Annexin II Is Required for Apical Transport in Polarized Epithelial Cells

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The sorting of apical proteins comprises an initial recognition step in the trans Golgi network and a final partitioning of the apical pool of proteins into at least two different types of vesicular carriers. One criteria of these carriers is the association or non-association of the protein content with lipid rafts. We have previously characterized a population containing the raft-associated sucrase-isomaltase-carrying vesicles (SAVs) and another one, the non-raft-associated lactase-phlorizin hydrolase-carrying vesicles (LAVs) that are targeted separately to the apical membrane. Here, we demonstrate biochemically and by employing confocal laser microscopy that the annexin II-S100A10 complex is a component of SAVs and is absent from LAVs. The unequivocal role of annexin II in the apical targeting of SI is clearly demonstrated when down-regulation of this protein by annexin II-specific small interfering RNA drastically decreases the apical delivery of SI in the epithelial cell line Madin-Darby canine kidney. The annexin II-S100A10 complex plays therefore a crucial role in routing SAVs to the apical membrane of epithelial cells.

The plasma membrane of epithelial cells is divided into two domains, an apical domain facing the lumen and a basolateral domain contacting adjacent cells and the underlying connective tissue. Both membrane domains are separated by tight junctions and contain a specific protein and lipid composition (for review, see Ref. 1). Components destined for the apical or the basolateral cell surface move along the secretory pathway to the TGN, where they are sorted into distinct vesicular carriers (2). Basolateral sorting signals have been identified in the cytosolic tails of a variety of transmembrane proteins that could redirect heterologous reporter molecules to the basolateral cell surface (3–6). The underlying sorting machinery is coupled to adaptor coat proteins that recognize these signals (7, 8). The apical sorting on the contrary is less well understood. In transmembrane proteins apical sorting signals have been detected in the cytosolic, transmembrane, and extracellular moiety of the polypeptide (9–12). Some early observations indicated that Triton X-100 insoluble lipid rafts are involved in this process, since most glycosylphosphatidylinositol-anchored proteins associate with rafts and are apically targeted in epithelial cells (13, 14). It is assumed that lipid rafts originate in the Golgi and are then sent in raft-containing vesicles to the apical surface. For some transmembrane proteins the apical delivery does not involve their association with lipid rafts, which indicates that more than one type of sorting mechanism is responsible for the apical targeting of membrane proteins (15, 16). We monitored the exocytic apical transport pathways in living cells with two hydrolases of the intestinal brush border as model proteins, YFP-tagged sucrase-isomaltase (SI) as raft-associated marker and the non-raft associated CFP-tagged lactase-phlorizin hydrolase (LPH) (17). Both marker proteins exit the TGN in post-Golgi carriers that pinch off two different vesicle populations, LPH- (LAVs) and SI-containing apical vesicles (SAVs). Furthermore, LAVs and SAVs segregate their cargo along different cytoskeletal tracks to the apical plasma membrane; in contrast to LAVs, SAVs also move along actin microfilaments to the cell surface and immunosolation of SAVs revealed that they contain the actin motor protein myosin Ia (18).

In the present study we identified the association of annexin II as a new component of the raft-containing SAV vesicle population. Annexin II belongs to a family that is characterized by the presence of a conserved structural element, the so-called annexin repeat, and a Ca2+-dependent binding to phospholipids (for review, see Ref. 19). Annexin II itself has a heterotetrameric structure consisting of two annexin II molecules which are non-covalently attached to a S100A10 (p11) dimer (20). It has been previously published that this complex interacts with membranes of the endosomal system and harbors a C-terminal actin binding site (21, 22). The formation of the annexin tetramer as well as its interaction with endosomal membranes are independent of calcium (23).

Here we demonstrate the association of annexin II with exocytic SAV vesicles that have left the Golgi apparatus. The expression of annexin II is an absolute prerequisite for the delivery of SI to the apical membrane of polarized epithelial cells, which indicates that annexin II plays an essential role in the exocytic transport of SAVs to the plasma membrane.
**EXPERIMENTAL PROCEDURES**

**Materials and Reagents**—Streptomycin, penicilllin, glutamine, Dulbecco’s modified Eagle’s medium (DMEM), methionine-free DMEM (denoted Met-free medium), fetal calf serum, and trypsin were purchased from BioWest (Essen, Germany). Pepstatin, leupeptin, aprotinin, trypsin inhibitior, and molecular mass standards for SDS-PAGE were purchased from Sigma (Deisenhofen, Germany). Soybean trypsin inhibitor was obtained from Roche Diagnostics (Mannheim, Germany). 1,2-[35S]Methionine (>1000 Ci/mmol) and protein A-Sepharose were obtained from Amersham Biosciences (Freiburg, Germany). Acrylamide, N,N,N’-methylenebisacrylamide, and TEMED were purchased from Carl Roth GmbH (Karlsruhe, Germany). Sodium dodecyl sulfate (SDS), ammonium persulfate, dithiothreitol, and Triton X-100 (TX-100) were obtained from Merck (Darmstadt, Germany). The pECFP-N1 and the pDsRed2-N1 vectors were purchased from Invitrogen/Clontech Laboratories, Inc., Heidelberg, Germany. Restriction enzymes were obtained from MBI Fermentas (St. Leon-Rot, Germany) and T7u polymerase was obtained from Qbiogene (Heidelberg, Germany). pH 7.4, triethanolamine (pH 7.4)) prior to SDS-PAGE analysis.

