Protein Kinase C δ Specifically Associates with Phosphatidylinositol 3-Kinase Following Cytokine Stimulation*

(Received for publication, March 14, 1996, and in revised form, April 22, 1996)

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Phosphatidylinositol (PI) 3-kinase is activated as a result of cytokine-induced association of the enzyme with specific tyrosine-phosphorylated proteins. PI 3-kinase lipid products, PI 3,4-P2 and PI 3,4,5-P3, have been shown, in vitro, to directly activate novel and atypical protein kinase C (PKC) isozymes. However, the mechanism by which PI 3-kinase may be involved in regulation of PKC isoforms in vivo is presently unknown. We investigated a possible relationship by looking for associations between these enzymes. We found that in a human erythroleukemia cell line, as well as in rabbit platelets, PI 3-kinase and PKCδ associate in a specific manner that is modulated by cell activation. Granulocyte-macrophage colony-stimulating factor treatment of cells caused increased association of PKCδ and PI 3-kinase as did treatment of platelets with platelet-activating factor. Results using two PI 3-kinase inhibitors, wortmannin and LY-294002, showed that the former inhibited this association, while the latter did not, suggesting that PI 3-kinase lipid products may not be a prerequisite for the PI 3-kinase/PKCδ association. Our results also suggest that tyrosine phosphorylation of PKCδ is not involved in its association with PI 3-kinase.

Cytokine stimulation of mitogenesis of hematopoietic cells is known to occur through at least two signaling pathways, both of which depend on tyrosine phosphorylation of key regulatory proteins; one is the p21ras/mitogen-activated protein kinase network and the other is the PI1 3-kinase pathway. Following ligand binding, the common β subunit of receptors for interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) becomes tyrosine-phosphorylated (1, 2). Several other signaling proteins including JAK-2 (3), STAT-5 (4), p46, and p52 Shc (5, 6), p42/44 mitogen-activated protein kinases (7, 8), and SH-PTP2 (9) become tyrosine-phosphorylated proteins (11–14). A tyrosine-phosphorylated 70-kDa substrate was shown to associate with PI 3-kinase following treatment of cells with IL-3 or GM-CSF (14), although this substrate was subsequently shown to be the tyrosine phosphatase, SH-PTP2, and its association may be indirect in a complex with Grb-2 (9).

The involvement of p21ras in mitogenesis is well understood, but the role of PI 3-kinase, which is thought to be essential as well (15), is less well characterized. Recent evidence suggests that two serine/threonine kinases, p70 S6 kinase (16, 17) and p70 S6 kinase (18, 19), are thought to be activated downstream of PI 3-kinase. In hematopoietic cells, we showed previously that IL-3, IL-5, and GM-CSF, as well as IL-4 and Steel factor all activate PI 3 kinase (14), and indeed, this signal is important in the ability of cytokines to inhibit apoptosis (19). An intriguing set of observations made in the past few years has suggested that PI 3,4-P2 and PI 3,4,5-P3 can activate several novel and atypical PKC isoforms (PKCε, δ, ζ, η, and θ) (20, 21). These results were obtained from in vitro assays, but the mechanism whereby PKC isoforms may be activated by PI 3-kinase is not known. The activation of PKC activity by cytokines has been reported in a few publications (22, 23), but it is not clear how this may occur. In the case of cytokines such as IL-3, IL-5, and GM-CSF, there is no evidence that a classical PI-phospholipase C pathway is operating, although evidence for increased production of diacylglycerol derived from phosphatidylinositol has been reported (24–26).

In an effort to further delineate pathways operating downstream of the related receptors for IL-3, IL-5, and GM-CSF, we have examined the role of PKC isoforms. This is a complex task, as there are at least 11 distinct family members that may be regulated by several independent mechanisms. In this report, we focus on the potential interaction of one specific PKC isoform, PKCδ, with the PI 3-kinase enzyme. We find that the two enzymes can be co-immunoprecipitated as shown both by immunoblotting and enzyme activities. Furthermore, the association is modulated by cytokines, particularly by GM-CSF, in a human hematopoietic cell line. In another system, platelets activated by platelet-activating factor (PAF), we can also demonstrate an increase in the association between the two enzymes following activation of the cells. In addition, increased tyrosine phosphorylation of PKCδ in response to FcεRI receptor activation in another cell type does not lead to any change in association between PKCδ and PI 3-kinase. Therefore, we have discovered an association between PI 3-kinase and one specific PKC isoform that is probably independent of tyrosine phospho-

*This work was supported by a grant from the Medical Research Council of Canada. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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The abbreviations used are: PI, phosphatidylinositol; IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; PAF, platelet-activating factor; PKC, protein kinase C; WM, wortmannin.
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rylation of PKCδ and is somehow modulated by specific receptor-mediated events.

