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Characterization of RAC3, a Novel Member of the Rho Family*

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The small GTP-binding proteins Rac1 and Rac2 are critically important in regulating multiple signal transduction pathways in eukaryotic cells. Here we report the isolation of a novel third Rac family member, Rac3. Rac3 differs from Rac1/2 at its carboxyl-terminal end, a domain associated with subcellular localization and binding to specific cellular regulators. RAC3 mRNA expression patterns differ from those of RAC2, which is hematopoietic specific and also from those of RAC1. The RAC3 gene was mapped to chromosome 17q23–25, a region frequently deleted in breast cancer. Rac3 protein levels are not affected by organization of the actin cytoskeleton but remarkably, are serum-inducible. Rac3 is an active GTPase, and this activity is regulated by Bcr. When constitutively activated, Rac3 is able to stimulate efficiently the c-Jun amino-terminal kinase signaling pathway. These findings support a role for Rac3 in intracellular signaling.

The small G proteins Rac1 and Rac2 are highly related GTPases belonging to the Rho subfamily of Ras proteins (1–3). Rho family members regulate the organization of the actin cytoskeleton. Specifically, activation of Rac is associated with actin reorganization accompanying the appearance of lamellipodia and membrane ruffles in fibroblasts (4, 5). In neuroblastoma cells, Rac1 stimulates the formation of lamellipodia leading to neurite development (6). Activated Rac stimulates F-actin uncapping and morphological transformation of platelets but inhibits receptor-mediated endocytosis (7, 8). In neutrophils and macrophages, Rac is essential for activation of a multiprotein complex that produces superoxide in phagocytic cells, the NADPH oxidase (9–11). Moreover, Rac1 regulates intracellular reactive oxygen species production in fibroblasts and the activity of the redox-dependent transcription factor nuclear factor- κ B (12, 13).

Rac participates in signal transduction from the membrane to the nucleus via two distinct mitogen-activated protein kinase cascades. Exposure of cells to endotoxins, proinflammatory cytokines, or hyperosmolarity effects the activation of Rac and subsequently p38, ultimately resulting in activation of

activating transcription factor 2 (14). A second stress-activated pathway involving Rac, the JNK¹/stress-activated protein kinase pathway, leads to c-Jun and activating transcription factor 2 activation (14–17). Activation of Rac also results in activation of the serum response factor, a transcription factor that binds to serum response elements found in the promoters of many growth factor-regulated genes (18). On a cellular level, Rac GTPases play an important role in cell cycle progression in response to mitogenic stimulation (17). Interestingly, overexpressed Rac1 complexes with and activates the 70-kDa ribosomal S6 kinase (pp70^{S6k}), which is necessary for the progression of cells through the G₁ phase of the cell cycle (19). Other experiments have demonstrated that Rac is essential for cellular transformation by Ras (20, 21).

A number of Rac-interacting regulators and effectors have been identified *in vitro*. Our laboratory was the first to isolate Bcr and Abr, large multidomain proteins with GTPase-activating protein activity toward Rac and the related Cdc42 (22–24). We have shown that ablation of the Bcr protein *in vivo* in null mutant mice results in deregulation of the production of superoxide generated by the NADPH oxidase, and we have implicated Bcr in the specific regulation of Rac2 *in vivo* (25). To date, no evidence for regulation of specific Rac1 functions by Bcr *in vivo* has been found (25). Unlike Rac2, Bcr is not hematopoietic specific (1–3, 22, 26), and therefore it is likely that *in vivo* Bcr also regulates other Rho family GTPases. Here we report the somewhat unexpected existence of a third human Rac species, Rac3. The finding that Rac3 is closely related to Rac1 and Rac2 yet is clearly distinct will allow us to investigate the specific role of this Rac species in the many processes attributed to Rac proteins.

