Glycosylation-dependent Collagen-binding Activities of Two Membrane Glycoproteins in MDAY-D2 Tumor Cells

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ABSTRACT

Two highly glycosylated membrane sialoglycoproteins designated P2A and P2B were isolated from the lymphoreticular tumor cell line called MDAY-D2 and shown to be structurally similar to the lymphocyte glycoprotein called leukosialin and to lysosome-associated membrane glycoprotein termed LAMP-1, respectively. The loss of sialic acid and polylactosamine sequences in glycosylation mutants of MDAY-D2 has been correlated previously with enhanced cell adhesion on extracellular matrix proteins. Since these two glycoproteins bear the majority of the sialylated oligosaccharides found in membrane fractions of MDAY-D2, they were tested for binding activity on extracellular matrix proteins. Both isolated glycoproteins bound to immobilized collagen type I with affinities that were dependent on their glycosylation. Enzymatic removal of sialic acid, polylactosamine, or complete asparagine-linked chains from purified P2B enhanced its binding to collagen, laminin, and fibronectin. In contrast, P2A bound specifically to collagen type I and the interaction required the presence of sialic acid residues which were sensitive to neuraminidase digestion but not to endoglycosidase F. The results suggest that oncodedvelopmental regulation of oligosaccharide expression on P2A and P2B glycoproteins may modulate their binding to extracellular matrix glycoproteins.

INTRODUCTION

Malignant transformation is often accompanied by changes in oligosaccharide expression (1, 2), and some of these changes may be associated with altered cell adhesion to the ECM (3, 4) and with metastatic potential of the tumor cells (5, 6). Control of cell proliferation (3, 4) and certain differentiated functions (7, 8) are regulated in part by specific contacts with ECM and loss of these contacts following malignant transformation may contribute to tumor cell proliferation, cell motility, and metastasis (4, 9).

Studies on the class 1 glycosylation mutants of the highly metastatic tumor cell line MDAY-D2 suggested that decreased expression of sialylated glycoconjugates may be related to the observed increase in cell attachment on collagen-, fibronectin-, and laminin-coated surfaces (10–12). The class 1 mutants synthesize glycoproteins and glycolipids which are deficient in sialic acid and galactose apparently due to a defect in transport of the sugar donor UDP-galactose into the golgi apparatus (13). Class 1 tumor cells were shown to be tumorigenic in syngeneic mice but nonmetastatic from a s.c. site. Suppression of the expression of sialylated glycoconjugates may be related to the nonadherent phenotype of MDAY-D2 cells (10).

The major sialylated glycoproteins in MDAY-D2 cells can be detected by 125I-L-PHA staining of membrane glycoproteins separated by SDS-PAGE and appear to have molecular weights of 80,000–160,000 (11, 13). The glycoproteins also stained with 125I-L-PHA indicating the presence of β1-6 branched complex type oligosaccharides. Digestion of membrane preparations with neuraminidase and endo-β-galactosidase reduced the size heterogeneity and suggested that only a few glycoproteins possessing L-PHA reactive oligosaccharides were present in MDAY-D2 cells. In an effort to identify these glycoproteins and their possible role in the malignant and/or adhesive phenotypes of MDAY-D2 cells, two major sialoglycoprotein were purified from MDAY-D2 cells and structurally characterized.3

In this report, the glycoproteins designated P2A and P2B were compared before and after glycosidase digestion for binding activity on immobilized ECM glycoproteins. P2A bound specifically to collagen type I and this activity appeared to be dependent on sialylation of O-linked oligosaccharides. P2B bound weakly to collagen fibronectin and laminin and this was enhanced by removal of sialic acid and polylactosamine present on N-linked oligosaccharides.

