Complex Formation between Tap and p15 Affects Binding to FG-repeat Nucleoporins and Nucleocytoplasmic Shuttling*

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Jun Katahira‡, Katja Straesser§, Takuya Saiwaki¶, Yoshihiro Yoneda‡, and Ed Hurt**

From the *Division of Immunology, Section of Cellular Interactions and Morphogenesis, Institute for Molecular and Cellular Biology, Osaka University, 1-3 Yamadaoka Suita, Osaka 565-0871, Japan, #Biochemie-Zentrum Heidelberg, University of Heidelberg, Im Neuenheimer Feld 328, D69120 Heidelberg, Germany, and the ‡Department of Cell Biology and Neuroscience, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

Mammalian Tap-p15 and yeast Mex67p-Mtr2p are conserved and essential mRNA export factor complexes that transport mRNPs through the nuclear pore. Here, we report that the small subunit p15 affects the binding of the large subunit Tap to repeat nucleoporins. BLAcore measurements revealed that recombinant Tap binds with high affinity (Kₐ in the nM range) to repeat nucleoporins and dissociates from them very slowly. In contrast, when recombinant Tap was bound to p15, the derived heterodimeric complex exhibited a significant lower affinity to FG-repeat nucleoporins (Kₐ in the μM range). Furthermore, when recombinant Tap lacking the N-terminal nuclear localization sequences (TapΔNLS) was microinjected in mammalian cells, it did not shuttle; however, TapNLS with bound p15 efficiently shuttles between nucleus and cytoplasm. We conclude that heterodimerization of Tap and p15 is required for shuttling of the functional Tap-p15 mRNA exporter complex.

Transport of macromolecules in and out of the nucleus occurs through the nuclear pore complexes (NPCs). Nuclear import and export require soluble transport receptors and nucleoporins (for review see Ref. 1 and 2). Import and export cargoes are recognized by importins or exportins, respectively, which belong to the importin-β type receptor family. The cargo-receptor complexes translocate through the NPC based on the direct binding of the importin-β type receptors to phenylalanine-glycine (FG)-repeat-containing nucleoporins (3–6). Although the mechanism of translocation through the pore is still unknown, several models exist. In one model, importin-β, which has different affinities to various FG-repeats, migrates through the NPC toward the nucleoplasm due to an affinity gradient (7). For transportin and NTF2 it was suggested that they translocate through the NPC by equally low affinities to the different nucleoporins (8–10).

Human Tap was first identified as the putative mammalian orthologue of the Saccharomyces cerevisiae mRNA exporter Mex67p (11) and to be necessary for the export of a viral RNA-export element called CTE (12). As does Mex67p, Tap shuttles between nucleus and cytoplasm and binds to poly(A)+ RNA in vivo (13). Tap exhibits a pronounced domain organization. The middle domain of Tap binds to p15 (13, 14), while the C-terminal domain binds to various FG-repeat-containing nucleoporins (13, 14). The N-terminal domain of Tap contains a basic NLS (13, 14), which is recognized by transportin (14) and an RNA-binding domain (13, 15) that exhibits a canonical RNP fold (16). Furthermore, in vivo Tap binds to a series of intranuclear proteins including Aly (Yra1p in yeast), which are recruited to the mRNA during splicing and mark the mature and thus export-eligible mRNA (17–20).

