Multiple C-terminal Motifs of the 46-kDa Mannose 6-Phosphate Receptor Tail Contribute to Efficient Binding of Medium Chains of AP-2 and AP-3*

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The interaction of adaptor protein (AP) complexes with signal structures in the cytoplasmic domains of membrane proteins is required for intracellular sorting. Tyrosine- or dileucine-based motifs have been reported to bind to medium chain subunits (μ) of AP-1, AP-2, or AP-3. In the present study, we have examined the interaction of the entire 67-amino acid cytoplasmic domain of the 46-kDa mannose 6-phosphate receptor (MPR46-CT) containing tyrosine- as well as dileucine-based motifs with μ2 and μ3A chains using the yeast two-hybrid system. Both μ2 and μ3A bind specifically to the MPR46-CT. In contrast, μ3A fails to bind to the cytoplasmic domain of the 300-kDa mannose 6-phosphate receptor. Mutational analysis of the MPR46-CT revealed that the tyrosine-based motif and distal sequences rich in acidic amino acid residues are sufficient for effective binding to μ2. However, the dileucine motif was found to be one part of a consecutive complex C-terminal structure comprising tyrosine and dileucine motifs as well as clusters of acidic residues necessary for efficient binding of μ3A. Alanine substitution of 2 or 4 acidic amino acid residues of this cluster reduces the binding to μ3A much more than to μ2. The data suggest that the MPR46 is capable of interacting with different AP complexes using multiple partially overlapping sorting signals, which might depend on posttranslational modifications or subcellular localization of the receptor.

The 46-kDa mannose 6-phosphate receptor (MPR46) mediates the transport of newly synthesized soluble lysosomal enzymes from the trans-Golgi network (TGN) to the endosomal-prefunctional compartment. Following the pH-induced dissociation of the complexes, the MP4 either return to the TGN or undergo cycling via the plasma membrane (1). Targeting information contained within the 67-residue cytoplasmic domain of this type I integral membrane glycoprotein is responsible for the directed intracellular transport of MPR46 between TGN, endosomes, and the plasma membrane as well as for retention by lysosomal delivery. Mutational analyses have identified several signals including a tyrosine (Tyr45,Arg-Gly-Val86) and dileucine-based motif (Leu64-Leu65), and two aromatic residues (Phe13 and Phe18) required for efficient sorting in the TGN or rapid internalization at the plasma membrane (2–4). Additionally, the di-aromatic Phe13,Trp19 motif and the phosphorylation of Ser34 have been reported to be important for endosomal sorting (5, 6). Finally, Cys34 has been shown to be a reversible palmitoylated residue that might anchor the tail to the lipid layer and form a cytoplasmic loop (7). Both the intact palmitoylation site and the correct length of the loop are critical to prevent targeting of MPR46 to degrading compartments (7, 8).

The signal structures in the cytoplasmic tail of the MPR46 form selective recognition sites for cytosolic proteins facilitating the incorporation of the receptors into transport vesicles. The best studied class of these cytosolic proteins comprises the family of adaptor proteins (AP; Ref. 9). AP-1 and AP-2 are heterotetramers comprising two large ~100-kDa chains (β1 and γ-adaptin for AP-1; β2 and α-adaptin for AP-2), a medium subunit of ~50 kDa (μ1 and μ2) and a small polypeptide of ~20 kDa (σ1 and σ2). AP-1 is involved in protein sorting at the TGN, whereas AP-2 mediates endocytosis from the plasma membrane. Recently, heterotetrameric AP-3 and AP-4 complexes have been identified (10, 11), which are proposed to be involved in sorting at the TGN and endosomal membranes. The AP-3 complex containing a μ3A isoform is ubiquitously expressed, whereas μ3B is a component of the neuronal-specific AP-3 variant. Biosensor analysis has demonstrated the presence of several distinct binding sites for AP-1 and AP-2 in the cytoplasmic tail of the MPR46, which do not depend on dileucine signals (12). Using the yeast two-hybrid system, μ1, μ2, and μ3 chains have been demonstrated to interact with triple repeat sequences of tyrosine-containing sorting signals of several integral membrane proteins (13). However, the composition of residues surrounding the tyrosine residue and the position of the tyrosine motif within the tail relative to the membrane appear to be important in determining μ chain specificity (13, 14). The subunit of the adaptor complexes responsible for recognition of the dileucine motifs is a matter of debate (13, 15, 16).

