Glycosyltransferase Changes upon Differentiation of CaCo-2 Human Colonic Adenocarcinoma Cells

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ABSTRACT

The spontaneous differentiation of CaCo-2 human colonic adenocarcinoma cells to enterocytes in culture is associated with a decrease in polylactosaminoglycan, particularly those attached to the lysosomal membrane glycoprotein h-lamp-1 (Youakim et al., Cancer Res., 49: 6889-6895, 1989). To elucidate the biosynthetic mechanisms leading to these alterations we have compared glycosyltransferase activities that are involved in the synthesis of polylactosaminoglycans and of the N- and O-glycan structures that provide the framework for the attachment of these chains. Glycosyltransferase activities in cell homogenates obtained from undifferentiated and differentiated CaCo-2 cells were assayed by high pressure liquid chromatography separation of enzyme products. The β-galactosidase activities and extremely high pyrophosphatase activities in differentiated cells were effectively inhibited by 5 mM γ-galactonolactone and 10 mM AMP, respectively. CaCo-2 cells contain most of the enzymes that are involved in N-glycan branching [N-acetylgalcosaminyl (GlcNAc) transferases I to V] with the exception of GlcNAc transferase VI. The levels of GlcNAc transferase I activities were comparable in undifferentiated and differentiated cells, but GlcNAc transferase II to V activities were significantly increased upon differentiation. The enzyme activities that are directly involved in the synthesis of linear polylactosaminoglycans (Galβ(1→4)GlcNAcβ(1→3)-repeating units), blood group I UDP-GlcNAc:Galβ(1→3)R β3-GlcNAc transferase and UDP-Gal:GlcNAc β4-Gal transferase, were found at similar levels in undifferentiated and differentiated CaCo-2 cells. Since GlcNAc transferase III activity is known to inhibit further branching and galactosylation, these results suggest that its increased activity in differentiated CaCo-2 cells may be partly responsible for the decreased synthesis of fucosylated polylactosaminoglycans. Differentiated cells showed a 2-fold increase in O-glycan core 2 UDP-GlcNAc:Galβ(1→3)R [GlcnAc to N-acetylgalactosamine (GalNAcβ)] β6-GlcNAc transferase activity. In contrast, O-glycan core 1 UDP-Gal-GlcNAc:Galβ(1→3)R β3-Gal transferase activity was found decreased. Several enzymes that are found in homogenates from normal human colon tissue are absent or barely detectable in CaCo-2 cells. These include blood group I UDP-GlcNAc:Galβ(1→3)R (GlcNAc to Gal) β6-GlcNAc transferase, O-glycan core 3 UDP-GlcNAc:GalNAc:Galβ(1→3)R β3-GlcNAc transferase and O-glycan core 4 UDP-GlcNAc:GlcNAcβ(1→3)GalNAcβ(1→2)R (GlcNAc to GalNAc) β6-GlcNAc transferase.

INTRODUCTION

CaCo-2 human colonic adenocarcinoma cells differentiate spontaneously into cells with the properties of enterocytes upon prolonged culturing (1). This differentiation is accompanied by the acquisition of a brush border and of hydrolytic enzymes typical of absorptive intestinal cells. CaCo-2 cells were previously shown to contain polylactosaminoglycans, which could be labeled with fucose and glucosamine. Although these are primarily associated with N-linked carbohydrate chains, a significant proportion of glucosamine-labeled glycopeptides were also found in alkali-labile O-linked oligosaccharides (2). The proportion of fucosylated polylactosaminoglycans known to carry oncodevelopmental antigens decreases significantly during differentiation (2). In particular, the lysosomal membrane protein h-lamp-1 was shown to be affected by these glycosylation changes (3).