EXPERIMENTAL PROCEDURES

Cloning and Sequencing of RAC3—A 350-base pair fragment from the coding region of mouse *rac1* was used to screen a K562 λ gt10 cDNA library. Four cDNAs were isolated and partially sequenced. The 5'-untranslated and coding region of cDNA clone R10 of 1.0 kb was sequenced completely on both strands.

Cell Lines—The K562, DU4475, HL60, SCaBER, Swiss 3T3, and COS-1 cell lines were obtained from the ATCC, Rockville, MD. The cell line GM04155 was from NIGMS Human Genetic Mutant Cell Repository, Camden, NJ, and 5838 was kindly provided by Dr. T. Triche. *Spodoptera frugiperda* Sf9 insect cells were from Invitrogen, San Diego.

Expression of mRNA—RNAs were isolated using the LiCl-urea method (27). Total RNAs (15 μ g) were run on guanidine thiocyanate-agarose gels (28), blotted to Hybond-N (Amersham Corp.), and hybridized as described (29). A multiple tissue Northern blot (CLONTECH) was used to analyze tissue distribution of RAC3 in human. For detecting RAC3, a 0.24-kb *Bam*HI probe from the 3'-untranslated region was used and blots were washed to 0.01 \times SSC at 65 °C. RAC1 was detected with a 0.21-kb *Nco*I-*Eco*RI probe and RAC2 with a 0.28-kb *Msc*I-*Pst*I probe, both of which included 3'-untranslated sequences.

Chromosomal Localization—Somatic cell hybrid and regional mapping panels for chromosome 17 were from the NIGMS Human Genetic

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The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EBI Data Bank with accession number(s) AF008591.

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¹ The abbreviations used are: JNK, c-Jun amino-terminal kinase; kb, kilobase(s); GST, glutathione S-transferase.

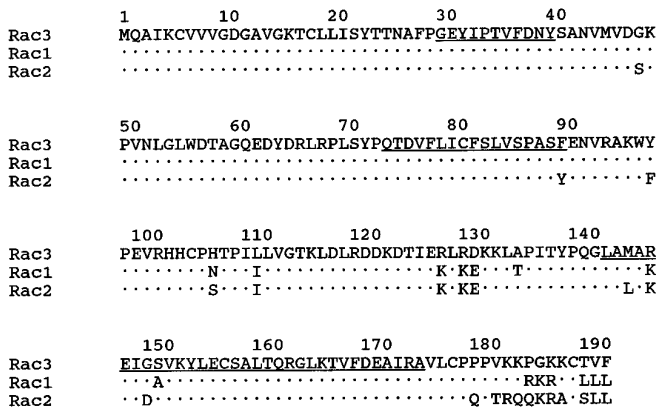


FIG. 2. Comparison of the primary sequences of Rac3, Rac1, and Rac2. The complete deduced amino acid sequence of Rac3 is shown as well as differences among Rac1, Rac2, and Rac3. Dots indicate amino acid residues identical to those of Rac3. Rac1 and Rac2 sequences are from Didsbury *et al.* (1). The effector domains are underlined.

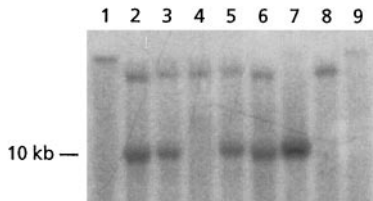


FIG. 3. Subchromosomal localization of RAC3 on chromosome 17. A 0.45-kb *Xba*I probe from the 3'-untranslated region of RAC3 was hybridized to *Eco*RI-digested DNAs from human-rodent somatic cell hybrids retaining different portions of chromosome 17. The location of the 10-kb *Eco*RI fragment is indicated to the left. DNAs include those of cell line GM10501 (17pter>p11.2), lane 1; GM10502 (17q23>q25), lane 2; GM10657 (17p13.1>q25), lane 3; GM10659 (17pter>q11.2), lane 4; GM10660A (17q11.2>q25), lane 5; GM10889 (17; microdeletion in 17p11.2), lane 6; IMR-91 (human cell line) lane 7; 3T6 (mouse cell line), lane 8; and RJK88 (Chinese hamster cell line), lane 9. The blot was washed to $0.01 \times$ SSC at 65 °C.

was detected as a single *Eco*RI fragment of around 10 kb in total human DNA (Fig. 3, lane 7), and somatic cell hybrids containing this fragment localized RAC3 to the q23–25 region of chromosome 17 (Fig. 3, lanes 2, 3, 5, and 6).

