**In Vivo Localization of Human Colon Adenocarcinoma by Monoclonal Antibody Binding to a Highly Expressed Cell Surface Antigen**

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**ABSTRACT**

We have produced a monoclonal antibody (SF-25) against a human hepatoma cell line (FOCUS) that strongly reacts with an antigen shared by all six colon adenocarcinoma cell lines. This cell surface antigen was uniformly expressed in all 17 human adenocarcinomas of the colon obtained at surgery but not on the normal adjacent mucosa counterpart. Other normal tissues were negative except for a population of cells in the distal tubule of the kidney as shown by immunoperoxidase staining and direct binding to membrane preparations. Binding of this M, 125,000 antigen to antibody is disrupted by detergents, sodium dodecyl sulfate, and paraformaldehyde fixation but not by treatment of FOCUS cells with trypsin. The SF-25 antibody when labeled with 125I shows a striking capacity by both biodistribution and nuclear imaging studies to localize human colon adenocarcinoma grown as solid tumors in nude mice. SF-25 may be useful in distinguishing between normal colon and the transformed phenotype.

**INTRODUCTION**

We have been investigating some of the antigenic changes associated with malignant transformation of hepatocytes (1). Since both the liver and gastrointestinal tract are derived from the endoderm (2), it is not unreasonable to assume that during dedifferentiation, common antigens may appear on both tissues. If these antigens are associated with the transformed phenotype, some MAbs produced against malignant hepatocytes might also detect similar antigens on adenocarcinomas of the colon. In this regard we have searched for and identified an antibody (SF-25) that exhibits such a phenomenon. In this report, we will present evidence that SF-25 detects a protein with a molecular weight of 125,000 on the cell surface. More importantly, this antigen is highly expressed in human adenocarcinomas of the colon and may be suitable for in vivo localization of tumor.

**MATERIALS AND METHODS**

Cell Lines. All cells used for immunization or monoclonal antibody testing were maintained in Earle's modified Eagle's medium (M. A. Bioproducts, Walkersville, MD) supplemented with 10% fetal bovine serum inactivated at 56°C, 10 µg of nonessential amino acids, 1000 U/ml of penicillin, and 100 µg/ml of streptomycin. Cells were harvested from the monolayer cultures by washing three times with 20 mM PBS, pH 7.2, followed by treatment with versene buffer in the absence of trypsin. Single cell suspensions thus obtained were used for immunization of BALB/c mice. The FOCUS cell line was developed in our laboratory (3) and all other cell lines were obtained from the American Type Culture Collection, Rockville, MD. These cell lines are listed in Table 1. Cell lines were tested for mycoplasma by DNA staining and all were found free of contamination (generously performed by the Mycoplasma Testing Laboratory, Massachusetts General Hospital).

Monoclonal Antibody Immunization and Fusion Protocols. The hepatocellular carcinoma cell line, FOCUS, was used for immunization of mice. An early passage of this cell line from the original tumor had been kept in liquid nitrogen. It was subsequently regrown and harvested from monolayer culture. Primary immunizations of female BALB/c mice were accomplished i.p. with 4.0 × 10^6 intact whole cells/ml in 50% complete Freund's adjuvant. After 6 to 10 weeks, the secondary immunizations were performed by an i.v. inoculation of 4.0 × 10^7 cells in 200 µl PBS. Splenocytes were fused with the parent myeloma cell line SP2O 3 days later. The resulting hybridomas were selectively maintained in hygromycin-amphotericin-thymine medium, then cloned by limiting dilution as previously described (4).

