Tumor-associated Antigens Common to Humans and Chemically Induced Colonic Tumors of the Rat

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ABSTRACT

The expression of human tumor-associated antigens CO17-1A, GA73-3, BR55-2, GICA 19-9, and CA50 of adenocarcinoma antigen was immunohistochemically studied in the colon mucosa of 70 Sprague-Dawley rats. Fifty were treated with 1,2-dimethylhydrazine (DMH) (with EDTA as a vehicle), ten were treated with EDTA only, and ten were untreated normal rats. The tumors were histogenetically divided as: (a) adenocarcinomas arising from villous adenomatous; (b) adenocarcinomas arising from lymphoid-associated mucosa (LAM); and (c) adenocarcinomas arising in flat mucosa. Adenocarcinomas arising in LAM had an intermediate expression. The expression of these antigens had no correlation to the localization of the tumor and to the differentiation. The expression of these antigens was similar in the non-lymphoid-associated normal colon mucosa of the untreated, EDTA-treated, and DMH-treated rats. In DMH-treated rats, LAM demonstrated increased expression (number of cells) and increased staining intensity of these tumor-associated antigens. In six of the 50 DMH-treated rats, only LAM expressed carcinoembryonic antigen. CA50 was not expressed in the tumors. The highest antigenic expression (number of cells) was observed in adenocarcinomas in villous adenomatous and the lowest in those arising in flat mucosa. Adenocarcinomas arising in LAM had an intermediate expression. The expression of these antigens had no correlation to the localization of the tumor and to the differentiation. The expression of these antigens was similar in the non-lymphoid-associated normal colon mucosa of the untreated, EDTA-treated, and DMH-treated rats. In DMH-treated rats, LAM demonstrated increased expression (number of cells) and increased staining intensity of these tumor-associated antigens. In six of the 50 DMH-treated rats, only LAM expressed carcinoembryonic antigen. CA50 was not expressed in the normal colon of untreated, of EDTA-treated, and of DMH-treated rats, nor was it in DMH-induced tumors. None of the tumor-associated antigens (GICA 19-9 and CA50 and carcinoembryonic antigen) was detected in serum. It is concluded that this animal model would be of value in the preclinical evaluations of monoclonal antibodies for therapy in humans.

INTRODUCTION

Spontaneously occurring CRCs in animals are rare (1). Only in the tamarin has a high frequency of spontaneous CRCs been reported (2). Since the first success by Druckrey et al. (3) in inducing colonic adenocarcinomas in the rat by a colonotropic carcinogen, many investigators have used this model to study the carcinogenesis in the colon mucosa of the rat. Histologically, histochemically, ultrastructurally, and cytokinetically, the chemically induced tumors have been claimed to resemble colonic tumors of humans (4–12). The chemically induced tumors of the rodents also elicit antitumor immune responses similar to those observed in humans with colonic neoplasms (13).

This model has been used preclinically to study effects of chemotherapy and immunotherapy (14, 15). Schmähl suggested that chemically induced autochthonous tumors should be used more often to analyze the efficacy of chemotherapy before being used in humans, since these tumors are of greater significance for treatment of human cancers than are heterologously transplanted tumors (16).

Autochthonous tumors in a non-immune compromised animal model might also be used to evaluate the effects of various biological therapeutics. Such a model should facilitate the introduction of biological treatment regimens in cancer patients. When MAbs are used for therapy, it is a prerequisite to have information on the expression of the TAA against which the MAbs are directed. Such a model should be even more valuable if the rodent tumors also express human TAA.

The expression of human TAA (CO17-1A, GA73-3, BR55-2, GICA 19-9, and CA50) can be detected in the various segments of normal colonic mucosa of Sprague-Dawley rats. DMH-induced colonic adenocarcinomas of the rat can be divided histogenetically into 3 types: adenocarcinomas arising in LAM; adenocarcinomas arising in villous adenomatous; and adenocarcinomas arising in the flat mucosa (17).