**Cell Culture, Biosynthetic Labeling of MDCK Cells, and Immunoprecipitation**—COS-1 and MDCK cells were grown in DMEM medium (Invitrogen Corp.) with 10% fetal calf serum at 37 °C. Plasmid and siRNA transfection of COS-1 and MDCK cells was performed with LipofectAMINE 2000 (Invitrogen). Metabolic labeling of MDCK-ML (30) or MDCK-SI (10) cells with [35S]methionine for 4 h, and immunoprecipitation with mAb anti-SI was performed essentially as described before (30). For surface precipitation biosynthetically labeled cells were incubated for 2 h at 4 °C in the presence of mAb anti-LPH or anti-SI followed by cell lysis and precipitation of the antigen-antibody complex with protein A-Sepharose by centrifugation. The precipitated aliquots were washed and mAb anti-LPH or anti-SI was added to the remaining supernatants to precipitate the internal mannose-rich and complex glycosylated stores of both enzymes. The immunoprecipitates were subjected to 6% SDS-PAGE and phosphoimages were analyzed with the Bio-Rad Quantity One software.

**RESULTS AND DISCUSSION**

To identify components that are involved in the transport and apical sorting process of LAVs and SAVs in epithelial cells, these post Golgi carriers were isolated separately from MDCK-LPH<sub>myc</sub> and MDCK-SI-YFP cells as described previously (18). Anti-myc was used for the immunoprecipitation of human SI a mixture of the mouse mAbs of hybridoma HBB 1/219, HBB 2/619, and HBB 3/605 was used (28). Human LPH was precipitated with mouse mAbs of hybridoma HBB 1/909 (28) and LMac 2, LMac 6, and LMac 8 (29).

**Construction of cDNA Clones**—The annexin II-cDNA (36) was inserted into the pECFP-N1, pEYFP-N1, or pDsRed1-N1 vectors (Clontech) using the unique restriction sites BamHI and XhoI. A SacI/SmaI fragment encoding the complete cDNA of myosin Ia, which was generously provided by D. Bikle (UCSF Comprehensive Cancer Center, San Francisco, CA) was inserted into pECFP-N1 (Clontech) using SacI and SmaI.

**Cell Polarity; Protein Transport and Annexins**

**Fig. 1.** Association of annexin II-S100A10 with SAVs. For a TGN accumulation of newly synthesized material, MDCK-LPH<sub>myc</sub> and MDCK-SI-YFP cells were incubated at 30 °C for 6 h followed by TGN release at 37 °C for 1 h (A and C). B, the 6-h incubation was performed at 15 °C for a pre-Golgi accumulation and at 20 °C followed or not followed by a TGN release step at 37 °C for 20 min. Cell homogenates were loaded onto a step sucrose gradient, and TGN-38-positive fractions were used for vesicle precipitation with mAb anti-GFP or anti-myc. The immunoprecipitates were separated by SDS-PAGE, transferred to a polyvinylidene difluoride membrane, and stained with monoclonal anti-annexin II or anti-S100A10 antibodies. C, LAVs and SAVs were immunolocalized in the absence or presence of EDTA to deplete Ca<sup>2+</sup> ions. D, the proportions of annexin II-S100A10 from three independent experiments were quantified.

