 1% Triton X-100, 2 mM Na\textsubscript{2}VO\textsubscript{4}, 1 mM phenylmethylsulfonyl fluoride, 5 μg/ml aprotinin, 5 μg/ml leupeptin (final concentrations). The lysates were incubated on ice for 15 min before centrifugation at 13,000 rpm for 15 min. The supernatant (2×) cell eq/ml) were incubated with 7 μl of the anti-PLD1 serum 04 and 0.5% bovine serum albumin, 1.2% Nonidet P-40, 20 μg/ml aprotinin, and 20 μg/ml leupeptin for 3 h at 4 °C on a rotator platform. Where indicated, the anti-PLD1 serum was neutralized with 10 μg/ml immunizing peptides for 2 h at 4 °C before use. This was followed by an incubation with 20 μg of protein A-Sepharose beads for 1 h at 4 °C. The beads were washed three times with ice-cold lysis buffer containing 1% Nonidet P-40 and boiled for 7 min at 100 °C in 2× Laemmli’s sample buffer. Immunoprecipitated proteins were electrophoresed on 8% SDS-PAGE.

**For immunoprecipitation under reducing conditions, the cell suspensions (6 × 10\textsuperscript{6} cells/ml) were mixed to an equal volume of boiling denaturing buffer A (2×) containing 125 mM Tris-HCl buffered to pH 6.8, 150 mM NaCl, 6% SDS, 5 mM Na\textsubscript{2}VO\textsubscript{4}, 1 μg pepstatin, 10 μg/ml aprotinin, 10 μg/ml leupeptin, and 4% β-mercaptoethanol (final concentrations) and incubated for 7 min at 100 °C. The lysates were centrifuged at 12,000 rpm for 2 min at room temperature. The supernatants were then filtered through Sephadex G-10 columns to remove the denaturing agents (27). 0.1% Nonidet P-40, 20 μg/ml aprotinin, 20 μg/ml leupeptin, and 5 μl of bovine serum albumin (0.01% w/v) were added to the eluates which were precleared with protein A-Sepharose and subsequently used for immunoprecipitation with the anti-PLD1 serum 03 as described above. Cytosolic and membrane fractions were prepared (24) and processed for immunoprecipitation of PLD1 as described previously by Grinstein and Furuya (28).

**Electrophoresis and Immunoblotting**—Samples were electrophoresed on 8% SDS-PAGE, proteins were transferred to Immobilon PVDF membrane (Millipore Corp.), and WB was performed as described (24). Membranes were incubated with anti-PLD1 serum 04 (1:2000) and exposed to peroxidase-conjugated anti-rabbit IgG (1:20,000) for 1 h at 37 °C in blocking solution or using the 4G10 anti-phosphotyrosine (Tyr(Phospho)) antibody (1:4000) as described previously (23). The membranes were covered with ECL detection reagents. Autoradiograms were obtained by exposing Kodak X-Omat film to membranes.

**RESULTS AND DISCUSSION**

We generated hPLD1 antipeptide antisera to examine the presence of hPLD1 in human HL-60 cells. To minimize proteolysis, the cell lysates were prepared by direct transfer of cell suspensions into boiling sample buffer. The samples were electrophoresed, transferred to PVDF membranes, and probed with the anti-PLD1 serum 03 and 04. rPLD1 (Fig. 1, A and B, lane 1) and rPLD2 (Fig. 1, A and B, lane 2) were added to the membrane samples before electrophoresis and immunoblotting with the anti-PLD1 sera. As shown in Fig. 1 the antibodies revealed a strong band at 120 kDa corresponding to rPLD1. rPLD2 was not recognized by the two anti-PLD1 sera. The presence of two immunoreactive bands in HL-60 granulocytes at 115 kDa and 120 kDa were consistently observed (lane 5). The immunoreactivity of the 120- and 115-kDa protein suggested the presence of two closely related PLD1 enzymes in HL-60 cells. The specificity of the two anti-PLD1 sera was demonstrated by the absence of the 120- and 115-kDa bands in immunoblots carried out with antigen-preneutralized antibodies (data not shown). The two immunoreactive bands at 120 and 115 kDa were detected in the membrane (lane 3) and to a lesser extent in the cytosolic (lane 4) compartments. Searches for hPLD1 isoforms revealed the presence of several closely related human PLD homologues (18, 19). DNA sequence analysis identified a second PLD1-related protein lacking 38 amino acids in the middle of the PLD1 sequence (amino acids 584–622). The 120- and 115-kDa PLD variants were named PLD1a and PLD1b, respectively (21). PLD1a and PLD1b are generated by alternative splicing of the PLD1 mRNA, and both forms are similarly sensitive to activation by small GTPases and protein kinase Ca (21). It is likely that the two bands revealed by the anti-PLD1 sera correspond to PLD1a and PLD1b.

