Temporal Association of the N- and O-Linked Glycosylation Events and Their Implication in the Polarized Sorting of Intestinal Brush Border Sucrase-Isomaltase, Aminopeptidase N, and Dipeptidyl Peptidase IV*

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The temporal association between O-glycosylation and processing of N-linked glycans in the Golgi apparatus as well as the implication of these events in the polarized sorting of three brush border proteins has been the subject of the current investigation. O-Glycosylation of pro-sucrase-isomaltase (pro-SI), aminopeptidase N (ApN), and dipeptidyl peptidase IV (DPPIV) is drastically reduced when processing of the mannose-rich N-linked glycans is blocked by deoxymannojirimycin, an inhibitor of the Golgi-located mannosidase I. By contrast, O-glycosylation is not affected in the presence of swainsonine, an inhibitor of Golgi mannosidase II. The results indicate that removal of the outermost mannose residues by mannosidase I from the mannose-rich N-linked glycans is required before O-glycosylation can ensue. On the other hand, subsequent mannose residues in the core chain impose no sterical constraints on the progression of O-glycosylation. Reduction or modification of N- and O-glycosylation do not affect the transport of pro-SI, ApN, or DPPIV to the cell surface per se. However, the polarized sorting of two of these proteins, pro-SI and DPPIV, to the apical membrane is substantially altered when O-glycans are not completely processed, while the sorting of ApN is not affected. The processing of N-linked glycans, on the other hand, has no influence on sorting of all three proteins. The results indicate that O-linked carbohydrates are at least a part of the sorting mechanism of pro-SI and DPPIV. The sorting of ApN implicates neither O-linked nor N-linked glycans and is driven most likely by carbohydrate-independent mechanisms.

Glycosylation of membrane and secretory glycoproteins comprises a cascade of steps that implicate a number of oligo- and monosaccharide transferases and commences in the lumen of the endoplasmic reticulum (ER) concomitant with protein translation and translocation (1–3). This initial glycosylation event, known as N-linked core glycosylation, involves the transfer of Glc\(_3\)Man\(_9\)GlcNAc\(_2\) unit to acceptor asparagine residues in the tripeptide sequon Asn-Xaa-Ser/Thr and is catalyzed by the enzyme oligosaccharyltransferase (1–3). N-Linked glycosylation is essential for the function, stability, folding, intracellular transport, and secretion of glycoproteins (4–7). Upon arrival to the cis-Golgi network, the initial mannose-rich core chains are trimmed by mannosidasises I and II of the cis-Golgi. In the medial and trans-Golgi formation of complex type of glycans ensues and is terminated by the addition of sialic acid in the trans-Golgi network (TGN) (1–3, 8, 9).

Another glycosylation event of many, but not all, membrane and secretory glycoproteins is O-linked glycosylation at particular serine or threonine residues. In contrast to N-linked glycosylation, O-glycosylation is a posttranslational event and occurs in the cis-Golgi (4, 10, 11). A consensus acceptor sequence, as the tripeptide Asn-Xaa-Ser/Thr in N-linked glycosylation, does not exist. However, comparison of amino acid sequences around a large number of O-glycosylation sites of several glycoproteins revealed a significantly increased frequency of proline residues at positions $-1$ and $+3$ relative to the glycosylated residues and a marked increase of serine, threonine, and alanine residues (12). It has been also suggested that stretches of serine and threonine residues in glycoproteins, such as in sucrase-isomaltase (SI, EC 3.2.1.48–10) (13), aminopeptidase N (ApN, EC 3.4.15.1) (14), glycosphin (15), or the low density lipoprotein receptor (16), are potential sites for O-glycosylation.

A role of O-glycosylation in the biological function of glycoproteins and in conferring stability and protection against proteolytic degradation has been proposed (16–18). A direct implication of O-glycosylation in the intracellular transport of proteins is unlikely, since acquisition of transport competence implicates a cascade of steps that occur in the ER and O-glycosylation is a cis-Golgi event. Consistent with this is the finding that truncation of the highly O-glycosylated stalk region of ApN does not affect the transport and targeting of this enzyme (19).