Expression of Human RAC3—The RAC3-specific probe was used to investigate RAC3 mRNA levels. In all of the human cell lines studied, a single mRNA of around 1.0 kb was detected (Fig. 4C), which is in close agreement with the size of the R10 cDNA. It was relatively abundant in the chronic myeloid leukemia cell line K562 and also expressed, albeit at a lower level, in the Ewing sarcoma cell line 5838, the promyelocytic cell line HL60, and the breast cancer cell line DU4475 (Fig. 4C, lanes 2–5). In concordance with previous reports, RAC2 mRNA of 1.4 kb was detected mainly in cell lines of hematopoietic origin (Fig. 4B), whereas two RAC1 mRNAs, of 2.4 and 1.1 kb, were present in all of the cell lines (Fig. 4A). To investigate the tissue-specific distribution of RAC3, the RAC3-specific probe was hybridized to a human multiple tissue Northern blot. Interestingly, the highest RAC3 expression levels were found in brain, although it was also detected in heart, placenta, and pancreas (Fig. 4E). A second, larger RAC3 mRNA was detected only in placenta (Fig. 4E, lane 3).

GTPase Activity of Rac3—Not all Rho family members have GTPase activity (32). To examine whether Rac3 was a functional GTPase it was expressed as a GST-fusion protein and compared with GST-Rac1. Both proteins were loaded with [γ - 32 P]GTP, and the rate of hydrolysis was measured using a filter binding assay. As shown in Fig. 5, the intrinsic GTPase activity of Rac3 was indistinguishable from that of Rac1. To

test whether Bcr can stimulate the GTPase activity of Rac3, baculovirus-expressed GST-Bcr was incubated with [γ - 32 P]GTP loaded GST-Rac3 and the rate of GTP hydrolysis measured. As shown in Fig. 5, Bcr stimulated the GTPase activities of Rac3 and Rac1 in a similar fashion.

Rac3-specific Antisera—To be able to detect Rac3 protein, antisera were raised against a carboxyl-terminal peptide of Rac3 containing a maximum degree of divergence with Rac1 and Rac2. Affinity-purified antibodies reacted only with GST-Rac3 (Fig. 6A, lane 2) but not with either GST-Rac1 or 2 (lanes 3 and 4), although all three extracts contained GST-Rac fusion proteins reacting with GST antibodies (Fig. 6A). Rac3 antibodies also clearly detected Rac3 overexpressed in COS-1 cells (Fig. 6B, lane 2) and endogenous Rac3 (lane 1).

Regulation of Rac3 Expression—Previous studies have shown that Rac1 expression levels can be modulated by the state of the actin network (2). To investigate this, endogenous Rac3 protein was analyzed in Swiss 3T3 cells. Treatment of these cells with 10^{-5} or 10^{-6} M cytochalasin B had no apparent effect on Rac3 levels (Fig. 6C, lanes 2–4), although this treatment caused a prominent morphological change in the cells caused by disruption of the actin cytoskeleton (not shown). Similarly, Rac3 levels were unaffected by disattachment from the substratum (lane 5). However, deprivation of cells from serum for 24 h caused a decrease in Rac3 levels (Fig. 6C, compare lanes 6 and 7). Stimulation of the serum-starved cells with 10% fetal bovine serum for 1 h resulted in a return to normal Rac3 levels (lane 8).