To elucidate the mechanisms responsible for the decrease in polylactosaminoglycans with differentiation, we compared the glycosyltransferase activities that are involved in the synthesis of polylactosaminoglycan chains (Fig. 1) and of the backbone structures of O- and N-linked oligosaccharides in UD3 and D CaCo-2 cells. The synthesis of core structures and of branches of N- and O-glycans requires distinct sets of glycosyltransferases (4, 5). However, most of the enzymes involved in the elongation of N- and O-glycans and in the addition of terminal antigens are the same for both types of glycans. We found increased activities for both O- and N-glycan branching enzymes and decreased activity of the transferase responsible for the synthesis of the O-glycan core 1 (Galβ3GalNAc-R) upon differentiation. Unexpectedly, the enzymes directly involved in polylactosaminoglycan biosynthesis, i.e., UDP-Gal:GlcNAc β4-Gal transferase (β4-Gal-T) and blood group I UDP-GlcNAc:Galβ4GlcNAc-R β3-GlcNAc transferase (β3-Gn-T), remain essentially unchanged with differentiation of CaCo-2 cells; blood group I UDP-GlcNAc: GlcNAcβ3Galβ-R (GlcNAc to Gal) β6-GlcNAc transferase, responsible for branching, was undetectable.

MATERIALS AND METHODS

Materials. AG 1-X8 (100-200 mesh, Cl– form) was purchased from Bio-Rad. Bovine serum albumin, Galβ3GalNAc, AMP, Triton X-100, γ-galactonolactone, Galβ3GalNAc, GlcNAcβ3Galβ-methyl, and GalNAcβ3-Galβ-methyl were purchased from Sigma. Acetonitrile (190 UV cutoff) was from Fisher Scientific Co. or Caledon Laboratories. UDP-N-[1-14C]acetylglucosamine was synthesized as described previously (6) and diluted with UDP-GlcNAc from Sigma. UDP-β4-14Cglactose was purchased from Amersham and diluted with UDP-Gal from Sigma.


Received 12/10/90; accepted 4/4/91.

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1 This research was supported by a grant from the Canadian Cystic Fibrosis Foundation to Harry Schachter (Hospital for Sick Children, Toronto), and by grants from the Canadian Cystic Fibrosis Foundation and the Canadian Research Council for Health and Colitis to A. H. and the Medical Research Council of Canada to I. B. 2 To whom requests for reprints should be addressed, at the Research Institute, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.
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Fig. 1. Pathways of polylactosaminoglycan synthesis. The enzymes involved in the synthesis of the blood group i antigen attached to R (R = N-linked or O-linked oligosaccharides) are present in CaCo-2 cells. The β6-GlcNAc transferase activity synthesizing the branch of the blood group i antigen is absent from CaCo-2 cells but is high in normal human colon.

(Manα3) Manβ-hexyl was synthesized by Dr. H. Paulsen, Hamburg, Germany. Manα6(14C)GlcNAcβ2 (Manα3) Manβ-hexyl was prepared from Manα6 (Manα3) Manβ-hexyl with purified rat liver GlcNAc transferase I and subsequent purification by AG 1-X8 and Bio-Gel P-4. It was shown that the purified enzyme attaches GlcNAc in β2-linkage only to the Manα3 residue of the substrate* (0,2+Fl, [2,24], [bis2,24], [26,24], and [bis26,24]) were isolated as reducing oligosaccharides from glycoproteins (7). GlcNAcβ6 (14C-GlcNAcβ4) (GlcNAcβ2) Manα-methyl was prepared from GlcNAcβ6 (GlcNAcβ2) Manα-methyl with hen oviduct microsomal GlcNAc transferase VI (8). [bis2,24mco], [2,24mco], and [bis2,24mco] were isolated as described before (8).

[14C]GlcNAcβ6 (GlcNAcβ3) Galβ-methyl was prepared by incubation of GlcNAcβ3 Galβ-methyl with pig gastric mucosa microsomal blood group 1 β6-GlcNAc transferase (9, 10) as follows: 3.2 μmol GlcNAcβ3 Galβ-methyl were incubated with pig gastric mucosal microsomes (4.8 mg protein) for 2 h at 37°C in a total volume of 1.32 ml containing 2.62 mM UDP-[1-14C]Galactose (3287 dpm/nmol), 9.0% Triton X-100, 76 mM MES buffer (pH 7), 1.5 mM AMP, and 76 μM GlcNAc. To stop the reaction, 8 ml 20 mM sodium tetraborate/1 mM EDTA, pH 9, were added. The mixture was passed through a 20-ml column of AG 1-X8, 100-200 mesh, Cl- form. The column was washed with 52 ml water, and the eluate was lyophilized. Enzyme product was purified twice by HPLC, using a Waters carbohydrate (propylamine) column. HPLC separations were carried out with an LKB or a Waters system as described (12, 13). The acetone signal was set at 2.225 ppm. Proton nmr spectra were recorded at 300 MHz using a Varian XL-300 spectrometer. The acetone signal was set at 2.225 ppm.