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2Monoclonal Antibody Binding to Membrane Preparations. Membrane...
Monoclonal Antibody Against Colon Adenocarcinoma

Fractions were prepared from normal human tissues as well as from colon adenocarcinomas and adjacent normal colon obtained from surgical specimens. Human colon adenocarcinoma (LS-180) or hepatoma cell lines (FOCUS) grown as solid tumors in nude mice served as a positive control. Tissues were homogenized with a Polytron homogenizer in ten volumes of 20 mM PBS, pH 7.2, containing 0.1% Na3P04 and were centrifuged at 20,000 x g for 30 min. Homogenization and centrifugation were repeated twice. Subsequently, the pellets were resuspended in PBS containing 20% glycerol and frozen at −80°C until use. For SDS-PAGE, the protein preparations were incubated for 5 min at 90°C in a SDS-PAGE buffer and 50 µg of protein was loaded at the top of a 10% SDS-polyacrylamide gel and separated according to Laemmli (13). The proteins were electrophoretically transferred onto nitrocellulose paper. The paper was then incubated with 1:100 dilution of SF-25 ascites fluid and subsequently with 125I-labeled sheep anti-mouse immunoglobulin F(ab′)2. The washed and dried paper was then exposed for autoradiography.

In Vivo MAb Distribution. 10 µCi of 125I-SF-25 was injected via the tail vein into nude mice bearing human colon tumors. For dual tracer studies (14), the mice were given simultaneous injections of 10 µCi of 125I-SF-25 and 1 µCi of 131I-B2TT, a nonspecific antibody. The mice were sacrificed and dissected at 24, 48, and 72 h after injection. Tumors, blood, thyroid, heart, lung, kidney, stomach, intestine, liver, and spleen were weighed on an analytical balance and assayed for radioactivity using a multichannel gamma counter (a window from 15 to 50 keV for 125I and a window from 50 to 330 keV for 131I). Results were expressed as follows: (a) uptake of antibody in tumor and tissues (cpm/mg); (b) ratios of specific activity in tumor compared to normal mouse tissues (cpm/mg tumor)/cpm/mg normal tissues); and (c) localization index, defined as the ratio of [125I]SF-25 to [131I]B2TT activity in tumor and in tissues divided by the same ratio in the blood (15).

Nuclear Imaging. For nuclear imaging studies 150 to 250 µCi of 125I-labeled intact antibodies were injected via the tail vein into nude mice when LS180 tumors reached an average size of 1.0 cm in diameter (range, 0.5–1.5 cm). The same amount of 125I-labeled intact B2TT was injected into tumor-bearing mice as a control. Nude mice were anesthetized with 0.1 ml 4% chloral hydrate per 10 g body weight via i.p. injection. Each nude mouse was then imaged 4 cm from the back with a gamma camera equipped with a 3-mm pinhole collimator and interfaced to a computer. Images were obtained at 6, 24, 48, 72, and 120 h. All data were recorded on a computer system and stored on floppy disks. No background subtraction nor computer smoothing was employed.

RESULTS

Monoclonal Antibodies. In total, 90 antibody screening clones were produced against antigens present on FOCUS cells using an indirect binding assay. Among the 90 clones, 18 were shown to react with human colon carcinoma cell lines, (data not shown). The SF-25 antibody of an IgG1 isotype was chosen for further investigation on the basis of additional specificity testing including reactivities to normal human lymphocytes, liver, colon, and other tissues by a direct radioimmunoassay described below.

SF-25 Cell Binding Studies. The binding specificity of SF-25 was investigated by a direct radioimmunoassay using a panel of cell lines. As shown in Fig. 1, SF-25 reacted with all the hepatoma cell lines tested (FOCUS, PLC/PRF/5, MAH-LAVU, SK-HEP-1, Hep G2, and Hep 3B) as well as Chang liver cells. More importantly, six of six adenocarcinoma of the colon cell lines including LS-180 expressed SF-25 antigen on their cell surfaces. Additional specificity testing revealed that SF-25 did not bind to normal human lymphocytes nor Vero cells (African green monkey kidney). The binding was weak with BT-20, C-33A, and AN3CA. Higher binding was observed with SK-MEL-5 and A-498 (see Table 1). Treatment of live FOCUS cells with 2.0% trypsin solution for 5 and 20 min did not reduce 125I-SF-25 binding [4,150 ± 150 (EDTA removed cells) vs. 4,870 ± 196 (5') vs. 4,541 ± 96 cpm (20'), respectively].

