p21-activated Protein Kinase 4 (PAK4) Interacts with the Keratinocyte Growth Factor Receptor and Participates in Keratinocyte Growth Factor-mediated Inhibition of Oxidant-induced Cell Death*

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Keratinocyte growth factor (KGF), a member of the fibroblast growth factor (FGF) family (also known as FGF-7), is an important protective factor for epithelial cells. The receptor for KGF (also called FGFR2-IIIb), which has intrinsic tyrosine kinase activity, is expressed specifically on epithelial cells and in the lung epithelium. Administration of KGF has been shown to protect the lung from various insults, but the mechanism of protection is not well understood. To understand the mechanism by which KGF exerts protective functions on epithelial cells, we used the yeast two-hybrid assay to identify proteins that interact with the KGF receptor (KGFR). Here we show that the cytoplasmic domain of KGFR interacts with p21-activated protein kinase (PAK) 4, which is a new member of the PAK family. The PAKs are regulated by the Rho-family GTPases Rac and Cdc42. PAK4 is the most divergent member of the PAK family of proteins and may have distinct functions. However, stimuli that regulate PAK4 activity are not known. Our data show that PAK4 can associate with the KGFR, which is dependent on KGFR tyrosine kinase activity. We show that a dominant negative mutant of PAK4 blocks KGF-mediated inhibition of caspase-3 activation in epithelial cells subjected to oxidant stress. Our data demonstrate that PAK4 is an important mediator of the anti-apoptotic effects of KGF on epithelial cells.
interacts with yeast G protein \( \alpha \)-subunits, which suggests that these PAK proteins may be regulated by heterotrimeric G proteins in mammalian cells. In Group II are PAK4 (16), PAK5, and PAK6 (19). Although overall human PAK4 resembles other PAK members in that it also contains an amino-terminal GTPase-binding domain and a carboxyl-terminal kinase domain, it lacks a G protein \( \alpha \)-binding domain or the ability to bind to Nck (16). Even within the GTPase-binding domain and the kinase domain, it shares only 50% similarity with other PAK members (16). Although a role for PAK proteins in the regulation of cytoskeletal organization is well described, PAK proteins, particularly those belonging to Group II, have been implicated in other distinct cellular processes (19). For example, PAK6 has been shown to bind to the androgen receptor and repress androgen receptor-mediated gene transcription in the presence of the ligand androgen (20). The different members of the PAK family have been shown to have different roles in the apoptotic response of cells. Although PAK2 promotes apoptosis (21, 22), PAK1 has been shown to protect cells from apoptosis induced by growth factor withdrawal (23, 24). Recently, PAK4 was shown to protect cells from apoptosis induced by multiple stimuli, including serum withdrawal, tumor necrosis factor-\( \alpha \) (TNF\( \alpha \)) treatment, or UV irradiation (25). Although PAK4 has been shown to be a target for Cdc42, extracellular stimuli that regulate endogenous PAK4 activity have not been identified. Here, using the yeast two-hybrid assay, we have identified an association between the KGFR and PAK4. Our studies suggest that this association may play an important role in the protective effects of KGF on epithelial cells.