In the present study we have examined the interaction of the entire cytoplasmic tail of the MPR46 (MPR46-CT) and various tail mutants with μ2 and μ3A using the yeast two-hybrid system. The results have revealed that both μ2 and μ3A bind to the MPR46-CT. The interactions are specific and depend on the presence of a complex configuration of different signals comprising not only the tyrosine and dileucine motif but also acidic amino acid residues localized between these motifs.
MATERIALS AND METHODS

[35S]Methionine and the prestained Rainbow protein marker were from Amersham Pharmacia Biotech Europe (Freiburg, Germany). Oligonucleotide primers for PCR were synthesized by NAPS (Göttingen, Germany). The following reagents were obtained commercially as indicated: restriction enzymes and T4 DNA ligase (New England Biolabs, Schwalbach, Germany); glutathione-agarose (Sigma); Pif and Taq DNA polymerase and the QuickChange site-directed mutagenesis kit (Stratagene Cloning System, La Jolla, CA); TNT® coupled reticulocyte lysate system (Promega Corp., Madison, WI).

Vectors—The Gal4-DNA binding domain vector pAS2 and the Gal4-activation domain vector pGAD424 were purchased from CLONTECH Laboratories (Heidelberg, Germany). The bacterial expression vector pGEX-4T-1 came from Amersham Pharmacia Biotech Europe and pSPP was purchased from Stratagene.

Yeast and Bacterial Strains—Yeast strains for two-hybrid system (MATCHMAKER) were purchased from CLONTECH. The yeast strain H7F6 was used for cotransformation of the Gal4 constructs and SFY526 was used for β-galactosidase assays. The Escherichia coli strains DH5α and BL-21 were obtained from CLONTECH and Amersham Pharmacia Biotech Europe, respectively.

Plasmids—The nuclear and mitochondrial medium-chain 2 (μ2) and -3A (μ3A) were kindly provided by Dr. Peter Schu (University of Göttingen, Göttingen, Germany) and Dr. Margret Robinson (University of Cambridge, Cambridge, United Kingdom), respectively.

Two-hybrid Plasmid Constructions—The cDNAs of wild type cytoplasmic tails of human MPR46 (MPR46-CT, Ref. 17) and human MPR300 (MPR300-CT, Ref. 18) were ligated in frame with the Gal4 activation domain of the pAS2 vector, using the QuickChange site-directed mutagenesis kit (Stratagene Cloning System, La Jolla, CA) to generate a polypeptide containing the C-terminal 164 amino acids of MPR46-CT (MPR46-CT-stopH63). The MPR46-CT-stopH63 cDNA was used as template with primers Y45-F (5′-CCGGATCCCGTCATGTCCTCACTTGGAA-3′) and ST63-R (5′-CCGGATCCCGTCATGTCCTCACTTGGACTC-3′) to amplify the wild type MPR46-CT or MPR300-CT and the Gal4 DNA binding domain (pAS2-MPR46/46300-CT). The PstI/II restriction site of the pSPUTK vector. The pSP64-Adaptor Subunit Binding to the MPR46 4299

RESULTS

Analysis of the Interaction of Wild Type MPR46 Cytoplasmic Tail with μ2 and μ3A Subunits—Reporter yeast cells were first transformed with a plasmid encoding a fusion protein between the wild type MPR46-CT or MPR300-CT and the Gal4 DNA binding domain (pAS2-MPR46/46300-CT). The strain was subsequently transformed with a plasmid encoding the μ2 or μ3A adabor subunit fused to the transcriptional activation domain of Gal4 (pGAD424-μ2 or -μ3A). After an incubation period of 5 days in the presence of 3-amino-1,2,4-triazole (5 mM), the cells expressing the MPR46-CT fusion protein with either μ2 or μ3A exhibited a strong growth in a medium lacking histidine, and positive β-galactosidase activity (Fig. 1). The MPR300-CT failed to interact with both μ2 and μ3A.

