Ran-binding Protein 1 (RanBP1) Forms a Ternary Complex with Ran and Karyopherin β and Reduces Ran GTPase-activating Protein (RanGAP) Inhibition by Karyopherin β*

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The nuclear accumulation of proteins containing nuclear localization signals requires the Ran GTPase and a complex of proteins assembled at the nuclear pore. RanBP1 is a cytosolic Ran-binding protein that inhibits RCC1-stimulated release of GTP from Ran. RanBP1 also promotes the binding of Ran to karyopherin β (also called importin β and p97) and is a co-stimulator of RanGAP activity. Yeast karyopherin β inhibits the GTP hydrolysis by Ran catalyzed by RanGAP. To further define the roles of RanBP1 and karyopherin β in Ran function, we explored the effects of RanBP1 and karyopherin β on mammalian proteins known to regulate Ran. Like RanBP1, karyopherin β prevented the release of GTP from Ran stimulated by RCC1 or EDTA. As with the yeast protein, mammalian karyopherin β completely blocked RanGAP activity. However, the addition of RanBP1 to this assay partially rescued the inhibited RanGAP activity. Kinetic analysis of the effects on RanGAP activity by karyopherin β and RanBP1 revealed a combination of competitive and noncompetitive interactions. Solution binding assays confirmed the ability of RanBP1 to associate with Ran and karyopherin β in a ternary complex, and RanBP1 binding was not competed out by the addition of karyopherin β. These results demonstrate that RanBP1 and karyopherin β interact with distinct sites of Ran and suggest that RanBP1 plays an essential role in nuclear transport by permitting RanGAP-mediated hydrolysis of GTP on Ran complexed to karyopherin β.

The nuclear import of proteins bearing nuclear localization signals (NLS)1 is mediated by several cytosolic factors. Recognition and docking of NLS substrates requires a heterodimeric complex termed importin (1) or karyopherin (2, 3). The α subunit of this complex (importin α (4), karyopherin α (5), Rh1/hSRP1α (6, 7), hSRP1/NPI-1 (8), or pendulin/OHOS31 (9)) is a 50–60-kDa protein that is necessary for NLS recognition. The β subunit of this complex (importin β (1), karyopherin β (3), p97 (10), or Kap95p (11)) docks the α-NLS-substrate complex at the nuclear pore through its interaction with nucleoporins (12). Whereas the α subunit enters the nucleus together with its import cargo, the β subunit remains at the nuclear envelope, indicating that the NLS receptor undergoes an association-dissociation cycle during nuclear transport (13).

Energy-dependent nuclear translocation of NLS-containing proteins requires the Ran GTPase (14) (originally TC4 (15)) and a 15-kDa Ran-interacting protein known as NTF2 or p10 (16, 17). Factors that directly control the nucleotide state of Ran include the nucleotide exchange factor, RCC1 (18), and a Ran-specific GTPase activating protein (RanGAP), designated in different organisms as RanGAP1 (19), Rna1p (20), or Fug1 (21). A family of proteins that bind to Ran:GTP has also been identified and includes RanBP1, which is a 29-kDa cytosolic protein (22), and RanBP2/NUP358, which is a 360-kDa nuclear pore protein (23, 24). These Ran-binding proteins (RanBPs) associate with GTP-Ran through one or more conserved Ran binding domains (RanBDs) (25). RanBDs inhibit GTP release from Ran and co-activate RanGAP activity (25). The function of RanBPs in nuclear transport remains unclear. However, in an in vitro nuclear import assay, RanBP1-depleted cytosol does not support import (26), and antibodies raised against a RanBD of RanBP2 inhibit transport (24). In addition, expression of an isolated RanBD blocks nuclear import in living cells, suggesting that the N and C termini of RanBPs are important for their function (27).

We and others have shown that the docking and translocation steps of nuclear transport are linked by the interaction of Ran with karyopherin β (12, 28). The Ran:karyopherin β interaction occurs in the presence of a RanBD, suggesting that they bind to different sites on Ran (28). However, Moroiou et al. (29) have recently proposed that the karyopherin β binding site for Ran is homologous to that of a RanBD, which implies that it associates with the same epitopes of Ran. Nonetheless, the two factors have opposite effects on Ran GTPase activity in the presence of RanGAP (30).

