Serological Reactivity in Cancer Patients to Human and Mouse Fetal Liver Cells

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ABSTRACT

The occurrence of antibodies to human and mouse fetal liver cells has been quantitated in the sera from patients with carcinoma of breast, colon, and lung and with malignant melanoma. Also, we have demonstrated cross-reacting murine antibodies in the sera from multiparous, antifetal, and pregnant mice, which bind to mouse fetal liver cells and/or several types of human tumor cells. A comparative evaluation of these antibodies with two immunological techniques has demonstrated a greater number of positive sera from cancer patients assayed by isotopic antiglobulin (25 of 27, or 92%) than by membrane immunofluorescence (12 of 17, or 71%). In the non-cancer control group, positive reactions were found in 11 and 31% by the two techniques, respectively. The specificity of such serological reactivity has been demonstrated by adsorption with fetal liver cells. These detected antibodies are not restricted to a particular type of human neoplasm, but rather to the presence of cancer. Because of their relative capacity of discrimination between benign and malignant conditions and because the assay for their detection is relatively simple, these techniques may provide alternative methods for diagnosis or monitoring of cancer patients.

INTRODUCTION

Increasing evidence indicates that the immunological cross-reactivity observed among human autologous and alloimmune tumor and fetal liver cells of similar histological origin may be due to the reexpression of organ-specific cell surface constituents normally present on fetal cells (6, 9, 12, 21, 24) and probably in limited amounts in adult proliferating tissues (19). In spite of the fact that such a concept has been recently questioned (38), a number of analogous reports on experimental tumor systems are also consistent with this interpretation (4, 7, 14, 16, 18, 37, 42). Tumor-associated antibodies of human breast carcinoma have been demonstrated to neutralize mouse mammary tumor virus (8) and also have been detected with the use of murine mammary carcinoma as target cells (28-30).

Relevant to these studies are our recent demonstrations that tumor-associated fetal antigens have detectable cross-reactivity among a number of tumors of various origins in the murine system (34), and this cross-reactivity has even been observed under xenogeneic conditions (1, 14, 15, 32, 33), which suggests that these tumor-associated fetal antigens are not species specific.

Cancer patients respond to neoantigens associated with autologous tumors (3, 17, 20), one of which is the fetal or tumor-associated fetal antigen. Therefore, we decided to test the hypothesis of reexpression of fetal constituents (and their respective immune response) as cross-reacting antigens between fetal and tumor cells of different species.

The objective of the present study was the investigation of the humoral response to tumor-associated fetal antigens by examination of the sera of patients with various types of cancers. We tested the possibility that antibodies or immune complexes from sera of cancer patients would bind to xenogeneic mouse as well as to allogeneic human FLC. Conversely, the possibility that isologous mouse antigens from sera would bind to xenogeneic human tumor cells was also tested.

The results of this study demonstrate the prevalence of cross-reacting specific antibodies to fetal determinants in sera of patients with several cancers as compared to the lack of reactivity in a non-cancer control group and a nonmalignant disease control group.

MATERIALS AND METHODS

Animals. First litters from 8- to 12-week-old BALB/c mice were used as the source of mouse fetal tissue. In all of our studies, 8- to 12-week-old BALB/c mice were used for immunization. All animals were obtained from Simonsen Laboratories, Inc., Gilroy, Calif.

Target Cells. Mouse FLC were obtained by dissection of fetuses from primiparous BALB/c mice at 15 days of gestation; the exception was determined as previously described (32, 34). Human fetal liver tissue from nonliving surgical specimens of 15- to 17-week-old fetuses was obtained from healthy patients undergoing therapeutic abortion and sterilization by elective hysterectomy. Appropriate informed consent for the use of the tissue was obtained. Both human and mouse FLC suspensions were prepared according to procedures reported earlier (34). Viability fluctuated at approximately 90% (eosin exclusion test). FLC suspensions were prepared and diluted to a concentration of 10⁶ viable cells/ml in PBS.