MATERIALS AND METHODS

Purification of P2A and P2B. The glycoproteins were purified from 50 ml of packed MDAY-D2 cells as described previously.2 Briefly, the pelleted cells were extracted at 4°C for 2 h with constant stirring in 200 ml of 50 mM Tris-HCl (pH 8.0)-0.15 M NaCl (buffer A) containing 1 mM EDTA, 1% Triton X-100, and 2 mM phenylmethylsulfonyl fluoride. The extract was centrifuged at 15,000 × g for 30 min and the supernatant was diluted 4-fold with buffer A. The extract was applied to a 25-ml column of WGA-Sepharose (4 mg lectin/ml Sepharose), preequilibrated in buffer A containing 0.2% Triton. The column was washed with 10 volumes of 10 mM Tris-HCl, pH 8.0, containing 0.4% sodium deoxycholate and 1 mM EDTA and eluted with the same buffer containing 5% N-acetylglucosamine. P2A and P2B were detected as L-PHA-reactive glycoproteins in the eluted fractions.3

The L-PHA-positive fractions eluted from WGA-Sepharose were pooled, concentrated to 5 ml by ultrafiltration using an Amicon P-10 membrane, and applied to a column (2.5 x 120 cm) of Bio-Gel A-5m (100–200 mesh). The column separated the material into two major L-PHA-reactive peaks which contained more than 90% of the applied glycoproteins and the fractions were designated P2A and P2B. P2A and P2B were each dialyzed against 20 mM NH4HCO3-0.01% SDS, 5 S. Laferté and J. W. Dennis. Purification of two glycoproteins expressing β1-6-branched Asn-linked oligosaccharides from metastatic tumor cells, submitted for publication.

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4 The abbreviations used are: ECM, extracellular matrix; DOC, deoxycholate; WGA, wheat germ agglutinin; L-PHA, leukosialin; GRGDPTL, Gly–Arg–Asp–Pro–Thr–Leu; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoreses; BSA, bovine serum albumin; ELISA, enzyme-linked immunoassay; NCAM, neural adhesion molecule; Gal, galactosyl; GalNAc, N-acetylgalactosamine; GlcNAc, N-acetyl-glucosamine; NeuNAc, N-acetylmuramic acid; RDG, Arg–Asp–Gly; GRGDSPK, Gly–Arg–Asp–Ser–Pro–Lys.

5 S. Laferté and J. W. Dennis. Purification of two glycoproteins expressing β1-6-branched Asn-linked oligosaccharides from metastatic tumor cells, submitted for publication.
lyophilized, resuspended in 2 ml SDS-sample buffer (0.03 M Tris-HCl, pH 6.8-5.5, 2-mercaptoethanol-5% glycerol-1.2% SDS), and subjected to preparative SDS-PAGE. A vertical strip of acrylamide was removed from each gel (0.35 x 16 cm), cut into 0.5-cm lengths, and extracted overnight in buffer A containing 0.1% SDS, and the extracted protein was counted for radioactivity. Regions of the gel corresponding to the glycoproteins were pooled and purified P2A and P2B were isolated by electrophoresis. The sample was dialyzed into 10 mm Tris, pH 7.4-0.15 M NaCl-0.4% DOC and concentrated to 3 ml by ultrafiltration. Protein determinations were carried out with BCA reagent (Pierce) using BSA as the standard.

Binding of 125I-labeled P2A and P2B to Collagen-Sepharose 4B. Twenty-five µg of P2A and P2B were radioliodinated with 250 µCi of Na125I (Amersham) and iodogen beads (Pierce) for 10 min at 20°C, followed by desalting on a Bio-Gel P-10 column developed in 10 mm Tris-HCl, pH 7.4-0.15 M NaCl-0.4% DOC. The specific activity was 6-12 x 10⁶ cpm/µg and the labeled glycoproteins were made 0.1% BSA and stored at 4°C.

CNBr-activated Sepharose 4B (Pharmacia) was coupled according to manufacturer’s instructions with rat tail collagen type I, collagen type IV (Sigma), human plasma fibronectin, or the chemically synthesized peptide GRGDSPK. Collagens were dissolved in 0.1 M acetic acid and then dialyzed into coupling buffer 0.1 M NaHCO₃, pH 8.0.