In this report we show that karyopherin β is a potent inhibitor of both RCC1 activity and RanGAP activity. We further show that the inhibition of RanGAP by karyopherin β can be reduced by the addition of RanBP1 or a functional RanBD. These results suggest that Ran can form a quaternary complex with a RanBP, karyopherin β, and RanGAP.

EXPERIMENTAL PROCEDURES

Proteins and Reagents—GST-fusion proteins of Ran, RanBP1, and RanBD (from RanBP1 or the RanBD3 of RanBP2) were expressed from pGEX2T in DH5α Escherichia coli by induction with isopropyl-1-thio-
ß-d-galactopyranoside and were subsequently purified by glutathione-Sepharose 4B (Pharmacia Biotech Inc.) (25). Where indicated, GST was cleaved from the purified proteins by incubation with thrombin as described by Richards et al. (27). Karyopherin β was expressed from the

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plasmid pET21B and purified using a nickel-nitrotriacetic acid column as described by Lounsbury et al. (28). The resulting karyopherin β lacks 12 amino acids at the N terminus and contains a His$_6$ tag and a T-7 tag. The creation of the E57K mutation of RanBP1 was described by Beddow et al. (25). The Ran exchange factor RCC1 was expressed as a GST-fusion protein (27). The murine homolog of RanGAP, Fug1, which exhibits efficient GAP activity toward Ran, was also expressed as a GST-fusion protein.

**GTP Release Assay**—Release of GTP from Ran in response to treatment with EDTA or RCC1 was accomplished as illustrated by Richards et al. (27). Briefly, Ran was loaded with [α-32P]GTP (3000 Ci/mmol, DuPont NEN), then incubated with a 10-fold volume of release buffer containing 50 mM Tris-HCl, pH 8.0, 2 mM GTP, 2 mM GDP, 1 mM dithiothreitol, 80 μM bovine serum albumin, plus either 10 mM MgCl$_2$ or 5 mM EDTA. At specified time points, [α-32P]GTP-bound Ran was quantified by filter binding and scintillation counting. RCC1-stimulated release of GTP from Ran was performed by the addition of GST-RCC1 to the release buffer containing 10 mM MgCl$_2$ (27).

**GAP Assay**—GAP assays were performed essentially as described in Ref. 27 with the following modifications. One μg of Ran was loaded with [γ-32P]GTP (3000 Ci/mmol, DuPont NEN), then incubated where indicated with RanBP1 and/or karyopherin β for 10 min at 25°C. The Ran complex was then diluted 10-fold into GAP buffer (40 mM Tris-HCl, pH 8.0, 8 mM MgCl$_2$, 80 μM bovine serum albumin, and 2 μM GTP) with or without 25 μM GST-Pug1 as the source of RanGAP activity. The final concentrations of proteins were 25 nM Ran, 20 nM RanBP1, and 34 nM karyopherin β. Samples were incubated at 25°C, and, at specified times, samples were filter-bound and quantitated by scintillation counting. Purified GST was used as a negative control for RanGAP activity.

**Solution Binding Assay**—The ability of proteins to associate in solution was determined by incubating a GST-fusion protein of either Ran or RanBP1 with one or more associating proteins. One μg of Ran was incubated in buffer containing 20 mM MOPS, pH 7.1, 1 mM EDTA, and 1 mM GTP. GTP-bound Ran was stabilized by adding 10 mM MgCl$_2$. GTP-bound Ran was mixed with 2 μg of RanBP1 and/or 5 μg of karyopherin β in 200 μl of RanBP binding buffer (20 mM MOPS, pH 7.1, 100 mM sodium chloride, 5 mM magnesium acetate, 5 mM dithiothreitol, 0.05% Tween 20) with 30 μl of glutathione-Sepharose. Samples were mixed by rotation for 30 min at 4°C. GST-fusion proteins bound to the glutathione-Sepharose were precipitated by centrifugation and washed twice with RanBP binding buffer. The resulting supernatants and pellets were separated by 10% SDS-PAGE and transferred to nitrocellulose. Untagged RanBP1 was detected by [α-32P]GTP-Ran binding in a Ran overlay assay as described in Ref. 31. Ran, GST-fusion proteins, and karyopherin β were detected by immunoblot using monoclonal anti-GST (Santa Cruz Biotechnology), anti-Ran (Transduction Laboratories), or anti-T-7 tag (Novagen) antibodies at a 1:5000 dilution. Proteins were visualized by chemiluminescence.

