The small GTPase RhoA is involved in the regulation of various cellular functions like the remodeling of the actin cytoskeleton and the induction of transcripational activity. G-protein-coupled receptors (GPCRs), which are able to activate Gαq/G11 and G12G13 are major upstream regulators of RhoA activity, and Gαq/G11 have been shown to couple GPCRs to the activation of Rho by regulating the activity of a subfamily of RhoGEF proteins. However, the possible contribution of Gαq/G11 to the regulation of RhoA activity via GPCRs is controversial. We have used a genetic approach to study the role of heterotrimeric G-proteins in the activation of RhoA via endogenous GPCRs. In perutis toxin-treated Gα12/Gα13-deficient as well as in Gα12/Gα13-deficient mouse embryonic fibroblasts (MEFs), in which coupling of receptors is restricted to Gαq/G11 and G12G13, respectively, receptor activation results in Rho activation. Rho activation induced by receptor agonists via Gαq/G11 occurs with lower potency than Rho activation via G12G13. Activation of Rho via Gα12/Gα13 is not affected by the phospholipase-C blocker U73122 or the Ca2+-chelator BAPTA, but can be blocked by a dominant-negative mutant of the RhoGEF protein LARG. Our data clearly show that Gα12/Gα13 as well as Gαq/G11 alone can couple GPCRs to the rapid activation of RhoA. Gαq/G11-mediated RhoA activation occurs independently of phospholipase C-β and appears to involve LARG.

The small GTPase RhoA plays a central role in the organizational aspect of the actin cytoskeleton due to its ability to stimulate the formation of actomyosin-based structures and to regulate their contractility (1). In addition to its role in the regulation of the actin cytoskeleton, RhoA has also been involved in various other cellular processes like the regulation of microtubule dynamics or transcriptional activity (1, 2). Analogous to other regulatory guanine nucleotide-binding proteins Rho functions as a molecular switch by cycling between an inactive GDP-bound form and an active GTP-bound form. In the active state RhoA relays extracellular signals to a number of downstream effectors. These include protein kinases like Rho kinase or citron kinase, lipid kinases like phospholipase D, or phosphatidylinositol 4-phosphate 5-kinase as well as non-

kinase proteins like rhothekin, rhophilin, or diaphanus (3). RhoA is activated through various receptors including those coupled to heterotrimetric G-proteins (4, 5). Activation of RhoA through G-protein-coupled receptors (GPCRs)1 involved in a variety of physiological regulatory processes (6). One of the best described cellular paradigms for GPCR-mediated RhoA activation is the RhoA-dependent actin stress fiber formation in fibroblasts activated by various GPCR agonists like lysophosphatidic acid or thrombin. However, a GPCR/Rho-mediated regulation of actin-based structures has also been shown to occur in many other eukaryotic cells. For instance, in neuronal cells activation of Rho through lysophosphatidic acid or thrombin receptors leads to the formation of contractile actomyosin filaments thereby inducing neurite retraction and cell rounding (7, 8). In vascular smooth muscle cells, the Rho-mediated pathway has been shown to contribute to the vasocostructor-induced actomyosin-based cell contraction (9, 10), and the same pathway appears to be centrally involved in the platelet shape change response (11).

