The discovery of a family of unique rho guanine nucleotide exchange factors (rhoGEFs), p115rhoGEF, or PDZrhoGEF, has suggested a mechanism of signaling by activated G protein-coupled receptors that activate rho has been obscure until recently (3). Thus, the discovery of a family of unique rho guanine nucleotide exchange factors (rhoGEFs), p115rhoGEF, or PDZrhoGEF, and LARG (leukemia-associated rhoGEF (6)) suggested a simple mechanism. They contain a regulator of G protein signaling (RGS) domain that binds activated G12 (7) and G13 (8) causing rhoGEF activation. Thus, the RGS-rhoGEFs are thought to serve as effectors of activated G12/13 and as molecular bridges between the heterotrimeric G protein α subunits and rho. A role for these proteins in cellular rho signaling by GPCRs, such as those for thrombin and LPA, has been suggested by studies with dominant negative constructs (9, 10) and inhibition of signaling by expression of the RGS domains, which act as G12/13 inhibitors (11). There is not, however, direct proof that these proteins mediate GPCR signals and no information is available about which rhoGEF(s) are downstream of which receptors.

rhol activation leads to actin rearrangements and stress fiber formation, gene transcriptional activation, neural process retraction, cell rounding, and smooth muscle contraction (reviewed in Ref. 1). Experimentally, rho activation can be detected directly by measurements of GTP-bound active rho precipitated from cell lysates with effector fusion proteins such as GST-rotokine (12) or indirectly by any of those functional readouts. The 1321N1 astrocytoma cells is a well studied model of thrombin-induced rho activation (13). Thrombin induces both cell rounding and enhanced cell proliferation in these astrocytoma cells by mechanisms that are independent of known second messengers but are blocked by rho inhibitors.

In this study, we use HEK293T cells and a human prostate cancer cell line, PC-3, to test the role of the three RGS-rhoGEFs, LARG, p115rhoGEF, or PDZrhoGEF, in receptor signaling. HEK293 and PC-3 cells express all three of these proteins with RNA for PDZrhoGEF and LARG being more abundant than that for p115. PC-3 cells overexpress the thrombin receptor (PAR1) and have an increased propensity to metastasize to bone compared with lines that have lower PAR1 expression (14). To demonstrate a role for rhoGEFs in GPCR signaling and to define the specificity of their actions, we prepared 21-nucleotide short interfering RNAs (siRNAs) targeting each of these RGS-rhoGEFs. We show that LARG mediates thrombin responses, while the LPA response is mediated by PDZrhoGEF.

**EXPERIMENTAL PROCEDURES**

**Materials**—The three myc-tagged human RGS-rhoGEF plasmids in pcdNAmyc and the SREI Luciferase rho reporter construct were described previously (7). The control Renilla luciferase construct, pRL-TK, was purchased from Promega. The C3 exotoxin expression construct in pcDNA3.1 was kindly provided by Dr. John Williams (University of Michigan).

siRNA design and synthesis has been described in detail (15). Briefly, 21-nucleotide synthetic RNA with the following sequences and their complementary strands (plus 3′ TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCTC-21-TT overhangs on each) were synthesized by the Qiagen siRNA synthesis service (Xenogene Inc.) and high performance liquid chromatography-purified. The sequence targeted was in the RGS domain for all three RGS-rhoGEFs: p115rhoGEF (CATACCATCT
HEKES-KOH, 2 mM magnesium acetate, pH 7.4, and heated to 90 °C for 1 min and then incubated at 37 °C for 1 h. Aliquots were then placed in small vials to make siRNA stock solutions at 300 ng/μl or about 20 μM and frozen at −20 °C.

LARG, p115-rhoGEF, and Gβ antibodies were purchased from Santa Cruz Biotechnology Inc. (N-14, catalog number sc-15439, C-19, catalog number sc-8492, T-20, catalog number sc-378). Affinity-purified polyclonal anti-PDZ-rhoGEF was generated with a synthetic peptide from rat PDZ-rhoGEF (GTRAP48, KTPERTSPSHRQPSD) as described previously (16). Secondary antibodies were bovine anti-goat IgG-horseradish peroxidase (catalog number sc-2352) and goat anti-rabbit IgG-horseradish peroxidase (catalog number sc-2054). The PAR1 agonist peptide SFLIRR was from Bachem (catalog number H-8365, King of Prussia, PA). HEK293T and PC-3 cell lines were gifts of Drs. J. Menon and K. Pienta of the University of Michigan.

