Unconventional Myosin VIIA Is a Novel A-kinase-anchoring Protein*

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To gain an insight into the cellular function of the unconventional myosin VIIA, we sought proteins interacting with its tail region, using the yeast two-hybrid system. Here we report on one of the five candidate interactors we identified, namely the type Iα regulatory subunit (RIα) of protein kinase A. The interaction of RIα with myosin VIIA tail was demonstrated by immunoprecipitation from transfected HER293 cells. Analysis of deleted constructs in the yeast two-hybrid system showed that the interaction of myosin VIIA with RIα involves the dimerization domain of RIα. In vitro binding assays identified the C-terminal “4.1, ezrin, radixin, moesin” (FERM)-like domain of myosin VIIA as the interacting domain. In humans and mice, mutations in the myosin VIIA gene underlie hereditary hearing loss, which may or may not be associated with visual deficiency. Immunohistofluorescence revealed that myosin VIIA and RIα are coexpressed in the outer hair cells of the cochlea and rod photoreceptor cells of the retina. Our results strongly suggest that myosin VIIA is a novel protein kinase A-anchoring protein that targets protein kinase A to definite subcellular sites of these sensory cells.

Myosin VIIA is an unconventional myosin, which plays a key role in both the eye and inner ear functions. Mutations in the MYO7A gene are responsible for Usher syndrome type 1B (USH1B),1 characterized by congenital sensorineural deafness, vestibular dysfunction, and retinitis pigmentosa (1). Mutations in this gene also underlie autosomal recessive and dominant forms of isolated deafness (2–4). In the retina, myosin VIIA is expressed in the photoreceptor cells and the pigment epithelium (5–7), where it is believed to be involved in the transport of opsins (8) and the distribution of melanosomes (9), respectively. In the inner ear, the expression of myosin VIIA is restricted to the sensory hair cells in both the cochlea (auditory apparatus) and the vestibule (balance organ) (5, 6, 10, 11). Myosin VIIA-defective mice (shaker-1 mutants) are deaf (12) and harbor a disorganization of the hair cell stereocilia, i.e. the mechano receptor structure (13). In addition, the uptake of aminoglycosides by the hair cells is impaired (14). Interestingly, a crucial role of myosin VIIA in phagocytosis has recently been demonstrated in the Dictyostelium discoideum (15), which suggests that the role of this protein in endocytosis has been conserved throughout evolution.

In addition to the eye and inner ear, myosin VIIA is expressed in a variety of organs or tissues including the olfactory epithelium, brain, choroid plexus, intestine, liver, kidney, adrenal gland, and testis (16, 17). However, the phenotypes associated with myosin VIIA mutations in humans and mice have so far revealed deleterious effects only in the inner ear and the eye.

The primary structure of myosin VIIA (Fig. 1A) is typical of unconventional myosins (18). Myosin VIIA is composed of a N-terminal motor head domain (aa 1–729) containing the ATP-binding site, a coiled-coil neck (aa 730–855) composed of five isoleucine/glutamine (IQ) motifs, a long helical tail (aa 856–2215) (10, 19). The tail segments of unconventional myosins contain domains that are believed to interact with other proteins, such as cargo molecules and components of the signal transduction pathways. The tail of myosin VIIA (Fig. 1A) begins with a short coiled-coil domain (79 aa), which has been shown, using the yeast two-hybrid system, to be implicated in the formation of myosin VIIA homodimers (2). This dimerization domain is followed by two large repeats (I and II) of about 460 aa each, with a poorly conserved Src homology 3 domain in between (19, 20). Each repeat is composed of a “myosin tail homology-4” (MYTH4) domain and a “4.1, ezrin, radixin, moesin” (FERM)-like domain (21), which characterizes the protein 4.1 superfamily. This family includes proteins 4.1, talin, filopodin, and merlin/schwannomin and the ERM proteins, ezrin, radixin, and moesin. The FERM domains of these proteins have been shown to bind, either directly or via an adaptor protein, to various integral membrane proteins (for a review, see Ref. 22). Accordingly, myosin VIIA could be one of the molecules that cross-link the cortical actin filaments to the plasma membrane (22–24).