**EXPERIMENTAL PROCEDURES**

**Interaction Cloning of Murine PAK4**—Duplex-A\textsuperscript{TM} yeast two-hybrid system (OriGene Technologies, Inc., Rockville, MD) was used to identify KGFR-interacting proteins. The KGFR cytoplasmic domain containing the tyrosine kinase domain was cloned into the yeast expression plasmid pEG202-NLS, and the resulting bait construct was named pNEGKGFRc. Expression of the cytoplasmic domain of the KGFR in the yeast strain EGY194 led to autophosphorylation of the receptor as judged by immunoprecipitation with an anti-phosphotyrosine antibody and Western blotting with an anti-KGFR antibody. We first ensured that the bait construct, pNEGKGFRc containing the LexA-KGFRc fusion, did not activate reporter genes due to autoactivation. Autoactivation of the reporter gene \( \text{lacZ} \) was checked by co-transforming EGY194 with pNEGKGFRc and the reporter plasmid pSH18-34. No activation of \( \text{lacZ} \) was observed with the LexA-KGFRc fusion protein. To identify KGFR-interacting proteins, EGY194 was first transformed with pNEGKGFRc and pSH18-34, and the pretransformed EGY194 was next transformed with a cDNA expression library constructed from cDNA derived from a 19-day-old post-coital mouse embryo fused to the B42 activation domain HA-tagged expression vector pJG4-5. After selecting clones potentially expressing interacting proteins, the specificity of the interaction was confirmed by a yeast-mating assay. The expression plasmid isolated from the putative positive clone was introduced into EGY194 (a strain), and a combination of the bait plasmid (pNEGKGFRc) and reporter plasmid (pSH18-34) was introduced into the Y2H strain EGY194. Appropriate controls were used in the mating assay. Among the positive clones, three independent clones contained sequences that matched with the sequence of human PAK4. Full-length cDNA of mPAK4 was cloned by 5' RACE.
plasmids—The chimeric trk/KGFR plasmid was kindly provided by Martin Sachs (Akt-r-29, MDC Max-Delbruck Center for Molecular Medicine, Berlin, Germany). The mutagenesis of the tyrosine residues of the amino-terminal domain of PAK4 into the 5'-GCCCATTTGTGCTTTTTATTAAAGCTCTATGTTGTTGATATCC-3' and 5'-GCCGGAGACCCCTGGC-3' and 5'-GGAGGGTTCTCGAGGAGTTGGCCAGAGGGTACCAAGGGTGCAGGGGTCTCCGAGtttGAGTT-3' and (iii) trk/KGFR(Y655F), 5'-CCACCTTTGGATCTCTGGAACACTCCaa-3' and 5'-GGGTGAGATCCaagAATTCCTCATTGGTTGATATCC-3'; and (ii) trk/KGFR(Y542F,Y543F), 5'-GGGTGAGATCCaagAATTCCTCATTGGTTGATATCC-3' and 5'-GGGTGAGATCCaagAATTCCTCATTGGTTGATATCC-3' and 5'-GGGTGAGATCCaagAATTCCTCATTGGTTGATATCC-3'.

Fig. 2. Association of mPAK4 with endogenous KGFR and trk/KGFR. A, association between endogenous KGFR and PAK4 proteins in HEK293 cells. HEK293 cells were serum starved for 3 h and left with or without KGFR (100 ng/ml; Roche Molecular Biochemicals) for 30 min. Cell extracts were immunoprecipitated with control Ig (con. Ig) or anti-KGFR, and immunoprecipitates were analyzed by immunoblotting with anti-human PAK4 (Cell Signaling). The blot was stripped and reprobed with anti-KGFR. Cell extracts were also directly analyzed with anti-PAK4 to assess PAK4 expression in the cells. B, association of HA-murine PAK4 (HA-mPAK4) with endogenous KGFR. HEK293 cells were transfected with HA-tagged mPAK4 (pHA-mPAK4). 36 h post-transfection, cells were stimulated with KGFR (100 ng/ml) for 30 min after 3 h of serum deprivation. Cells were lysed, and 0.4 μg of protein in the lysates was used for IP with anti-HA-coupled agarose (Roche Molecular Biochemicals). The immunoprecipitates were analyzed by Western blotting techniques using anti-KGFR (Santa Cruz Biotechnology). The membrane was stripped and reprobed with anti-HA to demonstrate expression of HA-mPAK4. The immunoprecipitates were analyzed by immunoblotting with anti-PAK4 (Cell Signaling). The blot was stripped and reprobed with anti-KGFR. Cell extracts were also directly analyzed with anti-PAK4 to assess PAK4 expression in the cells. C, association of HEK293 cells transfected with HA-tagged mPAK4 (pHA-mPAK4). 36 h post-transfection, cells were stimulated with KGFR (100 ng/ml) for 30 min after 3 h of serum deprivation. Cells were lysed, and 0.4 μg of protein in the lysates was used for IP with anti-HA-coupled agarose (Roche Molecular Biochemicals). The immunoprecipitates were analyzed by Western blotting techniques using anti-KGFR (Santa Cruz Biotechnology). The membrane was stripped and reprobed with anti-HA to demonstrate expression of HA-mPAK4. The immunoprecipitates were analyzed by immunoblotting with anti-PAK4 (Cell Signaling). The blot was stripped and reprobed with anti-KGFR. Cell extracts were also directly analyzed with anti-PAK4 to assess PAK4 expression in the cells.

