Membrane cofactor protein (MCP), a widely distributed complement regulatory protein, is expressed on the basolateral surface of polarized epithelial cells, and it is not endocytosed. The carboxyl-terminal tetrapeptide (FTSL) is required for polarized surface expression. The ability of this tetrapeptide to serve as an autonomous sorting signal has been analyzed by adding this sequence motif to the C terminus of an apical membrane protein, the influenza A virus hemagglutinin (HA). The recombinant protein HA-FTSL retained the apical localization of the parental HA protein. Substitution of the complete cytoplasmic tail of MCP for the cytoplasmic tail of HA resulted in the targeting of the chimeric protein (HA/MCP) to the basolateral surface suggesting that the carboxyl-terminal FTSL motif is a weak sorting signal that requires additional targeting information from the membrane-proximal part of the cytoplasmic tail of MCP for redirecting an apical protein to the basolateral membrane domain. In contrast to the native HA, the HA-FTSL protein was subject to endocytosis. The basolateral HA/MCP was also found to be internalized and thus differed from the basolateral MCP. This result suggests that the carboxyl-terminal FTSL motif serves as an internalization signal and that in native MCP sorting information outside the cytoplasmic tail counteracts this endocytosis signal. Substitution of a tyrosine for the phenylalanine dramatically increased the internalization with most of the HA-YTSL protein being present intracellularly. Our results are consistent with the view that the interplay of multiple sorting signals and the modification of a well known targeting signal (YTSL) by amino acid exchange (FTSL) determine the constitutive expression of MCP on the basolateral surface of polarized epithelial cells.

Epithelial cells fulfill important functions at the borderline between intracellular and extracellular compartments. To meet these requirements, they have a polarized organization that involves the separation of the plasma membrane into an apical and a basolateral portion (reviewed in Ref. 1). The two membrane domains have a different protein and lipid composition, which is maintained by a diffusion barrier made up from junctional complexes. A specialized sorting apparatus exists to ensure that proteins and lipids specific for either of the two surface domains are targeted correctly. As far as sorting signals are concerned, more information is available for basolateral proteins than for apical proteins. Sequence motifs for basolateral targeting are usually located in the cytoplasmic tail and often contain a tyrosine residue (2, 3). Many studies have reported a close relationship between basolateral sorting signals and determinants for coated pit localization (3, 4). Indeed the majority of basolateral proteins that have been identified so far and characterized in more detail are subject to endocytosis. An exception is membrane cofactor protein (MCP),1 which is not endocytosed though it is efficiently targeted to the basolateral plasma membrane of several polarized epithelial cells (5, 6).

MCP is a widely distributed regulatory protein that interacts with complement factors C3b and C4b deposited on self-tissue (7). It promotes the degradation of these factors by plasma serine protease factor I and thus protects the cell from complement-mediated damage. It also serves as a receptor for vaccine virus; PBS, phosphate-buffered saline; BSA, bovine serum albumin; FITC, fluorescein isothiocyanate; mAb, monoclonal antibody.

The abbreviations used are: MCP, membrane cofactor protein; HA, hemagglutinin; MDCK, Madin-Darby canine kidney; FPV, fowl plague virus; PBS, phosphate-buffered saline; BSA, bovine serum albumin; FITC, fluorescein isothiocyanate; mAb, monoclonal antibody.

1 The abbreviations used are: MCP, membrane cofactor protein; HA, hemagglutinin; MDCK, Madin-Darby canine kidney; FPV, fowl plague virus; PBS, phosphate-buffered saline; BSA, bovine serum albumin; FITC, fluorescein isothiocyanate; mAb, monoclonal antibody.
serosal compartment and therefore is able to protect the epithelial cell from complement-mediated lysis.

