Phosphatidylinositol 4,5-bisphosphate (PI(4,5)P₂) mediates cell motility and changes in cell shape in response to extracellular stimuli. In platelets, it is synthesized from PI4P by PIP5K in response to stimulation of a G-protein-coupled receptor by an agonist, such as the thrombin. In the present study, we have addressed the pathway that induces PIP5K Iα activation following the addition of thrombin. Under resting condition expressed PIP5K Iα was predominantly localized in a perinuclear distribution. After stimulation of the thrombin receptor, PAR1, or overexpression of a constitutively active variant of Goαq, PIP5K Iα translocated to the plasma membrane. Movement of PIP5K Iα to the cell membrane was dependent on both GTP-bound Rac and Rho, but not Arf, because: 1) inactive GDP-bound variants of either Rac or Rho blocked the translocation induced by constitutively active Goαq, 2) constitutively GTP-bound active variants of Rac or Rho induced PIP5K Iα translocation in the absence of other stimulants, and 3) constitutively active variants of Arf1 or Arf6 failed to induce membrane translocation of PIP5K Iα. In addition, a dominant negative variant of Rho blocked the PIP5K Iα membrane translocation induced by constitutively active Rac, whereas dominant negative variants of either Rac or Arf6 failed to block PIP5K Iα membrane translocation induced by constitutively active Rho. This implies that the effect on PIP5K Iα by Rac is indirect, and requires the activation of Rho. In contrast to the findings with PIP5K Iα, the related lipid kinase PIP4K failed to undergo translocation after stimulation by small GTP-binding proteins Rac or Rho. We also tested whether membrane localization of PIP5K Iα correlated with an increase in its lipid kinase activity and found that co-expressing of PIP5K Iα with either constitutively active Goαq, Rac, or Rho led to a 5- to 7-fold increase in PIP5K Iα activity. Thus, these findings suggest that stimulation of a G-protein-coupled receptor (PAR1) leads to the sequential activation of Goαq, Rac, Rho, and PIP5K Iα. Once activated and translocated to the cell membrane, PIP5K Iα becomes available to phosphorylate PI4P to generate PI(4,5)P₂ on the plasma membrane.

The synthesis of the membrane-bound phospholipid, phosphatidylinositol 4,5-bisphosphate (PI(4,5)P₂) is a critical step in signal transduction. PI(4,5)P₂ serves as a substrate for phospholipase C and phosphatidylinositol 3-kinase to generate lipid second messengers (1–3), directly interacts and regulates both actin-binding and PH domain-containing proteins (4–7), and functions as a cofactor for small GTP-binding proteins and phospholipase D (8–15). In mammalian cells, PI(4,5)P₂ is synthesized by two different pathways. The first involves a phosphatidylinositol-4-phosphate 5-kinase type I (PIP5K I) isoform, which phosphorylates the substrate phosphatidylinositol 4-phosphate (PI(4P) at the 5- position of the inositol ring (16, 17). The second pathway involves phosphorylation at the 5- position of phosphatidylinositol 5-phosphate (PI(5P) by a enzyme currently referred to as phosphatidylinositol-5-phosphate 4-kinase (PIP4K), but previously named phosphatidylinositol-4-phosphate 5-kinase type II (PIP5K II) or type C (PIP5K C) (16, 18). It is currently thought the pathway utilizing PIP5K I (α, β, or γ isoform) is the predominant mechanism of PI(4,5)P₂ synthesis in mammalian cells and, therefore, is a major regulator of actin organization, secretion, and endocytosis (19–22).

Although PIP5K I and PIP4K have homologous lipid kinases domains, they differ in substrate specificity and in vivo regulation (23). For example, only PIP5K I requires phosphatidic acid as a cofactor for maximal activity (24, 25). In vitro, PIP5K I can associate, in a nucleotide-independent fashion, with the small GTP-binding proteins Rho and Rac (26, 27). These GTPases can lead to the activation of PIP5K I, but this effect on lipid kinase activity may be limited to the GTP-bound form of the nucleotide-binding protein (28). There is evidence that the effect of Rac or Rho on PIP5K I is indirect and may be mediated by either Rho-kinase or the GTPase Arf (29–31). Consistent with these interactions in vitro, is the observation that the addition of a non-hydrolyzable GTP analog, GTP-S, stimulates PI(4,5)P₂ production in human placenta membrane and in rat brain (32, 33). In HeLa cells, Honda et al. (29) demonstrated that the small G-protein ADP-ribosylation factor, Arf, directly activates PIP5K Iα in the presence of phosphatidic acid, whereas Rho and Rac had no effect. In contrast, Tolias et al. (34) showed that the addition of recombinant Rac to permeabilized platelets led to PIP5K Iα activation and PI(4,5)P₂ production. Therefore, it appears that small GTP-binding proteins affect PIP5K I activity and PI(4,5)P₂ production. However, it is unclear which GTPase is predominantly responsible.

