Polycystin-1 Activation of c-Jun N-terminal Kinase and AP-1 Is Mediated by Heterotrimeric G Proteins*

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Autosomal dominant polycystic kidney disease (ADPKD) is a major inherited disorder that is characterized by the growth of large, fluid-filled cysts from the tubules and collecting ducts of affected kidneys, and by a number of extrarenal manifestations including liver and pancreatic cysts, heart valve defects, and cerebral, and aortic aneurysms (1–4). Approximately 85% of all cases of ADPKD are caused by mutations in the PKD1 gene, with most (if not all) of the remaining cases being caused by defects in the PKD2 gene. The PKD1 gene product, polycystin-1, appears to be a large membrane-associated glycoprotein (5–9) that is thought to play a role in cell-cell and/or cell-matrix interactions (10). Polycystin-1 is composed of a large N-terminal extracellular domain of about 3,000 amino acids, a multimeric domain spanning about 1,000 amino acids containing 11 transmembrane segments, and a C-terminal cytosolic domain of about 200–225 amino acids. Polycystin-2, the protein product of the PKD2 gene, appears to be a Ca2+-permeable, nonselective cation channel whose activity may be regulated by a direct interaction with the C-terminal cytosolic domain of polycystin-1 (11–14).

Sequence analysis of polycystin-1 has suggested that the C-terminal cytosolic domain of the protein is involved in protein-protein interactions and signal transduction (15). Biochemical analyses support this hypothesis, as transient transfection of the C-tail of polycystin-1 modulates Wnt signaling via stabilization of b-catenin (16) and activates the transcription factor AP-1 via c-Jun N-terminal kinase (JNK) and protein kinase C (17). Polycystin signaling has also been implicated in the regulation of a cell growth phenotype, as ADPKD renal epithelial cells are susceptible to abnormal proliferation in response to AMP (18–20). Furthermore, stable transfection of full-length polycystin-1 in Madin-Darby canine kidney cells suppresses spontaneous cyst formation and inhibits cellular growth rates and apoptosis (21). Despite these clues, however, the primary cystic events that initiate these signaling cascades have remained unclear.

A number of observations have suggested that heterotrimeric G proteins play a role in polycystin-1-mediated signaling. Polycystin-1 has been shown to bind and stabilize RGS7 (regulator of G protein signaling 7) (22), a member of the newly identified family of RGS proteins that are capable of regulating G protein-dependent signaling cascades by accelerating the hydrolysis of GTP bound to Go subunits of certain heterotrimeric G proteins (23). Furthermore, RGS7 has been identified as a candidate for a genetic modifier of bpk, a murine model of PKD that is similar to human autosomal recessive PKD (24). We have also shown that polycystin-1 binds and activates heterotrimeric G/i proteins in vitro (25). However, a direct link between polycystin-1-mediated signaling pathways and heterotrimeric G proteins has not been established.

To determine whether heterotrimeric G proteins mediate polycystin-1 signaling, we tested the effects of expression of the Gbq sequestering constructs, dominant-negative Gq12 and b-adrenergic receptor kinase C-terminal tail (bARK-ct), on polycystin-mediated JNK activation. The evidence demonstrated that polycystin-1 activates JNK signaling via Gbq subunits of heterotrimeric G proteins. We also showed that a dominant-negative p115RhoGEF construct inhibited AP-1 activation and that wild-type Gq12 and Gq13 subunits effectively...
augmented polycystin-1 signaling to AP-1. Gαi and Gαo family subunits were also found to be capable of stimulating polycystin-1 signaling to AP-1 but less effectively than Gα12 family subunits. These results, taken together with our previous in vitro G protein binding and activation studies (25), indicate that polycystin-1 can couple with and signal via heterotrimeric G proteins and thus is an atypical heterotrimeric G protein-coupled receptor.