Recent results indicate that p15 is crucial for nuclear mRNA export by Tap. However, p15, which is also called NXT1, was shown to be involved in Crm1-dependent nuclear protein export (21). Hence, p15 may play a role in multiple nuclear export pathways. Nuclear export of mRNAs in mammalian cells is stimulated by co-expression of p15 and Tap (22–24), and the complex formation of Tap and p15 was shown to be required for the stimulatory activity (25). The Tap-p15 complex is the functional orthologue of the yeast mRNA exporter Mex67p-Mtr2p, which indicates that the mRNA export pathway is conserved from yeast to human (13). Interestingly, a mutation of MEX67 that abrogates its interaction with Mtr2p leads to mislocation of Mex67p into the cytoplasm and concomitant nuclear accumulation of poly(A)+ RNA. This suggested that complex formation of Mex67p-Mtr2p is required for both pore association and mRNA export. Furthermore, complex formation between Mex67p and Mtr2p is required for nucleoporin binding in vitro (26). These findings led to the conclusion that Mtr2p could function in mRNA export by altering the affinity of Mex67p to repeat nucleoporins (26) and Mtr2p (27). Binding of Mex67p alone to FG-repeat nucleoporins has been also shown, but in this case it was not tested whether Mtr2p influences this interaction (27). On the other hand, Tap itself possesses a distinct affinity for FG-repeat nucleoporins. In this report, we show that p15 significantly decreases the affinity of Tap to various FG-repeats and enables the Tap-p15 heterodimer to translocate efficiently through the nuclear pores in both directions.

MATERIALS AND METHODS

Plasmid Construction—Construction of the Escherichia coli expression vectors for untagged p15 (pET9d-p15) and for the FG-repeat domain of CAN (aa 1462–1909, pGEX-CAN4H) was reported (13). DNA fragments encoding an 188–619 and 188–550 of Tap were amplified by PCR and subcloned into the BamHI and SalI sites of pGEX6P1 (Amersham Biosciences, Inc.). DNA fragments encoding the repeat domains of hCG1 (aa 216–377), Nup98 (aa 1–466), and p62 (aa 1–300) were amplified by PCR and subcloned into the expression vectors for untagged p15 (pET9d-p15) and for the FG-repeat domain of CAN (aa 1462–1909, pGEX-CAN4H) was reported (13). DNA fragments encoding an 188–619 and 188–550 of Tap were amplified by PCR and subcloned into the BamHI and SalI sites of pGEX6P1 (Amersham Biosciences, Inc.). DNA fragments encoding the repeat domains of hCG1 (aa 216–377), Nup98 (aa 1–466), and p62 (aa 1–300) were amplified by PCR and subcloned into the BamHI and SalI sites of pGEX-CAN4H.

Protein Expression and Purification—TapΔNLS, TapΔNLS-p15, and

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** To whom correspondence may be addressed. Tel.: 81-6-6879-3210; Fax: 81-6-6879-3219; E-mail: yyoneda@anat3.med.osaka-u.ac.jp.

§ To whom correspondence may be addressed. Tel.: 49-6221-54-41-98; Fax: 49-6221-54-41-73; E-mail: eg@eel.rez.uni-heidelberg.de.

** To whom correspondence may be addressed. Tel.: 81-6-6879-3210; Fax: 81-6-6879-3219; E-mail: yyoneda@anat3.med.osaka-u.ac.jp.

† To whom correspondence may be addressed. Tel.: 49-6221-54-41-73; Fax: 49-6221-54-41-69; E-mail: eg@eel.rez.uni-heidelberg.de.

‡ To whom correspondence may be addressed. Tel.: 49-6221-54-41-98; Fax: 49-6221-54-41-73; E-mail: eg@eel.rez.uni-heidelberg.de.

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TapaNLS C and TapαNLS G were expressed in E. coli strains BL21 (DE3) harboring pGEX6P1-TapαNLS alone, pGEX6P1-TapαNLS and pET9d-p15, or pGEX6P1-TapαNLS C. E. coli cells were harvested, resuspended with phosphate-buffered saline (8 mM Na2HPO4/1 mM KH2PO4/137 mM NaCl/3 mM KCl (pH 7.4) containing 1 mM DTT (PBS-DTT), and disrupted kinetically limiting. Thus, we conclude that the fluorescent labeling did not grossly interfere with the repeat binding ability of Tap. For microinjection and in vitro import assays, concentrations of the Alexa 546-labeled proteins were adjusted to 2 mg/ml in phosphate-buffered saline.