Both PIP5K I and PIP4K appear to localize to distinct subcellular compartments. PIP5K Iα has been reported to specifically localize at the plasma membranes or in the nucleus, phosphatidylinositol 4,5-bisphosphate; PIP5K, phosphatidylinositol-4-phosphate 5-kinase; PIP4K, phosphatidylinositol-5-phosphate 4-kinase; PI4P, phosphatidylinositol 4-phosphate; PI5P, phosphatidylinositol 5-phosphate; GTP-S, guanosine 5'-3-O-(thio)triphosphate; HA, hemagglutinin; PCR, polymerase chain reaction; EST, expressed sequence tag; PBS, phosphate-buffered saline.
whereas PIP4K has been reported to be present diffusely within the cell or to be present in the ER, actin cytoskeleton, cytosol, plasma membrane, or nucleus (35–38). We asked whether localization of PIP5K Iα played a role in its regulation, because its only known substrates are membrane-bound phospholipids. In the present study, we demonstrate that stimulation of the PAR1 receptor induces a translocation of PIP5K Iα from the Golgi to the cell membrane. This process involves heterotrimERIC G-proteins as well as both Rac and Rhos, but not Arf. Coincident with the intracellular translocation of PIP5K Iα, we found that its enzymatic activity increased 5- to 7-fold when co-expressed with either large or small GTP-binding proteins. Therefore, these results delineate a signaling pathway that is initiated by a G-protein-coupled receptor and leads to the production of PI4,5P2.

MATERIALS AND METHODS

Reagents and Antibodies—The anti-myc, anti-HA, or the biotinylated monoclonal anti-FLAG (M2) antibodies were purchased from Covance, the anti-GM 130 was purchased from Transduction Laboratories, and the anti-PAR1 monoclonal antibody was a gift from L. F. Brass (University of Pennsylvania, Philadelphia, PA (39)). The fluorescein isothiocyanate- and rhodamine-conjugated goat secondary antibodies were obtained from BIOSOURCE. Alexa 350, the cascade blue-labeled goat anti-rabbit secondary antibody, and Alexa 546, the red dye-conjugated streptavidin were purchased from Molecular Probes. The PI4P was obtained from Roche Molecular Biochemicals, and all remaining chemicals were obtained from Sigma Chemical Co.

Plasmid Construction—The human PIP5K Iα cDNA was generated by PCR using EST AA054379 (Genome Systems) as template and the following oligonucleotide primers: 5'-CG GCA G GTA CC CAC ACC ATG TCT CTT GCT GGT AAA-3' and 5'-GG CCG TCT AGA TTA CAA GTC TTC AGA AAT CAA CTT TTG TTC TAA ATA GAC GTC ACG CAC-3'. The primers incorporated BamH I and Xho I sites, as well as a carboxy-terminal myc epitope (EQKLISEEDL). This product was cloned into BraH II- and Xho I-digested pCMV 5 (a gift of Mark Stinski, University of Iowa).

Cloning of PIP4K (also known as PIP5K Type II or Type C) was performed by PCR using EST W00481 from Genome Systems. Full-length sequence revealed that two nucleotide changes that differed from the published sequence, and altered the predicted translated product. The encoded peptide differs at 171 and 173 residues relative to published sequence, and likely represent polymorphisms, because multiple independent EST clones (N28765, N33825, and THC154497) contained the identical sequence. The cDNA was amplified using PCR primers CG GCA G GTA CC CAC ACC ATG TCT CTT GCT GGT AAA-3' and 5'-GG CCG TCT AGA TTA CAA GTC TTC AGA AAT CAA CTT TTG TTC CGT CAA GAT GTG GCC CAC-3'. The resulting product was cloned into BraH II- and Xho I-digested pCMV 5 (a gift of Mark Stinski, University of Iowa).