From the biological point of view, it is interesting to know whether the carboxyl-terminal tetrapeptides (FTSL and YTSL) are functional only in the context of MCP or whether they are also active in the sorting of other membrane proteins. Therefore, the tetrapeptide sequences were added to the carboxyl terminus of the hemagglutinin (HA) of influenza A virus, and the recombinant proteins were analyzed for surface transport in epithelial cells as well as for endocytosis.

**EXPERIMENTAL PROCEDURES**

**Cell Culture—** MDCK cells (strain I) were grown in Dulbecco’s modified essential medium (Life Technologies, Inc.) supplemented with 10% fetal calf serum (Life Technologies, Inc.), 100 units/ml penicillin, and 100 μg streptomycin. Tissue culture-treated 0.4-μm pore size Transwell polycarbonate filters (Costar Corp., Cambridge, MA) were used for all experiments. Cells were seeded 5 days before experiments (2 × 10⁵ cells per 7.5-mm unit and 2 × 10⁶ cells per 24-mm unit). The polarity was determined by measurement of the transepithelial resistance using a Millipore ERS apparatus (Bedford, MA). MDCK cells formed a tight monolayer with an electrical resistance of 1,000–2,500 Ω cm². The different patterns of surface proteins on the apical and basolateral membranes of the polarized cell lines were verified by surface biotinylation.

**Construction of HA-MCP Chimeras and Stable Expression in MDCK Cells—** For recombinant DNA techniques, plasmid pSG5new was used. Cloning of the HA gene of fowl plague virus (influenza A/FPV/Rostock/34) into this vector (pSG5new:HA) has been reported previously (12). The mutant hemagglutinin HAnm7 has been described elsewhere (15). The MCP gene (isoform BC1) was excised from the pHAApr-1-neo-MCP-BC1 (14) by EcoRI and cloned into the EcoRI site of pSG5new. Chimeras were generated by a recombinant polymerase chain reaction technique (15) using synthetic oligonucleotides and pSG5new:HA and pSG5new: MCP-BC1 as templates. The sequences of the chimeric constructs were confirmed by the dideoxy chain termination method, using the ABI PRISM® Dye Terminator Cycle Sequencing Ready Reaction Kit (Perkin Elmer).

For stable expression, MDCK cells were cotransfected with either of the pSG5new plasmids, and the neomycin resistance-conferring plasmid pG1 at a ratio of 10:1 using the calcium phosphate method. Cells were screened for genetin resistance by addition of 1.0 mg of genetin (Sigma) per ml of medium. The selected cell clones were screened for expression of foreign proteins by immunofluorescence.

**Surface Biotinylation and Immunoprecipitation—** Filter-grown MDCK cells were washed three times with cold phosphate-buffered saline (PBS) containing 0.1 mM CaCl₂ and 1 mM MgCl₂. The apical or basolateral surface was incubated with 20 ml at 40 °C with 0.5 mM sulfo-N-hydroxysuccinimide-biotin (Pierce) by adding 1 ml of the biotinylating reagent to the respective filter chamber. The same volume of PBS containing 0.1 mM glycine was placed into the opposite filter chamber. After the double immunofluorescence staining, the samples were incubated with PBS containing 3% BSA and either of the monoclonal antibodies J4/48 (Dianova) directed against MCP (final concentration 2 pg/ml) or biotinylated goat anti-mouse Fab fragments (Sigma) at a dilution of 1:100 in PBS-BSA. After incubation with 60 min on ice, the antibody was removed by washing with PBS, and the cells were incubated with cell culture medium for 60 min either at 4 °C or at 37 °C to allow endocytosis of the antigen-antibody complex. Internalization was stopped by rapid cooling on ice. Surface-bound antibody was detected by an incubation for 60 min on ice with rhodamine-conjugated goat anti-mouse Fab fragments (Sigma) at a dilution of 1:100 in PBS-BSA. After washing with PBS, the cells were fixed and permeabilized for 5 min at −20 °C with methanol/acetone (1:1). Internalized antibodies were detected with FITC-labeled rat anti-goat IgG (Sigma) at a dilution of 1:500 in PBS-BSA. To avoid non-specific binding to the rhodamine-labeled goat Fab fragments bound to the cell surface, the FITC-labeled antiserum was preabsorbed with goat-IgG-agarose (Sigma). After the double immunofluorescence staining, the samples were mounted in Mountol and 10% 1,4-diazabicycloc(2,2,2)octane. Conventional epifluorescence was performed with an Axioshot microscope (Zeiss, Oberkochern, Germany). Pictures were taken with Kodak Tmax film (3200 ASA) exposed for identical times for both fluorochromes.