Preparation of Antisera. Mouse isoantisera to FLC were produced in male BALB/c mice by i.p. inoculations with 10⁶ viable (eosin-excluded) irradiated (5000 R) FLC. Antisera were collected by retroorbital sinus bleeding; sera

1 This work was done in part at the University of Southern California School of Medicine, Los Angeles, Calif. 90033.

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from 5 to 10 mice were pooled. Sera were also obtained from multiparous BALB/c mice and from normal (untreated) controls matched by age and sex. Human serum samples were obtained from freshly clotted venous blood drawn from cancer patients before surgery. At the time of serum sampling, all patients had disease restricted to local or regional lymph nodes sites in the absence of any distant spread of disease. Subsequent pathological evaluation was consistent with this preoperative staging. Control human sera matched by age and sex were collected in a similar manner from healthy nonhospitalized volunteers with no known medical illness. All sera used were heat inactivated at 56° for 30 min and were maintained at 4° until use. Dilutions of sera were made with PBS.

**Serum Adsorption.** Adsorption of sera prior to being tested with either technique was performed by mixing an indicated number (see tables and chart legend) of viable, irradiated (5000 R), either mouse or human FLC or mouse adult spleen cells with 0.2 ml of serum. After incubation for 1 hr at room temperature and then for 3 hr at 4°, the cells were sedimented by centrifugation for 10 min at 800 x g; the supernatant fraction was aspirated, centrifuged at 3000 x g for 5 min, and then collected and tested. A reaction was considered positive when the AR in the IAT was reduced by at least 20% more than any reduction achieved in the respective control serum adsorption as established by Sparks et al. (36) and Ting et al. (39). The percentage of adsorption was expressed as:

\[
\% \text{ removal} = \frac{AR \text{ unadsorbed} - AR \text{ after adsorption}}{AR \text{ unadsorbed} - 1} \times 100
\]

Relative amounts of antigen were calculated by comparison of the number of adsorbing cells required to remove 50% of the serum reactivity. In the immunofluorescence assay, the reaction was considered positive when the percentage of reacting cells was reduced to the same or less than the percentage of reacting cells with control serum.

**Indirect Membrane Immunofluorescence Test.** This test was performed on viable, single-cell suspensions of mouse FLC or human tumor cells. Briefly, the target cells free of buffer were incubated with test or control for 30 min, washed, and treated with fluorescein isothiocyanate-conjugated sheep anti-human IgG (Wellcome, Beckenham, England) or with rabbit anti-mouse IgG (Cappel Laboratories, Downingtown, Pa.) diluted 1:10 in PBS for 30 min and washed 5 times with PBS. Cell suspensions were then made in glycerol:PBS (1:1). Microscopic examination was done with a Leitz incident microscope with high-intensity UV lamp, with a combination of a BG 12 primary filter, a TK 510 dichroic mirror, a KP 490 excitation filter, and a K 515 suppression filter. Cell counts were made to determine the percentage of positive cells after the application of test serum, over and above those cells fluorescing after incubation with respective anti-y-globulin conjugate alone. A preparation was considered positive if the percentage of fluorescent cells exceeded that found in the controls. Positively scored cells showed complete equatorial or point staining of the cell surface, whereas dead cells showed diffuse cytoplasmic staining and were discounted.

**Iodination of Antiglobulins.** Aliquots containing chromatographically purified goat or rabbit anti-human IgG, 0.5 mg/ml, obtained from Cappel Laboratories (Lots 89361 and 89431) were labeled with \[^{125}\text{I} \] carrier free (Amersham/Searle, Arlington Heights, Ill.) by the modified chloramine-T technique (27). In an effort to avoid significant loss of antibody binding reactivity through excessive iodination, the specific activity of our preparations was kept between 100 and 800 \(\mu\text{Ci/mg}\), as suggested by Burdick and Wells (7). Preliminary binding studies confirmed the activity of this preparation before it was used in the IAT. To measure possible loss of antibody activity, we performed simultaneous labeling of anti-human IgG with chloramine-T and with lactoperoxidase (26) on several occasions. The results demonstrated no significant difference in antibody reactivity when tested.