Membrane Binding Studies. We examined the capability of 125I-SF-25 to bind to membrane preparations from FOCUS...
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Fig. 1. Display of [125I]SF-25 binding to antigens expressed on various tumor cell lines (Table 1). Note that all six colon adenocarcinomas and hepatoma cell lines as well as Chang liver express SF-25 antigen on their cell surfaces.

Table 1 Origin of cell lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Tissue of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS 180</td>
<td>Human, colon, adenocarcinoma</td>
</tr>
<tr>
<td>COLO 320</td>
<td>Human, colon, adenocarcinoma</td>
</tr>
<tr>
<td>SW 403</td>
<td>Human, colon, adenocarcinoma</td>
</tr>
<tr>
<td>WiDr</td>
<td>Human, colon, adenocarcinoma</td>
</tr>
<tr>
<td>Caco-2</td>
<td>Human, colon, adenocarcinoma</td>
</tr>
<tr>
<td>SK-CO-1</td>
<td>Human, ascites, colon adenocarcinoma</td>
</tr>
<tr>
<td>FOCUS</td>
<td>Human, liver, hepatoma</td>
</tr>
<tr>
<td>PLC/PRF/5</td>
<td>Human, liver, hepatoma</td>
</tr>
<tr>
<td>MAHLAVU</td>
<td>Human, liver, hepatoma</td>
</tr>
<tr>
<td>Hep G2</td>
<td>Human, liver, hepatoma</td>
</tr>
<tr>
<td>Hep 3B</td>
<td>Human, liver, hepatoma</td>
</tr>
<tr>
<td>SK-HEP-1</td>
<td>Human, ascites, hepatoma</td>
</tr>
<tr>
<td>Chang liver</td>
<td>Human, liver, epithelial-like morphology</td>
</tr>
<tr>
<td>A-427</td>
<td>Human, lung, adenocarcinoma</td>
</tr>
<tr>
<td>SK-LU-1</td>
<td>Human, lung, adenocarcinoma</td>
</tr>
<tr>
<td>Calu-3</td>
<td>Human, pleural effusion, lung adenocarcinoma</td>
</tr>
<tr>
<td>BT-20</td>
<td>Human, breast, adenocarcinoma</td>
</tr>
<tr>
<td>A-498</td>
<td>Human, kidney, adenocarcinoma</td>
</tr>
<tr>
<td>Caov-3</td>
<td>Human, ovary, adenocarcinoma</td>
</tr>
<tr>
<td>C-33A</td>
<td>Human, cervix, undifferentiated carcinoma</td>
</tr>
<tr>
<td>HeLa</td>
<td>Human, cervix, adenocarcinoma</td>
</tr>
<tr>
<td>SK-UT-1</td>
<td>Human, uterine, mesodermal tumor</td>
</tr>
<tr>
<td>AN3 CA</td>
<td>Human, endometrium, adenocarcinoma</td>
</tr>
<tr>
<td>JEG-3</td>
<td>Human, choriocarcinoma</td>
</tr>
<tr>
<td>SK-MEL-5</td>
<td>Human, lymph node, malignant melanoma</td>
</tr>
<tr>
<td>Vero</td>
<td>Monkey, kidney, fibroblast-like morphology</td>
</tr>
</tbody>
</table>

and LS-180 tumors as well as other normal human tissues as shown in Fig. 2. Specific binding (defined as the difference in cpm bound in the absence and presence of cold SF-25 antibody) was observed to both FOCUS and LS-180 membranes but not to membranes derived from other normal human tissues with the notable exception of kidney. Binding was inhibited by cold SF-25 but not by cold SF-55 which is another antibody against a highly expressed common cell surface membrane antigen (Fig. 3). Note that [125I]SF-55 demonstrates high binding of FOCUS and LS-180 as well as other normal tissues and serves as a good positive control for comparison with SF-25 (Fig. 2). We then performed membrane binding studies on surgical specimens of human colon adenocarcinomas and compared the results to the adjacent normal counterparts as shown in Fig. 4. A limited amount of surgical tissue was available for the studies compared to other normal human tissues obtained at autopsy. Specific binding of SF-25 to membrane preparations was observed in LS-180 tumors and human colon adenocarcinomas. In contrast, SF-25 showed no significant binding to membrane preparations of the normal colon mucosal counterpart (P < 0.01).

