Quantitative and Qualitative Characterization of Human Cancer-associated Serum Glycoprotein Antigens Expressing Epitopes Consisting of Sialyl or Sialyl-Fucosyl Type 1 Chain

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ABSTRACT

The levels of carbohydrate antigens having epitopes consisting of type 1 chain (R-Galβ1-GlcNAcβ1-Galβ1-R) in the sera of patients with various malignant and nonmalignant disorders have been investigated with the use of three monoclonal antibodies, N-19-9, FH-7, and FH-9. Serum levels of 2→3 sialylated Le* antigen and 2→6 sialylated Le* antigen, defined respectively by antibodies N-19-9 and FH-7, were found to be frequently high in patients with cancer of the digestive system, particularly pancreatic cancer. High levels of 2→3,2→6 disialylated Le* antigen, defined by antibody FH-9, were less frequent in cancer patients when compared with the other two antigens. In patients with nonmalignant disorders, especially renal and autoimmune diseases, serum levels of the two type 1 chain antigens defined by FH-7 and FH-9 were more frequently high than that defined by N-19-9. Molecular weights and other general biochemical characteristics of serum mucin carrying the type 1 chain determinants were not significantly different in cancer patients as compared with patients with nonmalignant disorders. However, the degree of glycosylation of the antigen, as assessed by its solubility in perchloric acid, showed significant differences; i.e., the mucin antigen carrying 2→6 sialylated Le* determinant in the sera of patients with nonmalignant disorders had the highest carbohydrate/protein ratio, followed by the mucin carrying the same determinant in the sera of cancer patients. Mucin antigen carrying 2→3 sialylated Le* antigen and 2→3,2→6 disialylated Le* antigen in cancer patients had the lowest carbohydrate/protein ratio among the four groups tested. Thus, the carbohydrate/protein ratio in the type 1 chain mucin antigens in sera of normal subjects is higher than that in sera of cancer patients (P < 0.05). This finding is in contrast to previous findings on the mucin antigens carrying the type 2 chain determinant (R. Kannagi et al., Cancer Res., 46: 2619-2626, 1986), in which the mucin antigen in cancer patients was found to have a much higher carbohydrate/protein ratio than that carrying the same antigenic determinants in patients with nonmalignant disorders.

INTRODUCTION

Analysis of glycoconjugates in human cancer tissues by using a combination of monoclonal antibodies has revealed the presence of a series of carbohydrate antigens having a repeating or modified lactosamine structure as the major cancer-associated antigens (for review, see Refs. 1–3). These antigens in the sera of patients with cancer have been utilized in diagnosis and therapy (4–10). In our previous study on type 2 chain antigens, using a set of monoclonal antibodies that can distinguish the fine structural differences among type 2 chain antigens, we reported that serum levels of sialylated Le*-i, defined by monoclonal antibody FH6, were frequently elevated in patients with lung adenocarcinoma, whereas levels of Le* were frequently high in patients with hepatocellular carcinoma (7). In this study, we have analyzed type 1 chain determinants in the sera of patients with various types of cancer, nonmalignant diseases, and normal subjects, using a set of monoclonal antibodies that can distinguish the fine structural differences among the sialylated and fucosylated type 1 chain antigens.

MATERIALS AND METHODS

Structures of Carbohydrate Antigens and Specificity of Monoclonal Antibodies Used in This Study. The structures of type 1 chain antigens and the specificities of the monoclonal antibodies used in this study are summarized in Table 1.

The essential difference between N-19-9 and FH-7 antibodies is that the former specifically recognizes the Le* antigen that is 2→3 sialylated at the terminal galactose (5), while the latter recognizes only the Le* antigen that is 2→6 sialylated at the penultimate N-acetylgalcosamine and does not show strict specificity toward the 2→3 sialylation at the terminal galactose (11). For this reason, the antigen defined by the antibody N-19-9 is referred to hereafter as 2→3 sialylated Le* antigen, and that defined by FH-7 as 2→6 sialylated Le* antigen. The antigen defined by FH-9 antibody is referred to as 2→3,2→6 disialylated Le* antigen, because 2→6 sialylation at the penultimate N-acetylgalacosamine, as well as 2→3 sialylation at the terminal galactose of the Le* antigen, is necessary for the FH-9 antibody to react with the antigen (12). Note that the essential difference between the specificities of N-19-9 and FH-7 is the location of only one sialic acid residue.