**Karyopherin β Binding Assay**—Ran was loaded with [α-32P]GTP (1 μCi/μmol) in the presence of 25 mM MOPS, pH 7.1, 1 mM EDTA. After 30 min at 4°C, 1 mM MgCl$_2$ was added, and the specific activity of GTP-Ran was determined by filter binding. Concentrations of [α-32P]GTP-Ran ranging from 0.2 nM to 23 nM were incubated in a final volume of 1 ml with 5 nM karyopherin β coupled to anti-T-7 protein A-Sepharose. Where indicated, 5 nM RanBP1 was also added. Proteins were mixed by rotation for 30 min at 4°C, then the beads were collected and washed by repeated centrifugation and resuspension in RanBP binding buffer. The washed pellets were quantitated by scintillation counting. Supernatants, containing free Ran, were filter-bound and quantitated by scintillation counting.

**Competition Assay**—Ran was loaded with [α-32P]GTP in the presence of 10 μM GTP as above. Binding assays were performed using affinity matrices containing either karyopherin β or GST-RanBP1 attached to glutathione-Sepharose (50 nM protein and 25 μl of Sepharose beads per sample). After the addition of an untreated competitor, radiolabeled GTP-Ran was added to a final concentration of 5 nM in 100 μl of RanBP binding buffer. Samples were mixed by rotation for 30 min at 4°C. Beads were collected by centrifugation and washed 3 times with RanBP binding buffer. The washed pellets were quantitated by scintillation counting.

**RESULTS AND DISCUSSION**

We demonstrated previously that Ran interacts with karyopherin β and that this interaction occurs in the presence of RanBP1 (28). These results suggested that karyopherin β interacts with Ran at a site different from that occupied by the RanBD. We therefore compared the individual and combined effects of karyopherin β and RanBP1 on the nucleotide state of Ran in the presence of RCC1 and RanGAP.

RanBP1 stabilizes the GTP-bound state of Ran in the presence of EDTA or RCC1 (25, 32). Using purified recombinant proteins, the ability of karyopherin β to inhibit GTP release from Ran was examined (Fig. 1). Karyopherin β prevented the release of GTP from Ran stimulated by EDTA (Fig. 1A) or by the Ran-specific exchange factor, RCC1 (Fig. 1B). These data demonstrate that the interaction between Ran and karyopherin β stabilizes Ran in the GTP conformation.

Because RanBP1 strongly promotes the binding of Ran to karyopherin β on an overlay assay (28), we asked whether karyopherin β forms a stable ternary complex with RanBP1 and Ran, and whether the affinity of karyopherin β for Ran is increased in the presence of RanBP1. To measure the interaction between Ran:GTP, RanBP1, and karyopherin β, solution binding assays were performed with purified recombinant proteins using GST-Ran and GST-RanBP1 glutathione-Sepharose affinity matrices. As shown in Fig. 2A, RanBP1 and karyopherin β associated independently with GST-Ran:GTP, and, when added together, they co-associated to a similar degree with GST-Ran:GTP. These results suggest that RanBP1 and karyopherin β do not compete for binding to Ran. There was no indication that RanBP1 promoted the binding of karyopherin β to Ran in this experiment. The difference in results obtained using a solution binding assay versus an overlay assay are possibly attributed to an increased GTP stabilization by RanBP1 in the overlay assay or a different conformation of karyopherin β when bound to nitrocellulose.