V12Rac3 Activates Endogenous JNK—To investigate whether activation of Rac3 would affect signaling, it was mutated to a constitutively activated form by replacing glycine at position 12 with a valine. Overexpression of V12Rac3 in COS-1 cells and the activation of endogenous JNK was examined by phosphorylation of GST-c-Jun. As shown in Fig. 7 (bottom), mock-transfected, V12Rac3-transfected, and osmotically shocked COS-1 cells contained comparable levels of endogenous JNK. Exposure of cells to 0.4 M sorbitol resulted in a maximal stimulation of 4-fold of endogenous JNK activity. Overexpression of the constitutively active Rac3 resulted in the activation of JNK as measured by the 2-fold increased phosphorylation of the GST-c-Jun substrate (Fig. 7, top).

DISCUSSION

We have identified a new member of the Rho family, Rac3, which has a high degree of amino acid identity with human Rac1 and Rac2 (92 and 89%, respectively). This raises the question of why three highly related proteins exist. Despite this close degree of relatedness, it is likely that each Rac species plays a distinct regulatory role *in vivo*, although there may be overlap both *in vitro* and *in vivo*. Differences among the three could be found in the regulation of their GTPase activity through interaction with other proteins or at the level of gene expression.

With respect to protein structure, experiments with mutant Rac proteins have delineated domains of functional importance for the interaction of both Rac1 and Rac2 with effectors and other regulatory molecules. Two effector sites are needed for *in vitro* activation of the NADPH oxidase component p67^{phox}, Rac-induced actin polymerization in fibroblasts, and interaction with p65^{PAK} *in vitro* (33). The amino-terminal effector site is identical in all three Rac proteins, and the carboxyl-terminal effector site in Rac3 is 94 and 91% identical to the homologous region in Rac1 and Rac2, respectively (Fig. 2 and Ref. 33). This suggests that Rac3 is also capable of binding p67^{phox} and p65^{PAK}, at least *in vitro*. In addition, the carboxyl-terminal residues have been identified as an important region for NADPH oxidase and JNK activation (34–36).

FIG. 4. Northern blot analysis of human RAC3, RAC1, and RAC2 expression. Sizes of the mRNAs detected are indicated to the left of each panel. Panels A–D, each lane contains 15 µg of total RNA. Cell lines include: GM04155 (lymphocytic leukemia), lane 1; K562 (myelocytic leukemia), lane 2; 5838 (Ewing sarcoma), lane 3; HL60 (promyelocytic leukemia), lane 4; DU4475 (breast cancer), lane 5; and SCaBER (bladder cancer), lane 6. Panels A, B, and C were hybridized to RAC1, RAC2, and RAC3 probes, respectively, as indicated under “Experimental Procedures.” In panel D, an ethidium bromide-stained gel serves as a loading control for panels A–C. Panel E shows a multiple tissue Northern blot of human poly(A) RNAs (CLONTECH) including: heart, lane 1; brain, lane 2; placenta, lane 3; lung, lane 4; liver, lane 5; skeletal muscle, lane 6; kidney, lane 7; and pancreas, lane 8. Panel E was hybridized to the RAC3 probe.