Preparation of Monoclonal Antibodies and Blood Samples. Two monoclonal antibodies, FH-7 (11) and FH-9 (12), which define fucosyl 2→6 sialosyl and 2→3,2→6 disialosyl type 1 chain antigens, respectively, were prepared as previously described. Antibody N-19-9, defining fucosyl 2→3 sialosyl type 1 chain, was purchased from Centocor (Malvern, PA). Patient serum samples were obtained from Kyoto University Hospital, Kyoto, Japan. Some serum samples were donated by Shimane University Hospital, Shimane, Japan, through the courtesy of Drs. Jiro Endo and Yoshinobu Yoshida. Serum samples from 348 randomly selected healthy individuals (18–65 years of age) were supplied primarily by the Otsuka Assay Institute, Tokushima, Japan.

Determination of Antigen Levels in Sera of Patients. The serum levels of 2→6 sialylated Le* antigen and 2→3,2→6 disialylated Le* antigen, defined by the monoclonal antibodies FH-7 and FH-9, were determined by the binding of 125I-labeled monoclonal antibody on polyacrylamide plastic beads that had been coated with the same monoclonal antibody and incubated with sera, according to the method described previously (7). Briefly, serum samples (20 μl) were mixed with 200 μl of 40 mM citrate buffer, pH 5.0, supplemented with 1% normal mouse serum, and incubated for 18 h with FH-7- or FH-9-coated beads at room temperature, with rotation. The beads were washed three times and incubated with 200 μl of 125I-labeled FH-7 (5 × 10⁶ cpm/tube) or FH-9 antibody (1 × 10⁵ cpm/tube) for 1 h at room temperature. The radioactivity adsorbed by the beads was measured after washing three times with the same buffer. Duplicate assays were performed for each sample. Pooled sera having high levels of the antigens were used as standards. The assay condition was linear up to 224 units/ml for both antibodies. The units of the reactive antigens were arbitrarily determined. Cut-off values were set to the mean ± 2 SD of the normal
RESULTS

Serum Levels of 2→3 and 2→6 Sialylated Leα Antigen, and 2→3,2→6 Disialylated Leα Antigen in Patients with Malignant and Nonmalignant Disorders. As shown in Fig. 1a, the levels of 2→6 sialylated Leα antigen, defined by FH-7 antibody, were high in a significant number of sera from cancer patients. The highest incidence of abnormal levels was noted in patients with pancreatic cancer, followed by patients with various cancers of the digestive system. Serum levels of 2→3 sialylated Leα antigen, as detected by N-19-9 antibody, were also high in patients with various malignant diseases, especially pancreatic cancer, as shown in Fig. 1b. The serum levels of 2→3,2→6 disialylated Leα antigen, defined by FH-9 antibody, were high in some patients with various cancers, as shown in Fig. 1c. The incidence of 2→3,2→6 disialylated Leα antigen was far less than that of 2→3 or 2→6 sialylated Leα antigen.

When the levels of 2→3 and 2→6 sialylated Leα antigens in patients with malignant and nonmalignant disorders were compared, it was evident that levels of 2→3 sialylated Leα antigen were higher than levels of 2→6 sialylated Leα antigen in sera of cancer patients, whereas the reverse was true in sera of patients with nonmalignant disorders. As shown in Table 2, the incidence of high levels of 2→3 sialylated Leα antigen defined by N-19-9 was as great as 36% in sera from cancer patients, while the incidence of high levels of 2→6 sialylated Leα antigen defined by FH-7 antibody was only 25% when determined with the same panel of sera taken from over 400 patients. On the other hand, the incidence of high levels of 2→3 sialylated Leα antigen was only 14% in patients with nonmalignant disorders, while the incidence of high levels of 2→6 sialylated Leα antigen was as high as 33% in these patients. It can be concluded that the level of 2→3 sialylated Leα antigen is elevated less frequently in patients with nonmalignant disorders than that of 2→6 sialylated Leα antigen. Similarly, the incidence of high levels of 2→3,2→6 disialylated Leα antigen in patients with nonmalignant disorders exceeded that of the 2→3 sialylated Leα antigen (Fig. 1c; Table 2).