The identification of proteins that interact with myosin VIIA tail is expected to provide helpful clues for understanding its role at the cell level. We used the yeast two-hybrid system to seek such interacting proteins. Five specific cDNAs were thereby isolated. Here we report on one of these that encodes the type Iα regulatory subunit (RIα) of cAMP-dependent protein kinase (PKA).

EXPERIMENTAL PROCEDURES

Plasmids—The bait used for the screening was the C-terminal 464-aa fragment of myosin VIIA (aa positions 1752–2215) derived from cDNA R358 (10) and cloned in-frame with the LexA DNA binding domain of LexA and GAL4BD, DNA binding domain of GAL4; GAL4AD, transcription activating domain of GAL4; 3-AT, 3-aminotriazole; AKAP, A-kinase-anchoring protein; PKA, cAMP-dependent protein kinase; C and R, catalytic and regulatory subunits of PKA, respectively; RIα and Iβ, type Iα and Iβ regulatory subunit of PKA, respectively; aa, amino acid(s); MYTH4, myosin tail homology-4; FERM, 4.1, ezrin, radixin, moesin; UTR, untranslated region; PBS, phosphate-buffered saline; OHC, outer hair cell; IHC, inner hair cell.

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1 The abbreviations used are: USHIB, Usher syndrome type 1B; LexABD, DNA binding domain of LexA; GAL4BD, DNA binding domain of GAL4; GAL4AD, transcription activating domain of GAL4; 3-AT, 3-aminotriazole; AKAP, A-kinase-anchoring protein; PKA, cAMP-dependent protein kinase; C and R, catalytic and regulatory subunits of PKA, respectively; RIα and Iβ, type Iα and Iβ regulatory subunit of PKA, respectively; aa, amino acid(s); MYTH4, myosin tail homology-4; FERM, 4.1, ezrin, radixin, moesin; UTR, untranslated region; PBS, phosphate-buffered saline; OHC, outer hair cell; IHC, inner hair cell.
Myosin VIIA Binds to RIα Subunit of PKA

Human Retina cDNA Fusion Library—Human retina poly(A)* RNA was purchased from CLONTECH (Palo Alto, CA). The cDNA library was constructed by generating random and oligo(dT)-primed cDNAs using the SuperScript cDNA synthesis kit (Life Technologies, Inc.). cDNAs were cloned downstream GALAID in pGAD-GE. About 7 × 10⁵ independent clones were obtained.

Yeast Two-hybrid Screening—A yeast two-hybrid screening was performed according to Vojtek et al. (26). Briefly, the yeast cells expressing the LexABD-bait fusion protein were transformed with the human retinal cDNA expression library (see above). The positive clones were rescued, retransformed into fresh L40 yeast cells, and confirmed by growth on plates lacking histidine and β-galactosidase assay. The positive clones were further analyzed by cotransformation with irrelevant baits, used as negative controls (see “Results and Discussion”).

DNA Sequencing and Sequence Analysis—DNA sequencing was performed using the Sequencer kit (U.S. Biochemical Corp.) on an Applied Biosystems ABI 377 or ABI 373 automatic DNA sequencer. Sequences were analyzed using the Wisconsin Package (Genetics Computer Group, Inc., Madison, WI).

Data base searches were performed with the BLAST 2.0 algorithm in the nonredundant nucleotide sequence data base (GenBankTM/EMBL/ DDBJ/PDB) and nonredundant peptide sequence data base (GenBankTM CDS translations/PDB/SwissProt/PIR/PRF) maintained at NCBI (available on the World Wide Web).