**RESULTS**

**Construction of Chimeric Proteins from MCP and the HA Protein of Influenza A Virus—** To know whether the carboxyl-terminal tetrapeptide of MCP functions as an autonomous sorting signal, we wanted to determine whether it is able to redirect an apical membrane protein to the basolateral membrane domain of polarized epithelial cells. For our analysis, we chose the HA protein of influenza A virus (strain FPV). The apical localization of this protein on epithelial cells is well documented (17). Furthermore, it has been shown to be excluded from coated pits (18). Therefore, foreign sequences introduced into the HA protein can be analyzed not only for basolateral targeting information but also for their ability to mediate endocytosis through coated pits. The chimeric proteins used in our study are shown in Fig. 1. In the HA/MCP chimera, the 11 amino acids of the cytoplasmic tail of the HA protein were replaced with the 26 amino acids of the cytoplasmic portion of MCP (isoform 1). In the HA-FTSL chimera, the carboxyl-terminal tetrapeptide of MCP (Phe-Thr-Ser-Leu) was added to the carboxyl terminus of HA. In the HA-YTSL and HA-ATSL chimeras, the phenylalanine residue of HA-FTSL was replaced with a tyrosine or an alanine, respectively.

Initial experiments had shown that it is difficult to generate stable MDCK cell lines constitutively expressing the wild type hemagglutinin of fowl plague virus. We reasoned that the pH sensitivity of the HA protein may be responsible for these difficulties. To be fusion-active, the influenza HA has to be proteolytically cleaved into the subunits HA₁ and HA₂. Following cleavage, a conformational change is induced if the HA protein encounters an acidic environment. If this structural rearrangement occurs within the membranes and HA, via its sialic acid binding activity, then close contact to another membrane, fusion of the two membranes is induced. If the conformational change occurs when the viral protein is not bound to a receptor of another membrane, the HA becomes irreversibly inactivated. In the case of FPV, cleavage of HA occurs by furin at the trans-Golgi network. The low pH of this compartment inactivates the viral protein. In the case of an FPV infection,
The parental proteins HA and MCP. MCP is shown in white boxes, HA in grey boxes. The luminal, transmembrane, and cytoplasmic domains are not drawn to scale.

Fig. 1. Diagram of the chimeric and mutant proteins as well as the parental proteins HA and MCP. MCP is shown in grey boxes, HA in white boxes. The luminal, transmembrane, and cytoplasmic domains are not drawn to scale.

another influenza A protein, M2, that functions as a ion channel prevents the inactivation by abolishing the pH gradient between the Golgi and the cytoplasm. To avoid these problems we used a mutant HA in which the furin cleavage site (Arg-Xaa-Lys/Arg-Arg↓) was abolished by site-directed mutagenesis. The KKRKKR sequence of the wild type protein was changed in the mutant protein to KKRNRK. After introduction of these mutations, it was possible to generate stable MDCK cells expressing the HA protein. As shown in Fig. 2, the mutant protein is present in the uncleaved form, even 4 h after synthesis. Like the hemagglutinin of human influenza viruses, addition of trypsin results in the cleavage of the HA protein present on the cell surface into the subunits HA1 and HA2. The mutant HA protein was used for the chimeric proteins mentioned above.