**Transfection of siRNAs into Cells**—For Westen blot analysis, HEK293 cells were transiently transfected in a 6-well plate with 2 μg/well of either active rhoGEF siRNAs (LARG, PDZ, p115) or mutant inverted siRNAs and 8 μl of LipofectAMINE 2000. After 72 h, protein lysates were prepared as described (17). For luciferase assays in 96-well plates, one rhoGEF plasmid DNA (p115 (2 ng), PDZ (5 ng), or LARG (5 ng)) was introduced into HEK293 cells with 30 ng of rhoGEF siRNAs or inverted mutant siRNAs with 0.2 μl of LipofectAMINE 2000 together with the dual luciferase reporters (SRE.L and pRL-TK) at 3 ng and 30 ng/well, respectively.

**Western Blot Analysis**—Western blot analysis is done with RGS-rhoGEF-specific antibodies and ECL detection as described previously (17). The same polyvinylidene difluoride membrane was stripped and re-blotted with anti-G protein β subunit antibody as loading control. Blots were quantitated as described previously (17).

**Luciferase Assays**—Twenty-four hours post-transfection with firefly and Renilla vectors, HEK293 cells were serum-starved (0.5% serum), and then at 48 h, luciferase activity was determined using the dual luciferase assay kit (Promega, Madison, WI) according to the manufacturer’s instructions. The ratio of firefly to Renilla luciferase counts was calculated. Data are expressed as the percent of the control value (samples without siRNA).

**GST-rotekin Pull-down Assay**—siRNA (si) or mutant controls (inv) were introduced (10 μg/10-mm dish) into HEK293 cells with 30 μl of LipofectAMINE 2000 in duplicate 100-mm dishes. Thirty-six hours after transfection, cells were switched to medium with 0.5% serum, then 18 h later stimulated with 300 nM thrombin for 5 min. Cells from each dish were lysed in 0.5 ml of lysis buffer containing 50 mM Tris, pH 7.5, 10 mM MgCl2, 0.5 M NaCl, 2% IGEPAL, and 5% sucrose. The active rhoA was precipitated with GST-rotekin beads (Cytoskeleton Inc., Denver, CO). Western blots with anti-rhoA antibody were done to assess the amount of active rhoA. Aliquots of total lysate were also analyzed for the amount of rho present.

**Cell Rounding Assay**—The day before transfection, PC-3 cells were grown on laminin-coated coverslips in 12-well plates until ~80% confluent. Cells were then transfected with 0.2 μg of EGFP cDNA. To disrupt rho signaling GFP was co-transfected with either a C3 exotoxin expression vector (0.5 μg) or with 2.0 μg of the indicated siRNA or inverted control along with 8 μl/well of LipofectAMINE 2000. At 45 h post-transfection, cultures were changed to serum-free medium and 6 h later treated with either buffer, thrombin (100 nM), or LPA (50 μM) for 30 min. Cells were then fixed with 4% paraformaldehyde for 10 min and GFP images obtained using an Olympus fluorescence microscope with a 20× objective. Fluorescent cells were counted (100–300 per coverslip) and the percentage of rounded cells determined. Cell rounding at 30 min was dose-dependent (EC50 80 nM for thrombin and 50 μM for LPA) and reversible upon removal of thrombin for 45 min (data not shown).

**Data Analysis and Statistics**—Quantitative data are means ± S.E. of three or more independent experiments and each luciferase experiment was conducted in triplicate. Two-way analysis of variance with post-tests (Graph Pad Prism 4.0, San Diego, CA) was used to evaluate statistical significance.