Fig. 3. Association of mPAK4 with different mutant forms of trk/KGFR. HEK293 cells were co-transfected with pHA-mPAK4 and ptrk/KGFR or the indicated mutants (mut). 36 h post-transfection, cells were serum starved and then stimulated with or without KGFR (100 ng/ml; Roche Molecular Biochemicals) for 30 min. 0.4 mg of lysate protein was used for IP with anti-HA-coupled agarose (Roche Molecular Biochemicals). The immunoprecipitates were analyzed by immunoblotting with anti-Bek (Santa Cruz Biotechnology). The membrane was stripped and reprobed with anti-Grb2 rabbit polyclonal antibody (SC-255A, Santa Cruz Biotechnology), anti-Grb2 monoclonal antibody (SC8034, Santa Cruz Biotechnology), anti-p-Grb2 phosphotyrosine (pY) antibody pY99 (SC7020 AC, Santa Cruz Biotechnology), and anti-Grb2 antibodies against the extracellular domain of TrkA (O6574, Upstate Biotechnology). Blots were visualized by enhanced chemiluminescence.
RESULTS

Cloning of Murine PAK4—To identify proteins that interact with FGFR2III-b/KGFR, we used the yeast two-hybrid system to screen for proteins that interact with the kinase (cytoplasmic) domain of KGFR. A murine embryonic cDNA library was screened for possible interactions with a chimeric bait comprising LexA and the cytoplasmic domain of KGFR. Among the several positive clones identified in this assay, three independent clones contained DNA fragments with open reading frames that were highly homologous to the carboxyl terminus of human PAK4. The corresponding full-length cDNA was cloned using 5’/H11032-RACE. Fig. 1A shows the predicted amino acid sequence of the full-length cDNA. Domain search revealed the presence of a p21 Rho-binding domain (PBD) and a protein kinase domain (PKD) in hPAK4 (GenBankTM Accession number NM_005884). The amino acid sequence was found to share 86% identity with that of hPAK4 (Fig. 1B) and less than 50% identity, only in the PKD domain, with the corresponding domain present in murine PAK1–3. We therefore consider this to be murine PAK4 (mPAK4; GenBankTM Accession number AY217016).