Immunoperoxidase Staining. Tissue expression of the antigenic determinants recognized by SF-25 in vivo was further investigated by the avidin-biotin complex immunoperoxidase staining reaction. Staining of tissue sections from 17 colon
adenocarcinomas along with normal mucosal counterparts were tested. Fig. 5 shows representative examples of typical staining patterns of colon adenocarcinomas compared to an adjacent normal colon mucosal counterpart using the same concentration of SF-25 on each section. Note that tumors demonstrate a diffuse cellular staining pattern. Indeed 17 of 17 cases (100%) of colon adenocarcinomas examined as fresh frozen specimens expressed SF-25 antigen in the primary tumor. Most if not all, tumor cells were stained as shown in Fig. 5; adjacent normal mucosa did not stain. A number of normal tissues were also found to be negative by immunoperoxidase staining including esophagus, stomach, small and large intestine, thyroid, lung, liver, pancreas, adrenal gland, skeletal muscle, and myocardium. In the kidney, no staining of the glomerulus, proximal tubule, or connective tissue was observed. Staining was present in a subpopulation of distal tubular cells and the pattern was diffuse and cytoplasmic. Sections of LS-180 tumors grown in nude mice and human adenocarcinoma of the colon fixed with paraformaldehyde and subsequently paraffin embedded did not stain indicating that the antigenic reactivity was disrupted by these procedures.

Identification of SF-25 Antigen. The presence of SF-25 antigen on the surface of FOCUS cells was examined by immunoprecipitation of 125I-labeled cell surface proteins. As shown in Fig. 6, a protein of approximately M, 125,000 was isolated from FOCUS cell membranes. Another M, 200,000 band is also seen but was not present in subsequent experiments. Also presented for comparison are two other MAb immunoprecipitations; AF-10 is a positive control and SF-22 is the negative control for antigens previously known to be present on these cells and subject to identification by this technique.4

We attempted to further characterize the SF-25 M, 125,000 cell surface antigen with [35S]methionine and [3H]glucosamine labeling experiments followed by capture with SF-25 antibody coupled to beads and subsequent SDS-gel electrophoresis. These experiments were unsuccessful despite varying incubation condition, pulse times autoradiographic times. We included in these experiments an analysis of AF-20 antigen as a positive control; the results have been published elsewhere (16). We were unable to identify SF-25 antigen by both direct and indirect Western immunoblots. We also reacted FOCUS cells with MAb to CEA, 17-1A, and 19.9 antigens (100 µg/ml, kindly supplied by Dr. Peter Dadonna Centocor, Malvern, PA) in the presence of [125I]SF-25; no inhibition of binding was observed.

In Vivo Biodistribution of SF-25. Nude mice bearing LS-80 colon tumors were injected i.v. with 125I-labeled SF-25, and the specific activity in tumor was compared to that in the normal mouse tissues (Fig. 7). The colon tumors showed a high uptake of radioactivity. As depicted in Table 2, tumor/tissue ratios were examined and at 48 h for example were found to be 32.4 ± 5.1 in intestine, 20.6 ± 6.2 in stomach, 9.5 ± 3.4 in liver, 12.6 ± 2.2 in spleen, 7.9 ± 2.0 in kidney, 6.3 ± 1.8 in lung, 9.7 ± 1.0 in thyroid, and 9.8 ± 1.8 in heart.

Further evidence of specific localization was established by
SF-25 clearly visualized xenographs of human colon cancer.

Representative imaging study demonstrating the localization of SF-25 in tumors at 48 h (Fig. 9, B and C). Radiolabeled 0.33 (72 h) [P < 0.001 when compared to normal tissues (0.97 blood were 1.81 ± 0.46 (24 h), 3.07 ± 0.34 (48 h), and 2.75 ± 0.33 (72 h)].