Membrane Recruitment of PIP5K Iα—A standard assay for phosphorylation of PIP4P was carried out in an incubation medium of 80 µl of buffer B containing 125 µM ATP, 125 µM PI4P, and 2.5 µCi of [γ-32P]ATP. The reaction mixtures were incubated at 37 °C for 20 min. After stopping the reaction with 1 v HCl (2 volumes) and extracting the radioactivity with an equal volume of chloroform-methanol (1:1, v/v), the 32P-labeled PI4,5P2 products were resolved by thin-layer chromatography using water-chloroform-methanol-NH4OH (25:70:100:15, v/v) as a solvent system. Immediately before chromatography, the thin-layer plates were coated with 1% potassium oxalate in water-methanol (1:1) and baked at 110 °C for 35 min. The transfer of radioactivity to phospholipids was visualized by exposure to iodine vapor. The regions of the TLC plates that contained PI4,5P2 spots were carefully excised, placed in a screw-capped scintillation vial, and then subjected to scintillation counting. Counts were normalized for immunoprecipitated myc-PIP5K Iα as determined by quantitative 125I-immunoblotting.

RESULTS

Stimulation of a G-protein-coupled Receptor Leads to the Membrane Recruitment of PIP5K Iα—Previous reports demonstrated that stimulation of the predominant thrombin receptor on human platelet, PAR1, leads to an increase in PI4,5P2 synthesis (41, 42). Using Cos-7 cells transfected with tagged PIP5K, we investigated whether stimulation of this G-protein-coupled receptor was also associated with an intracellular redistribution of PIP5K Iα. Under resting conditions, expressed PIP5K Iα was located adjacent to the cell nucleus (Fig. 1). Because of the eccentric perinuclear distribution, we simultaneously stained cells with antibodies against the Golgi marker, adaptin, as well as the epitope tag on PIP5K Iα. We found that resting PIP5K Iα was localized in proximity with γ-adaptin (Fig. 1). Confocal microscopy verified this localization and showed that PIP5K Iα colocalized most closely with a marker of the cis-Golgi cisternae, GM-130 (Fig. 2A). Thus, under resting conditions, PIP5K Iα is co-localized within the early trans-Golgi network. It should be noted that the Golgi has previously been described to contain PIP5K I activity (43, 44) and that this intracellular localization is also consistent with the related lipid kinase PI4Kβ (45, 43).
We next tested whether stimulation of the PAR1 thrombin receptor would alter the location of PIP5K Iα. As shown in Fig. 3, stimulation of PAR1 with the receptor-specific activating peptide SFLLRN resulted in the translocation of PIP5K Iα to the cellular membrane. After 1 h of stimulation with the peptide agonist, 30–40% of cells redistributed PIP5K Iα toward their plasma membrane. Additional studies using transfected HEK-293 cells yielded the same result (not shown). Therefore, these data indicate that stimulation of the thrombin receptor initiates a signaling cascade that can induce the movement of PIP5K Iα toward the cell membrane.

PAR1 is typically coupled to phospholipase C by Go q. To determine whether PAR1 mediated its effect on the intracellular distribution of PIP5K Iα via Go q, we tested whether the relocalization of PIP5K Iα could be mimicked by co-expression of PIP5K Iα with an active variant of the α subunit. The Q209L mutation in Go q (HA-Go q Q209L) is constitutively in the GDP-bound state. In 100% of cells expressing Go q Q209L and PIP5K Iα, PIP5K Iα was easily identified as being associated with the cell membrane (Fig. 4). Confocal microscopy of cells expressing active Go q and PIP5K Iα, verified PIP5K Iα was present on the cell membrane (Fig. 2B). Although these confocal images revealed that the majority of PIP5K Iα was now on the cell membrane, in some cells a fraction of PIP5K Iα was still localized with the Golgi. These results indicate that the subcellular distribution of the PIP5K Iα can be regulated by the thrombin receptor and at least one of the G-proteins which normally associate with it.

We also found that stimulation of the EGF receptor by 1-h stimulation of 25 ng/ml EGF initiated cell membrane association of PIP5K Iα (data not shown). This demonstrates that the relocalization of PIP5K Iα is not limited to stimulation of a G-protein-coupled receptor. In addition, we have found that expressed PIP5K Iα in Jurkat T-cells has a perinuclear distribution when the cells are plated on poly-L-lysine. However, PIP5K Iα translocates to the cellular membrane when the cells are plated on either fibronectin or C305 (an IgM antibody that binds and activates the T-cell antigen receptor). This implies that the signaling pathway leading to membrane association of PIP5K Iα ultimately involves effectors common to multiple receptor families, including G-protein-coupled, growth factor, immunoglobulin supergene, and integrin receptors.