EXPERIMENTAL PROCEDURES

Cells—TF-1 cells, a human erythroleukemia cell line (a kind gift from Dr. T. Kitamura, DNAX, Palo Alto, CA), were maintained in RPMI 1640 (Life Technologies, Inc.) with 10% fetal bovine serum (Intergen) and 2 mM L-glutamine. In experiments in which cells were stimulated with cytokines, human recombinant cytokines were used; IL-3 and GM-CSF were from R&D Systems and IL-5 as described above. RBL-2H3 cells (a kind gift from Dr. J. John Rivera, NIH) were maintained in RPMI 1640 with 10% fetal bovine serum. Cells were trypsinized and passaged every 3 days.

Cytokine Stimulation and Immunoprecipitations—TF-1 cells, grown in complete RPMI with IL-3, were placed in cytokine-free medium with 1% serum 18 h prior to assay. Cells (5 × 10⁶/300 μl) were washed three times in Hanks' balanced salt solution buffered with 20 mM Hepes, pH 7.4, and then preincubated in RPMI 1640 buffered with 20 mM Hepes, pH 7.4, at 37°C for 30 min. Recombinant human GM-CSF (50 ng/ml), IL-3 (100 ng/ml), or IL-5 (500 ng/ml) were added for 15 min. Cells were solubilized in 500 μl of solubilization buffer (50 mM Tris-Cl, pH 7.4, 1% Triton X-100, 100 mM NaCl, 2.5 mM EDTA, 10 mM NaF, 0.2 mM NaVO₄, 1 mM Na₃MoO₄, 40 μg/ml phenylmethylsulfonfluoride, 1 μg pepstatin, 0.5 μg leupeptin, 10 μg soybean trypsin inhibitor), centrifuged to remove debris, and then mixed with immunoprecipitating antibodies (anti-PKCδ mouse monoclonal (Transduction Laboratories; 2 μg/500 μl of solubilization buffer), anti-PKCε rabbit polyclonal IgG (Life Technologies, Inc.; 4 μg/500 μl of cell lysate), or anti-p85 rabbit polyclonal antisera (raised against the p85 SH2-glutathione 5-transferase fusion protein; a kind gift from Dr. M. Welham; 1 μg/500 μl of cell lysate) for 1 h on ice. Following addition of protein A-Sepharose beads (Pharmacia Biotech Inc.), samples were rotated at 4°C for 1 h. The beads were washed 5 times with cold solubilization buffer. For immunoblots, proteins were eluted with SDS sample buffer containing 2-mercaptoethanol and boiled at 90°C for 1 min prior to loading on 8.0% polyacrylamide gels using an acrylamide:sample buffer containing 2-mercaptoethanol and boiled at 90°C for 1 min prior to loading on 8.0% polyacrylamide gels using an acrylamide:

bis ratio of 118:1. Proteins were transferred onto nitrocellulose using an LKB Novablot semi-dry transfer apparatus. The nitrocellulose filters were incubated with Tris-buffered saline (50 mM bovine serum albumin, 1% ovalbumin, 0.05% NaN₃) when blotted with anti-phosphotyrosine antibody 4G10 (Upstate Biotechology Inc., Lake Placid, NY), anti-p85, or anti-p110 (Santa Cruz Biotechnology), or they were blocked using 5% skim milk powder for immunoblots with anti-PKCδ, -ε, -α, -β, -γ, or -ζ (Santa Cruz Biotechnology). PKCδ-3 Kinase Activity—Following immunoprecipitation as described above, beads were used to assay for PI 3-kinase activity as described (14, 27). Briefly, the beads were washed twice with solubilization buffer and three times with 10 mM Tris-Cl buffer, pH 7.4, Phosphatidylinositol (10 μg/sample) in 30 mM Hepes, pH 7.4, and 40 μl of kinase buffer (30 mM Hepes, pH 7.4, 30 mM MgCl₂, 50 μM ATP, 200 μM adenosine, [³²P]ATP 10 μCi/pmol) were added to the beads. The reaction was stopped after 15 min with 1 M HCl. Chloroform/methanol (2:1) was used to extract the lipid, and the labeled PI-3-P was separated by thin layer chromatography using oxalate-treated aluminum-backed silica gels (EM Scientific) and solvent comprised of NH₄OH:water:methanol:chloroform. Rabbit platelets were prepared as described (28).