**IAT.** The procedure described by Sparks et al. (36) was followed. Briefly, \(10^6\) FLC (0.1 ml) were incubated first with test sera or normal sera (0.1 ml) at 1:100 final dilution for 30 min at room temperature. After 8 consecutive washes with Hanks' balanced salt solution plus 10% of \(\gamma\)-globulin-free, heat-inactivated, immunoprecipitin-tested fetal calf serum (Grand Island Biological Co., Grand Island, N. Y.), the target cells were incubated with 2 \(\mu\)l of iodinated anti-human IgG at optimal concentration (0.5 mg/ml) for 15 min at 4°. Optimal concentration was determined by the maximum AR obtained through serial 10-fold increases of iodinated antiglobulins (range, 1.6 ng to 16 \(\mu\)g protein per tube). Thereafter, the target cells were washed 8 times with heat-inactivated, immunoprecipitin-tested, \(\gamma\)-globulin-free fetal calf serum, and after final sedimentation they were counted in a LKB-Wallace 8000 automatic \(\gamma\) counter. All tests were done in triplicate. Variation among replicates ranged between 5 and 12%. All tests included the following controls: target cells plus PBS, target cells plus normal serum, and target cells plus \[^{125}\text{I} \]-antiglobulin alone. Activities of test sera are expressed as cpm of \[^{125}\text{I} \]-antiglobulin bound to cells, or as the AR:

\[
AR = \frac{\text{cpm obtained by reaction with test serum}}{\text{cpm obtained by reaction with control serum}}
\]

As previously established (36, 39), a reaction was considered positive when AR \(=\) 2, weakly reactive when AR was from 1.8 to 2.0, and negative with an AR less than 1.8. Cell loss and viability resulting from the multiple washings were not found to be critical when determined by microscopic observation (eosin exclusion test).

**RESULTS**

**Comparison of the Two Assays.** A simultaneous evaluation of antifetal antigen reactivity detected in sera of cancer patients was performed by use of IAT and indirect membrane immunofluorescence assay on mouse and human FLC targets. The results of this study show consistency as summarized in Table 1. Data from the IAT indicate a greater number of positive reactions than that of immunofluorescence determinations (92 versus 71%, respectively) and a lower number of positive reactions (false-positive) among the non-cancer control group studied (11 versus 31%, respectively). Of the 5 control sera detected as positive by immunofluorescence, 3 of them showed a constant positive reaction with IAT. Of the 18 sera used in our control panel,
3 of them gave a consistent positive reaction in both tests used. Later, it was found that all of these persons were under replacement hormonal therapy for menstrual irregularities; furthermore, 1 of them was later found to have a pituitary tumor. Whether this therapy or other factors could account for these positive reactions has yet to be explored.

Specificity of Anti-FLC Reactivity in the Sera of Cancer Patients. A multiple approach was undertaken to demonstrate the specificity of this immune reaction. First, a comparison was made by parallel evaluation of IAT and immunofluorescence technique with sera from selected patients before and after adsorption with mouse FLC. The results show a significant reduction in antibody titer to FLC with both assays after such adsorption procedures. Human FLC-adsorbed sera tested with mouse FLC targets were each adsorbed with 6 x 10^9 human FLC. Reactivity to mouse FLC targets with IAT. AR of these already demonstrated a specific reaction to mouse FLC sera from breast carcinoma patients was carried out. The only by specific mouse FLC and not by adult spleen cells. Subsequently, these same sera were tested for residual reactivity to mouse FLC targets with IAT. AR of these human FLC-adsorbed sera tested with mouse FLC targets demonstrated significant reductions of 71 and 29%, compared with control serum. Furthermore, the human FLC used for these adsorptions were then reacted with anti-human IgG fluoresceinated conjugate. The resulting immunofluorescence reactions obtained with 1 patient's serum (N. D.) were more positive (80%) than the more limited activity (35%) of the second serum (C. J.). The sera of both patients were compared with cells incubated with control serum (20% or less).

We have also demonstrated that sera of breast carcinoma patients, known to react specifically with mouse FLC, also reacted with human FLC as targets in the IAT. The results depicted in Table 3 show that the serum of every patient tested gave a significantly positive titer compared with non-cancer control sera. These data also provide indirect proof of the cross-reactive nature of these fetal antigens.