**RESULTS AND DISCUSSION**

All three RGS-rhoGEFs are expressed in HEK293 cells as detected by both Western blot (Fig. 1A) and reverse transcription-PCR analysis (15). HEK293 cells also exhibit a substantial thrombin-stimulated rho activation (18 and Fig. 2). To assess the role of RGS-rhoGEFs in receptor signaling, we designed a series of synthetic oligo-siRNAs targeted against the RGS domain of the three human rhoGEFs. Two oligonucleotides each against LARG and PDZrhoGEF and 5 against p115rhoGEF were analyzed (15), and the most active and specific three siRNAs were used in this study. They suppress the expression of their cognate rhoGEF but do not affect either Gβ used as a loading control (Fig. 1A) or the other rhoGEFs (15). Their specificity is also demonstrated in a functional effect on rho-mediated gene expression. We used a modified SRE.L luciferase reporter construct (7), which responds to serum response factor-megakaryocytic acute leukemia transcription complexes but not serum response factor-ternary complex factor complexes (19) and provides a rho-dependent transcription response. Luciferase expression is strongly enhanced by transfected wild-type Gα13 and the constitutively active Gα13QL mutant (19- and 54-fold over reporter alone, respectively; data not shown), and by transfection of all three of the RGS-rhoGEFs (Fig. 1B). In each case, firefly luciferase expression is reduced to base line by co-transfecting C3 exotoxin (data not shown) consistent with the literature showing that Gα13 and rhoGEF-stimulated gene expression is rho-dependent (9, 18).
The rhoGEF-stimulated luciferase signal is also completely eliminated by 0.5 μM latrunculin B (not shown). Co-transfection of the siRNAs targeting LARG, p115rhoGEF, or PDZrhoGEF strongly and specifically reduced the luciferase response to the targeted RGS-rhoGEF but had minimal effects on luciferase expression stimulated by the other two RGS-rhoGEFs (Fig. 1B). As an additional control for specificity, an inverted control siRNA (−) for each of the active siRNAs (+) was included and had minimal effects. The incomplete inhibition of the luciferase response by the siRNAs may be due to: 1) a strongly amplified signaling cascade which is integrated over 48 h, 2) some maintained expression of RGS-rhoGEF in the presence of siRNA, or 3) incomplete overlap of transfection of the siRNA and the RGS-rhoGEF plasmid. The latter mechanisms seems unlikely given the nearly 90% transfection efficiency of these cells with a GFP reporter plasmid plus the virtually complete suppression of endogenous protein for LARG and p115rhoGEF. The data, however, indicate a substantial and specific suppression of RGS-rhoGEFs by these transfected siRNAs.

FIG. 2. LARG siRNA effect on thrombin receptor-stimulated rhoA activation. LARG siRNA or its mutant siRNA (LARGinv) were introduced (10 μg/dish) into HEK293T cells and thrombin-stimulated rho activation measured as described under “Experimental Procedures.” Cells were treated with (+) or without (−) thrombin (300 nM for 5 min). The active rho was precipitated with GST-rhotekin beads, and Western blots with anti-rhoA antibody were done to assess the amount of active rhoA. The top panel is a representative Western blot showing stimulation of active rhoA by thrombin in the control lanes (LARGinv), which was suppressed by LARG siRNA. The bottom panel shows quantitation of three independent rho pull-down experiments showing mean ± S.E. of scanned band densities. A statistical comparison of results with LARG, PDZ, and p115 RNAi is shown in Table I.

| Control (inv) | Active (si) |
|--------------|------------|
| LARG         | Mean 3.20  | S.E. 1.08 | n 3 | Mean 0.97 | S.E. 0.20 | n 3 |
| PDZ          | Mean 1.75  | S.E. 0.09 | n 4 | Mean 1.63 | S.E. 0.19 | n 5 |
| p115         | Mean 1.46  | S.E. 0.25 | n 4 | Mean 2.8  | S.E. 0.60 | n 6 |

*Significantly different from control by two-way analysis of variance (p < 0.05).

The rhoGEF-stimulated luciferase signal is also completely eliminated by 0.5 μM latrunculin B (not shown). Co-transfection of the siRNAs targeting LARG, p115rhoGEF, or PDZrhoGEF strongly and specifically reduced the luciferase response to the targeted RGS-rhoGEF but had minimal effects on luciferase expression stimulated by the other two RGS-rhoGEFs (Fig. 1B). As an additional control for specificity, an inverted control siRNA (−) for each of the active siRNAs (+) was included and had minimal effects. The incomplete inhibition of the luciferase response by the siRNAs may be due to: 1) a strongly amplified signaling cascade which is integrated over 48 h, 2) some maintained expression of RGS-rhoGEF in the presence of siRNA, or 3) incomplete overlap of transfection of the siRNA and the RGS-rhoGEF plasmid. The latter mechanisms seems unlikely given the nearly 90% transfection efficiency of these cells with a GFP reporter plasmid plus the virtually complete suppression of endogenous protein for LARG and p115rhoGEF. The data, however, indicate a substantial and specific suppression of RGS-rhoGEFs by these transfected siRNAs.