EXPERIMENTAL PROCEDURES

DNA Constructs—The sIg-PKD-MN6 (MN6) construct (obtained from Dr. G. Wals) (17) contains the C-terminal cytosolic tail of human polycystin-1 (amino acids 4077–4241) fused to the membrane targeting cassette, slg7 (Fig. 1). The slg7 cassette consists of the CD5 signal peptide, the CH2-CH3 domains of human IgG, and the CD7 transmembrane domain. MN6 terminates in the coiled-coil region of polycystin-1. The slg-PKD222 construct (Fig. 1) was made from a mouse polycystin-1 cDNA (obtained from Dr. G. Germino), which was subcloned downstream of slg7 in pCDNA1/Amp (Invitrogen) such that it encodes the C-terminal 222 amino acids of polycystin-1 (25). For controls, slg7 alone was inserted in pcDM12 (a derivative of pCDM8; Invitrogen) (slg0-12; control for slg-PKD-MN6) or pCDNA1/ Amp (slg0-1; control for slg-PKD222). The slg-PKD1284 polycystin-1 fusion construct (Fig. 1) was made from the 3′ portion of a mouse polycystin-1 cDNA clone (26) encoding amino acid residues 3,010–4,293, which was subcloned downstream of the CD5 signal sequence and the CH2-CH3 IgG domains in pCDNA1/Amp (Invitrogen). As a control, a stop codon was introduced in place of amino acid 3092 to create the construct slg-stop. The HA-JNK1i1 construct was obtained from Dr. L. E. Hasleby, bARK-ct and pRK5 were obtained from Dr. R. J. LeKowitz; dominant-negative (DN) and wild-type (WT) Gαo were obtained from Dr. T. Okamoto; and a vector encoding a GST-Jun-(1–32) fragment was obtained from Promega.

RESULTS

Dominant-negative bARK-ct and Gαi2 Constructs Inhibit JNK Activity Mediated by the C-terminal Cytosolic Tail of Human and Mouse Polycystin-1—Transfection of a human C-terminal cytosolic polycystin-1 construct into 293T cells was shown to activate c-Jun N-terminal kinase (JNK). Because JNK is known to be activated by Gβγ subunits (30, 31), 293T cells were cotransfected with cDNAs encoding a C-terminal polycystin-1 fusion protein, HA-JNK1i1, and a Gβγ-sequestering construct, the β-adrenergic receptor kinase C-terminal tail (bARK-ct) (32). Following transfection with the human C-tail MN6 construct (see Fig. 1), cells were lysed; HA-JNK1i1 was immunoprecipitated with an anti-HA antibody, and HA-JNK activity was determined by an immune complex kinase assay. JNK activity in MN6-transfected cells was increased >7-fold over that of control cells transfected with slg0 (Fig. 2A). Cotransfection of bARK-ct reduced JNK activity ~30% (Fig. 2A), suggesting that this JNK activation is mediated by Gβγ subunits.

Because overexpression of Gα subunits can also sequester Gβγ subunits, 293T cells were cotransfected with cDNAs encoding MN6, HA-JNK1i1, and a dominant-negative DN Gαi2 construct (see Figs. 1 and 2C). Cotransfection of Gαi2 reduced JNK activity in a dose-dependent fashion by an average of ~65% (Fig. 2B). A similar experiment was carried out using a wild-type (WT) Gαi2 construct. As seen in Fig. 2C, cotransfection of the WT construct inhibited JNK activation to nearly the same degree as the DN construct (~60% inhibition). The observation that both DN and WT Gαi2 subunits reduced polycystin-mediated JNK activity suggests that they inhibit signaling by sequestering Gβγ subunits.

To investigate the effects of these inhibitors on endogenous JNK activity, 293T cells were cotransfected with a murine polycystin-1 C-tail construct, slg-PKD222 (see Fig. 1), one of the inhibitor constructs, a c-Jun activation domain/GAL4 DNA binding domain fusion protein, and a GAL4 promoter-reporter construct (Fig. 3). Under these conditions, all three constructs completely inhibited endogenous JNK activation, supporting the idea that Gβγ subunits mediate polycystin-1-induced JNK

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activation from the C-tail constructs. The WT and DN inhibitors utilized in these studies were ineffective in inhibiting either endogenous JNK or HA-JNK1β activated by constitutively active MEKK, a kinase that acts upstream of JNK (34), demonstrating the specificity of inhibition by βARK-ct and the DN and WT Goi2 constructs (data not shown).