**The Role of Low Molecular Weight GTP-binding Proteins**—Although there is agreement that low molecular weight GTP-binding proteins contribute to PIP5K Iα activation, the identity of the relevant proteins is controversial. Because the low molecular weight GTP-binding proteins Rac and Rho become activated after stimulation of G-protein-coupled, growth factor, immunoglobulin supergene, and integrin receptors (42, 46–49), we tested whether the membrane localization of PIP5K Iα could be influenced by these proteins. As shown in Fig. 5, when PIP5K Iα was co-expressed along with constitutively GDP-bound variants of Rac (Rac L61) or Rho (Rho L63), PIP5K Iα was recruited from the Golgi to the cellular membrane in 100% of cells. This effect by Rac or Rho was regulated by the nucleotide-bound state, because overexpression of constitutively GDP-bound variants of either Rac (Rac V12N17) or Rho (Rho V12N17) did not alter the localization of PIP5K Iα.
Membrane Translocation of a PIP5K

**Fig. 5.** GTP-bound RAC or Rho can induce the membrane localization of PIP5K Iα. Cos-7 cells were transfected with myc-PIP5K Iα alone or along with constitutively inactive, or active, variants of Rac or Rho. Shown is PIP5K Iα transfected alone, along with constitutively inactive HA-Rac V12N17, constitutively active HA-Rac L61, constitutively inactive HA-Rho N19, constitutively active HA-Rho L63, or constitutively active HA-Arf1 QL. Cells were stained with anti-myc (panels on left) to detect PIP5K Iα, and with anti-HA (panels on right) to detect various small GTPases. Together, this figure demonstrates that either GTP-bound Rac, or Rho, can induce the membrane relocalization of PIP5K Iα. In contrast, GDP-bound Rac or Rho, and GTP-bound Arf, have no effect. The white bar corresponds to 30 μm.

**Fig. 6.** Rac and Rho have no effect on the localization of PIP4K. Cos-7 transiently transfected with myc-PIP4K alone, or with either constitutively active HA-Rac L61, or HA-Rho L63. Localization of myc-PIP4K is shown with anti-myc staining (panels on left). Staining of small GTPase is shown by anti-HA (panels on right). Similar results were obtained when myc-PIP4K was co-expressed with either constitutively GDP-bound HA-Rac V12N17 or HA-Rho N19. This figure shows that, in contrast to the their effect on PIP5K Iα, neither Rac nor Rho have effect on the intracellular distribution of PIP4K. The white bar corresponds to 30 μm.

N19) failed to induce the PIP5K Iα translocation (Fig. 5). Arf is another low molecular weight GTP-binding protein that has been shown to interact in vitro with PIP5K Iα. In contrast to the effect of Rac and Rho on PIP5K Iα intracellular localization, we found that neither constitutively GTP-bound variant of Arf1 (Fig. 5) or Arf6 (not shown) induced PIP5K Iα translocation. Therefore, this demonstrates that Rac and Rho, but not Arf, are capable of inducing membrane translocation of PIP5K Iα. This also shows that PIP5K translocation is regulated by which guanine nucleotide is bound to the low molecular weight GTP-binding protein.

Because PIP4K has also been reported to become stimulated after thrombin stimulation of platelets (38), we next tested whether small GTP-binding proteins also affected the intracellular distribution of this lipid kinase. In contrast to our findings with PIP5K Iα, neither the GTP- nor GDP-bound variants of Rac or Rho affected the localization of PIP4K (Fig. 6). Therefore, these observations suggest that, although Rac and Rho can contribute to the membrane localization of PIP5K Iα, they have no effect on the intracellular distribution of PIP4K.