It is well established that G-proteins of the G12-family, G12 and G13, can couple GPCRs to the activation of RhoA. Constitutively active mutants of Gα12 and Gα13 have been shown to induce actin stress fiber formation as well as other RhoA-dependent cellular effects (Ref. 12; for review see Ref. 6). Recent studies in reconstituted or co-transfected systems have demonstrated that a group of RhoGEF proteins, consisting of p115 RhoGEF, PDZ-RhoGEF, and LARG, interact with Gα12 and Gα13 through their RGS domains, thereby stimulating RhoA activity (13–16). Receptors, which activate G12G13 also couple to Gαq and G11. It has been a controversial issue, whether Gαq/G11-mediated signaling contributes to the activation of RhoA via GPCRs. While various reports show Rho-dependent effects of constitutively active Gαq mutants (Refs. 8 and 18; for review see Ref. 6) other studies demonstrated that active mutants of Gαq are not able to induce Rho-mediated processes (12, 17). The recent development of methods for the precipitation of the activated form of RhoA from cell lysates allowed to directly determine the effects of different G-protein α-subunits on Rho activity. It could be confirmed that constitutively active mutants of Gαq/Gα13 can induce RhoA activation (19, 20). However, again, conflicting data exist with regard to the potential role of Gαq/G11 in GPCR-mediated RhoA activation. In NIH3T3 and HEK293T cells, expression of constitutively active Gαq-family members results in an increased level of active RhoA (21–23). In contrast, expression of mutant Gαq in COS-7 cells

1 The abbreviations used are: GPCR, G-protein-coupled receptors; GST, glutathione-S-transferase; RBD, Rho-binding domain; PTX, pertussis toxin; LPA, lysophosphatidic acid; S1P, sphingosine 1-phosphate; PLC, phospholipase C; RhoGEF, Rho guanine nucleotide exchange factor; SRE, serum response element; MEF, mouse embryonic fibroblast; RGS, regulator of G-protein signaling; GST, glutathione S-transferase.

* This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. 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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do not induce activation of RhoA (24).

To study the role of different G-proteins under more physiological conditions we used Gq/G11- and G12/G13-double deficient embryonic fibroblasts (MEFs) to determine their role in the activation of Rho via endogenous receptors. Our data clearly show that Gq/G11 can couple GPCRs to the rapid activation of RhoA. This process occurs in a phospholipase C-β-independent manner and appears to involve the RhoGEF protein LARG.

**MATERIALS AND METHODS**

Reagents—Thrombin (T3399), LPA (L7260), Bradykinin (B3259), and U73122 were from Sigma-Aldrich (Dreieich, Germany). Pertussis toxin, BAPTA/AM, and Fura-2/AM were purchased from Calbiochem (Schwalbach, Germany).

Plasmids—HA-ΔDH/PH-LARG lacking the DH and the PH domain was generated by EcoNI and EcoRI digestion of full-length LARG and in-frame re-ligation using MungBean-nuclease and T4-DNA polymerase. Deletion was confirmed by sequencing (Li-cor 4200, Li-cor, Inc.). The modifying enzymes were purchased from New England Biolabs (Schwalbach, Germany), the ligase was obtained from Takara (Kusatsu, Japan), and the restriction enzymes (EcoRI digestion of full-length LARG and RI digestion of full-length LARG) were obtained from New England Biolabs (Schwalbach, Germany).

Cell Lines and Transfection—MEF cell lines were generated as described (25) and maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. Cells were transiently transfected using Lipofectamine (Invitrogen) according to the manufacturer's protocol. Serum starvation and pertussis toxin treatment were done for 4 h.

Western Blot Analysis—Lysates of MEFs were analyzed by Western blotting after SDS-polyacrylamide gel electrophoresis and visualized by chemiluminescence detection using sheep anti-mouse (Amersham Biosciences) or goat anti-rabbit antibodies (Cell Signaling, Frankfurt, Germany) coupled to horseradish peroxidase and were visualized using ECL reagent (Amersham Biosciences). Monoclonal antibodies against RhoA (26C4) or c-Myc (9E10) and rabbit polyclonal antibodies against Gα12 (A-20) and Gα13 (C-19) were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, USA). Anti-Gαq, rabbit polyclonal antibody was described previously (26). Monoclonal HA antibody was obtained from Covance Research Products. Antibodies raised in rabbit against p115-RhoGEF, PDZ-RhoGEF, and LARG were described previously (26).