**JNK Signaling via the Complete Multimembrane Spanning Region of Polycystin-1**—The results shown in Figs. 2 and 3 suggest that the C-terminal tail of polycystin-1 signals in a constitutive fashion, because the C-tail constructs do not contain extracellular polycystin-1 sequences. Many GPCRs utilize intracellular loops to initiate signaling, we wanted to determine whether a longer polycystin-1 construct containing all of the putative intra- and extracellular loops would behave in a manner similar to that of the human slg-PKD-MN6 and the murine slg-PKD222 constructs. Thus, a cDNA encoding the C-terminal 1,284 amino acids of murine polycystin-1 was fused to the extracellular portion of the slg7 membrane targeting cassette (lacking the CD7 transmembrane domain). This construct, slg-PKD1284 (see Fig. 1), encodes the complete, predicted multimembrane spanning and intra- and extracellular loops of polycystin-1 (8) and might be expected to function similarly to native polycystin-1.

Consistent with observations using the shorter C-terminal tail constructs, slg-PKD1284 also activated HA-JNK1β, βARK-ct (Fig. 4A) and DN Goi2 (data not shown) were both effective at blocking JNK activity, reducing this activation ~65 and ~35%, respectively. However, in contrast to our observations with the shorter polycystin-1 constructs, WT Goi2 caused a stimulation in JNK activity, which was more effective at lower amounts of the transfected WT Goi2 (Fig. 4B). The stimulation of JNK at low concentrations of WT Goi2 suggested that polycystin-1 may be capable of utilizing Goi2 for signaling and that the reduced JNK activation at higher concentrations of WT Goi2 may be due to sequestration of Gβγ by overwhelming amounts of the Ga subunits. Endogenous JNK was also completely inhibited by βARK-ct and DN Goi2 but showed some stimulation with WT Goi2 when activated by the slg-PKD1284 polycystin-1 construct (data not shown). Despite this stimulation of JNK activity by exogenous WT Goi2, we could only partially block polycystin-induced JNK activation with pertussis toxin. In four experiments in which inhibition was seen, HA-JNK1β activation by the mouse and human C-tail constructs was inhibited from 9 to 43% (mean = 25%). These results suggest that polycystin-induced JNK signaling is only partially mediated by Gt and may therefore involve other G protein families.

**AP-1 Signaling Is Mediated by the Go Subunits of Heterotrimeric G Proteins**—AP-1 can be activated by a number of signaling pathways, including the JNK pathway (35–37). Previous work (17) had shown that the human polycystin-1 C-tail can activate AP-1 in a JNK- and PKC-dependent fashion. We have seen that the slg-PKD1284 construct (data not shown), as well as the slg-PKD222, can activate AP-1 when assayed using a 7× AP-1 promoter. To identify the G protein families that can be activated by polycystin-1, wild-type Gt, Gαq, and G12 family α subunits were cotransfected into 293T cells with the slg-PKD222 construct, and AP-1 was assayed. At 100 ng of transfected Go construct, Goi2, and Goi3, were found to be quite effective at stimulating polycystin-1-induced AP-1 activity (Fig. 5A). Goi1, Goi2, Goi3, and Goi4 were much less effective com-
transfected with a total of 7 μg DNA, which included the indicated amounts of plasmid DNA with pRK5, or with a dominant-negative inhibitor of G12 family subunits, DN p115RhoGEF (DN p115). The DN p115 construct lacks the RhoGEF domain of p115RhoGEF, but contains the RGS domain, and therefore can bind to and inhibit Gα12 and Gα13 subunits (27, 38, 39). Fig. 6 shows two representative experiments (left and right) in which AP-1 activity in polycystin-transfected cells was inhibited −24 and 38% by the DN p115 construct, confirming that polycystin-induced AP-1 activity is mediated in part by endogenous Gα12 family heterotrimeric G proteins.