To assess the role of the RGS-rhoGEFs in receptor-mediated signaling, we used the thrombin-stimulated activation of rho as detected by precipitation of GTP-bound active rhoA with the effector domain fusion, GST-rhotekin.2 Thrombin stimulates rho activation in HEK293 cells (Fig. 2) probably via an endogenous PAR1 receptor (20). Transfection of HEK293 cells with the active LARG siRNA (si) shows an essentially complete

*Attempts to measure a thrombin-stimulated luciferase response in the HEK293 cells were unsuccessful. The prolonged activation needed to initiate a transcription response may not be possible given rapid desensitization of thrombin receptors.
block of thrombin-stimulated rho activation (Fig. 2). Table I quantitates the effects of the three rhoGEF siRNAs and their inverted controls. While this assay exhibits significant variability, only the LARG siRNA reduced the thrombin-stimulated rho activation significantly. To assess signaling by other receptors, we attempted similar measurements with LPA. While there was some stimulation of rhoA activation by LPA in HEK293 cells, it was substantially smaller than that induced by thrombin and not sufficient to permit analysis with the siRNAs. Thus we turned to a different cell line and a different rho response.

rho stimulates several types of cytoskeletal rearrangements. Stress fiber formation in NIH or Swiss 3T3 cells is a classic rho response (21). In other cell types such as the 1321N1 astrocytoma line, cell rounding is observed as a thrombin-stimulated G12/13-mediated rho response (10). We found that a similar cell rounding response occurs in the human prostate cancer cell line, PC-3. After thrombin stimulation, there was some appearance of stress fibers following phalloidin staining (data not shown), but no prominent effect was cell rounding (Fig. 3A).

The thrombin and LPA responses in PC-3 cells were then tested with the RGS-rhoGEP siRNAs which on Western blots show suppression of the appropriate rhoGEP (data not shown). As expected from the HEK293 data, the LARG siRNA nearly completely abolished the thrombin-stimulated PC-3 cell rounding response (Fig. 3B). This is mediated by the PAR1 type of thrombin receptor, since cell rounding stimulated by the PAR1 agonist peptide SPLLRRN was also inhibited by LARG siRNA (Fig. 3C). The negative control inverted LARG siRNA (--) did not affect thrombin-stimulated cell rounding. Also, the p115rhoGEP and PDZrhoGEP siRNAs did not inhibit the thrombin response indicating that LARG represents the primary downstream pathway from PAR1 to rho activation in PC-3 cells. Surprisingly, the LARG siRNA did not inhibit cell rounding induced by LPA but the PDZrhoGEP siRNA did (Fig. 3F). This shows that the LPA receptor uses a different RGS-rhoGEP to induce rho responses. It is known that PC-3 cells express LPA and LPA, but not LPA receptors (22), but we cannot presently say which LPA receptor is mediating this effect. The LPA data also provide additional controls; the LARG siRNA effect on thrombin responses is specific for thrombin and not other rho-activating stimuli, and the lack of effect of PDZrhoGEP siRNA on thrombin responses is not due to incomplete knockdown of the PDZrhoGEP protein as the siRNA was able to disrupt the LPA response.

The mechanism of specificity of PAR1 for LARG and LPA receptor for PDZrhoGEP is unclear. Recently, it has been suggested that thrombin and LPA receptors activate different members of the G12 family, G12a and G12b, respectively (23), and G12b is known to activate LARG (7). In addition to G protein selectivity, it is possible that there could be direct interactions between the RGS-rhoGEFs and the receptors. Both LARG and PDZrhoGEP have PDZ domains, which bind to plexin B1 and mediate semaphorin signaling (24–26). The carboxyl termini of LPA1 and LPA2 receptors (EDG2 and EDG4) have classical PDZ interaction motifs (S/T-F-X-L/V), so direct rhoGEP-receptor interactions may contribute to the specificity.

In summary, we provide the first direct demonstration that RGS-rhoGEFs mediate GPCR signaling to rho as well as showing receptor specificity in the use of RGS-rhoGEFs with PAR1 using LARG in both HEK293 and PC-3 cells and the LPA receptor using PDZrhoGEP in PC-3 prostate cancer cells. Since thrombin stimulates proliferation (27) and vascular endothelial growth factor secretion (28) of prostate cancer cells and prostate cancer metastasis to bone has increased levels of PAR1 (29), the ability to block receptor-stimulated rho signaling could represent an important approach to regulating cancer cell growth and metastasis.

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Thrombin and Lysophosphatidic Acid Receptors Utilize Distinct rhoGEFs in Prostate Cancer Cells
Qin Wang, Min Liu, Tohru Kozasa, Jeffrey D. Rothstein, Paul C. Sternweis and Richard R. Neubig

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