Enzyme Kinetics. K_{m} and V_{max} values were determined from 5 to 6 different substrate concentrations by linear double reciprocal Line-weaver-Burk plots.

RESULTS

Glycosyltransferases that assemble and elongate the branches of N-linked oligosaccharides and O-glycan cores were assayed in UD and D CaCo-2 cells. The enzymes; structures of their substrates and products; the HPLC conditions of product separation; and enzyme activities are summarized in Table 1. The assays were complicated by high pyrophosphatase activities observed especially in D cells. These activities were calculated from the total amount of free radioactive sugars arising from the breakdown of radioactive UDP-Gal or UDP-GlcNAc during the incubation. Without the addition of AMP, UD cells exhibited reasonable levels (<5%) of breakdown; however, pyrophosphatasases in D cells cleaved more than 80% of the nucleotide sugar donor. It was used essentially to add 10 mM AMP as a pyrophosphatase inhibitor to the assay. Under these conditions, less than 2% of the nucleotide sugars in both cell populations were degraded during a 1-h incubation.

The absorbance scans of HPLC graphs indicated that the


Nuclear Magnetic Resonance. Samples were prepared by exchanging twice with 99.8% D$_2$O (Aldrich) and twice with 99.96% D$_2$O (Merck, Sharpe and Dohme). Samples were dissolved in 99.96% D$_2$O as the internal standard. Proton nmr spectra were recorded at the Toronto Carbohydrate Research Centre with a Bruker 500-MHz spectrometer. The acetone signal was set at 2.225 ppm.

High Pressure Liquid Chromatography. HPLC separations were carried out with an LKB or a Waters system as described (12, 13). Acetonitrile/water mixtures were used as the mobile phase for all columns at a flow rate of 1 ml/min. To separate enzyme products with mco, hexyl, benzy, and methyl groups, a reverse phase C_18 column was used. Free reducing sugars or methylglycosides were separated on a propylamine (NH$_2$) column (Waters carbohydrate analysis column). Elution of compounds was monitored by measuring the absorbance at 195 nm and counting the radioactivity of collected fractions (12).