**DISCUSSION**

This study has demonstrated that polycystin-1 activates JNK and AP-1 signaling via Gα and Gβγ subunits of heterotrimeric G proteins and that polycystin-1 can couple with Gαi, Gαq, and Gα12 family proteins. Polycystin-1 contains sequence elements found in a number of GPCRs, including a latrophilin/CL-1-like GPCR proteolytic site (40). This GPCR proteolytic site domain has been identified in CIRL-l, a member of a large orphan receptor family that contains structural features typical of cell adhesion proteins and GPCRs (41). We showed previously that polycystin-1 also contains a polybasic domain in its C-terminal tail that can activate Gαq proteins *in vitro* (25). This domain lies in the most highly conserved region of polycystin-1 and is part of a sequence capable of forming stable binding interactions with heterotrimeric Gα/Gα proteins *in vitro* (25). Polycystin-1 has an unusual structure for a GPCR, as it is thought to have 11 transmembrane domains rather than 7 and thus would have to stimulating AP-1 (Fig. 5B and data not shown). To determine the contribution of endogenous Gα12 family subunits to polycystin-induced activation of AP-1, we tested the effect of the dominant-negative inhibitor of Gα12 family subunits, DN p115RhoGEF (DN p115). The DN p115 construct lacks the RhoGEF domain of p115RhoGEF, but contains the RGS domain, and therefore can bind to and inhibit Gα12 and Gα13 subunits (27, 38, 39). Fig. 6 shows two representative experiments (left and right) in which AP-1 activity in polycystin-transfected cells was inhibited −24 and 38% by the DN p115 construct, confirming that polycystin-induced AP-1 activity is mediated in part by endogenous Gα12 family heterotrimeric G proteins.

**FIG. 2.** Inhibition of human polycystin-1 C-tail-mediated HA-JNK1β activation by dominant-negative interfering constructs. 293T cells were cotransfected with sIg-PKD-MN6 or sIg-0, HA-JNK1β, and increasing amounts (shown in μg transfected DNA) of βARK-ct (A), DN Gα12 (B), or WT Gα12 (C). Cells were plated at 4 × 10⁵ cells per T25 flask, grown for 2 days, and transfected for 16 h. Each flask was transfected with a total of 7 μg of DNA, which included 2 μg of the inhibitor constructs or pKR5, 2 μg of sIg-PKD222 or sIg-0, 1 μg of pFR-Luc, 50 ng of pFA2-cJun, 10 ng of pRL-null, and pBS as the filler. To determine the level of activation of endogenous JNKs, cells were cotransfected with the c-Jun activation domain/GAL4 DNA binding domain construct (pFA2-cJun) and the luciferase reporter gene under the control of a GAL4 promoter (pFR-Luc). Following transfection, cells were lysed and JNK activation was determined by assaying firefly luciferase activity, and the values were normalized to *Renilla* luciferase activity. Data are expressed as relative luciferase units (RLUs). Independent experiments were carried out in triplicate (n = 3) or bars represent S.D. In all cases, the inhibitors significantly decreased JNK activation (p < 0.001), as determined by one-way ANOVA. The Western blot demonstrates expression of the polycystin constructs from one of the experiments.
be classified as an atypical GPCR.

GPCRs can signal through a number of pathways that lead to the activation of JNK and AP-1 (42). Pathways that activate Rac and/or Cdc42 and JNK via heterotrimeric G proteins have been described, including those activated by Go12 and Go13 subunits (43, 44), βγ subunits (30, 31), Go9 subunits (45), and possibly Gαq (46). In addition, AP-1 can be activated by JNK-independent pathways involving Gq and G12/G13 activation of Rho, the p38 MAPKs, and BMK1/ERK5 (47, 48). Work by others (17) has shown that the polycystin-1 C-terminal cytosolic domain can activate JNK via the small G proteins Rac-1 and Cdc42. Here we demonstrate the first evidence that polycystin-1 mediated signaling to JNK and AP-1 is regulated by heterotrimeric G protein subunits, possibly through a number of pathways.