The aim of the present study was to analyze the expression of human TAAs in these different histogenetic types in a search for an animal model to preclinically evaluate immunotherapy protocols with murine MAbs to be used for treatment of patients with CRC. This animal model seems to fulfill the requirements of a preclinical experimental system for biotherapy with special emphasis on the use of MAbs. The model might hopefully facilitate the introduction of MAB treatment protocols into the clinic.

MATERIALS AND METHODS

The material consisted of 50 male Sprague-Dawley rats (Anticimex, Stockholm, Sweden) weighing approximately 200 g. The animals were kept 5 rats/cage and were fed with a purine chow diet (R3; Ewos, Södertälje, Sweden). All rats were given injections s.c. with 21 mg/kg body weight of DMH hydrochloride salt (M, 133.02) (Kebo, Stockholm, Sweden) suspended in 1 ml of EDTA solution (as a stabilizing agent) once a wk for a period of 27 wk. At the end of this period the animals were sacrificed by exposing the rats to a CO2 chamber. The colons were dissected, fixed in 4% neutral buffered formalin, and stored at —70°C. Ten additional rats kept under the same conditions were used: MAb 17-1A (18, 19); MAb 73-3 (20); MAb 55-2 (21); MAb 19-9 (22, 23); and MAb C50 (24). Polyclonal anti-CEA was produced in rabbits (25, 26). The following murine MAbs against TAA on human colorectal cells were used: MAb 17-1A (18, 19); MAb 73-3 (20); MAb 55-2 (21); MAb 19-9 (22, 23); and MAb C50 (24). Polyclonal anti-CEA was produced from these 10 large tumors was also snap frozen in liquid nitrogen and stored at —70°C. Ten additional rats kept under the same conditions received EDTA for 27 wk once a wk. These rats were used as controls.

At the end of the experiment, ten normal Sprague-Dawley rats were sacrificed by injecting a lethal dose of Nembutal. The serum, the terminal ileum, and the colon from these rats were used as controls for serology and immunohistochemistry, respectively.

Monoclonal Antibodies

The following murine MAbs against TAA on human colorectal cells were used: MAb 17-1A (18, 19); MAb 73-3 (20); MAb 55-2 (21); MAb 19-9 (22, 23); and MAb C50 (24). Polyclonal anti-CEA was produced by the Ethical Committee of the Karolinska Institute, Stockholm, Sweden.

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The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact. The abbreviations used are: CRC, colorectal carcinoma; TAA, tumor-associated antigens; MAbs, monoclonal antibodies; DMH, 1,2-dimethylhydrazine (DMH); CEA, carcinoembryonic antigen; CC, columnar cells; GC, goblet cells; IC, intercalated cells; GLC, goblet-like cells; LAM, lymphoid-associated mucosa; IP, immunoperoxidase; IgG, immunoglobulin G (IgM defined similarly).

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in monkeys against human CEA (National Bacteriological Laboratory, Stockholm, Sweden) (25).

IP Procedure

Paraffin Sections. The tissues were fixed in 4% neutral buffered formalin, embedded in paraffin, and processed routinely. The IP procedure was performed as described (26) on 5-μm-thick paraffin sections, using an IgG avidin-biotin peroxidase kit (Vector Labs., Inc., Burlingame, CA) with diaminobenzidine as a substrate for peroxidase. With MAB C50, an IgM avidin-biotin peroxidase kit (Vector Labs.) was used. With the polyclonal monkey anti-CEA, goat anti-human IgG (cross-reacting with monkey IgG) and an IgG avidin-biotin peroxidase kit (Vector Labs.) were used.

Cryostat Sections. Cryostat sections (8 to 10 μm) were cut and dried overnight at 4°C. The sections were then fixed in −20°C acetone for 10 min. The IP procedure was carried out as described above.

Controls. Human CRCs, known to express the antigens CO17-1A, GA73-3, BR55-2, GICA 19-9, CA50, and CEA, were used as positive controls until a positive control could be established among the rat tumors. However, for MAB C50 and MAB anti-CEA, human tumors continued to be used as positive controls. Terminal ileum of the untreated rat, normal mouse serum diluted 1:400, and Tris-buffered saline were used as negative controls.