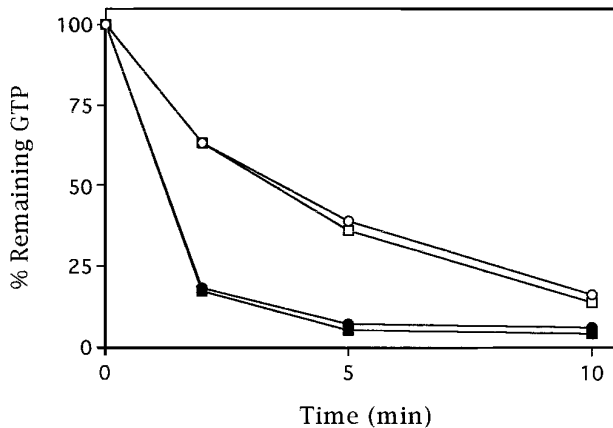
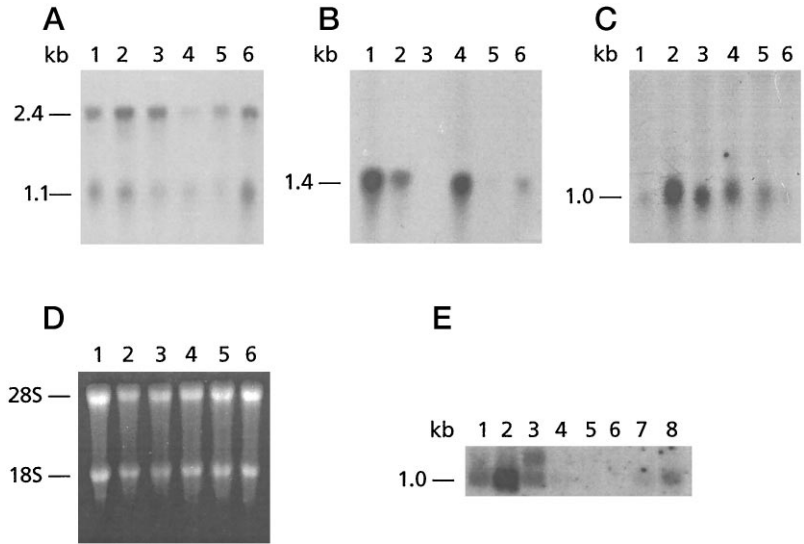


FIG. 5. GTPase activity of Rac3. GTPase activity of Rac3 (○) and Rac1 (□) with (filled symbols) or without (open symbols) Bcr. GST-Rac was loaded with [γ - 32 P]GTP, and hydrolysis of GTP was measured after 2, 5, and 10 min. Each point represents the average of two independent experiments, which gave nearly identical values.

Our experiments on the functional activity of Rac3 show that it is a GTPase. Like Rac1, it interacts with Bcr, which enhances its GTPase activity *in vitro*. COS-1 cells overexpressing a constitutively activated Rac3 show a physiologically significant 2-fold activation of endogenous COS-1 JNK compared with its 4-fold activation by osmotic stress. This demonstrates that Rac3 is able to participate in the stress activation pathway.

The greatest divergence among Rac3, Rac1, and Rac2 occurs at residues 180–192, which are also hypervariable regions in the Ras proteins (37). Indeed, the only functional difference demonstrated to date between Rac1 and Rac2 using an *in vivo* assay is that p67^{phox} interacts 6-fold better with Rac2 than with Rac1 (38). Therefore, this region may specify differences in *in vivo* binding activities among the three Rac proteins. All three Rac proteins contain a Cys-A-A-X-COOH sequence, in which A is an aliphatic residue and X is any amino acid. *In vivo* in Rac1/2, the cysteine residue becomes geranylgeranylated, followed by proteolytic removal of the A-A-X residues and carboxyl methylation of the isoprenylated cysteine (39). This post-translational modification is important for specific intracellular localization and interaction with target proteins (19, 40, 41). Thus, the identified differences between Rac3 and Rac1/2 in their very carboxyl-terminal end may define differences in subcellular localization and/or binding to specific regulatory molecules.