**Are Rac or Rho Critical for Gαq-mediated PIP5K Iα Recruitment to the Membrane?**—Because activation of both high, and low, molecular weight GTP-binding proteins lead to the translocation of PIP5K Iα, we examined whether they are components of the same signaling pathway. To begin to address this question, we tested whether dominant negative variants of Rac or Rho affected the ability of Gαq to induce membrane association of PIP5K Iα. As shown in Fig. 7, GDP-bound variants of either Rac or Rho functioned as competitive inhibitors (dominant negatives) and blocked the ability of Gαq to induce cell membrane association of PIP5K Iα. Triple staining verified the simultaneous expression of PIP5K, Gαq, and the dominant negative GTPase in all analyzed cells. Pharmacologic inhibition of Rho by C3-exotoxin also inhibited Gαq-initiated translocation of PIP5K Iα, confirming the necessity of Rho (not shown). These data imply that stimulation of the PAR1 receptor leads to the cellular membrane binding of PIP5K Iα through a pathway that involves both Rac and Rho.

Because the dominant negative variants of either Rac or Rho block Gαq-mediated PIP5K Iα translocation, both Rac and Rho participate in a single signaling pathway. Nobles and Hall (50) have previously demonstrated that activation of Rac leads to the activation of Rho. Thus, it is possible that the effect of Rac on PIP5K Iα localization is indirect and requires activation of Rho. To test this hypothesis, we expressed constitutively active Rac L61 alone, or along with dominant negative Rho N19, and analyzed the effect on the intracellular distribution of PIP5K Iα. Coexpression of Rac L61, Rho N19, and PIP5K Iα in the Cos-7 cells was confirmed by triple antibody staining (Fig. 8). As we had seen previously, constitutively active Rac induced membrane localization of PIP5K Iα; however, this effect was blocked by co-expression of a dominant negative Rho. This suggests that the effect on PIP5K Iα by Rac is mediated by activation of Rho.

We performed several different experiments to verify the specificity of our observations. First, we found that pharmacologic inhibition of Rho by C3-exotoxin also inhibited Rac-stimulated membrane translocation of PIP5K Iα (not shown). Second, we tested whether dominant negative Rac would block PIP5K Iα membrane translocation initiated by constitutively active Rho. As shown in Fig. 8, expression of dominant negative Rac did not influence Rho-stimulated PIP5K Iα membrane...
association. As a third test of specificity, we have found that dominant negative Arf6 N27 also did not influence PIP5K Iα translocation induced by either Rac or Rho. Together these three lines of evidence demonstrate that Rac and Rho are in a single signaling pathway that leads to the membrane localization of PIP5K Iα and that in these cells PIP5K Iα translocation is mediated most directly by Rho.

Effect of Large and Small GTP-binding Proteins on the Lipid Kinase Activity of PIP5K Iα  

To determine whether membrane localization of PIP5K Iα is associated with an increase in lipid kinase activity, we performed in vitro kinase assays using immunoprecipitated PIP5K Iα. As shown in Fig. 9, the ability of PIP5K Iα to generate PI4,5P₂ from PI4P increased 5- to 7-fold when it was co-expressed with activated large, or small, GTP-binding proteins. In contrast, constitutively inactive variants of Rac and Rho had an inhibitory effect on PIP5K Iα lipid kinase activity. GDP-bound Rac inhibited PIP5K Iα activity by 40% \( (p < 0.05) \) and GDP-bound Rho inhibited PIP5K Iα activity by 60% \( (p < 0.04) \). These experiments imply that the same signaling pathway that induces the relocalization of PIP5K Iα also induces an increase in its lipid kinase activity.

**DISCUSSION**

The goal of this work was to investigate the signaling pathway initiated by stimulation of a G-protein-coupled receptor leading to the activation of PIP5K Iα and production of PI4,5P₂. Our in vivo findings demonstrate a pathway that sequentially involves the activation of Gₐq, Rac, and Rho. This signaling pathway simultaneously results in the membrane recruitment and enzymatic activation of PIP5K Iα. We hypothesize that both relocalization and biochemical activation of PIP5K Iα are critical for its ability to regulate cell motility and shape change in response to extracellular stimuli.

Our observations extend previous data on the subcellular...
localization of PIP5K Iα. Using a variety of transfection or viral infection systems, other investigators have reported PIP5K Iα in the cell membrane, cytoplasm, and nucleus. To our knowledge, our data are the first to visualize an agonist-mediated translocation of this lipid kinase from one defined cellular location to another. Our data is consistent with previous cell fractionation studies of platelets that revealed that PIP5K enzymatic activity migrates after thrombin stimulation from a Triton X-100-soluble to -insoluble fraction (38).