Formation of HeLa cell homokaryons by Sendai virus and microinjection assay were carried out as reported (28). Thirty min after microinjection cells were fixed with formaldehyde and observed with a Zeiss Axioskop II fluorescence microscope.

For *in vitro* import assays Madin-Darby bovine kidney cells were used. Cytosolic extract was prepared from Ehrlich ascites tumor cells as reported previously (29). Cells grown on glass 8-well multitest slides (ICN Biomedicals) were treated with ice-cold transport buffer (20 mM Tris-HCl (pH 8.0)/1 mM DTT) and adjusted to 2 mg/ml in phosphate-buffered saline.

**Microinjection Experiments and in Vitro Import Assay**—Labeling of proteins with fluorescent dye was achieved with the Alexa 546 labeling kit (Molecular Probes) according to the manufacturer’s instructions. Unincorporated dye was removed by PD-10 gel filtration column chromatography (Amersham Biosciences, Inc.). All the purification steps except protease treatment were done at 4 °C. GST-TapaNLS C and GST-TapaNLS G co-expressed with untagged p15 were purified as described above except that the PreScission elution step was replaced by elution with 20 mM glutathione. The repeats of CAN, Nup98, and p62 were purified as described (13).

Pull Down Assays—Pull down assays were performed as reported previously (13, 30). Unbound proteins were precipitated with 10% trichloroacetic acid. After extensive washing, bound proteins were eluted by treating the resin with SDS-sample buffer. Aliquots corresponding to 50% of input of the bound and unbound fractions were loaded onto SDS-14% polyacrylamide gels and protein bands were separated by electrophoresis and visualized by Coomassie staining.

**Binding Assays**—Ligands (GST-fused nucleoporin repeats) were immobilized via anti-GST antibody covalently attached on CM5 research-grade sensor chips (BIAcore). Activation and blocking of sensor chips and immobilization of anti-GST antibody were done using the Amine-coupling and GST antibody kits (BIAcore) according to the manufacturer’s instructions. Analysis of protein-protein interactions was carried out in transport buffer containing 0.2% Tween 20 at a flow rate of 20 μl/min at 20 °C using a BIAcore 2000 system. Parallel injections of analytes over a GST-immobilized flow cell were subtracted from the data as background. Apparent *Kd* values for TapaNLS/p15-repeat binding were derived from Scatchard plots RU/concentration versus RU and linear regression analysis by Kypplot software (31, 32). The absence of mass transport limitation and/or rebinding was tested by injecting TapaNLS on sensor chips harboring different amounts of each GST-repeat at a flow rate of 20 μl/min at 20 °C. Since the sensorgrams were superimposable (data not shown), it can be concluded that the diffusion of the analyte from the bulk flow to the sensor chip surface is not kinetically limiting. Thus, *Kd* values for TapaNLS-repeat bindings were obtained by using standard kinetic equations supplied within the BIAevaluation 3.1 software.

**Biochemical Function of p15**

**Fig. 1. TapaNLS-p15 complex but not TapaNLS alone enters the nucleus without the aid of soluble factors.** Alexa 546-labeled TapaNLS (B and D) or TapaNLS-p15 complex (A and C) was incubated with digitonin-permeabilized Madin-Darby bovine kidney cells in the presence (A and B) or absence (C and D) of cytosolic extract and an ATP-regenerating system. After incubation at 30 °C for 30 min cells were fixed and observed with a fluorescence microscope (left panels). Average fluorescent intensities in the nuclei (arbitrary units) are 101 (A), 47 (B), 95 (C), and 28 (D). The same fields were viewed with phase-contrast (right panels).