To test the hypothesis that polycystin-1 modulates JNK and AP-1 activity via heterotrimeric G proteins, we assessed the ability of various polycystin-1 C-terminal constructs to activate JNK and AP-1 in the presence of specific inhibitors of G protein signaling. JNK activation mediated by C-terminal tail polycystin-1 constructs could be inhibited in some experiments up to 100% by dominant-negative inhibitors. Because transfection of a WT Go12 subunit also inhibited JNK activation, it was thought that overexpression of WT and DN Go subunits might be inhibiting JNK activation by competing for Gβγ subunits. Similar observations have been made in the yeast Saccharomyces cerevisiae, where overexpression of the Go subunit Gpa1 inhibits Gβγ signaling (49), and in COS-7 cells, where transient transfection of Go12 subunits interferes with Go12,Gqα11- and Go13,Gqα11-mediated signaling via competition for Gβγ complexes (50). Consistent with this idea, cotransfection of βARK-ct, a specific βγ scavenger, inhibited exogenously expressed HA-JNK1β by about 30% (Fig. 2) and completely inhibited endogenous JNK (Fig. 3).

The polycystin-1 assays made use of C-tail constructs that apparently function in a constitutively active fashion, because they lack extracellular polycystin-1 sequences. Constitutive activity of GPCRs has been observed previously (51). We also tested a larger fusion protein construct encoding amino acids 3,010–4,293 of murine polycystin-1. This construct, sIg-

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PKD1284, only lacks the N-terminal extracellular domain of polycystin-1 but contains all of the putative transmembrane domain segments (8) and all of the extracellular and intracellular loops, as well as the C-tail. Thus, the product encoded by this construct would be expected to adopt the native polycystin-1 structure over this region of the protein. As with the experiments involving the smaller C-tail constructs, slg-PKD1284 was also capable of stimulating JNK and AP-1. Furthermore, the slg-PKD1284-mediated JNK activation was effectively inhibited by βARK-ct and by DN Goα2. However, contrary to our observations utilizing the smaller C-tail constructs, the slg-PKD1284-mediated JNK activation could be stimulated somewhat by WT Goα2 at low concentrations (Fig. 4B). Despite this stimulation, we could only partially inhibit polycystin-1 JNK activation with pertussis toxin. Thus, to identify other G protein families that may be activated by polycystin-1, we transfected cells with three different G protein families in JNK/AP-1 signaling. Apparently, the C-tail alone is sufficient for coupling with and activating G protein signaling

Polycystin-1 has been shown to regulate Ca2+ flux through an interaction with polycystin-2 (12, 13). Polycystin-2 has similarity to the α1E-1 subunit of a voltage-activated calcium channel, a class of calcium channels whose activity is potentially regulated by Gβγ subunits (52, 53). Binding of Gβγ to the α1 subunit of these channels results in kinetic slowing and steady-state inhibition of the current. This inhibition may be due to competition (or in some cases cooperative interactions) between Gβγ and a channel β subunit that regulates membrane targeting and other biophysical properties of α1 channels.

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FIG. 6. Inhibition of mouse polycystin-1-induced AP-1 activity by DN p115. Endogenous AP-1 was assayed in 293T cells transfected as described under “Experimental Procedures,” with a total of 7 μg of DNA which included 3 μg of control or polycystin-1 construct, 1 μg of DN p115 or control plasmid, 1 μg of AP-1 reporter, 5 ng of RL-null, and pBS as the filler. Data for two independent experiments, each carried out in triplicate (n = 3), are expressed as direct firefly luciferase activity. AP-1 activity was inhibited by DN p115 ~24 and ~38%, representing 42 and 30% drops in fold increase, respectively. Error bars represent S.D. Significant differences between DN p115-inhibited and control samples are indicated by one asterisk (p < 0.05) or two asterisks (p < 0.01), as determined by one-way ANOVA. Western blots demonstrate expression of the polycystin-1 (Ig-PKD222) and control (Ig-0) constructs.

FIG. 7. Model of G protein-coupled polycystin-1 function. Our data demonstrate that polycystin-1-mediated JNK and AP-1 activation are regulated by the Go and Gβγ subunits of heterotrimeric G proteins. Gβγ subunits could potentially be involved in the regulation of polycystin-2 channel activity. The extracellular event that initiates polycystin-1-mediated G protein signaling remains unknown.
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