PAK4 Associates with KGFR in Mammalian Cells—We investigated whether endogenous KGFR and PAK4 associate with each other in HEK293 epithelial cells. HEK293 cell extracts were immunoprecipitated with anti-KGFR antibody or control immunoglobulin, and analysis of the immunoprecipitates by immunoblotting with anti-human PAK4 revealed the presence of PAK4 in immunoprecipitates obtained with the anti-PAK4 but not the control Ig (Fig. 2A). The association between the two proteins was detected in the absence of KGF and was not appreciably augmented upon treatment of the cells with KGF. Interaction between these two proteins was also detected when HA-tagged murine PAK4 was used (Fig. 2B). To further explore interactions between KGFR and PAK4, we expressed a chimeric receptor containing the extracellular ligand-binding domain of NGF (Trk) and the cytoplasmic domain of KGFR, which we termed trk-KGFR. The rationale for using the chimeric receptor was that, because epithelial cells do not express the NGF receptor, treatment of cells with NGF would allow us to specifically monitor the activity of the hybrid receptor without interference from the endogenous KGF receptor. Also, in the absence of an effective anti-KGFR antibody that could be used for immunoprecipitation, the anti-TrkA antibody was particularly useful. As shown in Fig. 2C, at a lower level of trk-KGFR expression, NGF-stimulation was required for co-immunoprecipitation of trk-KGFR and PAK4 (Fig. 2C). However, at higher levels of expression of the chimeric receptor, the
association was readily detectable with (Fig. 2C) or without (not shown) NGF stimulation. Because receptor tyrosine kinases are known to undergo ligand-independent activation (autophosphorylation) due to dimerization when the protein is overexpressed, it is possible that phosphorylation augments or stabilizes association between PAK4 and KGFR. We also found that the tyrosine residues 542 and 543, corresponding to tyrosine residues 653 and 654 in FGFR1 (which are autophosphorylation sites of KGFR), are critical for the association with PAK4 (Fig 3A). However, mutations of tyrosine residues 352 and 655 corresponding to tyrosine residues 463 and 766 in FGF receptor 1, the putative binding sites for Shc and PLC-γ, respectively, with FGF receptor 1 (26–28), did not affect association with PAK4. It is to be noted that, compared with the wild type receptor, these mutant receptors displayed reduced basal autophosphorylation, which may be due to reduced receptor dimerization when these residues are mutated.

Grb2 Participates in the Association between mPAK4 and KGFR—Grb2 is an adapter protein that associates with receptor tyrosine kinases and couples the activated receptor to downstream signaling molecules such as Ras (28, 29). The PAK family members have been shown to associate with the adapter protein Nck, which has similarities to Grb2 (30, 31). However, PAK4, the sequence of which is the most divergent of all PAK proteins, does not associate with Nck (16). We therefore investigated whether PAK4 has the ability to associate with Grb2. Because Nck and PAK1 have been shown to form a complex in the absence of growth factor stimulation (32), we investigated whether PAK4 exists in a complex with Grb2 in unstimulated cells. As shown in Fig. 4A, anti-Grb2 antibody-immunoprecipitated PAK4 and KGF had no effect on Grb2-PAK4 association. We also investigated whether endogenous KGFR associates with Grb2. Immunoprecipitation of HEK293 cell extracts with anti-Bek but not control Ig led to co-immunoprecipitation of Grb2 as revealed by immunoblotting of the immunoprecipitates with anti-Grb2 (Fig. 4B). If anti-Bek and anti-Grb2 have comparable affinities for their respective proteins, then a comparison of the amount of Grb2 co-immunoprecipitated with KGFR with the net Grb2 obtained by immunoblotting with monoclonal anti-Grb2 shows that a small fraction of Grb2 is complexed with KGFR in the cells, which probably reflects the level of KGFR expression in the cells. Also, we detected similar levels of Grb2 in the immunoprecipitate whether cells were left with or without KGF. To determine the importance of specific phosphorylation sites for KGFR-Grb2 association, HEK293 cells were transfected with expression vectors for trk-KGFR (wild type or individual mutants). We uniformly treated all cells with NGF to achieve maximum receptor activation, because overexpression of the wild type receptor consistently resulted in basal autophosphorylation and, therefore, only small differences between stimulated and unstimulated cells were expected (Fig. 3). As shown in Fig. 4C, the wild type receptor associated with Grb2 and the autophosphorylation site of the receptor was critical for this association. Again, the other tyrosine residues, Tyr352 and Tyr655, did not affect association with Grb2 and, similar to what was observed with PAK4, the mutation of Tyr352 actually augmented association of Grb2 with the receptor. The receptor-Grb2 complex also contained PAK4 (Fig. 4D). Because the endogenous KGFR was found to associate with both PAK4 and Grb2 in the absence of KGF stimulation of cells, and because for both associations the autophosphorylation sites in the KGFR were found to be critical for association, it is possible that the endogenous KGFR (at least a fraction of the receptor) in HEK293 cells exists in an autophosphorylated state. Also, because Grb2 is widely expressed in many species, including yeasts, it is possible that the association between KGFR and PAK4 is indirect and mediated by Grb2, because Grb2 has been shown to bind to receptor tyrosine kinases in yeast two-hybrid assays. Also, we were unable to co-immunoprecipitate KGFR and PAK4 when the recombinant proteins were expressed in bacteria, which reinforces our suspicion that Grb2 mediates association between the receptor and PAK4.