At first glance N- and O-linked glycosylation could be considered as independent events by virtue of the different structural requirements of the glycosylation sites, the temporal aspect (cotranslational versus posttranslational), and the different monosaccharide composition of the individual chains. Recent observations, however, suggested that at least an indirect association between the two events does exist. Here, inhibition of trimming of the mannose-rich chains of brush border lactase-phlorizin hydrolase (LPH, EC 3.2.1.23–62) (20) by deoxymannojirimycin (dMM), an inhibitor of cis-Golgi a-manno-
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Asidase I (21), was accompanied by generation of only N- rather than N- and O-glycosylated forms of LPH (17). In this very example, it was proposed that conformational alterations in LPH due to persisting mannose-rich type of glycosylation in the presence of dMM may render potential O-glycosylation sites in LPH inaccessible to Golgi transfers. It is not clear, however, whether the observed effect with LPH may be generalized to other O-glycosylated proteins.

In an effort to analyze the role of carbohydrate modification on the sorting of the brush border hydrolases, pro-SI, ApN, and dipeptidyl peptidase IV (DPPIV, EC 3.4.14.5), we used inhibitors of trimming of carbohydrate chains in the cis-Golgi and surprisingly found that dMM has generated similar effects on three different proteins as those observed with LPH. The O-linked glycosylation of pro-SI, ApN, and DPPIV was substantially affected. Moreover, the polarized sorting of SI and DPPIV, but not of ApN, was drastically altered from high sorting fidelity to the apical membrane to random distribution on both sides.

**EXPERIMENTAL PROCEDURES**

**Biological Material and Cell Lines**—Human intestinal biopsies (5–10 mg) were obtained for routine diagnosis by suction with a pediatric Watson capsule and processed as described elsewhere (22). The colon carcinoma Caco-2 cells (23) were cultured in Dulbecco’s modified Eagle’s medium containing 0.45% glucose and supplemented with 20% heat-inactivated fetal calf serum, 1% nonessential amino acids, and antibiotics (Life Technologies, Inc.).

**Immunological Reagents**—Monoclonal antibodies (mAbs) against human small intestinal brush border membrane hydrolases were a generous gift from Dr. H.-P. Hauri (Biocenter, Basel, Switzerland) and Dr. E. E. Sterchi (University of Bern, Bern, Switzerland) (24). The mouse mAb anti-ApN and anti-DPPIV were products of hybridomas (Roche Molecular Biochemicals). Enzymes were usually labeled at day 6 after confluence. When used, dMM, an inhibitor of mannosidase I (21), was accompanied by generation of only N- and O-glycosylated proteins.

**RESULTS**

**O-Glycosylation of ApN and DPPIV**

We have shown previously that pro-SI is an O-glycosylated molecule, whose O-glycosylation pattern is heterogeneous and correlates with the position of the individual subunits, sucrase and isomaltase, that comprise this enzyme complex (18). These data were obtained by employing a number of approaches, including enzymatic and chemical deglycosylation and lectin binding studies. Here, we extended these studies to ApN and DPPIV. First we demonstrate that ApN and DPPIV are O-glycosylated and that, as in the case of pro-SI and LPH, this glycosylation is also heterogeneous.

**Enzymatic and Chemical Deglycosylation of ApN and DPPIV**

ApN—Human ApN is synthesized in intestinal cells as a 130-kDa mannose-rich glycosylated precursor, which matures with a half time of 30–40 min to a complex glycosylated species of apparent molecular mass of 160 kDa (24, 29). The biosynthesis and processing of ApN in other species has been also studied (30). The full-length cDNA of the human enzyme has been cloned (14), and the amino acid sequence of the protein deduced from cDNA revealed a Ser/Thr-rich domain, which, as in SI, may provide potential O-glycosylation sites. However, no direct evidence from biosynthetic or structural analyses has been described so far.