**Vesicle Preparation and Precipitation**—For the enrichment of post-Golgi carriers, these post Golgi carriers were isolated separately from MDCK-LPH<sub>myc</sub> and MDCK-SI-YFP cells as described previously (18). Anti-myc was used for the immunoisolation of post Golgi carriers, these post Golgi carriers were isolated separately from MDCK-LPH<sub>myc</sub> and MDCK-SI-YFP cells as described previously (18). Anti-myc was used for the immunoisolation of post Golgi carriers.
the trypsinized peptide pattern of the scaffolding protein annexin II with a molecular weight of 36 kDa (GenBank™ accession NP004030). This result was confirmed by immunoblots in which the 36-kDa band was detected exclusively in the SAV vesicles using a mAb anti-annexin antibody (Fig. 1A). Furthermore, antibodies directed against S100A10, the binding partner of annexin II, labeled a polypeptide of 11 kDa in the SAV fractions indicating that the complete heterotetrameric complex of annexin II and S100A10 is associated with the vesicular membrane of SAVs. The next step was to assess the stage in the secretory pathway at which annexin II and S100A10 become associated with SAV. For this MDCK-SI-YFP and MDCK-LPHmyc cells were subjected to different temperatures at which the protein trafficking could be blocked in particular compartments. The cells were either cultured for 6 h at 15 °C to accumulate pre-Golgi vesicular elements or at 20 °C to achieve an arrest of the proteins in the TGN (31), which was followed by a 20 min TGN release at 37 °C. Vesicular fractions were isolated from the homogenates by sucrose-density centrifugation followed by immunoprecipitation and immunoblot. Fig. 1B demonstrates that the annexin II-S100A10 complex was detected exclusively on SI-carrying vesicles that were released from the TGN at 37 °C. Neither ER- nor Golgi-arrested material contained a component of the complex, which indicates that the annexin II-S100A10 tetramer attaches to SAVs after exit from the TGN.

To examine the role of Ca²⁺ in the association of annexin II-S100A10 with post-Golgi vesicles we probed SAVs immunoisolated in the absence or presence of the Ca²⁺-chelating agent EDTA by immunoblot with mAb anti-annexin II or mAb anti-S100A10. Fig. 1C shows that the coprecipitation of annexin II and S100A10 is not significantly affected when EDTA was included in the buffer used to isolate SAVs. This suggests that the annexin II tetramer still binds to SAVs at submicromolar Ca²⁺ concentrations. A similar observation was previously reported for the association of annexin II with early endosomes (23).

The binding of annexin II to post-Golgi vesicles was further

**Fig. 2. Confocal analysis of annexin II and LPH or SI in transiently transfected COS-1 cells.** COS-1 cells were transfected with LPH-CFP and anx2-YFP (A) or SI-YFP and anx2-CFP (B) or SI-YFP, anx2-DsRed, and myo1A-CFP (C). One day post-transfection the cells were incubated for 4 h at 20 °C to accumulate proteins in the Golgi apparatus followed by a TGN release at 37 °C for 20 min. This incubation was performed in the presence of 1.6 mM cycloheximide to inhibit protein synthesis. The red arrows and arrowheads indicate transport vesicles stained by annexin II; white arrowheads depict labeling at the plasma membrane. Scale bars, 10 μm; n, nucleus.
assessed using confocal microscopy of COS-1 cells that were cotransfected with different variants of annexin II fused to CFP, YFP, or DsRed, which does not alter complex formation with S100A10 (24), and either LPH-CFP or SI-YFP. One-day post-transfection the newly synthesized proteins were chased to the TGN at 20 °C followed by their release from this organelle at 37 °C. Finally, the cells were permeabilized to decrease the cytosolic background of annexin II before fixation. Confocal analysis revealed that annexin II, LPH, and SI were concentrated at the cell surface and in intracellular vesicular structures (Fig. 2). However, analysis of 216 vesicles of 15 cells cotransfected with LPH-CFP and annexin II-YFP revealed no overlap between LAVs, the vesicles stained by LPH, and annexin II (Fig. 2A), while from 353 vesicular carriers that were found in 15 cells cotransfected with SI-YFP and annexin II, about 70% were labeled with both markers (Fig. 2B). These data were further corroborated in COS-1 cells that have been cotransfected with the cDNAs of annexin II fused to DsRed, SI-YFP, and the actin motor protein myosin 1a fused to CFP. The latter protein has been previously demonstrated to be associated with SAVs (18). Fig. 2C shows the distinct labeling patterns of each of the transfected genes within the same cells and at the same time demonstrates that all three proteins could be detected together on some vesicular structures located outside the Golgi. This is in line with previous biochemical data in which a colocalization of annexin II and myosin 1a to SAVs was demonstrated (18). In eight of ten cells we also observed a significant staining of annexin II and myosin 1a in areas of the plasma membrane suggesting an association of a pool of these proteins with the plasma membrane.

Next, we examined the subcellular localization of annexin II in polarized epithelial cells by generating an MDCK cell line that stably expresses the annexin II-DsRed fusion protein (denoted MDCK-anx2Ds). A polarized monolayer of MDCK-anx2Ds cells was analyzed by confocal microscopy and revealed an accumulation of annexin II-DsRed in the cortical apical and basolateral domains as well as in intracellular vesicular structures (Fig. 3A). This corroborates previous observations of the subcellular distribution of the annexin II-S100A10 complex in MDCK cells (32) and suggests an involvement of this complex in transport processes to the apical as well as the basolateral membranes.