PAK4 Is Phosphorylated by Ligand-activated trk/KGFR—The association between PAK4 and KGFR (Fig. 1) prompted us to investigate whether PAK4 undergoes tyrosine phosphorylation in response to receptor activation. As shown in Fig. 5, activation of the hybrid receptor with NGF induced tyrosine

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**FIG. 6.** Dominant negative PAK4 (PAK4/NT) prevents inhibition of PARP cleavage by KGF. HEK293 cells were incubated in serum-containing medium with or without H2O2 (control). The caspase-3 inhibitor DEVD-fluoromethylketone was added at a concentration of 200 nM 1 h before the addition of H2O2 (1 mM). Cleavage was assessed by Western blotting as an indicator of PARP cleavage. A, PARP cleavage was assessed by Western blotting as an indicator of cellular apoptosis. β-actin expression was used as a loading control. B, densitometric analysis of PARP cleavage. C, interaction between KGFR and mPAK4/NT. HEK293 cells were transfected with trk-KGFR together with empty vector or expression constructs encoding HA-tagged full-length or mutant mPAK4. Extracts were immunoprecipitated with anti-PAK4 antibody and the immunoprecipitants were analyzed by sequential immunoblotting with anti-trkA and anti-HA. The experiment was performed twice with similar results.
phosphorylation of PAK4, which was clearly evident in cells that expressed higher levels of the chimeric receptor. The phosphorylation status paralleled that of the chimeric receptor. The bottom panel of Fig. 5 demonstrates equivalent expression of HA-PAK4 in all cells.

**Dominant Negative Mutant of PAK4 (PAK4/NT) Prevents KGF-mediated Inhibition of Oxidant-induced Poly(ADP-ribose) Polymerase (PARP) Cleavage**—Because our data suggested an important role for PAK4 in cellular protection by KGF, we investigated whether interference of PAK4 function would influence anti-apoptotic functions induced by KGF in HEK293 cells. For this purpose, we treated HEK293 cells with H$_2$O$_2$, which has been shown to induce pro-apoptotic pathways in these cells (33). Because apoptosis is associated with caspase-3 activation, a focal point of different pro-apoptotic pathways, we investigated the state of protein PARP, a substrate of caspase-3, in the cells under different conditions of treatment. Also, to inhibit the functions of endogenous PAK4, we overexpressed the N-terminal fragment of PAK4 lacking the kinase domain, the inactivation of which imparts dominant negative functions to PAK4 (16, 34). As shown in Fig. 6, treatment of cells with H$_2$O$_2$ promoted cleavage of the PARP protein. Cleavage of PARP was inhibited in the presence of the caspase-3 inhibitor DEVD-fluoromethylketone or KGF. However, when the PAK4 dominant negative mutant was expressed in the cells, KGF was unable to inhibit PARP cleavage. Furthermore, Fig. 6C shows that the PAK4 mutant is able to interact with the KGF receptor. By binding to the receptor, the mutant is probably able to disrupt KGF signaling to downstream pathways.

**Discussion**

In this study, we have identified PAK4 as a KGFR-interacting protein using a yeast two-hybrid assay. We show that this interaction has functional relevance, because expression of a dominant negative mutant of PAK4 prevented the inhibition of oxidant-induced caspase-3 activation by KGF in epithelial cells. It is interesting to note that just as mice deficient in the KG receptor show organ malfunction with evidence of enhanced apoptosis of developing organs such as the lung (9, 10), *Drosophila* lacking the protein Mushroom Body Tiny (MBT), the closest known homolog of PAK4, also shows defects in organ development in the embryonic stage and during injury in adults.

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