Analysis of the Chimeric Proteins for Surface Transport in Polarized Epithelial Cells—MDCK cells stably expressing either of the chimeric proteins were analyzed whether they express the foreign protein on the cell surface. Cells grown on coverslips were fixed with paraformaldehyde, and surface expression was analyzed by immunofluorescence microscopy using a monoclonal antibody (2A11-H7) directed to the HA protein of FPV. As shown in Fig. 3, the chimeric proteins HA/MCP, HA-ATSL, and HA-FTSL were found on the surface of the recombinant MDCK cells as was the parental HA protein. No surface expression was detected with the HA-YTSL protein (not shown). Permeabilization of the cells with saponin indicated that this protein was present intracellularly (Fig. 3, panel f). The pattern of fluorescence suggests that this protein is present in vesicular structures as is observed with proteins that are internalized by endocytosis. The surface-expressed chimeric proteins were analyzed whether they are present on the apical or on the basolateral domain of the plasma membrane. For this purpose, the cells were cultured on filters. Polarized cell monolayers were cooled to 4 °C and either the apical or the basolateral surface proteins were labeled by adding the nonmembrane-permeating reagent sulfo-N-hydroxysuccinimide-biotin to the respective filter chamber. Following immunoprecipitation with mAb 2A11-H7, the proteins were analyzed by SDS-polyacrylamide gel electrophoresis, and biotinylated proteins were detected with streptavidin-peroxidase. As shown in Fig. 4, the HA protein as well as the chimeric proteins HA-FTSL and HA-ATSL were found predominantly on the apical surface of MDCK cells. In contrast, strong labeling of the HA/MCP protein was detectable only on the basolateral surface. This result indicates that the cytoplasmic portion of MCP contains sorting information that is sufficient for targeting of the HA protein to the basolateral plasma membrane. The FTSL sequence alone that is essential for the basolateral transport of MCP is not sufficient to redirect the apical HA protein to the basolateral membrane domain. To confirm these results, the distribution of the chimeric proteins on MDCK cells was analyzed by indirect immunofluorescence using a confocal laser-scanning microscope. Filter-grown MDCK cells were fixed without disruption of the plasma membrane. The fixed cells were incubated from both the apical and the basolateral side with mAb 2A11-H7 and a FITC-conjugated second antibody. A vertical section (side view) of the cells is shown in Fig. 5. Strong fluorescence signals were detected in the apical surface of MDCK cells expressing...
Protein was internalized during an incubation period of 60 min. Cellular staining revealed that a substantial amount of the detectable on the surface of MDCK cells. However, the intracellularly. With the HA-FTSL mutant, bound antibody was also shown). As shown in Fig. 6, after incubation at 37 °C, the internalized protein-antibody complexes were detected with a second antibody at 4 °C. After permeabilization of the cells, the HA protein or the chimeric proteins HA-FTSL or HA-ATSL, respectively, were incubated with mAb 2A11-H7 at 4 °C, and the cells were kept on ice for 60 min or warmed to 37 °C to allow uptake experiment. The proteins at the surface of living cells were incubated with 2% paraformaldehyde, the apical and basolateral surfaces were incubated with mAb J4/48 (specific of MCP) of 2A11-H7 (specific for HA) and a FITC-conjugated second antibody. Analysis was performed with a laser-scanning microscope. Confocal immunofluorescence micrographs of the vertical profile (side view) through the monolayers are shown.

In contrast, the HA/MCP mutant resembled the HA-FTSL mutant with respect to endocytosis, i.e. fluorescence was detectable both by surface and intracellular staining. These results indicate that both the carboxyl-terminal FTSL motif and the MCP cytoplasmic tail act as internalization signals in the context of the influenza hemagglutinin, whereas MCP, the protein they are derived from, is not endocytosed.