**Fig. 2. TapaNLS-p15 complex but not TapaNLS alone migrates through the NPC in both directions.** Alexa 546-labeled TapaNLS (C and D, middle panels, red), TapaNLS-p15 complex (A and B, middle panels, red), GST-TapaNLS C-p15 (E and F, middle panels, red) or GST-TapaNLS-p15 (G and H, middle panels, red) were microinjected into the nucleus (A, C, E, G) or the cytoplasm (B, D, F, H) of Sendai virus-induced HeLa cell homokaryons together with an injection marker (Alexa 488-labeled goat antimouse IgG; left panels, green). Injected nuclei are marked by arrow heads (A, C, E, G). After incubation at 37 °C for 30 min cells were fixed with formaldehyde, and the intracellular localization of the injected proteins was examined with a fluorescence microscope. The same cells were also viewed with phase contrast (right panels).
RESULTS

TapΔNLS-p15 Complex Enters the Nucleus without the Aid of Soluble Factors—The C-terminal domain of Tap (aa 540–619) binds directly to nucleoporins and confers to Tap the ability to translocate through the nuclear pore (13, 33–35). However, \textit{in vitro} Tap requires its N-terminal NLS and transportin for nuclear import (14). To find out whether p15 can confer transportin-independent shuttling of Tap, fluorescently labeled TapΔNLS lacking the transportin binding site (14) either alone or complexed with p15 was tested in an \textit{in vitro} nuclear import assay. This revealed that TapΔNLS can enter the nucleus only when bound to p15 (Fig. 1A). In contrast, free TapΔNLS is only inefficiently imported and has the tendency to accumulate at the nuclear periphery (Fig. 1B). Unexpectedly, nuclear import of TapΔNLS-p15 was still observed when cytosol (containing karyopherins and Ran) and an energy-regenerating system were omitted from the \textit{in vitro} assay (Fig. 1C).

Under these conditions, GST-GFP-M9 import substrate was not imported into the nucleus unless cytosol and an ATP-regenerating system were added (data not shown), indicating that not only the soluble transport factors (i.e.; transportin and Ran) as well as energy are deprived. Under the same conditions, TapΔNLS alone did not enter the nucleus (Fig. 1D). These data indicate that upon complex formation with p15 TapΔNLS gains the ability to translocate through the nuclear pore and no longer requires transportin/RanGTP for nuclear import. In the light of this finding, the role of the N-terminal NLS of Tap remains unclear. Transportin could be required for the rapid re-import of free Tap and/or for nuclear import of newly synthesized Tap only. Another possibility is that transportin is required for efficient release of mRNP cargoes from Tap-p15, since the N-terminal NLS and the RNA-binding domain of Tap are adjacent to each other.

\textit{TapΔNLS Shuttles between the Nucleus and Cytoplasm Only in Association with p15}—To analyze nucleocytoplasmic shuttling of TapΔNLS-p15 \textit{in vivo}, fluorescently labeled TapΔNLS, either alone or in complex with p15 were microinjected into the cytoplasm or nucleus of HeLa cell homokaryons. When free TapΔNLS was injected into one of the several nuclei of a homokaryon, it was not exported (Fig. 2C). Similarly, TapΔNLS injected into the cytoplasm of a homokaryon was not imported into the nucleus (Fig. 2D). In contrast, the TapΔNLS-p15 complex, regardless of the injection site, was able to translocate through the nuclear pores in both directions and rapidly accumulated in the nuclei (Fig. 2A and B). The ability of Tap-p15 to shuttle depends on the ability of TapΔNLS to bind to FG-repeat nucleoporins, since TapΔNLS lacking its C-terminal domain but bound to p15 (GST-TapΔNLSΔC-p15), showed a reduced binding to FG-repeat Nups (see below) and lost the ability to shuttle between the nucleus and cytoplasm (Fig. 2E and F). The inability of GST-TapΔNLSΔC-p15 to shuttle is not due to the larger complex size caused by the GST tag, since GST-TapΔNLS-p15 is still able to translocate through the nuclear pores (Fig. 2G and H). Taken together, our results show that complex formation with p15 enables Tap to translocate through the nuclear pores in both directions.