Assays for GlcNAc Transferases (Table 1). The standard assay mixture for GlcNAc transferases contained the following ingredients in a total volume of 40 μl: 0.125 mM GlcNAc; 0.125 mM MES, pH 7; 0.125% Triton X-100; 12.5 mM MnCl$_2$; 10 mM AMP; 5 mM γ-galactonolactone (only for substrates with terminal Gal at the nonreducing end as indicated in Table 1); 0.87 mM UDP-[1-14C]GlcAcβ2-mannose (5486 dpm/nmol); substrate (as indicated in Table 1); and 10 μl cell homogenate (0.057 ± 0.068 mg protein/ml for D or UD cells, respectively). β6-GlcNAc transferases that do not require MnCl$_2$ (GlcNAc transferase V, blood group 1, core 2, and core 4 β6-GlcNAc transferases) were measured in the absence of exogenous MnCl$_2$ to reduce any enzyme reactions requiring MnCl$_2$. Mixtures were incubated for 1 h at 37°C. Reactions were stopped by the addition of 400 μl 20 mM sodium tetraborate/1 mM EDTA, pH 9, and freezing. Mixtures were passed through Pasteur pipets filled with AG 1-X8, 100-200 mesh, CF$_3$ form. After these were washed with 2.6 ml water, eluates were lyophilized, taken up in 200 μl water, and stored at -20°C. We used 100 μl for HPLC analysis. Results from assays lacking the acceptor were routinely subtracted in the calculations of activities.
Table 1. Glycosyltransferase changes upon differentiation of CaCo-2 cells: summary of enzymes assayed in CaCo-2 cells, structures of substrates and products, HPLC conditions, and enzyme activities.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Product</th>
<th>Retention time (min)</th>
<th>Col.</th>
<th>% AN</th>
<th>Activity (nmol/h/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gn-T I</td>
<td>0.5 mM M6(Gm3) M6-hex</td>
<td>M6(Gm32Gm3) M6-hex</td>
<td>35</td>
<td>C18</td>
<td>12</td>
<td>11.0 12.2</td>
</tr>
<tr>
<td>Gn-T II</td>
<td>0.25 mM [0.2+F]</td>
<td>[2,2+F]</td>
<td>14</td>
<td>NH3</td>
<td>74</td>
<td>ND</td>
</tr>
<tr>
<td>Gn-T III</td>
<td>1 mM [2,2mco]</td>
<td>[bis2,2mco]</td>
<td>25</td>
<td>C18</td>
<td>16</td>
<td>7.8 15.7</td>
</tr>
<tr>
<td>Gn-T IV</td>
<td>0.5 mM [26,24]</td>
<td>[bis26,24]</td>
<td>38</td>
<td>C18</td>
<td>16</td>
<td>2.9 10.2</td>
</tr>
<tr>
<td>Gn-T V</td>
<td>1 mM [2,2mco]</td>
<td>[2,2mco]</td>
<td>65</td>
<td>C18</td>
<td>16</td>
<td>2.6 4.9</td>
</tr>
<tr>
<td>Gn-T VI</td>
<td>0.2 mM [2,24]</td>
<td>[2,24]</td>
<td>80</td>
<td>NH3</td>
<td>70</td>
<td>ND</td>
</tr>
<tr>
<td>Core 1 β3-Gal-T</td>
<td>2 mM GAα-Bn</td>
<td>GAβ3GAα-Bn</td>
<td>12</td>
<td>C18</td>
<td>1</td>
<td>ND</td>
</tr>
<tr>
<td>Core 2 β6-Gn-T</td>
<td>2 mM GAβ3GAα-Bn</td>
<td>GAβ3GAα-Bn</td>
<td>31</td>
<td>C18</td>
<td>10</td>
<td>38.3 21.4</td>
</tr>
<tr>
<td>Core 3 β3-Gn-T</td>
<td>2 mM GAα-Bn</td>
<td>GAβ3GAα-Bn</td>
<td>28</td>
<td>C18</td>
<td>10</td>
<td>8.9 20.1</td>
</tr>
<tr>
<td>Core 4 β6-Gn-T</td>
<td>2 mM GAβ3GAα-Bn</td>
<td>GAβ3GAα-Bn</td>
<td>26</td>
<td>C18</td>
<td>10</td>
<td>0.46 0.64</td>
</tr>
<tr>
<td>Elongation β3-Gn-T</td>
<td>4 mM GAβ3GAα-Bn</td>
<td>GAβ3GAα-Bn</td>
<td>30</td>
<td>C18</td>
<td>10</td>
<td>0.09 0.04</td>
</tr>
<tr>
<td>i β3-Gn-T</td>
<td>4 mM GAβ4Gn</td>
<td>GAβ3GAβ4Gn</td>
<td>20</td>
<td>NH3</td>
<td>86</td>
<td>ND</td>
</tr>
<tr>
<td>I β6-Gn-T</td>
<td>2 mM Gβ3Gβ3-methyl</td>
<td>Gβ3Gβ3-methyl</td>
<td>64</td>
<td>NH3</td>
<td>86</td>
<td>ND</td>
</tr>
</tbody>
</table>

substrate Galβ3GalNAcα-Bn was degraded by the action of β-galactosidases in D cells to GalNAcα-Bn. Degradation of Galβ3GalNAcα-Bn was barely detectable in UD cells. β-Galactosidase activity measured with Galβ-p-nitrophenyl substrate in D was 250% of the activity in UD cells. The optimal pH of β-galactosidase activity in both UD and D cells was pH 4.3 or below. This indicates that the β-galactosidases probably originate from the lysosomes. However, the addition of 2.5 or 5 mM...
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γ-galactonolactone inhibited breakdown of Galβ3GalNAc-Bn (Fig. 2) and concomitantly increased the activity of core 1 β3-Gal-T, while the core 2 β6-GlcNAc-T remained unchanged. 5 mM γ-galactonolactone was therefore routinely added to all Gal transferase assays and enzyme assays involving substrates with terminal Gal.