RT-PCR—Cytoplasmic RNA from MEFs was isolated using the Qiagen RNaseasy Midi kit according to the manufacturer's protocol. Cytoplasmic RNA was reversely transcribed using oligo-dT primers and the SuperScript™ II System from Invitrogen. PCR was performed with specific primers hybridizing to specific regions of cDNAs of various G-protein-coupled receptors, which if possible were encoded by different exons using Taq polymerase (Invitrogen). The following primers were used: 5'-TCCACCGGCCCATTGACTATTTCA-3' and 5'-CTGCCGGCTGTTTCTCTTGCTAT-3'.

**Measurement of Intracellular [Ca2+]**

For fluorescence-based imaging of [Ca2+] cells were cultured on glass coverslips. MEFs were loaded for 30 min with 2 μM Fura-2/AM (Calbiochem) in HEPES-buffered saline (pH 7.4) containing 135 mM NaCl, 6 mM KCl, 1 mM MgCl2, 1 mM
CaCl₂, 5.5 mM glucose, 10 mM HEPES, and 0.2% (w/v) bovine serum albumin. Coverslips were analyzed on a monocromator-equipped (Polychrome IV, TILL-Photonics, Germany) inverted microscope (Axiovert 135, Carl Zeiss, Germany). The fluorescence was recorded with a 12-bit CCD camera (IMAGO, TILL-Photonics) and TILLvision v4.0 software. Fura-2 fluorescence was excited at 340, 358, and 380 nm and filtered through a Fura-2 corresponding long-pass filter, and the 340/380 fluorescence ratio determined. After subtraction of background signals, the 340/380 fluorescence ratio was determined as described (27).

Immunofluorescence—Cells were fixed in 4% paraformaldehyde and stained as described previously (28). Antibody dilutions were monoclonal anti-HA (Covance Research Products) 1:290, BODIPY FL phallacidin (B-607, Molecular Probes; Eugene) 1:150, TRITC-conjugated clonal antibody (26C4) and anti-Myc antibody (9E10), respectively (Santa Cruz Biotechnology).

Rho Pull-down Assay—Activation of Rho was determined by a modified method described by Ren and Schwartz (29). MEF cells were seeded on 10-cm dishes and were either transfected with Myc-tagged RhoA and indicated plasmids or left untransfected for assessment of endogenous GTP-Rho. After serum starvation and pertussis toxin treatment for 24 h, cells were stimulated via endogenous receptors by thrombin (1 unit/ml), LPA (5 mM) and bradykinin (100 nM), and lysates were analyzed by Western blotting with an antibody against Gᵣ. Complete ADP-ribosylation after PTX treatment is indicated by the decreased mobility of Gᵣ-type G-proteins in urea-containing SDS-polyacrylamide gels. Data shown are representative of at least three independently performed experiments.

**RESULTS**

Mouse embryonic fibroblast cell lines were generated from wild-type embryos as well as from embryos double deficient for Gᵣᵩ₁₁ and Gᵣ₁₂/Gᵣ₁₃ (30, 31). Western blot analysis of lysates from these cell lines confirmed the absence of Gᵣᵩ₁₁ and Gᵣ₁₂/Gᵣ₁₃ in respective cells (Fig. 1A). We then determined, whether the different MEF cell lines express receptors for various ligands, which have been shown to induce the activation of Gᵣᵩ₁₁ as well as Gᵣ₁₂/Gᵣ₁₃-like the lysophospholipids lysosphosphatidic acid (LPA) and sphingosine 1-phosphate (S1P), bradykinin, or proteases like thrombin (Fig. 1B). By using RT-PCR, we found that wild type as well as Gᵣᵩ₁₁- and Gᵣ₁₂/Gᵣ₁₃-deficient MEFs express receptors for sphingosine 1-phosphate (S1P₁, S1P₂, and S1P₅), LPA (LPA₁ and LPA₂), bradykinin (B₂) as well as for thrombin (PAR-1). No expression was found for S1P₄, S1P₅, or LPA₃ receptors as well as PAR-2, -3 or -4 receptors. S1P₂ and S1P₅ receptors have been shown to couple to G₁₂/G₁₃, Gᵣᵩ₁₁, as well as to Gᵣ₁₁-type G-proteins (32), and there is good evidence that LPA₁ and LPA₂...
receptors have a very similar G-protein coupling pattern (33). Similarly, the thrombin receptor PAR-1 has also been shown to couple to all three G-protein families (11, 34–36). Notably, the pattern of expressed receptors did not differ between all three cell lines indicating that they are well suited for a comparative analysis of receptor-mediated effects.