Among the sera taken from patients with nonmalignant disorders, high levels of 2→6 sialylated Leα antigen were observed frequently in sera of patients with renal and autoimmune diseases, in which elevated levels of 2→3 sialylated Leα antigen were rarely observed (Fig. 1a and b; Table 2).

Serum Levels of 2→6 Sialylated Leα Antigen in Nonmalignant Renal and Autoimmune Diseases. Among renal and autoimmune diseases, abnormally high serum levels of 2→6 sialylated Leα antigen were observed frequently in patients with chronic glomerulonephritis and nephrosis (mostly lipid nephrosis), systemic lupus erythematosus, rheumatoid arthritis, and Sjögren’s syndrome, as shown in Fig. 2. This is interesting because no elevated levels of any carbohydrate antigen have ever been reported in these disorders. The serum levels of 2→6 sialylated Leα antigen correlated well with the clinical course in some patients with systemic lupus erythematosus (data not shown). It is possible, however, that these diseases may be associated with a high level of a nonspecific compound in sera (see “Discussion”).

Comparison of Incidence of Type 1 Chain and Type 2 Chain Antigens in Sera of Patients with Malignant and Nonmalignant Disorders. When the incidence of these type 1 chain antigens was compared with that of the type 2 chain antigens, as shown in Table 2, it was evident that the positive incidence of these antigens in cancer patients was very similar. However, when the incidence of type 1 chain antigens in sera of patients with

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Table 1  Structures of the type 1 chain carbohydrate* antigens and the specificities of the monoclonal antibodies used in this study

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Antibody (isotype)</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leα</td>
<td>—OH</td>
<td>—OH</td>
<td>Fucα1→4</td>
<td></td>
</tr>
<tr>
<td>2→3 Sialyl Leα (CA19-9)</td>
<td>NeuAcα2→3</td>
<td>—OH</td>
<td>Fucα1→4</td>
<td></td>
</tr>
<tr>
<td>2→6 Sialyl Leα (lgG1)</td>
<td>—OH, or</td>
<td>NeuAcα2→6</td>
<td>Fucα1→4</td>
<td></td>
</tr>
<tr>
<td>2→3,2→6 Disialyl Leα (lgG3)</td>
<td>NeuAcα2→3</td>
<td>NeuAcα2→6</td>
<td>—OH</td>
<td></td>
</tr>
<tr>
<td>2→3,2→6 Disialyl Leα (lgG2a)</td>
<td>NeuAcα2→6</td>
<td>NeuAcα2→6</td>
<td>—OH</td>
<td></td>
</tr>
</tbody>
</table>

*Gal, galactose; GlcNAc, N-acetylgalactosamine; Glc, glucose; Cer, ceramide; Fuc, fucose; NeuAc, acetylenuraminic acid.

2 Abbreviations used are: PCA, perchloric acid; Leα, lactotetrasaccharide.
nonmalignant disorders was compared with that of type 2 chain antigens, as shown in Table 2, it was evident that the false positive incidences of type 1 chain antigens (14, 33, and 27%) are remarkably higher than those of type 2 chain antigens (2 and 4%). Note that the panel of sera from patients with malignant and nonmalignant disorders used in the previous study and in the present study is essentially the same.

Overlap of Positive Incidence of Type 1 and Type 2 Chain Antigens in Sera of Patients with Malignant Disorders. In most of the sera of cancer patients tested, the 2→3 sialylated Le\(^a\) antigen showed the highest positive incidence among the type 1 chain antigens. Although the serum levels of 2→3 and 2→6 sialylated Le\(^a\) antigens showed a good correlation in some cancers, combining the determination of these two antigens and/or 2→3,2→6 disialylated Le\(^a\) antigen in sera still increased the detection rate of cancer. However, the incidence of false positive cases in patients with nonmalignant disorders increased significantly when false positive incidence of all three type 1 chain antigens was cumulated. When combined determination of type 1 and type 2 chain antigens was performed, the rate of detection of cancer greatly increased (as shown in Fig. 3), since no correlation was observed between the two types. In this case, the false positive incidence did not increase much, since the incidence of type 2 chain in nonmalignant disorders was consistently low.