Activities of β4-Gal and core 1 β3-Gal-T, the core 2, core 4, and blood group I β6-GlcNAc-T, and core 3 β3-GlcNAc-T were present in all five samples of normal human colonic homogenate, but there were considerable variations of the levels of all six transferase activities between samples. This may be due to the fact that colonic homogenates represent heterogeneous cell populations. Three of these activities (Table 1), i.e., core 3 β3-GlcNAc-T, core 4 β6-GlcNAc-T, and blood group I β6-GlcNAc-T, were absent from CaCo-2 cells or present at only very low levels. Fig. 3 shows that the blood group I β6-GlcNAc-T has high activity in the normal human colon but is absent from CaCo-2 cells.

Of the GlcNAc transferases that attach the branches to N-linked oligosaccharides, activities of GlcNAc-T I to V were detectable in CaCo-2 cells while GlcNAc-T VI was absent (Table 1).

GlcNAc-T I activities were high (11 to 12 nmol/h/mg) and at a similar level in UD and D cells. GlcNAc-T II, III, IV, and V activities appeared to be increased in D cells (Table 1). GlcNAc-T II was increased 2-fold using [0,2+F] as the substrate. In the absence of GlcNAc-T VI, the tetraantennary [26,24] oligosaccharide is a specific substrate for GlcNAc-T III and showed a 2-fold increase of this enzyme in D cells (Table 1). [2,2meo] was used as the substrate to measure both GlcNAc-T III and GlcNAc-T IV activities in the same assay (Fig. 4). GlcNAc-T III was increased more than 3-fold, and GlcNAc-T IV was increased more than 7-fold in D cells (Table 1).

GlcNAc-T V assays were carried out in the absence of additional MnCl2 to reduce the action of GlcNAc transferase III, using [2,24] as the substrate. The assays indicated an almost 3-fold increase of GlcNAc-T V in D cells (Table 1). However, low levels of the product of GlcNAc-T III action, [bis2,24], were also detected (not shown).

The enzymes assembling the repeating units of poly lactosaminoglycans, i β3-GlcNAc-T and β4-Gal-T, were found at a comparable level in UD and D cells (0.81 and 0.62 nmol/h/mg for the i β3-GlcNAc-T and 50.3 and 58.8 nmol/h/mg for the β4-Gal-T) (Table 1). Enzyme kinetics for the β4-Gal-T indicates similar Km (6.3 mm for UD and 7.1 mm for D) and Vmax (167 nmol/h/mg for UD and 250 nmol/h/mg for D) values.

The core 1 β3-Gal-T that synthesizes O-glycan core 1 (Galβ3 GalNAc-), using GalNAc-Bn as the substrate, showed a re-
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The activity of GlcNAc-T III, the enzyme that introduces the bisecting GlcNAc linked to the β-Man residue of N-linked oligosaccharides (22), was elevated in differentiated CaCo-2 cells, along with the other branching enzymes. It has been shown that the presence of the bisected GlcNAc has a profound effect on oligosaccharide conformation (23) and blocks further branching (24), lectin binding (25), and galactosylation (26). Bisected structures have also been found in differentiated HL 60 cells associated with decreased high molecular weight oligosaccharide chains (21). It seems possible, therefore, that the increased GlcNAc-T III activity observed in differentiated cells prevents subsequent reactions, including elongation to polylactosaminoglycans. GlcNAc-T III may thus be an important regulator of polylactosaminoglycan synthesis. Other factors may also be involved. As protein determinants are possible biosynthetic controlling factors (23, 27, 28), proteins may carry their individual carbohydrate structures. It is possible that proteins undergo qualitative and quantitative changes upon differentiation, and these changes influence lactosaminoglycan synthesis. However, the decrease in polylactosaminoglycans with differentiation was clearly demonstrated for a specific glycoprotein, h-lamp-1 (3). This decrease was not due to a change in the amount of protein but to glycosylation changes. Another possibility for the decrease in fucosylated polylactosaminoglycans may be increased degradation of these chains in D, changes in the subcellular organization or intracellular transport, or changes in the activity of glycosyltransferases that add terminal carbohydrate residues. Sialyltransferases have been reported to increase upon differentiation of rat intestinal cells (29), HL 60 cells (30), and human myeloblasts (31). If polylactosaminoglycan chains became hypersialylated or increasingly substituted with blood group antigens, extension would likely be inhibited. However, for Chinese hamster ovary cells it has been suggested that the addition of terminal α3-Gal and α3-sialic acid does not compete with polylactosaminoglycan synthesis, probably because these reactions take place in different subcellular compartments (32). The subcellular distribution of terminal transferases in CaCo-2 cells is not known.