The localization indices derived from the ratio of specific to nonspecific activity in tumor divided by the same ratio in the blood.

Fig. 9. Nuclear imaging by [125I]SF-25 of nude mice bearing LS-180 generated adenocarcinomas of the colon. A, imaging of a tumor bearing animal with the nonrelevant 125I-labeled B2TT monoclonal antibody; B and C, two animals imaged with [125I]SF-25; D, the same mouse as in B (in reversal) illustrating the size of the tumors. All imaging was performed at 48 h in this experiment.

DISCUSSION

We have studied an antigen expressed on the surface of malignant cells which may be useful for in vivo localization of adenocarcinoma of colon. The antigen identified by MAb SF-25 appears to be novel and not previously described. Some of the more interesting features of this antigen are: (a) Its homogeneous expression on colon adenocarcinomas in vivo and uniform distribution in most if not all tumor cells. (b) The epitope to which SF-25 binds is disrupted by mild fixation, denaturing gels and detergent extraction. (c) The epitope resides on a cell surface protein and probably is present in the cytoplasm as well with a molecular weight of approximately M, 125,000 as shown by 125I-labeling experiments (Fig. 6). Cell surface binding was not disrupted by 2% trypsin exposure. Most other previously described antigens associated with gastrointestinal malignancies have on further characterization revealed a mucin glycoprotein or glycolipid structure (17-22). In this regard, some of the characteristics of the SF-25 antigen may be due in part to the immunizing cell type. The FOCUS cell line was derived from a human hepatocellular carcinoma and does not secrete large amounts of mucin glycoproteins (3). (d) The antigen is closely associated with the malignant phenotype and appears not to be expressed on adjacent normal colon or other normal tissues with the exception of a subpopulation of distal tubular cells of the kidney. SF-25 binds to all colon and hepatoma cell lines tested as well as several others. Thus, the epitope is not confined to a specific tumor cell type but instead is most closely associated with malignant transformation in general.

The SF-25 antigen appears different from those previously described antigens associated with adenocarcinomas of the colon. For example, the well-characterized CEA is a glycoprotein of higher molecular weight (22, 23). CA 19-9 recognizes a carbohydrate determinant (sialylated lacto-N-fucopentose II; a hapten of the human Lea blood group antigen) found on both mucin glycoprotein and lipid (24, 25). CO 29.11 detects also a sialylated Lea antigen but is directed towards a different epitope and has a higher binding affinity than CA 19-9 (26). Furthermore, antibodies to CEA and 19-9 do not inhibit the binding of SF-25 to its epitope on FOCUS cells. Similarly, DU-PAN-2 detects a mucin-like antigen isolated from a human pancreatic adenocarcinoma (18). Monoclonal antibodies directed against
such antigens do not uniformly react with all adenocarcinomas of the colon by immunoperoxidase staining (27) or by direct binding assays. In addition, CEA, and antigens recognized by CA 19-9, CO 29.11, and DU-PAN-2, represent cell products that are secreted or shed into cell culture supernatants from the immunizing cell type. They are often in the serum of patients with a variety of gastrointestinal malignancies (26, 28–30). In contrast we have not identified SF-25 antigen in cell culture supernatants from hepatoma and colon adenocarcinoma cell lines or in the serum of patients with gastrointestinal malignancies by a “simultaneous sandwich” homologous immunoradiometric assay (31).

Another well-characterized monoclonal antibody, designated B72.3 was produced against a membrane rich fraction of a metastasis derived from a mammary carcinoma (32). This antibody detects a large mucin glycoprotein TAG-72 (tumor-associated glycoprotein) of >$M_r$ 1,000,000 (17). The antigen was expressed in only one of 18 colon cancer cell lines (33) but in vivo it was detected in 80–85% of colon adenocarcinomas and their metastasis (33, 34). The in vivo distribution was found to be quite heterogenous as shown by immunoperoxidase staining of formaldehyde fixed paraffin embedded tissue specimens. Binding of B72.3 to its epitope on TAG-72 was substantially reduced by neuraminidase digestion and this suggests that sialic acid is an important structural component of the epitope (17). TAG-72 antigen was also found in the serum of patients with gastrointestinal malignancies (35). Another antibody produced against a membrane-enriched fraction of a biopsy from a primary colon adenocarcinoma has also been described (36). However expression of this antigen appears to correlate with a more differentiated state and therefore is highly expressed on normal colon and less on the transformed phenotype.