Characterization of Type 1 Chain Antigens in Sera of Patients with Malignant and Nonmalignant Disorders. The 2→3 and 2→6 sialylated Le\(^a\) antigens had very high molecular weights, as ascertained by molecular sieve column chromatography. The average molecular weights of 2→3 and 2→6 sialylated Le\(^a\) antigens (approximately 1–2 x 10^6 as calculated from CL-6B and CL-2B column chromatography) were very similar. Essentially the same gel filtration patterns of the serum antigens were demonstrated in the presence of 6 M guanidine chloride or 1 M potassium chloride (data not shown).

The average molecular weights of the 2→6 sialylated Le\(^a\) antigen in patients with malignant and nonmalignant disorders were essentially the same, as indicated in Fig. 4.

On ion-exchange chromatography, 2→3 and 2→6 sialylated Le\(^a\) antigens were eluted at the same position (0.2–0.25 M NaCl), after most of the serum protein had already been eluted, showing that the antigens had a relatively strong negative charge compared with other serum proteins. The behavior of 2→6 sialylated Le\(^a\) antigens from sera of patients with malig-
Fig. 2. Levels of 2→6 sialylated Le\(^a\) antigen in sera of patients with various nonmalignant renal and autoimmune diseases. Sera having a high level of the antigen in "other autoimmune diseases" include samples from patients with Sjögren's syndrome.

Fig. 3. Coincidence of presence of three type 1 chain antigens and two type 2 chain antigens in the sera of patients with various cancers. Antigen profiles of sera that showed high levels of at least one of the five antigens are shown.
SERUM TYPE 1 CHAIN ANTIGENS

Fig. 4. Sepharose 6B column chromatography of serum 2→6 sialylated Leα antigen. a, pooled sera collected from patients with cancers; b, pooled sera from patients with nonmalignant autoimmune diseases (mostly systemic lupus erythematosus); c, pooled sera from patients with nonmalignant renal disorders (mostly nephrosis). ●, 2→6 sialylated Leα; ○, protein concentration.

DISCUSSION

Serum levels of sialylated fucosylated type 2 chain antigens defined by monoclonal antibodies FH6 and AH6 were previously described (7). In this study, the serum levels of type 1 chain antigens 2→3 sialylated Leα detected by antibody N-19-9, 2→6 sialylated Leα defined by monoclonal antibody FH-7, and 2→3,2→6 disialylated Leα antigen defined by FH-9 have been compared. All the results are based on the same sandwich method which was previously used (7). The detectability of serum antigens by monoclonal antibodies depends greatly on the specificity, affinity, and avidity of the antibodies used, as well as on the method of detection used. Therefore, the value of serum antigen levels is entirely "relative" rather than "absolute."

Serum levels of type 1 chain antigens such as 2→3 sialylated Leα antigen detected by N-19-9 or CSLEA-1 antibody and 2→3 sialylated Leα antigen detected by C50 antibody, have been shown to be elevated in patients with cancers of the digestive system, especially pancreatic cancer (4, 6, 10, 13, 14). The serum levels of 2→6 sialylated Leα antigen and 2→3,2→6 disialylated Leα antigen, described in this paper, show a very similar elevation in cancer. These results are based on the simultaneous assay of these antigens using essentially the same set of sera. This is expected, because these type 1 chain antigens are closely related structurally, and are synthesized through the concerted action of a similar set of glycosyltransferases. Similar
 Table 3 Effects of chemical and enzymatic treatments on the serum 2→6 sialylated Le\(^a\) antigen