The MPR46-CT-Binds Directly to the μ2 and μ3A Subunits in ViVo—To confirm the results obtained with the two-hybrid system, the interaction between the in vitro translated [35S]methyl labeled μ2 and μ3A with MPR46-CT and MPR300-CT expressed and purified as GST fusion protein was examined. Densitometric evaluation of the coprecipitated μ2 subunit and μ3A correction by unspecified binding to GST alone revealed that about 4.3% of total μ2 was specifically recovered on glutathione-agarose beads (Fig. 2A). About 17% of the total μ3A was coprecipitated with the MPR46-CT fusion protein, whereas the in vitro translated [35S]methionine labeled luciferase used as a...
Adaptor Subunit Binding to the MPR46

Interaction of Mutant MPR46-CT with μ3A—When the various MPR46-CT mutants were coexpressed with μ3A in SFY 526 cells, quantification of the interaction measured by lacZ reporter gene activity revealed that the deletion of the dileucine motif (MPR46-CT StopH63) reduced β-galactosidase activity by 42% (Fig. 4). The MPR46-CT StopV48 and StopA44 mutants as well as the alanine substitution (Y45A/V48A) in the entire or in the truncated receptor tail (StopH63-Y45A/V48A) interacted weakly with μ3A (10–27% of β-galactosidase activity of the wild type MPR46-CT). The N-terminal deleted mutant MPR46-CT Δ1–16 activated β-galactosidase similarly to the wild type tail. In control cells coexpressing lamin C, no interaction with μ3A was observed (Fig. 4).

The Cluster of Acidic Amino Acid Residues in MPR46-CT Contributes to μ2 and μ3A Interaction—To determine whether

![Diagram](image-url)

**Fig. 1.** Interaction of MPR-CT with μ2 and μ3A. Wild type cytoplasmic tail of MPR46 or MPR300 fused to the Gal4 DNA binding domain (pAS2) were coexpressed in HF7c cells with μ2 or μ3A fused to the complementary Gal4 activation domain (pGAD424). The cells were grown for 5 days at 30 °C in the presence of 5 μM 3-AT on plates with (+His) or without histidine (–His) and tested for expression of β-galactosidase activity (blue color).

![Diagram](image-url)

**Fig. 2.** Binding of in vitro translated μ2 and μ3A to wild type MPR46-CT and MPR300-CT. A, equimolar amounts (0.7 nmol) of GST or wild type GST-MPR46-CT fusion protein were incubated either with 35S-labeled μ2 (lanes 2 and 3), luciferase (lane 5), or μ3A (lanes 7 and 8) for 2 h at 4 °C following absorption to glutathione-agarose beads for 1 h. After washing the beads, the bound radioactive proteins were detected by SDS-polyacrylamide gel electrophoresis and autoradiography. One fifth of the total amount of the in vitro-translated μ2 (lane 1), luciferase (lane 4), and μ3A (lane 6) were applied on the gel for comparison. B, GST or wild type GST-MPR300-CT fusion protein (25 μg) were incubated with 35S-labeled μ2 (lanes 10 and 11) or μ3A (lanes 13 and 14) as described above. Ten percent of the total amount of in vitro translated μ2 (lane 9) and μ3A (lane 12) was applied on the gel for comparison. Bound μ2 (lanes 3 and 11) or μ3A (lanes 8 and 14) was quantified using a phosphorimager and expressed as percentage of total μ2 or μ3A, respectively. Binding was corrected by the unspecific binding of 35S-labeled μ2 (lanes 2 and 10) or μ3A (lanes 7 and 13) to GST, respectively. Autoradiograms of one representative experiment out of three are shown.
the cluster of acidic amino acids (residues 50–62) is responsible for the reduced binding of mutant MPR46-CT StopV48 to μ2 and μ3A in comparison with the StopH63 mutant as well as for residual adaptor subunit binding in the StopH63-Y45AV48A mutant, substitutions of acidic residues in the context of the entire tail were tested (Fig. 5). The coexpression of the mutant MPR46-CT containing double substitution of Glu55, Glu56, and the quadruple substitution of Glu55, Glu56, Glu58, and Glu59 by alanine with μ2 reduced β-galactosidase activity by 22 and 31%, respectively (Fig. 5C). These mutations impaired the interaction with μ3A more strongly (20 and 18% of β-galactosidase activity of the wild type MPR46-CT). The substitution of Glu55, Glu56, Glu58, Glu59, Asp51, and Asp52 by alanine reduced the interaction both with μ2 and μ3A to 26 and 5%, respectively, of wild type MPR46-CT.