Schwartz and colleagues (28) were the first to demonstrate that PIP5K Iα is regulated by small GTP-binding proteins. Their in vitro observations were that PIP5K Iα catalytic activity in cell lysates increased in the presence of GTP-bound Rho but not in the presence of either GDP-bound Rho or GTP-bound Rac. Consistent with this observation, Oude Weernink et al. (30) found that Rho-kinase may be the direct mediator of this effect. Although there is agreement in the literature that small GTPase regulates PI4,5P2 synthesis, the specific GTPase responsible for expression experiments, and 3) potential disparate effects between different isozymes of small GTPases.

Under basal conditions, we have found that the majority of PIP5K Iα is localized to the Golgi. Our findings are in contrast to those published by Shibasaki et al. (35) who found that adenovirus-expressed PIP5K Iα was bound to the cell membrane, and its expression was associated with extensive actin changes even in the absence of stimulation. This discrepancy in results might at least partially be due to the adenovirus. Adenovirus infection alone has been previously shown to induce actin organization and cell spreading (51–54). Our studies indicate that PIP5K Iα only supports cell spreading and actin changes after the kinase has been stimulated and translocated to the cell membrane.²

Our findings are consistent with two previous publications demonstrating that PIP5K Iα is associated with the Golgi (43, 44). This indicates that it co-localizes with PI4K, the lipid kinase that generates the predominant PIP5K substrate, PI4P (45, 55). After stimulation of the PAR1 receptor, we have found that PIP5K Iα relocates to the plasma membrane. Our results are consistent with previously established observation that PI4,5P2 is most abundant in the plasma membrane (56, 57). It is conceivable that several small GTP-binding proteins contribute to the localization of these lipid kinases and that some are required for trafficking to the Golgi and others for transport to the cell membrane to coordinate polyphosphoinositide synthesis.

How GTP-bound Rho recruits PIP5K Iα to the cell membrane is unclear. Several investigators have demonstrated that Rho family members shuttle on and off the membrane; this association is regulated by their GTP/GDP-bound state (58–60). It is conceivable that Rho is constitutively bound to PIP5K Iα and that GTP binding merely serves to help translocate the complex to the cell membrane where it can phosphorylate PI4P to generate PI4,5P2 on the plasma membrane. We have found that the in vitro activity of immunoprecipitated PIP5K Iα is increased when it has been co-expressed with GTP-bound Rho. This demonstrates that Rho-mediated membrane recruitment PIP5K Iα alone is not sufficient to also explain the resultant increased production of PI4,5P2. Therefore, this implies that the membrane recruitment and the increase in lipid kinase activity, although both are mediated by GTPases, have a separate mechanism of action. Consistent with this hypothesis, we have found that catalytically inactive PIP5K Iα is still capable of being recruited to the cell membrane.²

In conclusion, our results support the hypothesis that stimulation of a G-protein-coupled receptor leads to the sequential activation of heterotrimeric G-proteins, Rac and then Rho. Once Rho becomes activated, it induces the activation and membrane recruitment of PIP5K Iα to generate PI4,5P2. In contrast, heterotrimeric G-proteins, Rac and Rho, appear to have no effect on PI4K activation or localization. The mechanism of its regulation, as well as the identification of other signaling components of the PIP5K Iα activation pathway, are areas of active investigation.

REFERENCES

1. Berridge, M. J., and Irvine, R. F. (1984) Nature. 312, 315–321
2. Berridge, M. J., and Irvine, R. F. (1989) Nature 341, 197–205
3. Auger, K. R., Serunian, L. A., Solhoff, S. P., Libby, P., and Cantley, L. C. (1989) Cell 57, 167–175
4. Anderson, R. A., and Marchesi, V. T. (1985) Nature 318, 295–298
5. Fukami, K., Endo, T., Inamura, M., and Takenawa, T. (1994) J. Biol. Chem. 269, 1518–1522
6. Janmey, P. A. (1994) Annu. Rev. Physiol. 56, 169–191

² N.-E.-H. Chatah and C. S. Abrams, unpublished observation.
G-protein-coupled Receptor Activation Induces the Membrane Translocation and Activation of Phosphatidylinositol-4-phosphate 5-Kinase I α by a Rac- and Rho-dependent Pathway

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J. Biol. Chem. 2001, 276:34059-34065.
doi: 10.1074/jbc.M104917200 originally published online June 28, 2001

Access the most updated version of this article at doi: 10.1074/jbc.M104917200

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