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Serum 2→6 sialylated Le(^a) level (units/ml)</th>
<th>Neuraminidase</th>
<th>(\alpha)-Fucosidase</th>
<th>Endo-(\beta)-galactosidase</th>
<th>Pronase E</th>
</tr>
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<tbody>
<tr>
<td>5,650</td>
<td>Pancreatic cancer</td>
<td>112</td>
<td>2</td>
<td>102</td>
<td>42</td>
<td>13</td>
</tr>
<tr>
<td>2,526</td>
<td>Stomach cancer</td>
<td>156</td>
<td>0</td>
<td>137</td>
<td>78</td>
<td>31</td>
</tr>
<tr>
<td>10,092</td>
<td>Nephrosis</td>
<td>186</td>
<td>1</td>
<td>NT(^a)</td>
<td>102</td>
<td>NT</td>
</tr>
<tr>
<td>11,241</td>
<td>SLE</td>
<td>220</td>
<td>6</td>
<td>NT</td>
<td>98</td>
<td>NT</td>
</tr>
</tbody>
</table>

Alkaline treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>No treatment</th>
<th>0.05 N</th>
<th>0.1 N</th>
<th>0.2 N</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,650</td>
<td>Pancreatic cancer</td>
<td>112</td>
<td>108</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>3,431</td>
<td>Colon cancer</td>
<td>230</td>
<td>198</td>
<td>77</td>
<td>19</td>
</tr>
<tr>
<td>10,092</td>
<td>Nephrosis</td>
<td>186</td>
<td>196</td>
<td>154</td>
<td>112</td>
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<tr>
<td>11,079</td>
<td>Nephrosis</td>
<td>156</td>
<td>132</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td>11,241</td>
<td>SLE</td>
<td>220</td>
<td>203</td>
<td>86</td>
<td>33</td>
</tr>
</tbody>
</table>

\(^a\) NT, not tested; SLE, systemic lupus erythematosus.

**Fig. 6.** Comparison of PCA extractabilities of serum 2→6 sialylated Le\(^a\), 2→3,2→6 disialylated Le\(_a\), and 2→3 sialylated Le\(^a\) antigens in patients with cancers. Antigen recovered in the 0.6 N PCA extract as a percentage of the amount of antigen in the original serum was calculated and plotted. Bars marked "N" show mean ± SD of the PCA recovery of each antigen in the sera of normal individuals. N.S., not significant.

**Fig. 7.** Comparison of PCA extractabilities of serum 2→6 sialylated Le\(^a\) (a) and sialylated Lex-i (b) antigens in the sera of patients with cancers and with nonmalignant diseases. Bars marked "N" show mean ± SD of the PCA recovery of each antigen in the sera of normal individuals. N.S., not significant.

To a low level of 2→3 sialyl Le\(^a\) antigen found in sera of patients with blood group Le(a-b-) status, a low level of 2→6 sialyl Le\(^a\) antigen has been found in Le(a-b-) individuals (data will be presented elsewhere). Thus, the incidence of high levels of both 2→3 and 2→6 sialyl Le\(^a\) antigen in sera is affected by Lewis and secretor status of the individual.

The major difference between the incidence of 2→3 and 2→6 sialylated Le\(^a\) antigens is that the latter is more frequently found in patients with nonmalignant disorders, such as pancreatitis, renal, and autoimmune diseases. Among the tested type 1 chain antigens, the incidence of 2→6 sialylated Le\(^a\) antigen in patients with nonmalignant disorders was highest, followed by 2→3,2→6 disialylated Le\(_a\) antigen and 2→3 sialylated Le\(^a\) antigen. This indicates that 2→6 sialylated Le\(^a\) antigen...
is significantly less specific to cancer than is 2→3 sialylated Le\(^a\) antigen.

Recently, we found that normal pancreatic tissue contains a greater amount of 2→6 sialylated Le\(^a\) antigen than 2→3 sialylated Le\(^a\) antigen, whereas the reverse is true in pancreatic cancer cells. This could explain why the incidence of serum 2→6 sialylated Le\(^a\) antigen is lower in patients with pancreatic cancer and higher in patients with pancreatitis than the incidence of serum 2→3 sialylated Le\(^a\) antigen. The tissue origin of 2→6 sialylated Le\(^a\) antigen in patients with renal and autoimmune disease remains to be elucidated.