**DISCUSSION**

Studies using the yeast two-hybrid system have established that tyrosine-based sorting signals in cytoplasmic domains of membrane receptors are important for the interaction with μ1, μ2, and μ3 subunits of adaptor complexes AP-1, -2, and-3, respectively (10, 13, 14). In the present study, we have examined the full-length cytoplasmic tail of the MPR46 containing several independent signal structures including tyrosine- and dileucine-based motifs (residues 45–48 and residues 64 and 65, respectively), aromatic residues (residues 13, 18, and 19), and clusters of acidic amino acids (residues 50–62) for its capability to interact with medium chains of AP-2 and AP-3 in the yeast two-hybrid system. Here we report that the tyrosine motif and a distal cluster of acidic amino acid residues but not the dileucine signal within the MPR46 tail are sufficient for effective binding to μ2. In contrast, the interaction of the receptor tail with μ3A depends on a complex C-terminal structure comprising tyrosine and dileucine motifs as well as a strong hydrophilic sequence.

The phenylalanine residues 13 and 18 as well as the tyrosine-based motif 46YRGV48 have been shown to mediate the internalization of the MPR46 from the cell surface (3). Whereas the former signal overlaps with the specific endosomal sorting signal 18FW19, the tyrosine motif has the characteristics of the consensus motif YXXφ (where Y is tyrosine, X is any amino acid, and φ is a bulky hydrophobic amino acid) which can be found within the cytoplasmic domains of many endocytic transmembrane proteins recognizing μ2 (13, 20). Recently, crystalization studies of μ2 complexed with tyrosine-containing internalization signal peptides have revealed that the peptides are bound to an extended conformation with separate pockets for both Y and φ residues (21). Consistent with the prediction that the dileucine signals, which are characteristically surrounded by polar and/or charged residues, will not be able to bind to the hydrophobic pocket structure of μ2 (21), the dileucine signals of CD 3γ have been proposed to interact with β2 adaptor subunits (16). However, surface plasmon resonance data have demonstrated the binding of dileucine-based sorting signals within the cytoplasmic tail of the major histocompatibility class II invariant chain to the μ2 chain of AP-2 (18). Here we show that the dileucine motif of the MPR46 tail is not critical for the interaction with μ2 in agreement with studies testing the binding of AP-2 to MPR46 tail peptides (15). Furthermore, the present data with C-terminal truncated MPR46 tails or with substitution of Tyr15 and Val18 by alanine in the context of the entire tail showed that, in addition to the tyrosine motif, a second signal in the stretch of amino acids 49–63 is required for efficient μ2 binding. Indeed, this study demonstrates that the substitution of six acidic residues within the compact cluster of acidic amino acids in this region (50DDQLGS2) prevents the interaction with μ2. The positive electrostatic surface potential near the YXXφ binding site of μ2 (21) may support this interaction. Additionally, the acidic residues may also be important in vivo for the binding of the MPR46-CT to μ2 because these amino acids are part of a casein kinase-2 phosphorylation site at Ser27 (23). Since the nonphosphorylated MPR46 are not cycled via the plasma membrane (6), these receptors should fail to interact with AP2. Both a tyrosine-based motif and a cluster of acidic