Proteins were coupled at a ratio of 10 mg protein/g Sepharose with a 70-80% efficiency as determined by A280 before and after coupling. The coupled Sepharose was equilibrated with 10 mm Tris, pH 7.4-1 mm CaCl₂-1 mm MnCl₂-0.1% Triton X-100 and 50-µl aliquots were incubated with P2A or P2B, 2 x 10⁶ cpm, on ice for 2 h. The beads were washed 5 times with the Tris buffer and eluted with buffer containing 0.2 M NaCl at 4°C for 30 min. Eluted samples were diluted with 2 x SDS-PAGE sample buffer and separated on a 7.5% polyacrylamide gel under denaturing conditions which were dried and exposed to X-ray film.

Glycosidase Digestions. Aliquots of iodinated P2A and P2B (5-10 ng) were incubated at 37°C overnight with 0.2 unit endoglycosidase F from Flavobacterium meningosepticum (Boehringer) in 20 µl of 10 mm Tris-HCl, pH 7.4-0.4% DOC for 16 h. For neuraminidase and endo-β-galactosidase digestion, aliquots of P2A and P2B in the same buffer were diluted with an equal volume of 50 mM sodium acetate, pH 5.0, and incubated at 37°C overnight with either 5 µU of endo-β-galactosidase (Escherichia freundii; Miles) or 50 µU neuraminidase (Clostridium perfringens; Sigma type X). The glycosidase digestions produced a characteristic shift in the molecular weights of P2A and P2B on SDS-PAGE. Neuraminidase and endoglycosidase F digestions under these conditions eliminated WGA and L-PHA reactivity, respectively, for both purified P2A and P2B and for crude membrane preparations of the glycoproteins. Undigested samples were incubated in buffer alone.

P2A and P2B Binding to Collagen-coated ELISA Plates. ELISA plates were coated overnight at 4°C with 2.5 µg/well of rat tail type I collagen or type IV prepared by the pepsin method (Sigma). The wells were blocked for 30 min at 20°C with 1% BSA in 10 mm Tris-HCl (pH 7.5)-1 mm MgCl₂-1 mm CaCl₂ and then washed in the same buffer. 125I-Labeled P2A or P2B preincubated with either buffer, neuraminidase, glycopeptidase F, or endo-β-galactosidase was diluted in the Tris buffer containing 1% BSA, such that 10⁵ cpm were added to each well. Following incubation at room temperature for 4 h, wells were washed 5 times with Tris buffer, the wells were cut out, and the radiolytic content of each well was measured in a gamma counter.

**RESULTS**

**P2A and P2B Glycoproteins.** The purified glycoproteins P2A and P2B were distinct from one another as indicated by amino acid sequencing of the amino ends. Secondly, endoglycosidase F digestion of the purified glycoproteins indicated different contents of N- and O-linked oligosaccharides and this was confirmed by lectin binding and monosaccharide composition (Table 1). Finally, rabbit polyclonal antiserum raised against P2B did not recognize purified P2A.

Based on these analysis, P2A appeared to be structurally similar to human (14, 15) and rat leukosialin (16, 17), a lymphoid cell surface glycoprotein with a high content of O-linked oligosaccharides. Amino end sequence homology of the glycoproteins indicated different contents of O-linked oligosaccharides. Amino acid compositions for P2A and P2B were compared to an average of 204 proteins.

**Table 1 Characteristics of P2A and P2B**

<table>
<thead>
<tr>
<th>P2A</th>
<th>P2B</th>
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<tbody>
<tr>
<td>Migration on SDS-PAGE</td>
<td>Migration on SDS-PAGE</td>
</tr>
<tr>
<td>(M)</td>
<td>(M)</td>
</tr>
<tr>
<td>Native</td>
<td>90,000-120,000</td>
</tr>
<tr>
<td>Neuraminidase</td>
<td>120,000-140,000</td>
</tr>
<tr>
<td>Neuraminidase + endo-β-galactosidase</td>
<td>100,000-120,000</td>
</tr>
<tr>
<td>Endoglycosidase F</td>
<td>65,000-75,000</td>
</tr>
<tr>
<td>N-Linked content (%)</td>
<td>15-25</td>
</tr>
<tr>
<td>O-Linked content (%)</td>
<td>20-30</td>
</tr>
<tr>
<td>Amino acid composition</td>
<td>High, Ser, Thr, Pro</td>
</tr>
<tr>
<td>Lectin binding</td>
<td>WGA, L-PHA, PNA*</td>
</tr>
<tr>
<td>Tissue distribution by Western blotting</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Peanut agglutinin (PNA) bound only following neuraminidase digestion. WGA reacts with α₂—3 sialylated structures (38) and L-PHA binds to β₁-6-branched complex type oligosaccharides (39). * ND, not determined.