Serology

An enzyme-linked immunosorbent assay was used (National Bacteriological Laboratory, Stockholm, Sweden) to detect CEA (27). A solid-phase radioimmunoassay kit was used for serum GICA 19-9 analyses (International, Cis, Cedex, France) as well as for CA50 (Pharmacia, Uppsala, Sweden) (28). The normal value in humans for CEA is <5 ng/ml, for GICA 19-9 is <37 units/ml, and for CA50 is <17 units/ml.

Evaluation of the Antigenic Expression

Staining Pattern. The staining patterns in different cells were recorded. The definitions of the various immunohistochemical staining patterns observed in the cytoplasm are as follows: Golgi apparatus, a punctate (dot-like) staining adjacent to the nucleus; supranuclear cytoplasm, a band-like zone in the cytoplasm above the nucleus; perinuclear cytoplasm, the cytoplasm surrounding the nucleus; diffuse cytoplasm, the entire cytoplasm stained homogenously; and apical, luminal part of the cytoplasm is stained.

Intensity of the Reaction. The intensity of staining in the whole preparation was semiquantitatively scored from weak to strong (+/++/+).

Quantification of the Reaction. The number of tumor cells expressing the various TAAs was semiquantitatively assessed in 10 high-power fields (×40) of nonnecrotic tumor areas. The expression was high when >75% of the cells were stained, moderate when 25 to 75% of the cells were stained, and low when <25% of the cells were stained. Lack of reaction was recorded as 0%.

RESULTS

Normal Colon

Histology and Immunohistochemistry. The expression of the TAAs in the colonic mucosa of untreated, EDTA-treated, and the normal colonic mucosa in DMH-treated rats was similar.

In the upper part of the crypts (varying from ½ to ⅔ of their length) of the entire colon, the Golgi apparatus of the CC was stained with MABs 17-1A, 73-3, and 19-9, while in 10 to 75% of the GC (having a homogenous mucus), the mucus was stained with the same MABs as well as with MAB 55-2. The cytoplasm of the CC in the cecum stained diffusely with MAB 55-2, while in the ascending colon, the Golgi apparatus of those cells was stained with MAB 55-2.

Different patterns of antigenic expression were, however, found in the lower part of the crypts in the four colonic segments in the three groups of rats, which are schematically presented in Fig. 1, a to d. The IC (i.e., small, tall, thin, sometimes triangular cells lying amidst Goblet cells of the cecum and Goblet-like cells, having a reticulated mucus, of the ascending colon) were evident only in immunohistochemically stained sections. In the cecum and ascending colon, the Golgi apparatus of the IC cells was stained with MABs 17-1A, 73-3, and 19-9. With MAB 55-2, the IC cells of the cecum were unstained in contrast to a characteristic intense diffuse cytoplasmic staining observed in the IC cells of the ascending colon. The Goblet-like cells of the ascending colon were not stained with all the MABs used.

In only 6 of the 40 DMH-treated rats, a few normal CC and
Table 1  Localization of DMH-induced adenocarcinomas in the colon of rats and
the degree of differentiation

<table>
<thead>
<tr>
<th>Site</th>
<th>Lymphoid associated</th>
<th>Villous/tubulo-villous</th>
<th>Flat mucosa</th>
<th>Uncertain type</th>
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<td>Poor</td>
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<td>Total</td>
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<td>9</td>
<td>5</td>
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HUMAN TAA IN RAT COLONIC ADENOCARCINOMAS

The expression of the antigens in the nonvacuolated colonic tumor cells was found in the supranuclear cytoplasm. In addition, MAb 17-1A showed a diffuse cytoplasmic staining, while only a few cells showed a diffuse cytoplasmic expression with MAbs 73-3, 19-9, and 55-2. The signet ring cells had a variable staining pattern. Some cells showed the expression of the antigens in the vacuole, while in others the antigens were located in the supranuclear cytoplasm, or the cells were completely negative. The extracellular mucin showed a variable expression of all the antigens. The staining intensity varied from very weak to strong (+/++/++/++). The number of positive cells varied from 0 to >90%. The expression of the antigens did not vary with the primary site of the tumor origin. No tumors expressed the antigens CA50 and CEA. The squamous cell carcinoma of the middle ear in one of the rats did not express any of the 5 studied antigens.