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**TABLE I**

| Adaptor Subunit Binding to the MPR46 | Value |
|-------------------------------------|-------|
| MPR46-CT wild type | 0.4 ± 0.1 |
| MPR46-CT wild type | 0.5 ± 0.1 |
| MPR46-CT Δ1-16 | 17.6 ± 1.0 |
| MPR46-CT S6H63 | 20.7 ± 2.4 |
| MPR46-CT S6V48 | 16.6 ± 1.0 |
| MPR46-CT S6T44 | 4.4 ± 0.6 |
| MPR46-CT S6A44 | 0.7 ± 0.2 |
| MPR46-CT Y45AV48A | 13.0 ± 0.5 |
| MPR46-CT S6H63 | 10.4 ± 2.2 |
| Y45AV48A | 0.5 ± 0.0 |
| Lamin C | 0.5 ± 0.0 |
| Gal4 | 0.3 ± 0.1 |
| MPR300-CT wild type | 0.5 ± 0.0 |

*a Data are means ± S.D. of three independent transfectants in duplicate.
*b Single plasmid transformation.
residues have also been reported to function as independent signals within the cytoplasmic tail of furin to mediate TGN localization and internalization from the cell surface (24, 25). Residues 2–16 of the MPR46 tail, which have been reported to affect AP-2 binding (12), are not important for MPR46 tail binding to the m2 chain, suggesting that these juxtamembrane residues may be involved in the binding of other AP-2 subunits. In contrast to the coprecipitation of m2 with the MPR300-CT, this interaction could not be demonstrated in the two-hybrid assay. The reason for these discrepancies is unclear.

AP-3 has been shown to be involved in a clathrin-independent transport of membrane proteins to lysosomes in mammalian cells or to the vacuole in yeast, and to lysosome-related storage granules arising from the endocytic pathway like melanosomes in melanocytes, synaptic vesicles in neurons, as well as synaptic-like microvesicles in neuroendocrine cells (26–30). Using the yeast two-hybrid system, tyrosine-based sorting motifs YXXf of LAMP I and CD63 have been shown to interact with m3A and m3B chains (10, 27) whereas in the cytoplasmic tails of LIMP II, tyrosinase, and vacuolar alkaline phosphatase or Vam3p, dileucine residues and acidic clusters were found to be important for AP-3 binding (26, 28, 31). Interestingly, we show for the first time the requirement for multiple C-terminal motifs within the cytoplasmic tail of the MPR46 comprising tyrosine- and dileucine-based signals, and clustered acidic amino acid residues to interact efficiently with m3A. Quantification of m3A interactions with various MPR46 tails by measurement of lacZ reporter gene activities revealed that the different signals were not additive but appeared to function in a cooperative manner. In addition, the data showed that the acidic residues Glu55, Glu56, Glu58, and Glu59 are more critical for efficient binding to m3A than to m2. At least two signals located in the cytoplasmic tail of LIMP II, tyrosinase and syntaptotagmin, have also been reported to be critical for correct intracellular sorting (28, 30, 32). It is likely that the structural distance between the tyrosine- and dileucine-based motifs and the acidic cluster in the cytoplasmic tail of MPR300 as well as their position with respect to the membrane (33, 34) compared with the MPR46 tail may be responsible for the failure of the MPR300 tail to bind to m3A.

Our present data are in contradiction to studies in which the MPR46 tail peptide immobilized on a sensor surface fails to bind AP-3 complexes (28). However, similar discrepancies have been reported for the m3A/AP-3 binding to the LAMP I tail (27, 28). The different results obtained with our two-hybrid approach and with the plasmon resonance technique using the MPR46 tail (28) might be explained by the usage of m3A compared with purified AP-3 complexes from brain cytosol containing m3B. Another possibility might be the formation of receptor tail dimers in the two-hybrid system resembling prevalent dimeric MPR46 forms present in membranes (35), which might facilitate the binding of m3A dimers. The physiological significance of MPR46 binding to m3A, which preferentially interacts with lysosomal membrane proteins, is unclear. However, sub-
stitution of Cys\textsuperscript{34} or deletion of amino acid residues 20–23 or 24–29 as well as of the C-terminal end of the cytoplasmic tail interfere with endosomal sorting processes (7, 8, 22) and might direct the MPR46 to organelles for degradation in an AP-3-dependent manner.

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