**Summary of glycoprotein characterization.** Estimates of N- and O-linked content are based on glycosidase digests and monosaccharide composition. Amino acid compositions for P2A and P2B were compared to an average of 204 proteins.

ECD proteins in the presence of low NaCl. The iodinated glycoproteins were incubated with Sepharose beads coupled with fibronectin or collagen types I or IV and the bound radioactivity was eluted with 0.2 M NaCl and visualized following SDS-PAGE. This procedure allowed a qualitative assessment of the bound radioactivity and confirmation of the glycosidase digestions. The second assay measured direct binding of the radiolabeled glycoproteins to ELISA plates coated with titered amounts of ECD proteins.

P2A bound specifically to collagen type I-Sepharose and not to fibronectin and collagen type IV. In contrast P2B bound weakly to collagen type I but did not appear to bind to fibronectin or collagen type IV (Fig. 1). Reapplication of unbound P2A and P2B to fresh collagen type I-Sepharose showed little additional binding indicating that the amount of affinity matrix used in the assay was saturating (Fig. 1B). Binding of P2A and P2B to ELISA plates coated with ECD glycoproteins was dependent on the ECD concentration and confirmed the specificities observed for binding to ligand-coupled Sepharose (Fig. 2).

**Sialic Acid on P2A Required for Binding to Collagen.** Neither...
type I (Fig. 2). Endoglycosidase F digestion removed N-linked oligosaccharides, as indicated by the increased mobility of collagen-bound P2A separated by SDS-PAGE (Fig. 1A). The endoglycosidase F-treated P2A retained its diffuse appearance on SDS-PAGE due to the presence of sialylated O-linked oligosaccharides.

Neuraminidase-treated P2A showed reduced binding to collagen-Sepharose and to collagen-coated ELISA plates (Figs. and 1 and 2). Since sialic acid associated with N-linked oligosaccharides would be removed by endoglycosidase F digestion, the sialic acid residues on O-linked structures of P2A appear to be required for collagen binding. Reduced and alkylated P2A showed a similar loss of collagen-binding activity suggesting that the native conformation of the glycoprotein is required for binding (Fig. 2).

N-Linked Sialic Acid and Polylactosamine Reduce P2B Binding. Compared to P2A, P2B bound poorly to the ECM glycoproteins. However, endoglycosidase F-digested P2B (i.e., M, 40,000) showed increased affinity for collagens, laminin, and fibronectin (Figs. 1 and 2). Similarly, the removal of polylactosamine sequences or sialic acid from P2B also enhanced binding to the ECM glycoproteins. Therefore, the binding affinity of P2B for these ECM glycoproteins appeared to be reduced by the presence of sialic acid residues which may be linked to polylactosamine sequences associated with N-linked oligosaccharides.

The considerable size heterogeneity observed for P2B separated by SDS-PAGE was reduced by endo-β-galactosidase digestion (Fig. 1A). This suggested that subpopulations of purified P2B differing in polylactosamine content might be distinguished by their binding affinities for ECM glycoproteins. To test this hypothesis, purified P2B was applied to type I collagen-Sepharose and eluted in a stepwise manner with increasing concentrations of NaCl. P2B could be partially eluted with 20 mM NaCl, while endoglycosidase F-digested P2B remained bound (Fig. 3). Raising the NaCl concentration to 50 mM was sufficient to elute most of the bound P2B, both untreated and endoglycosidase F digested. A comparison of untreated P2B eluted from the collagen-Sepharose with increasing salt concentrations indicated that a higher molecular weight subfraction of P2B eluted first (Fig. 3). This supports the conclusions drawn from the studies using glycosidases and further suggests that polylactosamine sequences as well as sialylation may reduce the binding affinity of P2B for collagen.