The inhibition of receptor-stimulated PLD activity by selec-
tive inhibitors of tyrosine kinases is well documented (23). Increased PLD activity was also detected in the anti-Tyr(P) immunoprecipitates of neutrophil lysates previously primed with granulocyte-macrophage colony-stimulating factor and stimulated with fMLP (formylmethionylleucylphenylalanine) (29). Furthermore, granulocyte PLD activity was increased by a treatment with tyrosine phosphatase inhibitors such as V4'-OOH.\(^2\) The molecular mechanisms that regulate these processes are, however, poorly understood as it remained unclear whether PLD itself, or one or more of its cofactors, were subject to regulation by tyrosine phosphorylation. To assess the role of tyrosine phosphorylation in the activation of PLD, we immunoprecipitated PLD using the anti-PLD1 serum under nonreducing and under denaturing conditions. HL-60 granulocytes were incubated with V4'-OOH (100 \(\mu\)M) or an equal volume of the diluent for the indicated times. The samples were prepared by direct transfer of the cell suspensions to an equal volume of ice-cold 2 \(\times\) nondenaturing lysis buffer. The lysates were incubated with the PLD1 antibodies (prenatalized or not with the peptide antigen), and the immune complexes were precipitated by the addition of protein A-Sepharose beads. The amounts of precipitated PLD1 and the presence of tyrosine-phosphorylated proteins in the precipitates were monitored, following transfer to PVDF membranes, by successive immunoblotting with anti-PLD1 and anti-Tyr(P) antibodies, respectively. Although PLD1 could be immunoprecipitated by the anti-PLD1 serum after the second immunization (Fig. 2A, lane 2) immunoprecipitation of PLD1 was more efficient after the fifth immunization (Fig. 2A, lanes 3-7). As shown in Fig. 2A, two major bands corresponding to PLD1a and PLD1b were detected at 120 and 115 kDa, respectively. The two forms of PLD1 were recovered in the supernatant when the immunoprecipitations were carried out with a normal rabbit serum (Fig. 2A, lane 1) or with the preevaluated PLD1 antibodies (Fig. 2A, lane 8). The membrane was then stripped and re-probed with anti-Tyr(P) antibodies (Fig. 2B). A 120-kDa tyrosine-phosphorylated protein was reproducibly observed in PLD1 immunoprecipitates. Several other tyrosine-phosphorylated peptides of 160, 140, 135, 90, and 75–80 kDa were also detected in PLD1 immune complexes. Phosphorylation of the 120-kDa band as well as the presence of the other phosphorylated proteins in the PLD1 immune complexes was time-dependent reaching near-maximal levels between 5 and 10 min after the addition of V4'-OOH. PLD1a, PLD1b, and the associated tyrosine-phosphorylated proteins were not detected in the immunoprecipitates carried out with a normal rabbit serum (Fig. 2, A and B, lane 1) or with the preevaluated PLD1 antibodies (Fig. 2, A and B, lane 8).

To examine whether the 120-kDa tyrosine-phosphorylated protein is PLD1 itself or an associated protein, cell lysis and immunoprecipitation with the anti-PLD1 serum were conducted under reducing conditions as described under “Experimental Procedures.” A representative blot for PLD1 under these conditions is shown in Fig. 3A. Both PLD1a and PLD1b were detected in the PLD1 immunoprecipitates. Similar amounts of PLD1a and PLD1b were immunoprecipitated from control (lane 1) and V4'-OOH treated cells (lane 2). As compared with unstimulated cells, a major 120-kDa tyrosine-phosphorylated protein was observed in the immunoprecipitates derived from V4'-OOH-stimulated cells (Fig. 3B, lane 2) but not from unstimulated granulocytes (Fig. 3B, lane 1). Neutralization of the anti-PLD1 serum with the immunizing peptides specifically eliminated PLD1a and PLD1b in the immunoprecipitates (Fig. 3A, lane 3) as well as the 120-kDa phosphorylated protein (Fig. 3B, lane 3). Tyrosine phosphorylation of PLD1b was hardly detectable probably because of the small amounts of PLD1b in the PLD1 immunoprecipitates. These experiments were also performed using the reverse protocol, immunoprecipitation with anti-Tyr(P) antibodies and blotting with anti-PLD1 antibodies (Fig. 4). Because of the large amounts of tyrosine-phosphorylated proteins in lysates derived from V4'-OOH-treated cells and the low abundance of the PLD1 enzymes, we conducted two rounds of immunoprecipitations. A first immunoprecipitation was carried out with the anti-PLD1 serum under nonreducing conditions because the efficiency of immunoprecipitation of PLD1 was higher under these conditions (data not shown). The PLD1 immune complexes were collected and boiled in lysis buffer containing SDS and \(\beta\)-mercaptoethanol. These manipulations would be expected to disrupt most, if not all, protein-protein interactions. After removing the denaturing agents (27), the tyrosine-phosphorylated proteins were immunoprecipitated with agarose-conjugated anti-Tyr(P) antibodies, and the amounts of PLD1 in the immunoprecipitates were assessed by WB. A representative blot of these experiments is shown in Fig. 4A. The presence of PLD1a and PLD1b in the anti-Tyr(P) immunoprecipitates was evident after stimulation with V4'-OOH (lane 2) but not in unstimulated cells (lane 1). Moreover, the PLD1 proteins were not detected in the immune complexes when the first round of