In Vivo Two-hybrid Analysis—pNLX3-BdC1 (1752–2006) was expressed in E. coli strain M15 according to the manufacturer’s instructions (Qiagen). Biotinylated fusion proteins in PinPoint Xa vectors were produced in E. coli strain HB101 following the protocol of the PinPoint protein purification kit (Promega). Grown bacterial cultures were pelleted and resuspended in buffer B (10 mM Tris-HCl, pH 7.5, 150 mM NaCl, 5 mM MgCl₂, 10% glycerol) with protease inhibitors (0.5 mM phenylmethylsulfonyl fluoride, 2 μg/ml aprotinin, 2 μg/ml soybean trypsin inhibitor, 1 μg/ml pepstatin). Cell lysates containing biotinylated myosin VIIA fusion peptides or an unrelated control protein (chloramphenicol acetyltransferase) were incubated with tetrameric avidin resin (TetraLink resin, Promega) on a rotating wheel at 4 °C overnight. After incubation, the coated resin was washed three times with buffer B supplemented with 0.1% Nonidet P-40 (Sigma). In vitro binding assays, 100 μl of a bacterial cell lysate containing His₃-RIα (1–286) in buffer B with 0.05% Nonidet P-40 were incubated with 3–6 μl of the coated resins for 2 h at 4 °C on a rotating wheel. The quantity of the protein bound to resin was visualized on a Western blot in order to adjust the amounts of coated resins in the binding experiments. After incubation, the resin was washed five times with 1 ml of buffer B and resuspended in 50 μl of Tris-buffer HS (pH 7.5, 250 mM NaCl, 10 mM MgCl₂, 1 mM EDTA, 10% glycerol, 1% Nonidet P-40). Bound proteins were eluted from the resin by boiling in SDS gel-loading buffer, separated by electrophoresis on SDS-polyacrylamide gel (12%) (27), electrotransferred to nitrocellulose sheets, and then submitted to immunoblot analysis. The blot was blocked in 5% powdered nonfat milk. To reveal His₃-RIα (1–286), the blot was incubated with monoclonal antibodies against the polyhistidine tag at 1:2000 dilution (anti-RGS-His, Qiagen). Monoclonal antibodies against the polyhistidine tag at 1:2000 dilution (anti-RGS-His, Qiagen) were used for detection. To visualize the amounts of biotinylated peptide/proteins used in each binding assay, the same blot was incubated with horseradish peroxidase-conjugated streptavidin at 1:2000, washed three times, the blot was incubated with monoclonal antibodies against myosin VIIA were preincubated with protein A-agarose (Amer sham Pharmacia Biotech) on a rotating wheel. The quantity of the protein bound to resin was visualized on a Western blot in order to adjust the amounts of coated resins in the binding experiments. After incubation, the resin was washed five times with 1 ml of buffer B and resuspended in 50 μl of Tris-buffer HS (pH 7.5, 250 mM NaCl, 10 mM MgCl₂, 1 mM EDTA, 10% glycerol, 1% Nonidet P-40). Bound proteins were eluted from the resin by boiling in SDS gel-loading buffer, separated by electrophoresis on SDS-polyacrylamide gel (12%) (27), electrotransferred to nitrocellulose sheets, and then submitted to immunoblot analysis. The blot was blocked in 5% powdered nonfat milk. To reveal His₃-RIα (1–286), the blot was incubated with monoclonal antibodies against the polyhistidine tag at 1:2000 dilution (anti-RGS-His, Qiagen). Monoclonal antibodies against the polyhistidine tag at 1:2000 dilution (anti-RGS-His, Qiagen) were used for detection. To visualize the amounts of biotinylated peptide/proteins used in each binding assay, the same blot was incubated with horseradish peroxidase-conjugated streptavidin at 1:2000 dilution (Amer sham Pharmacia Biotech) were used for detection. To visualize the amounts of biotinylated peptide/proteins used in each binding assay, the same blot was incubated with horseradish peroxidase-conjugated streptavidin at 1:2000 dilution (Amer sham Pharmacia Biotech). The protein bands were revealed with the ECL chemiluminescence system. The band intensity was measured using the ImageQuant software (Molecular Dynamics, Sunnyvale, CA). The protein bands were revealed with the ECL chemiluminescence system. The band intensity was measured using the ImageQuant software (Molecular Dynamics, Sunnyvale, CA).
glycerol, 5% β-mercaptoethanol), and boiled for 5 min. After centrifugation, the supernatant was subjected to SDS gel electrophoresis (27) in a 4–20% acrylamide gradient. Proteins were electrotransfered to nitrocellulose sheets. Blots were incubated overnight with 5% nonfat dry milk in Tris-buffered saline containing 0.05% Tween 20. Antibodies to Rλ and to myosin VIIA were diluted at 1:1000 and 1:5000, respectively. Horseradish peroxidase-conjugated goat anti-rabbit antibodies (Bio-Rad) and the ECL chemiluminescence system (Amersham Pharmacia Biotech) were used for detection.