There is, however, one previously described MAb with some similar features to SF-25. The 17.1A antibody was produced against a colorectal adenocarcinoma cell line (37) and detects a labile antigen sensitive to methanol, ethanol, and formaldehyde fixation and paraffin embedding (38). Also, the antigen is resistant to neuraminidase treatment and binding activity is abolished by protease treatment which suggests that the 17.1A binding domain is a nonmucin, non-sialic acid structure. Furthermore, the antigen is displayed on the distal convoluted tubular cells of the kidney like SF-25 and is expressed on most adenocarcinomas of the colon in situ by immunoperoxidase staining of fresh frozen tissue sections; the molecular weight, however, is about $M_r$ 40,000 (31). Nonetheless, MAb 17.1A appears different from SF-25 antigen not only in its molecular weight but also since it is highly expressed on normal colon and small bowel as well as pancreas, gallbladder, cystic duct, and sweat glands (38). Furthermore, 17.1A antibody does not inhibit the binding of $^{125}$I-SF-25 to its epitope on FOCUS cells. The 17.1A IgG$_2a$ antibody has been of particular interest since it apparently has potential for in vivo immunotherapy of colon adenocarcinoma (39–42). Recently a chimeric mouse-human hybridoma has been produced by recombinant DNA techniques and the hybrid demonstrates the same biological and antigen binding properties as the native molecule (43).

Finally, there are a number of other monoclonal antibodies described that react with adenocarcinomas of the colon both in vitro and in vivo (44–49). Some of them are directed against glycoprotein determinants (44, 48) and limited specificity testing to date suggest that they are quite different from SF-25. Such antibodies have been produced in an attempt to distinguish between the antigenic properties of the normal colon epithelial cell and its transformed phenotype. In this regard a mucin glycoprotein antigen designated large external antigen has recently been described (44); it appears to be constitutively expressed on colon cancer by immunoperoxidase staining of fresh tissue but was not found on adjacent normal colon. This antigenic determinant identified by MAb ND-1 was neuraminidase sensitive and is expressed on fetal colon and biliary epithelium as well as normal cervix and uterus. The authors speculate that large external antigen is a mucin glycoprotein associated with the malignant phenotype.

MAb SF-25 proved to be an excellent antibody for tumor localization in vivo using the nude mouse model. We are led to believe from our observations detailed in Figs. 5 and 7–9 that the following properties of the SF-25 antibody-antigen interaction may be responsible for its ability to localize tumors. In the first place, the SF-25 antigen is uniformly expressed in all (17/17) adenocarcinomas of the colon studied thus far and not on adjacent normal colon. We are presently trying to confirm that the epitope recognized by SF-25 is a primary gene product by means of molecular cloning. Secondly, the antigen is displayed on the cell surface as shown by direct binding studies with live cells (Fig. 1). $^{125}$I cell surface labeling experiments followed by immunoprecipitation provides further evidence for its location on the surface of malignant cells. This cell surface location is likely to be crucial for epitope accessibility to $^{125}$I-labeled SF-25 binding in vivo. Thirdly, there appears to be little heterogeneity of antigen distribution among tumor cells within the colon tumor or between different tumors (Fig. 5). Finally, this antigen is not shed into culture medium from colon adenocarcinoma cell lines or present in serum of patients bearing colorectal cancers in amounts detectable by a radioimmunometric assay. Thus, radiolabeled antibody may reach the tumor cell surface without being trapped in immune complexes. SF-25 shows sufficient sensitivity and specificity to be considered as a potential tumor targeting agent. It may also contribute to a better understanding of the antigenic differences displayed on the cell surface between normal and transformed colon cells.

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