In further experiments we used LPA, bradykinin and thrombin to stimulate cells through their endogenous receptors. To study the role of Gq/11 and G12/13 in GPCR-induced Rho activation, we restricted coupling of receptors to these two G-protein families by pretreating cells with pertussis toxin (PTX), which uncouples receptors from Gi-type G-proteins. Fig. 2C shows that PTX treatment completely ADP-ribosylated α-subunits of Gi, in G12/13-deficient cells under the used experimental conditions. As expected, none of the stimuli was able to induce Ca2+ transients in G12/13-deficient cells whereas Ca2+ transients were induced in wild-type and G12/13-deficient cells (Fig. 2A and data not shown). In pertussis toxin-treated G12/13-deficient cells, in which coupling of receptors is restricted to G12/13, thrombin, and LPA resulted in an activation of RhoA (Fig. 2B). This confirms that G12/13 are able to mediate receptor-dependent RhoA activation independently of any signaling via Gq/11. Bradykinin, which induced Rho activation in PTX-treated wild-type cells had no effect on Rho activity in G12/13-deficient cells, suggesting that the bradykinin B2 receptor is not coupled to G12/13, but may induce Rho activation through Gq/11 (Fig. 2B). To test the potential ability of Gq/11 to mediate receptor-dependent Rho activation more directly, we tested the effect of thrombin, LPA, and bradykinin on RhoA activation in PTX-pretreated G12/13-deficient cells, in which coupling of receptors is restricted to G12/13. All three receptor agonists were still able to activate RhoA through Gq/11 (Fig. 2B).

Next we assessed whether Gq/11-mediated RhoA activation requires a functional phospholipase C-β or increases in intracellular free [Ca2+]. Receptor-mediated Rho activation in PTX-treated G12/13-deficient cells was not inhibited by the phospholipase C-β inhibitor U73122 or the Ca2+-chelator BAPTA, although both agents completely blocked receptor-mediated induction of Ca2+ transients in the same cells (Fig. 3). These data indicate that GPCRs can mediate RhoA activation via Gq/11 in a phospholipase C-β-independent manner.
To further characterize \( G_{12}/G_{13} \) and \( G_{q}/G_{11} \)-mediated RhoA activation through GPCRs, we determined concentration-response relationships for thrombin-induced RhoA activation in PTX-treated wild-type, \( G_{q}/G_{11} \)-, and \( G_{12}/G_{13} \)-deficient cells (Fig. 4A and B). Thrombin-induced RhoA activation in PTX-treated wild-type cells and in \( G_{q}/G_{11} \)-deficient cells with half-maximal and maximal concentrations of \( 10^{-4} \)–\( 10^{-3} \) and \( 10^{-2} \) units/ml, respectively. However, when G-protein coupling was restricted to \( G_{12}/G_{11} \) in PTX-treated \( G_{12}/G_{13} \)-deficient cells, thrombin was considerably less potent, and maximal RhoA activation was observed only at thrombin concentrations of 1 unit/ml. While both \( G_{12}/G_{13} \) and \( G_{q}/G_{11} \) can mediate RhoA activation, receptor-dependent activation through \( G_{q}/G_{11} \) requires agonist concentrations about two orders of magnitude higher than activation through \( G_{12}/G_{13} \).