Titration of Antifetal Reactivity in the Sera of Cancer Patients. The relative concentration of antifetal antibodies present in the sera of cancer patients was determined by use of IAT with serum at various dilutions. The results of a representative serum titration, with a maximum reactivity detectable at a serum dilution of 1:100, is presented in Chart 1. With 1 exception (carcinoma-of-breast patient whose peak was at serum dilution of 1:20), a serum dilution of 1:100 gave a consistent maximum reaction as compared to respective control serum counterpart. Another approach

### Table 1

<table>
<thead>
<tr>
<th>Test sera</th>
<th>Isotopic antoglobulin assay FLC</th>
<th>Membrane immunofluorescence FLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma of the breast</td>
<td>10/11^a</td>
<td>10/10^a</td>
</tr>
<tr>
<td>Carcinoma of the lung</td>
<td>8/8</td>
<td>0/1</td>
</tr>
<tr>
<td>Carcinoma of the colon</td>
<td>3/3</td>
<td>1/2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3/3</td>
<td>1/2</td>
</tr>
<tr>
<td>Ocular melanoma</td>
<td>1/2</td>
<td>0/2</td>
</tr>
<tr>
<td>Total no. of cancer patients</td>
<td>25/27^b (92)</td>
<td>12/17 (71)</td>
</tr>
<tr>
<td>Control</td>
<td>3/18</td>
<td>5/14</td>
</tr>
<tr>
<td>Benign lesion</td>
<td>0/9</td>
<td>0/2</td>
</tr>
<tr>
<td>Total no. of controls</td>
<td>3/27 (11)</td>
<td>5/16 (31)</td>
</tr>
</tbody>
</table>

^a Number of positive subjects per total number of subjects tested.

^b Control versus cancer patient groups were significantly different at p < 0.01 and p < 0.05 values for IAT and immunofluorescence test, respectively, as determined by the Wilcoxon test.

^c Numbers in parentheses, percentages of patients.

### Table 2

<table>
<thead>
<tr>
<th>Test sera N. D.</th>
<th>Type of cell</th>
<th>No. of cells used for adsorption (× 10^6)</th>
<th>% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse FLC</td>
<td>Mouse FLC</td>
<td>Mouse FLC</td>
<td>3.0^b</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>1</td>
<td>10^d</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>1</td>
<td>6^d</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>1</td>
<td>6^d</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>1</td>
<td>2^d</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>1</td>
<td>0^d</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>1</td>
<td>0^d</td>
</tr>
</tbody>
</table>

^a Sera dilutions of 1:100 were used for testing reactivity of IgG class.

^b Mean of 2 separate experiments, triplicate samples of each; S.E. were less than 10% of the mean.

^c SC, mouse adult spleen cells.

^d No significant reduction in AR or cpm at cell number tested, as determined by Student's t test.

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Table 3
Isotopic anti-IgG determination of cancer sera reactivity to human FLC surface determinants

<table>
<thead>
<tr>
<th>Test sera</th>
<th>cpm</th>
<th>anti-125I (experimental/control)</th>
<th>AR</th>
<th>p^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. S.</td>
<td>7087/2665</td>
<td>2.7</td>
<td>≤0.005</td>
<td></td>
</tr>
<tr>
<td>N. D.</td>
<td>4830/2665</td>
<td>1.8</td>
<td>≤0.001</td>
<td></td>
</tr>
<tr>
<td>E. B.</td>
<td>6016/2665</td>
<td>2.3</td>
<td>≤0.005</td>
<td></td>
</tr>
<tr>
<td>A. H.</td>
<td>5459/2665</td>
<td>2.0</td>
<td>≤0.001</td>
<td></td>
</tr>
</tbody>
</table>

^a All sera from breast cancer patients were tested at 1:100 dilution.
^b Probability of significant difference from control serum, as determined by Student's t test.
^c Average of triplicate samples; S.E. less than 10% of the mean.

circulating mouse antibodies to fetal antigens are summarized in Table 4. Sera were taken from fetal liver immune, multiparous, pregnant, and normal control animals. Mouse fetal liver immune serum gave detectable antibody titers to ocular melanoma, malignant melanoma, breast carcinoma, lung carcinoma, and glioblastoma human target cells. No immunofluorescence reaction was observed for human colon carcinoma cell targets. Multiparous serum showed a positive reaction with all types of cancer cells tested. Sera from pregnant mice showed a marginal reaction to lung carcinoma and glioblastoma tumor cells, and stronger reactions were found on colon, breast, malignant melanoma, and ocular melanoma target cells. Normal mouse serum gave no reactivity by immunofluorescence to any human tumor cells assayed.