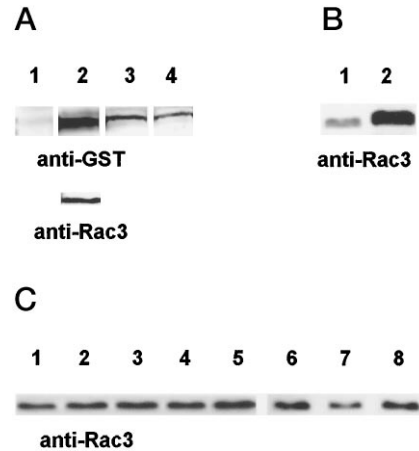


FIG. 6. Regulation of Rac3 protein levels in Swiss 3T3 cells. Panel A, protein extracts were prepared from insect cells overexpressing GST-Rac3, GST-Rac1, and GST-Rac2, and analyzed on a Western blot using GST (top) and Rac3 (bottom) antibodies. Extracts were from mock-transfected Sf9 cells, lane 1, and cells expressing GST-Rac3, lane 2; GST-Rac1, lane 3; and GST-Rac2, lane 4. Panel B, protein extracts from mock-transfected COS-1 cells, lane 1, and cells overexpressing Rac3, lane 2, were immunoblotted using Rac3 antibody. Panel C, Swiss 3T3 cells were treated with: nothing, lane 1; 0.1% dimethyl sulfoxide, lane 2; 10⁻⁵ M cytochalasin B, lane 3; 10⁻⁶ M cytochalasin B, lane 4; trypsin, lane 5; nothing, lane 6; serum deprivation, lane 7; serum deprivation followed by stimulation for 1 h with 10% FCS, lane 8. Total cellular extracts (10 µg of protein/lane) were analyzed on a Western blot using Rac3 antibody. Results shown for the serum starvation are representative of three independent experiments.

Prominent differences among Rac1, 2, and 3 were found in expression levels in tissues and cell lines. The highest RAC3 mRNA expression in human tissues studied was in brain. In contrast, little or no RAC2 mRNA is found in brain (1–3). Both Bcr and its cognate Abr have GTPase-activating protein activity toward Rac proteins (22–24). Because the expression levels of both BCR and ABR are highest in brain (22), Rac3 may be a main target of these GTPase-activating proteins.

Using highly specific Rac3 antisera, Rac3 protein could be identified unambiguously. Previous experiments have shown rac1 mRNA expression levels are affected by the organization of the actin cytoskeleton (2). However, treatment with cytochalasin B, which disrupts actin cytoskeletal organization, did not have a significant effect on Rac3 protein levels, suggesting a functional difference between Rac3 and Rac1. Alternatively, it is possible that Rac3 and Rac1 protein levels are unaffected by

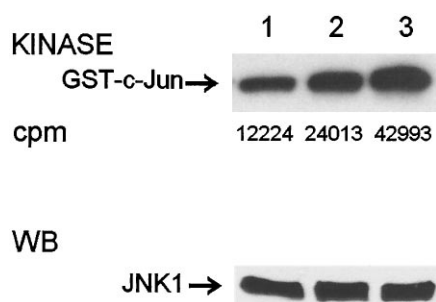


FIG. 7. Activation of endogenous JNK by activated Rac3. COS-1 cells were mock-transfected (lane 1) or transfected with V12RAC3 (lane 2). Treatment of cells with 0.4 M sorbitol for 1 h was used as a positive control for JNK activation (lane 3). Kinase reactions were performed in anti-JNK1 immunoprecipitates using GST-c-Jun as substrate (top). Phosphorylation levels of GST-c-Jun are indicated in counts/min (cpm). Levels of JNK1 protein were analyzed in total cellular lysates from transfected COS-1 cells using a Western blot (bottom). Similar data were obtained in two independent experiments.

this treatment. Surprisingly, Rac3 expression was down-regulated in quiescent fibroblasts and was clearly induced by serum stimulation. This suggests the Rac3 promoter is serum-responsive. To date, of the extended Rho family, only RhoB was shown to be serum-inducible; there have been no reports indicating that either Rac1 or Rac2 expression is modulated by serum. RhoB is closely related to RhoA and RhoC on an amino acid level. In contrast to RhoA and RhoC, RhoB does not have a clearly defined function in actin cytoskeletal reorganization, but rather it appears to be involved in cell proliferation (42, 43).

In view of the increasing evidence for critical roles of Rho family members in actin reorganization and cellular signaling including cancer, it will be of interest to define the specific role of Rac3 in these processes. This, in addition to our finding that RAC3 is located at chromosome 17q23–25, a region frequently deleted in breast cancer (44, 45), provides further impetus to investigate Rac3 expression and activity in this type of malignancy.

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