Immunohistofluorescence—Adult guinea pig inner ears were fixed for 3 h in 4% paraformaldehyde in PBS, pH 7.4, and then decalcified for 4 days in 10% EDTA-PBS at 4 °C. Human retinas were fixed in 4% paraformaldehyde-PBS overnight at 4 °C. After three washes with PBS, the samples were immersed in 20% sucrose-PBS for 12 h at 4 °C and then frozen in Tissue-Tek O.C.T. embedding medium (Miles). Cryostat sections (10–14 μm) were processed as described previously (6). The polyclonal antibodies against the Rλ (sc-906) and Rβ (sc-907) regulatory subunits of PKA were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA); these antibodies are partially cross-reacting. The inner ear hair cells were identified using the affinity-purified polyclonal anti-myosin VIIA antibody (6). The specificity of the immunolabeling was verified by omission of the first antibody and use of the preimmune serum.

RESULTS AND DISCUSSION

Yeast Two-hybrid Screening for Interacting Partners of the Myosin VIIA Tail Identifies the Rλ Regulatory Subunit of Protein Kinase A—The presence of a FERM domain at the C-terminal end of myosin VIIA is expected to target this molecule to cell membrane proteins and possibly serves as a “cargo binding domain” (21). This domain is preceded by a MyTH4 domain of unknown function. The same tandem arrangement of the two domains is present in other motor proteins, namely myosin X, myosin XV, and a plant kinesin (18, 19, 29, 30), suggesting that the association of these domains has a functional significance. Therefore, two peptides covering the C-terminal MyTH4 and FERM domains (repeat II), which differed by their N termini, were tested for their ability to be used as baits in a two-hybrid screen. They were expressed as a fusion protein with LexABD in the pNLX3 vector. The longer peptide (aa 1698–2215) caused a strong activation of the two reporter genes on its own and could not be used. The shorter peptide (aa 1698–2215) caused a strong activation of the two reporter genes on its own and could not be used. The shorter peptide (aa 1698–2215) gave a weak activation of the histidine reporter genes on its own and could not be used. The shorter peptide (aa 1698–2215) could not be used. The shorter peptide (aa 1698–2215) could not be used. The shorter peptide (aa 1698–2215) could not be used. The shorter peptide (aa 1698–2215) could not be used.

To test the specificity of their interaction with the bait, the 141 plasmids were isolated, retransformed into yeast strain AMR70, and mated with the L40 strain containing either the LexABD-bait or theLexABD-lamin C, which served as a negative control. For 27 (19%) of these plasmids, upon coexpression with the LexABD-bait, the His α LacZ + phenotype could not be confirmed. Sixty-nine (49%) plasmids showed also an interaction with LexABD-lamin C and were discarded. The remaining 45 plasmids were analyzed further. They were used to transform the Y187 strain, which was mated with the HF7 strain expressing the GAL4BD in fusion with the bait (GAL4BD-bait in pAS2). This switch from LexABD- to GAL4BD-bait fusions eliminates false positives that may arise as a result of binding to the junction region between LexABD and the bait. Finally, clones that would be able to interact with various FERM domains were eliminated by mating these 45 transformed Y187 yeasts with the HF7 strain carrying either the entire or the N-terminal part (containing the FERM domain) of merlin/schwannomin in fusion with GAL4BD (pGBT10-DH3 and pGBT10-DH1, respectively).