Binding to GRGDSPK-Sepharose. Since many of the cell attachment receptors recognize RGD-containing peptide sequences present in glycoproteins such as fibronectin and vitronectin (20–22), P2A and P2B were compared for their ability to bind to an immobilized GRGDSPK. Similar amounts of endoglycosidase F-digested 125I-labeled P2B bound to collagen type I and GRGDPTL-Sepharose 4B while P2A did not bind to the peptide (Table 2). The same result was obtained using a peptide-Sepharose column coupled with a 5 times higher peptide:Sepharose ratio. Approximately 25% of applied P2B, both endoglycosidase F-digested and untreated samples, bound to the column, while <1% of the applied P2A was retained on the column. Since removal of N-linked oligosaccharides from P2B did not appear to be required for binding to the RGD peptide, it is possible that the conformational context of the peptide sequence in ECM glycoproteins may also influence P2B access or binding.

P2B differed in peptide size from that of both the α or β subunits of the fibronectin or vitronectin receptors (20, 21), LFA-1 or IIb/IIIa, the latter found on lymphocytes and platelets, respectively (22). Since P2B appears to be structurally
related to lysosomal associated membrane proteins, RGD recognition by these glycoproteins may play a role in trafficking of intracellular vesicles or movement of proteins containing RGD sequences into or out of specific vesicular compartments. These activities might also be modulated by oligosaccharide processing on P2B.

DISCUSSION

Some of the commonly observed changes in oligosaccharide structures following malignant transformation or tumor progression include increased sialylation of available galactosyl and GalNAc residues (5), increased branching of complex type asparagine-linked oligosaccharides (6, 23), increased expression of unsubstituted GalNAc and Galβ1-3GalNAc presumably on O-linked (24, 25), and neoeexpression of embryonic and blood group antigens (2). Studies on the glycosylation mutants of MDAY-D2 have suggested that loss of sialic acid and galactose or decreased branching of complex type asparagine-linked oligosaccharides are directly related to loss of metastatic potential (6, 26). To begin to understand how oligosaccharide expression may affect malignant tumor cell growth, membrane glycoproteins that had previously been identified on SDS-PAGE as the major L-PHA/WGA-reactive species were purified from metastatic MDAY-D2 lymphoma cells and structurally characterized. Since previous studies on the class 1 glycosylation mutants of MDAY-D2 also suggested that loss of sialic acid and/or poly lactosamine may be associated with increased cell adhesion on ECM glycoproteins (10–12), purified P2A and P2B were tested for ECM-binding activity. P2A bound specifically to collagen type I and P2B bound weakly to collagen type I. The sialic acid on P2A and P2B had opposing effects on the binding activities of the two purified glycoproteins. Sialylated O-linked on P2A appeared to be required for collagen binding and loss of sialylated poly lactosamine containing N-linked structures on P2B enhanced its binding on a number of ECM substratum. MDAY-D2 cells were previously shown to be nonadherent on
fibronectin, laminin, and collagen type IV but could attach to collagen type I which may be due to the presence of P2A (11, 12). Loss of sialic acid and galactose in the glycoconjugates of the class 1 mutants was associated with enhanced cell adhesion on fibronectin, laminin, and collagen type IV but little change on type I. Based on the binding characteristics of purified P2A and P2B, the cellular attachment phenotypes of MDAY-D2 and the class 1 mutants are exactly as expected.

Developmentally regulated changes in oligosaccharide processing on fibronectin (27) and NCAM (28) have been shown to alter or modulate their binding affinities. Enzymatic removal of polylactosamine from the N-linked oligosaccharides of placentalfibronectin enhanced binding to gelatin making its binding profile similar to that of adult fibronectin which lacks polylactosamine (27). Interestingly, increased polylactosamine content in asparagine-linked oligosaccharides has been associated with increased malignancy in human thyroid carcinomas (29). Polylactosamine sequences in N-linked structures of the BWS147 lymphoma were shown to be preferentially associated with the β1—6-linked antenna (30). Therefore increased expression of polylactosamine content in N-linked structures may be related in part to increased branching at the trimannosyl core of complex type oligosaccharides which may in turn reduce the binding affinity of P2B for ECM glycoproteins.