We first assessed the O-glycosylation pattern by employing a strategy that combines enzymatic and chemical deglycosylation of precursor and mature forms of ApN and compared the apparent molecular weights of the deglycosylation products. First, the glycoprotein was enzymatically deglycosylated of its N-linked sugars by using the combination endoglycosidase F/N-glycopeptidase F (endo F/GF), which removes complex and mannose-rich N-linked carbohydrates. Endo H, which cleaves mannose-rich glycans, was used when mannose-rich glycoproteins were analyzed. In either case, the resulting molecular form(s) were further treated with TFMS, a chemical reagent that cleaves O-glycosidic linkages (28). A further reduction in the apparent molecular weight of an enzymatically N-deglycosylated species provides an ample evidence for the presence of O-linked sugars in the treated protein. The results are shown in Fig. 1. Immunoprecipitation of biopsy samples with mAb anti-ApN revealed a 130-kDa labeled protein after 30 min of chase. This band corresponded to the mannose-rich precursor of ApN (denoted ApN<sub>pm</sub>) as assessed by its sensitivity to treatment with endo H and its conversion to a 100-kDa polypeptide (Fig. 1A, lanes 1 and 2). A similar digestion process was obtained with endo F/GF (Fig. 1A, lane 3), supporting the endo H data that the 130-kDa polypeptide is N-glycosylated of the mannose-rich type. Treatment of the endo F/GF product with TFMS did not produce a further shift in the size of the 100-kDa band (Fig. 1A, lane 4), indicating that the 130-kDa protein is not O-glycosylated. After 4 h of chase, a predominantly labeled endo H-resistant 160-kDa ApN band could be detected, which corresponded to the complex glycosylated mature form of ApN (Fig. 1A, lanes 5 and 6) (this form will be referred to throughout as ApN<sub>cm</sub>). When this immunoprecipitate was treated with endo F/GF, a diffuse band pattern was obtained that, however, could be resolved into at least two bands (Fig. 1A, lane 7; see also Fig. 2).
SDS-PAGE on 6% slab gels and fluorography. Proteins were treated or not treated with endo F/GF and subjected to digestion and immunoprecipitation with mAb anti-ApN. The isolated pulse-labeled with [35S]methionine for 30 or 120 min, followed by solubilization and immunoprecipitation with mAb anti-ApN. The isolated proteins were treated or not treated with endo H, endo F/GF, and endo B, followed by TFMS. The proteins were subjected to SDS-PAGE on 6% slab gels and fluorography. B, biopsy specimens were continuously labeled with [35S]methionine for 15 min and chased for the indicated times with cold methionine. Detergent extracts of the labeled tissues were immunoprecipitated with mAb anti-ApN. The immunoprecipitates were treated or not treated with endo H, endo F/GF, and endo F/GF followed by TFMS. The proteins were subjected to SDS-PAGE on 6% slab gels and fluorography. B, biopsy specimens were continuously labeled with [35S]methionine for 30 or 120 min, followed by solubilization and immunoprecipitation with mAb anti-ApN. The isolated proteins were treated or not treated with endo H and endo F/GF revealed essentially similar molecular species of an apparent molecular mass around 85 kDa (Fig. 2, lanes 2 and 3). TFMS treatment of the N-deglycosylated DDPIV did not generate a further shift in its size indicating that the 85-kDa species is devoid of O-glycosidically linked glycans. By contrast, the mature 124-kDa DDPIV form obtained within 4 h of chase (Fig. 2, lane 5) is heavily O-glycosylated as assessed by the combined endo F/GF and TFMS treatments. N-Deoxyglycosylation generated a diffuse band of an apparent molecular mass ranging between 90 and 110 kDa (Fig. 2, lane 7). TFMS treatment converted this heterogeneous form to a band of an apparent molecular weight smaller than the lowest band periphery of the N-deglycosylated product (Fig. 2, lane 8, and compare this band with the band in lane 7). The result demonstrates that the N-deglycosylated protein contains O-glycosidically linked oligosaccharides, which have been eliminated by TFMS. Altogether, the chemical and enzymatic treatments provide an evidence for O-glycosylation of ApN and DDPIV. Further, the observed multiple and heterogeneous band patterns in N-deglycosylated ApN and DDPIV suggest the presence of several populations of differently O-glycosylated species of these glycoproteins, which could be converted to one unglycosylated species upon TFMS treatment. The existence of several populations of N- and O-glycosylated glycoproteins has been also reported for two other brush border enzymes, LPH (17, 20) and SI (18). In all these cases, a possible association between the differentiation state of intestinal cells and the various glycoforms is favored. Association between Processing of Mannose-rich N-Linked Carbohydrates and O-Glycosylation