\textit{Tap Exhibits Different Affinities to Various FG-repeats in the Presence or Absence of p15}—It is well documented that Tap can interact directly with FG-repeat-containing nucleoporins CAN/ Nup214 and hCG1 via its C-terminal domain (aa 507–619) (13, 33). Since p15 is necessary for shuttling of Tap \textit{in vivo}, p15 could modulate the FG-repeat binding ability of Tap. To test this possibility, the binding of TapΔNLS alone or the TapΔNLS-p15 complex to nucleoporin repeats was analyzed \textit{in vitro}. As reported earlier, purified TapΔNLS can bind to the FG-repeat domains of CAN and hCG1 (Fig. 3A and B, lanes 2–4). In addition to these FG-nucleoporins, TapΔNLS also bound efficiently to the FXFG-repeats of p62 and GLFG-repeats of Nup98 (Fig. 3, C and D, lanes 2–4; see also Ref. 14). In contrast to the strong binding of TapΔNLS to FG-repeats, binding of TapΔNLS complexed to p15 was weaker since most of the complex was recovered in the unbound fraction (Fig. 3, A–D, lanes 5–7 and 13–15). We conclude that complex formation with p15 reduces the affinity of Tap to nucleoporin repeats.

To obtain quantitative data on the binding of TapΔNLS \textit{+/−} p15 to repeat nucleoporins, we performed BIAcore measurements. Repeat sequences from the different nucleoporins were immobilized on a sensor chip and varying concentrations of TapΔNLS or TapΔNLS-p15 complex were injected. Free TapΔNLS bound very efficiently to all of the repeat sequences tested and dissociated extremely slowly (Fig. 4A). The $K_d$ value of free Tap to nucleoporin repeats lies in the nM range, showing that Tap alone binds very strongly to repeat nucleoporins (Fig. 4A, inset). In contrast, the TapΔNLS-p15 complex showed a weaker and transient interaction with the different nucleoporin repeats; accordingly, \textit{−}10 times more TapΔNLS-p15 com-
plex had to be used in the Biacore binding assays. Strikingly, the sensorgram exhibited almost a rectangular shape indicative of an extremely high dissociation rate of Tap-p15 from the repeat sequences (Fig. 4B, left panels). Since the on/off rates for TapNLSp15 from FG-repeats (except CAN4 repeats) were too fast to be reliably calculated by kinetic analysis, the apparent dissociation constants (K_d) were obtained by Scatchard analysis. The TapNLSp15 complex binds to nucleoporin repeats with a K_d in the µM range (see Fig. 4B, right panels). The efficient binding of Tap to repeat sequences requires the C-domain of Tap, since deletion of this domain significantly reduced the amount of Tap-p15 bound to repeats (Fig. 4C). However, a residual but significant binding of Tap-p15 to several repeat nucleoporins is evident (See also Fig. 2, E and F). This residual binding may result in nuclear rim localization observed in microinjected cells (see Fig. 2, E and F). The observed lower on-rate of TapNLSp15 to CAN4 FG-repeats in comparison to other tested FG-Nups is not understood at present. This could be due to a lower amount of immobilized GST-CAN4 on the sensor chip or may be a peculiarity of the CAN4 FG-repeat construct. In summary, p15 decreases the affinity of Tap to nucleoporin repeats about 1,000-fold. These data indicate that p15 functions to modulate the interaction of Tap with FG-repeat nucleoporins by making this association more transient.