An alternative explanation for this apparent heterotrimeric
association is that the GST-Ran was in sufficient excess that both RanBP1 and karyopherin β were bound to different Ran molecules. To exclude this possibility, we performed an inverse experiment in which the ability of GST-RanBP1 to indirectly precipitate karyopherin β was tested. GST-RanBP1 did not interact with karyopherin β directly (Fig. 2B, lane 3). However, when untagged Ran:GTP was added to the assay, karyopherin β was precipitated in an amount comparable with that observed for the GST-Ran affinity matrix (Fig. 2B, lane 4). Similar results were seen when a GST-RanBD from RanBP2 (not shown) or RanBP1 was used as the affinity matrix (Fig. 2B, lane 5). Therefore, the observed interaction of RanBP1 with karyopherin β must be mediated through binding to Ran. Together these data demonstrate that a heterotrimeric complex can form between Ran:GTP, RanBP1, and karyopherin β.

RanBP1 did not cause any detectable increase in the association of Ran with karyopherin β (Fig. 2A). To determine whether RanBP1 alters the affinity of karyopherin β for Ran, a quantitative binding assay was performed. The amount of [α-32P]GTP:Ran bound to karyopherin β (attached to an anti-T-7:protein A-Sepharose affinity matrix) was measured in the presence or absence of RanBP1 over a range of Ran concentrations. In the absence of RanBP1, karyopherin β interacted with Ran with a $K_d$ of approximately 3.5 nM (Fig. 3A). The affinity of Ran for karyopherin β did not change significantly in the presence of RanBP1, although the available Ran binding sites increased by 12%. This slight augmentation may arise if RanBP1 protects the karyopherin β–Ran complex from denaturation.

Moroiana et al. (33) have proposed that the region of karyopherin β that binds to Ran is homologous to the RanBD, implying that karyopherin β and the RanBD interact with the same site on Ran. Our observation that RanBP1, karyopherin β, and Ran can form a ternary complex suggests that the binding sites for RanBPs and karyopherin β on Ran must be distinct. If the binding sites for RanBP1 and karyopherin β were the same, the two proteins would compete for binding to Ran. To test this possibility directly, [α-32P]GTP-Ran was mixed with affinity matrices of GST-RanBP1 or karyopherin β that contained increasing amounts of untagged competitor. The amount of Ran able to associate with the affinity matrices in the presence of competitor was then quantified. Whereas RanBP1 competed efficiently with GST-RanBP1 for binding to Ran, RanBP1 did not disrupt the association between Ran and karyopherin β (Fig. 3B). Likewise, karyopherin β did not compete with GST-RanBP1 for binding to Ran (Fig. 3B).

Our laboratory and others have shown that RanBP1 is a co-activator of RanGAP activity (25, 32). Floer and Blobel have since shown that karyopherin β inhibits RanGAP activity (30).
Because Ran is capable of interacting with both RanBP1 and karyopherin β, we explored the possibility that the inhibition of RanGAP activity by karyopherin β could be attenuated by the addition of RanBP1.

To determine the individual and combined effects of RanBP1 and karyopherin β on RanGAP activity, [γ-32P]GTP:Ran was first incubated with the Ran-associating protein(s), then subjected to GTP hydrolysis stimulated by the murine homolog of RanGAP, Fug1 (21). Fug1 stimulated rapid hydrolysis of GTP by Ran, and the rate of hydrolysis was increased 2–4-fold by the addition of RanBP1 (Fig. 4A). Karyopherin β efficiently inhibited the RanGAP activity of Fug1, although maximal inhibition required more than stoichiometric concentrations of karyopherin β. When Ran was incubated with both RanBP1 and karyopherin β prior to exposure to RanGAP, a reduction of the inhibition by karyopherin β was observed (Fig. 4A). The rescue of GAP activity by RanBP1 was not complete, and the two proteins exhibited a mixture of noncompetitive and competitive interactions with RanGAP, suggesting that allosteric interactions occur between RanBP1, karyopherin β, Ran, and RanGAP (Fig. 4B).