Similarly, polysialic acid sequences in NCAM isolated from embryonic tissue reduces homotypic binding compared to NCAM from adult tissues which have less polysialic acid (28). Homotypic binding of NCAM appears to be mediated through protein domains and polysialic acid on the molecule reduces the affinity of the interaction possibly by altering protein conformation. The binding of P2B to ECM proteins appears to be modulated in a similar manner with sialic acid and polylactosamine sequences on asparagine-linked carbohydrates reducing binding to collagen, laminin, and fibronectin. The similarities of these systems suggest that binding affinities of several adhesion-mediating glycoproteins may be modulated together by changes in the activities of glycosyltransferases in the processing pathway for asparagine-linked oligosaccharides. Since oligosaccharide processing and expression of embryonic carbohydrate antigens are temporally and spatially regulated during embryogenesis (2), carbohydrate-dependent changes in the activity or specificity of adhesion glycoproteins may influence cell motility, proliferation, and differentiation. These are also the parameters that change as a result of tumor progression and appear to directly affect metastatic potential (31).

Since distinct α2—6 and α2—3 sialyltransferases act on O- and N-linked oligosaccharides (32), the sialylation of structures on P2B and P2A that modulate their affinity for collagen may be controlled independently. Consequently, a shift in the distribution of sialic acids between O- and N-linked structures may radically change the adhesion properties of the cells. For example, attachment variants of the Esb lymphoma were found to have unchanged levels of total sialic acid; however, lectin-binding studies suggested that the distribution of sialic acid on O- and N-linked structures may be altered and could account for the change in attachment and metastasis phenotypes (33). The sialylation of peanut agglutinin- and soybean agglutinin-reactive oligosaccharides (i.e., Gal-GalNAC and GalNAC, respectively) has been shown to be directly related to the invasive and metastatic potential of BWS147 lymphoma sublines (34). The metastatic sublines with sialylated O-linked structures were generated by fusing nonmetastatic BWS147 cells with activated T-cells. Segregants that lost sialic acid on the O-linked oligosaccharides also lost invasive and metastatic potential. Similarly, the acquisition of sialylated peanut agglutinin-reactive oligosaccharides on M, 90,000—130,000 glycoproteins in B16 melanoma cells maintained in suspension culture has been associated with increased metastatic potential (35). These experimental models and our results suggest that an increased content of sialylated O-linked structures may affect the metastatic potential of tumor cells by altering the activity of adhesion-mediating glycoproteins such as P2A.

Stimulation of lymphocytes results in an increase in NeuNAcα2-3Gal sialyltransferase and a decrease in NeuNAcα2-6GalNAc transferase activities concordant with changes in oligosaccharide expression on leukosialin (36). It remains to be determined whether stimulation-related changes in oligosaccharide expression on leukosialin affect cellular interactions with ECM glycoproteins. Interestingly, leukosialin and the immunologically distinct GP1b have been shown to be deficient on lymphocytes and platelets, respectively, from individuals with Wiscott-Aldrich syndrome (37). GP1b is structurally similar to leukosialin and P2A, showing a high content of O-linked oligosaccharides, and appears to be involved in...
platelet adhesion to Von Willebrand factor. Since neuraminidase-treated normal lymphocytes showed a loss of gpL115/leukosialin and the appearance of a larger band in SDS-PAGE similar to a species observed in the Wiscott-Aldrich patients, it was suggested that a glycosylation defect may explain the dysfunction of two distinct glycoproteins in these patients (37). Based on our observations with P2A, a defect in glyclosylation leading to incomplete sialylation of O-linked oligosaccharides may inhibit binding activity of the sialoglycoprotein(s) and this in turn may affect lymphocyte function.

In conclusion, the glycosylation state of two membrane glycoproteins, P2A and P2B, directly affected their binding affinity for ECM glycoproteins. This suggests that the oncodevelopmental state or cellular program of oligosaccharide processing may regulate the binding affinity of adhesion-mediating proteins such as P2A and P2B and influence cellular processes during development and tumor cell metastasis.

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