The fact that RhoA activation via \( G_{q}/G_{11} \) occurred independently of phospholipase C-\( \beta \) prompted us to consider the involvement of RGS domain-containing RhoGEF proteins, which have been suggested to directly link \( G_{q}/G_{11} \) to Rho activation. Of the three members of this subgroup of RhoGEF proteins, p115RhoGEF, PDZ-RhoGEF, and LARG, we found only LARG to be expressed in MEFs (Fig. 5A). This is consistent with the much wider expression pattern of LARG compared with p115RhoGEF and PDZ-RhoGEF, which are mainly found in hematopoietic and neuronal cells, respectively (26, 37, 38). To test the potential role of LARG in \( G_{q}/G_{11} \)-mediated Rho activation, we constructed a mutant of LARG lacking the DH and PH domains required for its RhoGEF activity (Fig. 5B). Expression of \( \Delta DH/PH \)-LARG in PTX-treated \( G_{q}/G_{13} \)-deficient cells efficiently blocked rapid actin stress fiber formation induced by LPA (Fig. 5C). Furthermore, expression of \( \Delta DH/PH \)-LARG also dramatically reduced the cellular F-actin content in the presence of 10% fetal calf serum (Fig. 5C). Similarly, \( \Delta DH/PH \)-LARG was found to block activation of Myc-tagged RhoA in response to thrombin and LPA in PTX-treated \( G_{12}/G_{13} \)-deficient cells (Fig. 5D). These data suggest that LARG is critically involved in the phospholipase C-\( \beta \)-independent RhoA activation via \( G_{q}/G_{11} \).
**Gq/G11 Mediate RhoA Activation**

Many GPCRs have been shown to be able to mediate the activation of the small GTPase RhoA (6, 15). Activation of RhoA via GPCRs is involved in a variety of functions like regulation of cell movement, cell shape, and cell growth. Receptors that stimulate RhoA activity couple to G12/G13, Gq/G11, and G1-type G-proteins. The fact that Rho activation through GPCRs is not affected by PTX and since receptors coupling only to G1-type G-proteins are unable to stimulate Rho activity suggests that Gq is unlikely to be directly involved in RhoA activation via GPCRs (5, 6). It has been difficult to evaluate the relative roles of G12/G13 and Gq/G11 receptors. Since there are currently no specific inhibitors of these G-protein subtypes available. Multiple evidence has accumulated that G12 and G13 can mediate the activation of RhoA, and the recently described RhoGEF proteins, p115-RhoGEF, LARG, and PDZ-RhoGEF have been shown to link G12/G13 to RhoA activation (13–16). It is not clear whether Gq/G11 are indeed directly involved in the rapid receptor-mediated RhoA activation by extracellular signals. Studies in platelets lacking Goq/G11 demonstrated that receptor-mediated RhoA activation does not necessarily depend on activation of Gq/G11 (39). Sagi et al. (24) reported that a constitutively active mutant of Goq was unable to induce RhoA activation. In contrast, several recent reports clearly show that transient transfection of constitutively active mutants of Goq in NIH3T3 cells or in HEK293T cells results in elevated levels of active RhoA (21–23). Since these studies rely on the effects of transfected constitutively active mutants of Goq, family members, they do not necessarily prove a direct involvement of Gq proteins in RhoA activation exerted by extracellular signals via receptors. We therefore chose a genetic approach to study the activation of RhoA through endogenous receptors in PTX-treated MEFs lacking either Goq/G11 or Gq12/G13. In these cells, receptor coupling is restricted to G12/G13 and Gq/G11, respectively. Our data confirm that RhoA activation is potently induced through Gq12/G13. More importantly however, they provide genetic evidence that Gq/G11 proteins can also mediate the rapid RhoA activation via endogenously expressed GPCRs.