\footnote{\(^2\) As described previously (25), in two independent experiments the levels of the phosphatidylethanol in intact HL-60 cells increased from 0.011 \(\pm\) 0.01% of tritium label in control cells to 0.955 \(\pm\) 0.11% of tritium label in cells stimulated with 100 \(\mu\) M V4'-OOH for 10 min.
immunoprecipitation was carried out with preneutralized anti-PLD1 serum (lane 3). The same membrane was stripped and reprobed with anti-Tyr(P) antibodies (Fig. 4B). A tyrosine-phosphorylated protein detected at 120 kDa in V^4+-OOH-stimulated cells (Fig. 4B, lane 2) was superimposable with PLD1a (Fig. 4A, lane 2). In contrast, no tyrosine-phosphorylated proteins could be detected in unstimulated cells (lane 1) or when immunoprecipitations were performed with neutralized anti-PLD1 serum (lane 3). Taken together these results demonstrate that PLD1a and possibly PLD1b can be tyrosine-phosphorylated upon stimulation of intact HL-60 cells with V^4+-OOH.

Biochemical studies have detected PLD activities in both the membrane and the cytosolic fractions of HL-60 cells (11). The differential regulation of the membrane-associated and of the cytosolic PLD activity by Rho and ARF proteins suggested the presence of distinct PLD isoforms. We analyzed the presence and the distribution of PLD1a and PLD1b in the different cellular compartments of HL-60 granulocytes. In these experiments the membranes and the cytosols were prepared (24). PLD1 was immunoprecipitated from the lysates derived from 2 × 10^7 cell eq with the anti-PLD1 serum, and the amounts of PLD1a and PLD1b in the immunoprecipitates were determined by blotting with the anti-PLD1 antibodies. A representative blot from three different experiments with similar results is presented.
brane PLD immunoprecipitates. In the cytosolic fractions, two bands at 135 and ~85 kDa were detected but we did not observe the presence of a 120-kDa tyrosine-phosphorylated protein. The protein could not be detected by WB because of the small amount of PLD1 proteins in the immunoprecipitates obtained from cytosolic protein fractions (Fig. 5A). In the membrane fractions, a major 120-kDa phosphotyrosine protein was detected and was superimposable with PLD1 (Fig. 5, A and B). Several major unidentified tyrosine-phosphorylated proteins in the 160-, 85–100-, and 75–80-kDa regions were also recovered in the PLD1 immunoprecipitates. We also immunoprecipitated the membrane-bound and cytosolic PLD1 under denaturing conditions (28). A doublet at 120 kDa and 115 kDa in the membrane fractions of V4+-OOH-stimulated or unstimulated HL-60 cells was detected by the anti-PLD1 serum (Fig. 5C). The cytosolic PLD1 was hardly detectable by WB (data not shown). In this particular experiment the membrane-bound PLD1b was not clearly detected in the immune complexes obtained from V4+-OOH-treated cells but was present in two other similar experiments (see Fig. 3 and data not shown). These same membranes were probed for the presence of phosphotyrosine. In the membrane PLD1 immunoprecipitates, a 120-kDa tyrosine-phosphorylated band was detected in cells stimulated with V4+-OOH. The tyrosine-phosphorylated band was perfectly superimposable with PLD1a and showed a similar shape (Fig. 5, C and D). The data indicate that the membrane-bound PLD1a is tyrosine-phosphorylated. Because of the low amount of cytosolic PLD1 proteins, it was not possible using this protocol to determine whether or not they were tyrosine-phosphorylated. Although these observations indicate that PLDs with similar antigenic properties can exist as soluble and membrane-associated proteins, the presence of additional PLD isoforms not recognized by our PLD1 antibodies is not excluded.

In summary, the anti-peptide antibodies raised against PLD1 recognize PLD1 but not PLD2. PLD1a and its spliced form PLD1b are expressed in HL-60 granulocytes. Both enzymes are associated with the membrane fractions, and only very small amounts of PLD1 are detected in the cytosolic fractions. Stimulation of HL-60 cells with V4+-OOH increased the phosphorylation of PLD1 and its association with several tyrosine-phosphorylated proteins. This finding is consistent with the hypothesis that PLD is complexed to several proteins in stimulated cells. PLD1 stimulation requires many cofactors for activation in vitro including the small GTPase RhoA and ARF in vitro (21). The increased levels of PLD activity in the membrane compartment is, at least in part, the result of the small GTPase translocation to membranes upon cell activation with various agonists (24), but the specific effect of protein tyrosine phosphorylation on PLD functionality, biochemical properties, and cofactor requirement is yet to be defined. The availability of PLD1-selective antibodies should help resolve this issue.

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