We have demonstrated before that impaired processing of cotranslationally added mannose-rich N-linked sugars in the cis- and medial Golgi by inhibitors of mannosidases I and II is associated with drastic reduction, if not complete blocking, of the O-linked glycosylation of human intestinal LPH (20). A possible conformational interference of unprocessed N-linked sugar chains with potential O-glycosylation sites lying in their vicinity was proposed. This has inspired us to further examine other heavily O-glycosylated proteins such as ApN, DDPIV, and pro-SI, with the ultimate goal of analyzing the role of N-linked...
Effects of Variations in the O- and N-Linked Glycosylation Patterns on the Polarized Sorting of Pro-SI, ApN, and DPPIV

Pro-SI, ApN, and DPPIV are apically sorted proteins in intestinal cells. In Caco-2 cells, pro-SI and ApN follow predominantly the direct sorting pathway to the apical membrane, while DPPIV follows both the direct and the transcytotic pathways (32). The significant effects of dMM on the O-glycosylation and swainsonine on the N-linked glycosylation of pro-SI, ApN, and DPPIV have inspired us to investigate these events in the context of polarized sorting of these proteins.
For this purpose, we performed cell surface immunoprecipitations of pro-SI, ApN, and DPPIV using Caco-2 cells that have been cultured on membrane filters and biosynthetically labeled for 6 h in the presence or absence of dMM and swainsonine. Cell surface immunoprecipitations were performed by adding mAbs directed against pro-SI (upper horizontal panel), ApN (middle horizontal panel), and DPPIV (lower horizontal panel) to the apical (denoted a) or basolateral (denoted b) compartments. The immunoprecipitates were then analyzed by SDS-PAGE on 5% (pro-SI) and 6% (ApN and DPPIV) slab gels, followed by fluorography. B, the proportions of pro-SI, ApN, and DPPIV appearing at the apical and basolateral membranes in the presence or absence of dMM and swainsonine were calculated from densitometric scans of the fluorogram shown in A and those of two more experiments.

Fig. 4. Polarized sorting of pro-SI, ApN, and DPPIV in the presence or absence of dMM and swainsonine. A, Caco-2 cells were cultured on membrane filters and labeled 6 days after confluence with [35S]methionine for 6 h in the presence of 5 mM dMM (middle vertical panels) or 4 μg/ml swainsonine (right vertical panels) or in their absence (left vertical panels). Cell surface immunoprecipitations were performed by adding mAbs directed against pro-SI (upper horizontal panel), ApN (middle horizontal panel), and DPPIV (lower horizontal panel) to the apical (denoted a) or basolateral (denoted b) compartments. The proportions of pro-SI, ApN, and DPPIV appearing at the apical and basolateral membranes in the presence or absence of dMM and swainsonine were calculated from densitometric scans of the fluorogram shown in A and those of two more experiments.