FeR1 Cross-linking in RBL-2H3 Cells—RBL-2H3 cells were trypsinized and washed in RPMI with serum. Cells were passaged every 3 days. Following immunoprecipitation as described above, beads were used to assay for PI 3-kinase activity as described (14, 27). Briefly, the beads were washed twice with solubilization buffer and three times with 10 mM Tris-Cl buffer, pH 7.4, Phosphatidylinositol (10 μg/sample) in 30 mM Hepes, pH 7.4, and 40 μl of kinase buffer (30 mM Hepes, pH 7.4, 30 mM MgCl₂, 50 μM ATP, 200 μM adenosine, [³²P]ATP 10 μCi/pmol) were added to the beads. The reaction was stopped after 15 min with 1 M HCl. Chloroform/methanol (2:1) was used to extract the lipid, and the labeled PI-3-P was separated by thin layer chromatography using oxalate-treated aluminum-backed silica gels (EM Scientific) and solvent comprised of NH₄OH:water:methanol:chloroform. Rabbit platelets were prepared as described (28).

RESULTS AND DISCUSSION

The association of PKC isoforms δ and ε with PI 3-kinase was examined in the erythroleukemia cell line TF-1. Cell lysates from TF-1 cells, immunoprecipitated with antibodies to either PKCδ or PKCε and analyzed by immunoblotting with antibodies to the p85 or the p110 subunits of PI 3-kinase, showed that

PI 3-kinase was being co-immunoprecipitated (Fig. 1, A and B, and Fig. 2). In reciprocal experiments, immunoprecipitation with antibody to p85 co-immunoprecipitated PKCδ and -e, as detected by immunoblotting. Other PKC isoforms found in TF-1 cells include α, β, μ, ζ, and δ. None of the latter PKC isoforms were found to co-immunoprecipitate with PI 3-kinase subunit p110, revealing a similar pattern of PI 3-kinase association with PKCδ, C, the same blot washed and reprobed with anti-PKCδ to verify equal amounts of immunoprecipitated PKCδ in all samples. These blots are representative of three independent experiments. lppt, immunoprecipitate.

\(^{2}\) S. L. Ettinger and V. Duronio, unpublished observations.

Fig. 1. Anti-PKCδ immunoprecipitates from TF-1 cell lysates contain PI 3-kinase. A, control samples indicate a basal level of PI 3-kinase association with PKCδ. This association is dramatically enhanced by stimulation with GM-CSF, slightly with IL-5, and not at all with IL-3. B, the same blot washed (without stripping) and reprobed with antibody to PI 3-kinase subunit p110, revealing a similar pattern of PI 3-kinase association with PKCδ, C, the same blot washed and reprobed with anti-PKCδ to verify equal amounts of immunoprecipitated PKCδ in all samples. These blots are representative of three independent experiments. lppt, immunoprecipitate.
Studies should be done to test additional times.

To investigate whether the PI 3-kinase co-immunoprecipitated with PKCδ or PKCe remains active, anti-PKCδ and anti-PKCe immunoprecipitates were analyzed for PI 3-kinase activity in vitro. GM-CSF stimulation of the cells led to increased PI 3-kinase activity associated with PKCδ compared with control samples or IL-5- or IL-3-stimulated cells (Fig. 3A), thereby correlating with the detection of PI 3-kinase in immunoblots. Anti-PKCe immunoprecipitates also contained active PI 3-kinase; however, the PI 3-kinase activity was not affected by cytokine treatment of cells.

We next studied the role of PI 3-kinase activity in mediating the association with PKCδ, taking advantage of two potent inhibitors of PI 3-kinase, wortmannin (WM) and LY-294002. Cells were pretreated with 100 nM WM or 50 μM LY-294002 prior to cytokine stimulation, conditions that are known to inhibit the majority of PI 3-kinase activity (29, 30).3 WM decreased the association of PKCδ with PI 3-kinase in all cases (Fig. 3A and B), but LY-294002 had no effect (data not shown). The relative decreases were consistently more pronounced in GM-CSF- and IL-5-treated cells than in IL-3-treated cells. WM is known to bind covalently to the active site of the p110 subunit, while LY-294002 is a competitive inhibitor. The contrasting results between WM and LY-294002 suggest that the PI 3-kinase/PKCδ association is not modulated by the lipid products of PI 3-kinase activity but may be affected by alterations of the p110 subunit caused by WM. Alternatively, we cannot rule out the possibility that WM is having its effect on the PI 3-kinase/PKCδ association independently of its effect on PI 3-kinase activity. Other inhibitory effects of WM have been described (31), and in our laboratory we have recently shown that WM has inhibitory effects on other kinases that are not seen with concentrations of LY-294002 that cause an equivalent inhibition of PI 3-kinase activity.3

Recent reports have described tyrosine phosphorylation of PKCδ following stimulation with 12-O-tetradecanoylphorbol-13-acetate, carbachol, substance P, or FcεRI cross-linking (32-34). In TF-1 cells, a faint band is detected in anti-phosphotyrosine blots of anti-PKCδ immunoprecipitates, and this band comigrates with PKCδ (data not shown). However, we have been unable to detect any differences in the levels of tyrosine phosphorylation following cytokine stimulation. Phosphoamino acid analysis of PKCδ will be necessary to confirm whether PKCδ is being tyrosine-phosphorylated to any significant extent. In another system, we have confirmed the results of Haleem-Smith et al. (34), showing that cross-linking of the FcεRI receptor in RBL-2H3 cells leads to a large increase in tyrosine phosphorylation of PKCδ (Fig. 4A), but interestingly, no PI 3-kinase was present in PKCδ immunoprecipitates, either before or after receptor activation (Fig. 4B). Together, these results strongly suggest that the association between PI 3-kinase and PKCδ that we have observed is independent of PKCδ tyrosine phosphorylation and is therefore not likely to be mediated by the SH2 domains of the PI 3-kinase p85 subunit.