In this context it has been proposed that cytosolic annexin II acts as a link between the actin-cytoskeleton and endocytic or exocytic membranes (33). To determine whether this linker plays a role in the intracellular dynamics of SAVs, we reduced intracellular annexin II in MDCK-anx2Ds cells by RNAi to specifically suppress annexin II. A dramatic reduction of annexin II-DsRed in the RNAi-treated samples is indicated in Fig. 3A,

![Fig. 3. SiRNA-mediated annexin II gene silencing inhibits the apical surface delivery of SI in polarized MDCK cells. A, distribution and depletion of annexin II in MDCK cells. Membraneous (arrowsheads) and cytosolic (arrows) staining of anx2-DsRed is depicted in confocal x/y-scans, transmitted light, or x/z-scans of polarized MDCK-anx2Ds cells. Anx2-DsRed is specifically depleted in MDCK-anx2Ds cells, while no effect was observed by nonspecific luciferase siRNA. B, Western blot of annexin II and vimentin from cell lysates of MDCK-SI cells transfected or non-transfected with siRNA. C, MDCK-SI were grown on transmembrane filters and biosynthetically labeled with [35S]methionine for 4 h in the presence or absence of RNAi. Cell surface immunoprecipitation of SI from the apical (a) or basolateral (b) membranes was performed with mAb anti-SI. The immunoprecipitates were subjected to SDS-PAGE followed by phosphoimaging analysis. D, the proportions of mannose-rich (SIh) and complex glycosylated SI (SIc) from three independent experiments were quantified. MDCK (E) or COS-1 (F) cells were transiently transfected with SI-YFP and annexin II siRNA. The cells were treated as described for Fig. 2 and analyzed by confocal microscopy. Arrows indicate the intracellular accumulation of SI-YFP-positive vesicles after siRNA treatment. Membrane-bound SI-YFP staining could be observed in the control experiment with luciferase siRNA. Scale bars, 10 μm; ap, apical; n, nucleus.](image-url)
which is comparable with the observations made by Zobiack et al. (24) with the corresponding RNAi construct. In a further approach RNAi was applied to decrease the amount of annexin II in MDCK cells expressing SI. After transfection of double-stranded annexin-siRNA into polarized cells grown on filter membranes, we analyzed the apical or basolateral delivery of SI by surface immunoprecipitation. By reducing the intracellular levels of annexin II the proportion of SI that has been delivered to the apical domain is significantly decreased (Fig. 3, C and D). Nevertheless, a shift in the polarity behavior of SI to the basolateral membrane did not occur by annexin II depletion. This indicates that annexin II is involved in the transport process and not in the sorting event of SI.

The observation that only a minor proportion of newly synthesized SI reaches the apical membrane after RNAi treatment raised the question for the final destination of SI under annexin II depleted conditions. Therefore, we applied RNAi on MDCK-SI-YFP cells. SI-YFP fluorescence was monitored after a temperature-dependent TGN exit as described above. In siRNA-transfected cells fluorescent staining of the apical membrane was significantly decreased, and SI-YFP-labeled vesicular structures appeared intracellularly (Fig. 3E). This suggests that annexin II depletion leads to the accumulation of SI-YFP in intracellular compartments. For a better resolution on a single focal plane, we further cotransfected COS-1 cells with an SI-YFP expression plasmid and annexin II siRNA. Here, we could also identify intracellular, submembraneous vesicles that were accumulated in the cellular periphery (Fig. 3F). However, the cell membrane was not labeled by SI-YFP. Taken together, the biochemical and confocal data indicate that a decrease in annexin II results in a blockade of the intracellular transport of raft-containing SAVs at a stage before vesicle fusion with the plasma membrane occurs. In fact it is well known that the annexin II-S100A10 tetramer interacts with lipid rafts in a cholesterol-dependent manner (34), and it has been published recently that S100A10 is also implicated in membrane trafficking of the background K+ channel TASK-1, the epithelial Ca2+ channels TRPV5 and TRPV6, and the tetrodotoxin-insensitive voltage-gated Na+ channel (35–37). In the latter case it binds directly to the amino terminus of the Na+ channel and promotes the translocation of this transmembrane protein to the plasma membrane, producing functional channels (36). A different binding motif, however, is required at the C termini of TASK-1, TRPV5 and TRPV6 for a specific interaction with S100A10 (35, 37).

As a conclusion our observations suggest a role for the annexin II-S100A10 complex in the trafficking of SI to the apical membrane of epithelial cells. Whether the SI polypeptide interacts directly with the complex or through a network of associated partners in raft-transporting SAVs remains to be elucidated. Annexin II is not the only member of the annexin superfamily that is involved in apical trafficking. Previous data demonstrated the function of annexin 13b in the delivery of the influenza virus hemagglutinin from the TGN to the apical plasma membrane (38, 39), which further suggests the presence of different apical transport pathways with diverse mechanisms in epithelial cells.

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