Interestingly, we observed a clear difference in the potencies by which thrombin induced RhoA activation via G12/G13 and Gq/G11. Rho activation through Gq/G11 required agonist concentrations about two orders of magnitude higher than Rho activation via G12/G13. The observed potency difference for ligand-induced Rho activation could be due to different efficiencies by which the activated receptor couples to different G-protein subfamilies. For example, the thromboxane A2 receptor, which coupled to Gq/G11 and G12/G13 has been shown to preferentially activate G12/G13 in platelets (35). However, it is not known whether this is a general feature of Gq/G11- and Gq/G12-mediated receptors. Alternatively it is conceivable that RhoGEF proteins are less sensitive to regulation via Goq/G11 than through Gq12/G13.

While it is well established that G12/G13-mediated RhoA activation involves RhoGEF proteins like PDZ-RhoGEF, LARG, and p115-RhoGEF, the mechanism of Gq/G11-mediated Rho activation is less clear. We could not observe any effects of Ca2+-chelators or of the phospholipase C-β inhibitor U73122 on Gq/G11-mediated Rho activation (see Fig. 3A), indicating that Gq/G11 mediates Rho activation in a manner independent of β-isomers of PLC. This is consistent with data showing that activation of protein kinase C (PKC) or elevation of intracellular Ca2+ is not able to promote RhoA activation and that inhibition of PKC does not interfere with Rho activation by an active mutant of Goq (23). If PLC is not involved in Gq/G11-mediated RhoA activation, it is tempting to speculate that Gq/G11 may activate RhoA by a mechanism analogous to G12/G13. Interestingly, recent data suggest that the RGS domain of LARG but not of p115 RhoGEF can interact with Goq when complexed with AIc4 to mimic the transition state of GTP hydrolysis (21). In contrast, the constitutively active mutant of Goq (Q229L) did not show a considerable interaction with the RGS domains or the full-length versions of LARG, PDZ-RhoGEF, or p115RhoGEF (23–40). However, mutants of PDZ-RhoGEF and p115RhoGEF which lack the N-terminal region including the RGS domain were able to interact with Goq (Q229L) (23). In functional experiments, it was shown that expression of full-length LARG but not of a LARG mutant, which lacks the PDZ and RGS domain, enhances RhoA activation by constitutively active Goq (21), suggesting that an interaction of the RGS domain with Goq is involved in RhoA activation. However, expression of the RGS domains of LARG and PDZ-RhoGEF did not interfere with Goq(Q229L)-induced serum response element (SRE) activation, an effect, which is mediated by Rho (23, 41). Thus, while there is some evidence that active Goq can interact with LARG and other RGS domain containing RhoGEF proteins, the exact mode of this interaction still remains elusive. In our study, we used a LARG mutant that lacks the RhoGEF domain (∆DH/PH-LARG) to study the potential involvement of LARG in receptor-mediated, Gq/G11-dependent RhoA activation. Expression of ∆DH/PH-LARG blocked receptor-mediated RhoA activation as well as actin stress fiber formation in PTX treated G12/G13-deficient cells, suggesting that LARG is critically involved in Gq/G11-mediated RhoA activation. Whether the mechanism of LARG-mediated Rho activation by Gq/G11 is identical to that by G12/G13 remains to be elucidated.

In summary, based on a genetic model our data clearly demonstrate that both, G12/G13 and Gq/G11, can mediate the activation of RhoA via G-protein-coupled receptors. The Gq/G11-mediated Rho activation occurs independently of β-isomers of phospholipase C and involves the RhoGEF protein LARG.

Acknowledgment—We thank M.A. Caligiuri for providing the LARG cDNA.

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Gq/G11 Mediate RhoA Activation
Receptor-dependent RhoA Activation in G\textsubscript{12/13}-deficient Cells: GENETIC EVIDENCE FOR AN INVOLVEMENT OF Gq/G11
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J. Biol. Chem. 2003, 278:28743-28749.
doi: 10.1074/jbc.M304570200 originally published online May 27, 2003

Access the most updated version of this article at doi: 10.1074/jbc.M304570200

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