In general, the incidence of type 1 chain antigens in patients with nonmalignant disorders is higher than the incidence of type 2 chain antigens, as determined by assay of the same sera.

Serum glycoproteins carrying these type 1 chain determinants show mucin-like biochemical properties. This finding is consistent with the previous report (15). The behavior of 2→6 sialylated Le\(^a\) antigen in sera of patients with nonmalignant disorders, as analyzed by gel filtration and ion exchange column chromatography, was essentially the same as the behavior of the same antigen in sera of cancer patients. The most striking difference was found in the solubility of the mucin carrying type 1 chain and that carrying type 2 chain determinants. The extractability in 0.6 N PCA of the serum mucins carrying type 1 chain determinants was in the following order: 2→6 sialylated Le\(^a\) antigen in patients with nonmalignant disorders > 2→6 sialylated Le\(^a\) antigen in cancer patients > 2→3,2→6 disialylated Lc\(_{a}\) antigen in cancer patients > 2→3 sialylated Le\(^a\) antigen in cancer patients. Solubility of serum glycoproteins in 0.6 M perchloric acid has been found to be roughly correlated with the carbohydrate content (16). It is suggested, therefore, that type 1 chain serum mucin in patients with nonmalignant disorders is more glycosylated than in cancer patients. This is in contrast to our previous findings with serum type 2 chain antigens, which showed a higher degree of glycosylation in cancer-associated mucin than that associated with nonmalignant disorders (7).

The reason for this discrepancy between the findings on type 1 and type 2 chains remains unknown. It can be noted that most of the type 1 chain determinants are closely related to Lewis blood group; even the Lc\(_a\) antigen is supposed to be an Le\(^a\) substance. In contrast, the fucosylated type 2 chain determinants described in this paper are not directly related to blood group substances, whereas the carbohydrate structures of the type 2 chain determinants studied in the previous report (7) and in this study are all related to a well-known developmental antigen, SSEA-1 (17–19).

In general, blood group substances, i.e., carbohydrate human alloantigens, are present in normal mature cells. Malignant cells display incomplete synthesis of these alloantigens as well as aberrant modification of the alloantigens (1). On the other hand, embryonic antigens are usually present only in immature cells, and frequently appear during the course of malignant transformation (1).

Probably, type 1 chain determinants are present on well-developed, highly glycosylated mucin in normal tissue and are released into the bloodstream in patients with nonmalignant disorders. This could explain why the mucin carrying type 1 chain determinants in patients with nonmalignant disorders has a higher carbohydrate/protein ratio. In cancer cells, modified blood group substances such as the 2→3 sialylated Le\(^a\) antigen determinant are carried by serum mucin, which could be relatively less glycosylated because of the incomplete synthesis associated with malignant transformation. This could explain why serum mucin carrying the type 1 chain determinant in cancer patients has a lower carbohydrate/protein ratio. Mucin carrying the type 2 chain determinant could be an embryonic type of mucin with a high carbohydrate/protein ratio, which reappears associated with the malignant transformation (20).

This hypothesis also explains why the incidence of type 2 chain determinants is much lower than that of type 1 chain determinants in patients with nonmalignant disorders.

The results of affinity chromatography clearly indicate that the serum mucin carrying type 1 chain determinants can be classified into several molecular species according to the distribution of antigenic determinants at the surface of the molecule. We suggest that, among these molecular species, the mucin carrying homogeneous 2→3 sialylated Le\(^a\) antigen has the highest cancer specificity, and the mucin carrying homogeneous 2→6 sialylated Le\(^a\) antigen is specific for nonmalignant disorders. The mixed type of mucin carrying both antigens is present in sera of patients with either malignant or nonmalignant disorders.

Collectively, these findings indicate that subtle differences in the linkage of sialic acid residues greatly affect the cancer specificity of carbohydrate antigens, and that serum mucin-like glycoproteins carrying type 1 chain determinants are very heterogeneous and can be classified into several characteristic molecular species, each of which has a different physiological significance.

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