In previous work, it was concluded that the polylactosaminoglycans of CaCo-2 cells were highly branched, based upon the pattern of products obtained following endo-β-galactosidase digestion (2). It is possible that the mixture of products obtained following endo-β-galactosidase digestion resulted from incomplete degradation of linear polylactosaminoglycans due to extensive substitutions with fucose residues. No branching activity to form the blood group I antigen (10) was found in the present study, although there was considerable core 2 β6-GlcNAc-T activity. The β6-GlcNAc-T synthesizing the I antigen is present in normal human colonic tissue homogenate which consists of a mixture of different cell populations. The activities synthesizing core 2, 1 antigen, and core 4 are probably due to the same enzyme in mucin-secreting tissues (9). Apparently, this β6-GlcNAc-T in CaCo-2 cells is similar to the enzyme in human leukocytes (13) but has a different specificity than the enzyme from pig gastric or human colonic mucosa inasmuch as it lacks the activities to synthesize core 4 and I antigen.

The β3-Gal-T that actively synthesizes O-glycan core 1 (Galβ3 GalNAco-) (18, 33, 34) in UD cells is reduced to about one-half upon differentiation in D cells. Enzyme kinetics suggests that the same enzyme is expressed in both UD and D cells but that there is less enzyme protein in D cells. Core 2 β6-GlcNAc-T [synthesizing core 2, GlcNAcβ6 (Galβ3) GalNAc-] (35, 36, 37) is significantly increased in differentiated CaCo-2 cells, probably due to an increase in enzyme protein. The core 2 β6-GlcNAc-T has previously been found to be significantly elevated in the less mature granulocytes and blast cells from
patients with chronic and acute myelogenous leukemia (13). Piller et al. (38) reported a dramatic increase in core 2 β6-GlcNAc-T activity upon activation of lymphocytes by anti-CD3 antibody or interleukin 2. This enzyme appears to be developmentally regulated and may be important in the differentiation process. CaCo-2 cells have only low levels of the β6-GlcNAc-T synthesizing core 4 (GlcNAcβ6 [GlcNAcβ3] GalNAc-) (6) which in various mucin-secreting tissues, including human colon, accompanies core 2 β6-GlcNAc-T activities at fairly high levels. It is possible that two β6-GlcNAc-T exist with different specificities, and at least one of them is regulated during differentiation. Alternatively, tissues may contain endogenous factors regulating enzyme specificity.

O-Glycan cores are usually made by the attachment of a 3-linked residue prior to introducing the 6-linked branch (18). Human glycoproteins have been reported to contain O-glycans with the GlcNAcβ6 GalNAc- structure (39, 40). In normal human colon or in CaCo-2 cells we could not detect an enzyme that can synthesize the GlcNAcβ6 GalNAc-R linkage without the β3-linked GlcNAc. It is possible that this linkage was made from core 2 (GlcNAcβ6 [GlcNAcβ3] GalNAc-R) by the action of β-galactosidase, because human cells studied in this report and previously (13) contained a high activity of a β-galactosidase capable of cleaving a β3-linked galactose.

Normal human colonic mucins contain a high proportion of oligosaccharides with the core 3 (GlcNAcββ3 GalNAc-R) structure (41, 42). The lack in CaCo-2 cells of the β3-GlcNAc transferase activity synthesizing core 3, an activity characteristic of normal colon tissue (6), suggests that this enzyme is turned off in colon adenocarcinoma cells. However, these cells, although capable of O-glycan synthesis, have properties analogous to those of intestinal columnar cells and may therefore not contain the spectrum of enzymes found in colon goblet cells that synthesize mucins.

ACKNOWLEDGMENTS

The authors thank Ji-Mao Yang for technical assistance.

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