**DISCUSSION**

Protein transport from the trans-Golgi network to the basolateral surface of polarized epithelial cells is mediated by vesicular transport involving clathrin-coated vesicles. Such vesicles are also transport intermediates for the protein traffic from the plasma membrane to endosomes (4). Formation of clathrin-coated vesicles requires the binding of specific assembly proteins. AP-1 is characteristic for coated pits and vesicles derived from the trans-Golgi network, AP-2 functions in the formation of endocytic vesicles (19). The adaptor complexes AP-1 and AP-2 promote the assembly of the clathrin cage at the respective membrane. In addition, they bind to the cytoplasmic domain of membrane proteins thus directing these proteins into the transport vesicles (2). The interaction with the adaptor complexes is mediated by sorting signals within the cytoplasmic tail of the membrane proteins. The most common targeting signal for both basolateral transport and endocytosis is based on a tyrosine residue within the motif Y-X-X-O with O representing a large aliphatic amino acid (3). Previous studies on the role of this tetrapeptide signals for basolateral targeting or for internalization were performed mostly with proteins that contained this sequence motif at an internal position of the cytoplasmic tail. It is established that nearby amino acids may modulate the sorting signal. In addition to the primary sequence, the secondary structure and the position within the tail have been suggested to be important factors that may control the recognition of the signal (20). Studies on the G protein of vesicular stomatitis virus have revealed that a certain separation (≥5 amino acids) between the basolateral targeting signal and the transmembrane domain is required for the motif to be functional (21). Our work addressed the question whether the tetrapeptide signal also functions in a carboxyl-terminal position.

Studies with MCP had shown that the FTSL sequence at the very carboxyl terminus is essential for the basolateral targeting of this complement-regulatory protein (6). Substituting a tyrosine for the phenylalanine residue did not affect basolateral targeting. However, it resulted in efficient endocytosis. The native protein with the FTSL motif was not endocytosed at a detectable rate. This result indicated that in MCP the tetrapeptide sorting signal was modulated such that it was functional in basolateral targeting but not in endocytosis. However, it was not known whether the carboxyl-terminal FTSL sequence alone is able to redirect the influenza hemagglutinin to the basolateral surface of polarized MDCK cells.

**Analysis of the Chimeric Proteins for Endocytosis**—MCP is a basolateral protein that is not endocytosed (6). The HA protein is an apical protein that is excluded from coated pit localization (18). Therefore, it was of interest whether the chimeric proteins were also refractory to internalization. In addition, we wanted to find out whether the poor surface expression of the HA-YTSL mutant was due to endocytosis. To examine this possibility, we analyzed the chimeric proteins for endocytosis by an antibody uptake experiment. The proteins at the surface of living cells were incubated with mAb 2A11-H7 at 4 °C, and the cells were either kept on ice for 60 min or warmed to 37 °C to allow endocytosis to occur. Surface-bound antibodies were detected by incubation of the living cells with a rhodamine-conjugated second antibody. With cells maintained at 4 °C, neither of the proteins were detected intracellularly (not shown). As shown in Fig. 6, after incubation at 37 °C, the HA-ATSL mutant was detected on the surface, but not intracellularly. With the HA-FTSL mutant, bound antibody was also detectable on the surface of MDCK cells. However, the intracellular staining revealed that a substantial amount of the protein was internalized during an incubation period of 60 min at 37 °C. Intracellular fluorescence was also observed with the HA-YTSL mutant. In contrast to HA-FTSL, the latter chimeric protein was not detectable by surface staining. This result confirms that HA-YTSL indeed is very efficiently internalized. The HA-MCP mutant resembled the HA-FTSL mutant with respect to endocytosis, i.e. fluorescence was detectable both by surface and intracellular staining. These results indicate that both the carboxyl-terminal FTSL motif and the MCP cytoplasmic tail act as internalization signals in the context of the influenza hemagglutinin, whereas MCP, the protein they are derived from, is not endocytosed.
for the basolateral localization of an otherwise nonpolarized membrane protein but not for the basolateral transport of an apical protein. Substitution of the complete cytoplasmic tail of MCP for the cytoplasmic domain of the HA protein resulted in the polarized expression of the chimeric protein (HA/MCP) on the basolateral surface. Therefore, amino acids of the cytoplasmic tail different from the FTSL sequence also contain basolateral targeting information. Whether this information is contained in a sequence motif or in the secondary structure is not known. In connection with the FTSL motif, it creates a strong basolateral targeting signal that is sufficient to redirect an apical protein to the basolateral surface.