Because the Ran binding domain (RBD) of RanBP1 alone confers co-activation of RanGAP activity (25), the ability of this domain to reverse the inhibition of RanGAP by karyopherin β was examined. As shown in Fig. 4C, the RanBD of RanBP1 rescued RanGAP activity to the same extent as full-length RanBP1. A RanBD from RanBP2 (RanBD3) was also able to partially rescue RanGAP activity (not shown), suggesting that the inhibition of RanGAP by karyopherin β can also be reversed at the nuclear pore complex. As predicted, RanBP1 containing a mutation that prevents high affinity binding to Ran (RanBP1 E37K) was not able to reverse the inhibition of RanGAP by karyopherin β (Fig. 4C). Together these results demonstrate that RanBP1 in the cytoplasm and RanBP2 at the nuclear pore can allow the interaction of Ran with RanGAP even in the presence of karyopherin β.

Taken together, these results suggest that Ran can form a quaternary complex with RanBP1 (or RanBP2), karyopherin β, and RanGAP. The binding sites on Ran for RanBP1 and karyopherin β must therefore be distinct, and it is unlikely that karyopherin β contains a Ran binding domain homologous to that of RanBP1, as was proposed by Moroianu et al. (33).

The ability of RanBP1 to partially reverse the block of RanGAP activity imposed by karyopherin β suggests an important function for RanBP1 in the nuclear transport cycle. A current model for nuclear transport proposes that Ran:GTP participates in the formation of a complex with NTF2, nucleoporins, and the NLS receptor (α and β karyopherin) bound to nuclear cargo (12). Nucleotide exchange on Ran within this complex triggers disassembly of the α subunit and the NTF2, but the karyopherin β will remain tightly associated with Ran:GTP. However, as we and others have shown, the Ran-karyopherin β complex is refractory to RanGAP activity, and the intrinsic GTPase activity of the Ran protein is far too slow to allow nuclear transport to proceed (30). The flaw in this model is therefore that all the Ran within the cell would rapidly become trapped in a dead-end complex with karyopherin β. We propose that the essential function of RanBP1 (and RanBP2) in nuclear transport is to bind to the Ran-karyopherin β complex and trigger GTP hydrolysis by RanGAP, thereby permitting a new transport cycle to begin. It will be of interest to test this model in intact cells to determine whether depletion of RanBP1 leads to the accumulation of a stable Ran-karyopherin β complex.

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Note Added in Proof—After acceptance of this paper for publication, Gorlich et al. (Gorlich, D., Pante, N., Kutay, U., Aebi, U., and Bischoff, F. R. (1996) EMBO J. 15, 5584–5594) reported that the inhibition of RanGAP by karyopherin β/importin β was not reversed by RanBP1. The karyopherin β used in our study lacked 12 amino acids at the N-terminus. Because we were concerned that this deletion might have altered the properties of the karyopherin β, we reconstructed the full-length open reading frame using synthetic oligonucleotides, and expressed a GST-fusion of the protein. We found that the full-length karyopherin β bound Ran with an affinity about 10-fold higher than that of the Δ(1–12) deletion protein. The full-length karyopherin β formed a ternary complex with Ran and RanBP1, as does the Δ(1–12) protein. Full-length karyopherin β also completely inhibited RanGAP activity. Finally, in our hands, RanBP1 was able to partially reverse the inhibition of RanGAP by karyopherin β, but the effect was less dramatic than that with the Δ(1–12) protein (30% recovery versus 80% recovery, under the conditions tested). These results confirm the conclusions described above. To establish that the N-terminal domain of karyopherin β is both necessary and sufficient for Ran binding, we constructed a second GST-fusion protein consisting of residues 1–330. This fusion protein, which lacks the sequences proposed by Moroianu et al. (33) to constitute the Ran binding site, was fully capable of binding Ran:GTP. Together, these data strongly implicate the N-terminal 12 amino acid residues of karyopherin β both in Ran binding and in the modulation of RanGAP activity by RanBP1. They show that the Ran binding domain of karyopherin β is in the N-terminal region and bears no similarity to the Ran binding domain of RanBP1.
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