**DISCUSSION**

Previous work has revealed that p15 is required for nuclear mRNA export (see Introduction). Here, we report a biochemical function for p15. Our data show that binding of p15 to Tap affects the affinity of the Tap-p15 complex to nucleoporin repeats. This enables the Tap-p15 complex to shuttle between the nucleus and the cytoplasm. How could p15 perform its function to modulate the binding of Tap-p15 to repeat nucleoporins? Interestingly, the middle domain of Tap, which binds to p15, and p15 itself show homology to NTF2, which was shown to bind directly to FG-repeat nucleoporins (13, 26, 36). Furthermore, a Mex67p-Mtr2p complex that lacks the C-domain of Mex67p, is still able to bind to repeat nucleoporins (26). In accordance with these observations, recent structural data of the Tap-p15 heterodimer indicates that the middle domain of Tap acts synergistically with the C-terminal NPC-binding domain in binding to nucleoporin repeats as well as in shuttling (25). This analysis also showed that p15 contributes only indirectly to repeat binding of Tap, most likely by stabilizing the overall NTF2-like fold of the M-domain of Tap. These structural

Fig. 4. Real time analysis of the interaction between TapNLSp15 complex and various repeats. A, GST-CAN4, GST-hCG1, GST-Nup98, and GST-p62 were immobilized on CM5 sensor chips through covalently coupled anti-GST antibodies. Injection of these GST fusion proteins resulted in average binding signals of 95 RU (GST-CAN4), 795 RU (GST-hCG1), 380 RU (GST-Nup98), and 599 RU (GST-p62). The indicated concentrations of TapNLSp15 were then injected over the sensor chip with immobilized GST (average binding signal of 498 RU) were subtracted from the data to eliminate contributions due to minor refractive index changes and background binding. Apparent binding constant values (K_d) obtained from each binding reaction are indicated in each graph. B, sensorgrams illustrating binding of various concentrations (6.0, 4.5, 2.3, 1.5, and 1.1 µM) of TapNLSp15 to immobilized repeats (left panels). Scatchard plot analysis of the data (right panels). Sensor responses at equilibrium (R_eq) were determined for each protein concentration from each sensorgram, and R_eq/concentration of TapNLSp15 values were plotted as a function of R_eq. The slopes of the curves obtained by linear transformation yields the dissociation constants K_d (insets). C, GST-Nup98, GST-p62, GST-hCG1, and GST-CAN4 were immobilized on a CM5 sensor chip as in A. Purified TapNLSp15 complex (5.98 µM, gray boxes) and TapNLSp15 (5.98 µM, black boxes) were then injected over the sensor chip. Control injections over a sensor chip with immobilized GST were subtracted from the data as background, and the RU value at equilibration was obtained as R_eq values. Data are presented as average values of three experiments ± S.D.
tural studies furthermore revealed a hydrophobic pocket in M-domain of Tap, which binds to a single phenylalanine residue of nucleoporin FG-repeats. Thus, the Tap-p15 heterodimer may move through the NPC by consecutive low affinity interactions with repeat nucleoporins.

It is not clear whether Tap functions as a monomer in vivo. If so, the measured in vitro affinities of the Tap monomer could be meaningful. Accordingly, Tap with bound mRNP cargo could be first recruited to the nucleoplasmic side of the NPC due to its strong affinity to repeat nucleoporins. p15 would then associate to trigger the release of Tap from these high affinity binding sites due to an increased dissociation rate. If p15 stays permanently bound to Tap during pore passage, Tap-p15 would efficiently pass through the NPC channel by hopping between different repeat nucleoporins due to its comparably low affinities as suggested for transportin and NTF2 (10). Alternatively, multiple association/dissociation cycles of p15 and Tap may move through the NPC by consecutive low affinity interactions with repeat nucleoporins. Since the C-terminal repeat binding domain of Tap alone is able to mediate NPC translocation in vitro (35), it is likely that both the C-domain and the M-domain of Tap act in concert as NPC shuttling devices. The correct folding of the middle domain of Tap, which requires binding to p15, may affect the overall conformation of the Tap-p15 heterodimer and hence might be a prerequisite for efficient shuttling of this mRNA export factor through the nuclear pores.

In summary, we have shown that p15 is a crucial co-factor of Tap that affects the interaction of Tap with repeat-containing nucleoporins. Thus, the Tap-p15 complex gains the capability to translocate efficiently through the NPC, which is the basis for export of mRNA from the nucleus to the cytoplasm.

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