Cryostat Sections

In 10 tumors, cryostat sections were compared with the formalin-fixed paraffin sections. In the nonvacuolated cells, a diffuse cytoplasmic staining pattern was predominant in the cryostat sections in contrast to a supranuclear cytoplasmic expression.
staining pattern seen in the paraffin sections. Other staining characteristics were similar in both methods.

The expression of the antigens in the various histogenetic types of adenocarcinomas is presented in Table 2.

Adenocarcinomas Arising in Villous Adenomas. The well-differentiated adenocarcinoma showed a high (>75%) expression of the antigens CO17-1A, GA73-3, and GICA 19-9, while BR55-2 was negative. Four of seven moderately differentiated carcinomas showed a moderate expression (25 to 75%) of all the antigens (Fig. 3). The poorly differentiated adenocarcinoma showed moderate (25 to 75%) expression of the antigens CO17-1A, GA73-3, and GICA 19-9 and poor (<25%) expression of the antigen BR55-2.

Adenocarcinomas Arising in Lymphoid-associated Mucosa. Two of two well-differentiated adenocarcinomas showed a high (>75%) expression of all the antigens, while two of two poorly differentiated adenocarcinomas showed poor (<25%) expression of all the antigens. However, the moderately differentiated adenocarcinomas showed a variable expression (<1% to >75%) of all the antigens (Figs. 4 and 5).

Adenocarcinomas of Uncertain Origin. Most carcinomas of uncertain origin (moderately or poorly differentiated) were either negative or had a low to moderate expression of the antigens (<25 to 75%). None had a high expression of any antigens.

Serology

CEA, GICA 19-9, and CA50 in serum of untreated as well as of DMH-treated rats were not detectable.

DISCUSSION

Only CEA has been extensively studied in rats (29). Steplewski described the expression of GICA 19-9, Le\(^a\), Le\(^b\), and a glycolipid antigen detected by Mab MCF 53-2-29 in the normal colon and spontaneous CRC of the cotton top tamarin, Saguinus oedipus oedipus (30). This study is the first report showing the expression of the human TAAs CO17-1A, GA73-3, BR55-2, and GICA 19-9 in DMH-induced adenocarcinomas of rats.

The expression of these TAAs was similar in the normal colon of untreated and EDTA-treated animals as well as in the normal appearing colonic mucosa of DMH-treated rats except for LAM. Thus, the expression of these antigens was not altered in the normal colonic mucosa by tumor growth elsewhere in the colon. The histochemical (7), cytokinetic (31), and ultrastructural (11) changes described in the normal colonic mucosa of the DMH-treated rats were not paralleled by a change in the expression of the antigens studied. The present findings are similar to those obtained with the same MAbs in the normal colonic mucosa of humans with or without concomitant colorectal tumors (26).

The expression of CO17-1A, GA73-3, BR55-2, and GICA 19-9 apparently correlated with the histogenetic types of the adenocarcinomas. The highest antigenic expression was observed in adenocarcinomas arising in villous adenomas. In 80% of the tumors, >50% of the cells were stained by MAbs 17-1A and 73-3. In 60% of the adenocarcinomas arising in lymphoid plaques, >50% of the cells expressed the antigens CO17-1A and GA73-3. In adenocarcinomas arising in the flat mucosa, only 40% of the tumors had a similar (i.e., >50%) expression.

Antigenic (CO17-1A, GA73-3, BR55-2, and GICA 19-9) expression in the tumors was similar in the three segments of the colon. Thus, no correlation was seen between the expression of TAA and the anatomical location of the tumors. The degree of differentiation could also not be correlated with the expression of the antigen. Similar results were reported in humans (26).