DISCUSSION

N- and O-linked glycosylations exert various fundamental roles that relate to biological function, processing, trafficking, and sorting of membrane and secretory proteins. A large number of these proteins are both N-glycosylated at particular Asn residues and O-glycosylated at either Ser or Thr residues (1–4). These glycosylation types are the outcome of distinct temporal events, and are structurally different (3, 4, 10–12). A direct or an indirect linkage between these processes has not been so far demonstrated, except for brush border LPH (20). Here it could be demonstrated that O-glycosylation does not proceed to completion, or is perhaps blocked, as a result of impaired processing or complete inhibition of the processing of the first mannose residues in the cis-Golgi by dMM, an inhibitor of cis-Golgi a-mannosidase I (21). This rather unexpected finding appeared initially to represent a special case of LPH. We postulated then that the unprocessed mannose-rich chains in the presence of dMM may stericly hinder the addition of glycan chains to neighboring potential O-glycosylation Ser or Thr residues. The present report, however, clearly documents that this phenomenon is not restricted to LPH alone. Three structurally and functionally different proteins of the brush border membrane have been examined with inhibitors of the
processing of mannose-rich chains. In all these cases, inhibition by dMM of the processing of the first four mannose residues of the mannose-rich sugar chains results in a substantial impairment of O-glycosylation. How do these results accommodate with the role of glycosylation in general and with our knowledge of the structure of the analyzed brush border proteins in particular?

All the proteins analyzed are extensively N- and O-glycosylated. The potential N-glycosylation sites vary from 16 for pro-SI (1827 amino acids) (13, 18) and LPPI (1927 amino acids) (34), to 10 for ApN (966 amino acids) (14), and 9 for DPPIV (766 amino acids) (35) and are almost evenly spread all over the ectodomains of these proteins. Many of the potential O-glycosylation sites are found in stalked regions, which are located in close proximity to the membranes and also among potential N-glycosylation sites (13, 14, 19, 34, 35). By virtue of the large number of N-linked glycosylation sites, it is likely that a particular structure of the mannose-rich N-linked glycans, which exist earlier in the biosynthesis than O-glycosidically linked sugars, elicit specific constraints on the processing of the O-linked sites. The results obtained with two different inhibitors of mannosidases I and II of the cis-Golgi compartment strongly suggest that the accessibility of potential O-glycosylation sites to galactosyl- or N-acetyl-galactosaminytransferases requires a reduced number of mannose residues of neighboring N-linked chains. A completely unprocessed N-linked mannose-rich chain in the presence of dMM may sterically reduce or hinder the glycosylation of a neighboring potential O-glycan site. Processing of the mannose-rich chains by mannosidase I appears to be sufficient for O-glycosylation to ensue, since inhibition of mannosidase II and subsequently further processing steps by swainsonine remains without marked effects on normal O-glycosylation of the four brush border proteins. Since the drastic impairment in O-linked glycosylation is only observed when mannosidase I, but not mannosidase II, is inhibited, our data suggest that the outermost four mannose residues cleaved by mannosidase I (21) are critically important or may be rate-limiting in determining the extent of O-glycosylation. Furthermore, the results suggest that O-glycosylation does not commence before processing of the mannose-rich chains by mannosidase I is achieved.