We thereby identified five independent prey clones that 1) grew well on histidine-free plates with 3 mM 3-AT and displayed strong β-galactosidase activity, when coexpressed with the bait, and 2) showed no interaction with the reporter genes in coexpression with lamin C or merlin/schwannomin. This strongly suggested that the proteins encoded by these clones are binding partners of myosin VIIA. Sequencing of the cDNA inserts of the five clones showed in all of them an open reading frame in direct fusion with the GAL4AD. One of them, clone D10, contained a fragment of the human cDNA coding for the regulatory subunit Rλ of PKA (GenBank℠ accession number M33336; Ref. 32).

The cDNA fragment that is present in clone D10 starts by 90 nt of the 5′-UTR, followed by the first 857 nt of the Rλ coding sequence. The 90 nt of the 5′-UTR form an open reading frame (30 aa) in frame with the Rλ coding sequence. The structure of the regulatory subunits (R) of PKA comprises a N-terminal region involved in homodimerization, a hinge that binds to the active site of the catalytic subunit (C) in the absence of cAMP, and two contiguous cAMP-binding domains, A (aa 145–262) and B (aa 263–381). D10 encodes the first 286 aa of Rλ, which is all except for the C-terminal cAMP-binding domain (see Fig. 3).

Immunoprecipitation experiments performed on lysates from transfected HEK293 cells expressing the entire myosin VIIA tail (see “Experimental Procedures”) confirmed the interaction of the endogenous PKA Rλ subunit to myosin VIIA, and also showed the coimmunoprecipitation of the β isoform of RI (Rβ) (Fig. 2). The existence of Rα-Rβ heterodimers (33) in these cells may account for the Rβ coimmunoprecipitation, although a direct binding of the Rβ subunit to myosin VIIA cannot be excluded.

The Dimerization Domain of Rλ Is Involved in the Binding to Myosin VIIA—The PKA holoenzyme is composed of two
myosin VIIA binds to RI$\alpha$ subunit of PKA

Myosin VIIA Binds to RI$\alpha$ Subunit of PKA

In a first attempt to localize the binding site of peptide D10 within the bait, using the yeast two-hybrid system, several truncated or mutated versions of the bait were generated (Fig. 1B), namely two C-terminal truncated baits (BdC1 (aa 1752–2006) and BdC2 (aa 1752–1931), and BdN2 (aa 2007–2215)); and mutated bait BG2137E, carrying the Gly$^{2137}$$\rightarrow$ Glu mutation. The blot was first developed with the anti-RGS-His antibody (bottom) to reveal the bound His$_6$-RI$\alpha$-(1–286) (arrowhead) and then stripped and incubated with streptavidin-horseradish peroxidase conjugate (top) to visualize the biotinylated myosin VIIA peptides. His$_6$-RI$\alpha$-(1–286) binds to the resins coated with the original bait, the BG2137E mutated bait, or the N-terminally truncated peptide BdN1. In contrast, the C-terminally truncated peptides BdC1 and BdC2 fail to interact with His$_6$-RI$\alpha$-(1–286). Positions of the molecular size markers are shown on the left.