The expression of the TAAs (GA73-3, BR55-2, and GICA 19-9) has previously been studied in human CRC (26). GA73-3 had usually a diffuse expression in the cytoplasm and occasionally in the Golgi apparatus. BR55-2 and GICA 19-9 were usually seen in the apical region of the tumor cells and occasionally in the rest of the cytoplasm. Thus, the expression of

Table 2 Immunohistochemical staining for the human TAAs CO17-1A, GA73-3, BR55-2, GICA 19-9, CA50, and CEA and proportion of positive cells (percentage) in the various types of DMH-induced adenocarcinomas of the colon of rats

<table>
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<tr>
<th>Mabs against</th>
<th>% of positive cells</th>
<th>Adenocarcinoma arising in lymphoid plaque (n = 20)</th>
<th>Adenocarcinoma arising in villous adenoma (n = 9)</th>
<th>Adenocarcinoma arising in flat mucosa (n = 5)</th>
<th>Adenocarcinoma of uncertain origin (n = 10)</th>
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<tbody>
<tr>
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HUMAN TAA IN RAT COLONIC ADENOCARCINOMAS

Fig. 3. Invasive adenocarcinoma arising in a villous adenoma (inset). Note the intense staining with MAb 73-3 in the supranuclear cytoplasm (probably corresponding to the Golgi area). The arrow in the inset corresponds to the gland shown. × 1000.

Fig. 4. Invasive adenocarcinoma arising in a lymphoid-associated mucosa (inset). Note the intense positivity of MAb 17-1A in the supranuclear cytoplasm. × 1000.

Fig. 5. Invasive adenocarcinoma arising in a lymphoid-associated mucosa (inset) (the same tumor as in Fig. 4) showing diffuse cytoplasmic positivity of MAb 55-2 in some of the tumor cells (arrow). × 1000.

Fig. 6. Invasive adenocarcinoma arising in a flat mucosa (inset) with uninvolved normal colonic mucosa at the right side (arrowhead). MAb 19-9 positivity in the supranuclear cytoplasm of some invading cells (arrow). × 1000.

demonstrate CEA in the sera of the tumor-bearing rats. None of the six DMH-treated rats with positive CEA expression in the normal colonic mucosa expressed CEA in their tumors. Interestingly, these six rats had poorly differentiated adenocarcinomas. The low degree of differentiation may explain the absence of CEA in the tumors in those rats (34). Furthermore, CEA being a complex glycoprotein for which at least 15 different determinants have been described, anti-CEA antibodies may differ in their reactivity (29, 35, 36).

Although the antigen GICA 19-9 could be detected in the tumors, we were unable to detect it in the serum. Similar findings have been reported in some humans with gastrointestinal tumors (37). Furthermore, there was no immunohistochemical evidence in the rat tumors of secretion of the antigen at either the luminal or the stromal aspect of the tumors.

Current therapy for metastatic CRC in humans remains investigational with no agreed standard therapeutic approach. In recent years interest has been focused on the use of immunotherapy with MABs. The results of clinical trials indicate that murine MAb 17-1A may induce tumor regression or inhibit tumor progression in humans with metastatic CRC (38).

Douillard et al. (39) proposed the use of murine MABs
generated against DMH-induced rat TAA to evaluate the therapeutic effects of MAbs in a transplantable tumor of rat origin and to extrapolate to the human situation. The rat model described in the present study may be more suitable to analyze the therapeutic efficacy of MAbs in colorectal carcinoma. In our model, the MAbs were directed against human TAA, and the therapeutic efficacy could be evaluated in autotransplanted tumors. Thus, this system might be more appropriate for the human situation as compared with that of Douillard et al. Moreover, it has previously been shown that this rat tumor might respond to immune signals. A lower incidence of autochthonous tumors. Thus, this system might be more appropriate for analyzing the therapeutic efficacy of MAbs in colorectal carcinomas, and the therapeutic efficacy could be evaluated in autotransplanted tumors. This, in turn, might be of benefit to human colorectal cancer patients.

REFERENCES


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