Though the FTSL motif was unable to convey basolateral sorting information onto the HA protein, it affected its internalization. Although the native hemagglutinin is not endocytosed, the chimeric protein (HA-FTSL) was subject to endocytosis. Information residing in the transmembrane domain has been shown to exclude the native HA protein from the incorporation into coated pits (18). The carboxyl-terminal FTSL motif is strong enough to override this negative transport signal. This finding makes the HA-FTSL protein an interesting model protein to analyze the interaction of an apical membrane protein with adaptor complex proteins involved in the formation of clathrin-coated pits and endocytosis. An expected substitution of a tyrosine residue for the phenylalanine created an even stronger endocytosis signal. In fact, internalization of this chimeric protein was so efficient that we were unable to detect it by surface staining. Internalization from the apical side is usually less efficient than endocytosis from the basolateral membrane domain. A reason for this difference has been shown to be the slower maturation of coated pits at the apical surface (22). From the efficient internalization, we conclude that the HA-YTSL mutant is transported to the basolateral surface of MDCK cells. With respect to the question whether a tetrapeptide sorting signal at the carboxyl-terminal position of an apical protein is functional in basolateral transport and endocytosis, the answer is positive as far as the internalization process is concerned. Basolateral targeting is only achieved with a strong (-YTSL) but not with a weak (-FTSL) signal.

Interestingly the HA/MCP chimera that was transported to the basolateral surface of MDCK cells was also endocytosed. Thus, substitution of the cytoplasmic tail of a protein that is not endocytosed (MCP) for the cytoplasmic domain of another protein that is not endocytosed (HA) resulted in a chimeric protein that is internalized. This finding can be explained by assuming that the FTSL motif in the HA/MCP protein acts as an internalization signal as it does in the HA-FTSL protein. The resistance of native MCP to endocytotic uptake then implies that this protein contains transport information outside the cytoplasmic tail that counteracts the FTSL signal and thus prevents endocytosis. This view is supported by the finding that the YTSLe motif was a stronger internalization signal in the context of the HA protein than it was in MCP. Although HA-YTSL could not be detected by surface staining, MCP-YTSL was readily detectable on the surface of MDCK cells. The signal of MCP that counteracts endocytosis might reside either in the transmembrane domain or in the ectodomain being a linear sequence motif or an element of the secondary structure.

Taken together, our results are consistent with the view that multiple sorting signals are contained in MCP. Apart from the carboxyl-terminal tetrapeptide there is sequence information in the membrane-proximal part promoting basolateral targeting. In addition there is sorting information outside the cytoplasmic tail preventing endocytosis. Multiple sorting signals have also been reported for other proteins. For example, the 46-kDa mannose 6-phosphate receptor has been shown to...
contain a common binding site for adaptors AP-1 and AP-2 and
two separate binding sites for AP-1 and AP-2, respectively (23).
Though basolateral targeting and internalization signals
partly overlap, the combination of multiple signals and the
modulation of individual signals (e.g. FTSL versus YTSL) al-

ows to direct a protein to a defined location, i.e. in the case of
MCP it allows the constitutive expression at the basolateral
surface of polarized epithelial cells.

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Importance of the Carboxyl-terminal FTSL Motif of Membrane Cofactor Protein for Basolateral Sorting and Endocytosis: POSITIVE AND NEGATIVE MODULATION BY SIGNALS INSIDE AND OUTSIDE THE CYTOPLASMIC TAIL

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