To determine if PI 3-kinase associates with PKC isoforms in any other signaling systems we next investigated rabbit platelets treated with the potent agonist, PAF. PAF-treated platelets also showed an increase in PI 3-kinase protein co-immunoprecipitated with PKCδ, compared with controls, as

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3 M. P. Scheid and V. Duronio, submitted for publication.
determined on immunoblots using anti-p85 antibodies (Fig. 5A). This association was again inhibited by WM. The PI 3-kinase was active in the PKC\textsubscript{\textdagger} immunoprecipitates as determined by an \textit{in vitro} PI 3-kinase assay (Fig. 5B).

We also characterized the serine/threonine kinase activity in anti-p85 immunoprecipitates and to date have found Ca\textsuperscript{2+}-independent protein serine/threonine kinase activity as evidenced by phosphorylation of a Ser-containing peptide substrate corresponding to the PKC\textsubscript{\textdagger} pseudo-substrate site. There were no increases in kinase activity in response to calcium, and the activity was at least partially lipid-dependent. These features are consistent with the characteristics of PKC\textsubscript{\textdagger} and PKC\textsubscript{\texte} activities. We are investigating this further to determine the role PI 3-kinase may play in regulation of the PKC activity, particularly that of PKC\textsubscript{\textdagger}.

The importance of PI 3-kinase in signal transduction has been pointed out in numerous publications over the past few years. There have been many proteinsshowntoassociatewith PI 3-kinase following stimulation of cells, generally as a result of tyrosine-phosphorylated proteins associating via the PI 3-kinase p85 SH2 domains. This type of association is known to result in PI 3-kinase activation, independent of the tyrosine phosphorylation of the p85 subunit itself (35). We demonstrate here for the first time that at least two members of the PKC family of enzymes, PKC\textsubscript{\textdagger} and PKC\textsubscript{\texte}, also associate with PI 3-kinase, and in the case of PKC\textsubscript{\textdagger}, the association is increased upon stimulation of hematopoietic cells with GM-CSF or upon activation of platelets. In our system, PKC\textsubscript{\textdagger} appears to be constitutively tyrosine-phosphorylated to a small extent, as seen on immunoblots. However, we cannot discern differences in levels of tyrosine phosphorylation with cytokine stimulation. Several PKC isoforms contain the consensus sequence recognized by PI 3-kinase SH2 domains in the p85 subunit including PKC\textsubscript{\textdagger}, which has YNYM (36), and PKC\textsubscript{\texte}, which has YEMM (37). However, the lack of increased tyrosine phosphorylation of PKC\textsubscript{\textdagger} following cytokine stimulation, along with the lack of PKC\textsubscript{\textdagger}/PI 3-kinase association in a system in which PKC\textsubscript{\textdagger} is heavily tyrosine-phosphorylated suggests that we are observing an association that is unlike previously demonstrated interactions with PI 3-kinase. However, we do not know whether we are observing a direct interaction or one that also involves other proteins.

In the TF-1 cells, IL-3, IL-5, and GM-CSF are each able to provide a complete mitogenic stimulus, while only GM-CSF and, to a lesser extent, IL-5 are able to cause increased PI 3-kinase/PKC\textsubscript{\textdagger} association. Coupled with the finding that PAF activation of platelets is able to increase the association, the results suggest that the functional role of this interaction may be unrelated to the mitogenic effect of cytokines. There have been conflicting reports regarding the role of PKC\textsubscript{\textdagger} in mitogenesis (38, 39). Furthermore, as suggested by Myers et al. (40),
the association of PI 3-kinase with various proteins may be unrelated to a role for that enzyme in mitogenesis. One might also speculate that the PI 3-kinase/PKC association could be related to the effects of GM-CSF and perhaps IL-5 on inducing differentiation, effects that are distinct from those of IL-3. Further studies will be required to delineate the exact function of this novel association as well as other systems in which this type of regulation may be occurring.

Acknowledgments—We thank David Fong for technical assistance and Dr. Michael Gold for helpful discussions.

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J. Biol. Chem. 1996, 271:14514-14518.
doi: 10.1074/jbc.271.24.14514

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