RI$\alpha$ Binds to the C-terminal FERM Domain of Myosin VIIA—In a first attempt to localize the binding site of peptide D10 within the bait, using the yeast two-hybrid system, several truncated or mutated versions of the bait were generated (Fig. 1B), namely two C-terminal truncated baits (BdC1 (aa 1752–2006) and BdC2 (aa 1752–1931), and BdN2 (aa 2007–2215)); and mutated bait BG2137E, carrying the Gly$^{2137}$$\rightarrow$ Glu mutation. The blot was first developed with the anti-RGS-His antibody (bottom) to reveal the bound His$_6$-RI$\alpha$-(1–286) (arrowhead) and then stripped and incubated with streptavidin-horseradish peroxidase conjugate (top) to visualize the biotinylated myosin VIIA peptides. His$_6$-RI$\alpha$-(1–286) binds to the resins coated with the original bait, the BG2137E mutated bait, or the N-terminally truncated peptide BdN1. In contrast, the C-terminally truncated peptides BdC1 and BdC2 fail to interact with His$_6$-RI$\alpha$-(1–286). Positions of the molecular size markers are shown on the left.

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Myosin VIIA Binds to RIα Subunit of PKA

To circumvent the difficulty in determining the binding site within myosin VIIA using the yeast two-hybrid system, in vitro binding experiments were performed. The bait, its truncated or mutated versions, and an unrelated control protein (chloramphenicol acetyltransferase) were expressed with an N-terminal biotin tag in bacteria (see “Experimental Procedures”). These peptides were immobilized on an avidin-coupled resin and tested for their ability to bind the His6-RIα-(1–286). The biotinylated baits bound to the resin and the associated proteins were eluted and analyzed on Western blots (Fig. 4). Peptide His6-RIα-(1–286) was found to bind to the resin coated with the bait but not to the resin alone or coated with the control protein (Fig. 4). The resin coated with the C-terminally truncated bait peptides BdC1 (aa 1752–2006) or BdC2 (aa 1752–1931) failed to interact with His6-RIα-(1–286). In contrast, peptide BdN2, comprising the C-terminal 209 aa of the bait (aa 2007–2215), retained His6-RIα-(1–286). Interestingly, the bait carrying the G2137E mutation was also observed to bind to His6-RIα-(1–286) (Fig. 4). These results establish that 1) RIα binds to myosin VIIA within the last 209 aa of the C-terminal FERM domain and 2) the G2137E mutation, which has been found in an USH1B-affected patient, does not affect this interaction.

Sequence analysis detected no homology between myosin VIIA FERM domain and any AKAP domain. More than 20 AKAPs have been identified (42). Although the primary sequence of their PKA binding sites varies substantially, their predicted secondary structure indicates that they form an amphipathic α-helix (36, 43). Their hydrophobic surfaces have been shown to play a key role in the interactions of AKAPs with RI or RII PKA regulatory subunits (36, 44). Interestingly, helical wheel analysis (PEPWheel program) revealed that within the myosin VIIA FERM domain, several sequences (containing 14–18 aa) are predicted to fold into an amphipathic α-helix, i.e. between aa positions 2007 and 2024, 2053 and 2066, and 2193 and 2207.

It has been proposed that AKAPs also act as scaffolds for assembling multiprotein complexes. In particular, AKAPs may assemble signaling complexes through association with multiple enzymes and potential substrates (35, 42). Since the tail of myosin VIIA contains at least three domains probably involved in protein-protein interactions, namely two FERM domains and a putative Src homology 3 domain, we propose that myosin VIIA also acts as a scaffolding organizer. Interestingly, whereas myosin VIIA does not contain any clear consensus motif for PKA phosphorylation (see Ref. 45), partial sequences of the four other putative ligands of the myosin VIIA tail that have been isolated so far have revealed such a motif in at least one of them.2

Myosin VIIA and RIα Are Coexpressed by Some but Not All Sensory Cells of the Retina and Inner Ear—The expression of RIα was studied by immunohistochemistry on tissue sections

2 P. Küssel-Andermann, A. El-Amraoui, S. Safieddine, J.-P. Hardelin, S. Nouaille, J. Camonis, and C. Petit, unpublished results.
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