One main aspect of the present work is that related to the implication of glycosylation, in particular O-glycosylation in the trafficking and polarized sorting of the brush border proteins pro-SI, ApN, and DPPIV. The observation that O-glycosylation could be substantially affected in the presence of dMM, i.e., when particular mannose residues are not cleaved, opens up the possibility to investigate in a simple and straightforward set up the role of O-glycosylation in sorting. Recent studies have demonstrated that carbohydrates, N- or O-linked, carry sorting information to the apical membrane (36–38). However, a general concept on the significance of the glycosylation events in polarized sorting cannot be drawn, in particular since only a few studies have addressed the role of N- and O-glycosylation of proteins naturally occurring in epithelial cells. In addition, it is not obvious how glycosylation correlates with sorting and what carbohydrate structures are implicated in the sorting event. It is clear that modifications in the N-linked carbohydrate structure of glycoproteins from mannose-rich to complex type precede polarized sorting in the trans-Golgi network. In addition, many proteins acquire O-linked glycosylation prior to transport to the TGN. Should carbohydrates play a role in the sorting at all, one may expect that the complex type as well as O-glycosylated may be involved. Our paper shows that modification of the N-linked glycosylation is not effective in the context of apical sorting of a number of heavily N-glycosylated brush border enzymes. By contrast, elimination or reduction of O-glycan units in the presence of dMM affects the sorting behavior drastically. In their predominantly mannose-rich type of glycosylation, pro-SI(dMM) and DPPIV(dMM) follow a random pattern of delivery to the apical and basolateral membranes. It is obvious that O-linked glycans are directly implicated in apical sorting. On the other hand, the sorting signal of ApN appears not to involve sugar chains, since ApN(dMM) and ApN(su) are delivered with similar fidelity to the apical membrane as their fully glycosylated wild type ApN counterpart. This result supports data, in which deletion of the potentially O-glycosylated Ser/Thr-rich stalk domain of ApN has no effects on the sorting behavior of the mutant (19) and indicates that sorting motifs other than O-linked glycans are responsible for apical targeting of ApN. The strong role of O-glycans in the sorting of pro-SI and DPPIV does not exclude, however, that the sorting of these proteins may implicate additional structural motifs that may function to tune up the apical sorting of these proteins. This may explain why a slightly more apical than basolateral delivery of pro-SI(dMM) and DPPIV(dMM) still occurs despite the removal of O-glycans. One possible mechanism of apical sorting has been described for the pig species of pro-SI, ApN, and DPPIV (39), which involves association of these proteins with glycolipid microdomains or rafts. If O-glycosylation is implicated in this mechanism, then at least the apical delivery of ApN would implicate different sorting signals and mechanism, since ApN(dMM), which is largely devoid of O-linked glycans, is targeted correctly to the apical membrane.

Unlike basolateral sorting, apical sorting appears to imply signals of different types, structure, and location, emphasizing the diversity of mechanisms responsible for this process. It has been proposed that the heavily O-glycosylated stalked region of the neurotrophin receptor is implicated in its sorting to the apical membrane, since deletion of this region leads to a mistargeting of the mutant protein to the basolateral membrane and suggesting the existence of a suppressed basolateral signal in this protein (38). A similar situation does not prevail with pro-SI(dMM) and DPPIV(dMM), suggesting that except for apical sorting signals no other motifs are present in these proteins. Due to the presence of GalNAc residues in O-linked carbohydrates, these chains could be considered as an exquisite candidate for binding specific sorting elements. The leguminous lectin-like VIP 36 protein, for example, is a resident of the Golgi apparatus that has been located to glycolipid rafts and is presumably involved in the sorting of some GPI-anchored proteins to the apical membrane (40).

Our results do not exclude a partial O-glycosylation occurring at Ser or Thr residues in SI, ApN, and DPPIV in the presence of dMM. The slight differences in the electrophoretic patterns obtained upon endo F/GF treatment of DPPIV(dMM) as compared with DPPIV (and to a lesser extent those of SI(dMM) and ApN(dMM)) suggest that some O-glycosylation still occurs. Nevertheless, an interaction with potential sorting elements, may not be as avid as with completely processed O-chains to ensure a high sorting fidelity.

While O-glycans are strongly implicated in apical sorting of pro-SI and DPPIV, partial modification of the N-glycan units to a hybrid type in the presence of swainsonine remains without significant effect on the sorting of these proteins. This is direct evidence that N-linked complex type of glycosylation per se is not an essential factor for correct sorting to the apical membrane. Moreover, it is not clear and also experimentally not established yet, how N-linked mannose-rich residues would mediate polarized sorting, particularly since many proteins are targeted to the apical membrane regardless of their N-glycosy-
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