A direct test of the same panel of fetal liver reactive mouse sera plus the sera of a group of selected breast cancer patients were evaluated on allogeneic human tumor

to defining comparative titers in the sera of different patients was undertaken by adsorption experiments with mouse FLC. These experiments were done in such a way that, by increasing the number of cells used in each adsorption, we were able to determine an estimation of the relative antibody titer in each serum. Sera from breast carcinoma patients were tested after such an adsorption for residual activity on mouse FLC as targets with the IAT. The results of a representative experiment are summarized in Chart 2. Assuming a constant antigenic density on the FLC used for adsorptions, we concluded that serum from 1 patient (N. D.) required approximately 7 × 10^8 FLC to reduce the titer by 50% as compared to 8 × 10^6 FLC needed to achieve a similar reduction in the serum from a second patient (C. J.). As expected, the data indicate that control (normal) serum was unaffected by a similar treatment with even 10^8 FLC. Furthermore, immunofluorescence evaluation of these same sera adsorbed as described above also showed greater reduction of titers in 1 breast cancer patient's serum (N. D.) than in that of the second (C. J.).

Detection of Mouse Antibody to Fetal Antigens On Human Tumor and Mouse FLC. Results of analyses for
cells and xenogeneic adult and fetal mouse liver cells. Their specificity was determined by means of specific adsorption experiments with mouse FLC. Aliquots of adsorbed and unadsorbed sera were tested for residual reactivity. Results of the respective immunofluorescence reactions (Table 5) can be summarized as follows. (a) When human tumor cells were used as targets, the results indicated that sera from cancer patients and from FLC-immunized, multiparous, and pregnant mice showed detectable levels of antifetal reactivity. The specificity of these reactions was demonstrated by the fact that their respective adsorbed counterpart sera show a lack of or lower reactivity when retested. Serum from a breast carcinoma patient (N. D.) was an exception to this pattern of reaction, showing lack of detectable reduction after adsorption. As expected, no detectable antibody reactivity was observed with serum from a patient with a benign lesion (C. W.) when assayed before and after adsorption on human tumor target cells. Nor was reactivity observed with control, normal human, or mouse serum. (b) Results of the reactions on mouse FLC targets demonstrated that all sera reacted positively to FLC targets, with the exception of those from controls (human and mouse) and patients with benign lesions whose serum was negative in all tests performed. It was also shown that mouse FLC adsorbed antibody reactivity from a given positive-reacting human or mouse serum. (c) Results of the reactions on mouse adult liver cells demonstrated negative reaction in almost all sera tested.

**DISCUSSION**

The results of this study demonstrate the presence of detectable human IgG antibodies to murine and human FLC in the sera of most patients (25 of 27) harboring a variety of malignant neoplasms. In contrast, only a limited number (3 of 18) of non-cancer-related sera showed this reactivity. In addition, no sera (0 of 9) were reactive from patients suspected of harboring cancer that subsequently could not be confirmed. This study has also demonstrated a good relationship for both detection techniques used. A comparative evaluation indicates that IAT is 10 to 20 times more sensitive compared with the indirect immunofluorescence test. Similar enhanced sensitivity of IAT has been reported by Wood and Barth (43). We tentatively attribute the discrepancies found in the results from both tests to (a) decreased sensitivity known to result from the greater concentration of antiglobulin protein used in the immunofluorescence test (7); (b) the possible differing specificity of antiglobulins used from 2 different manufacturers; or (c) the fact that detection of a protein by fluorescence microscopy depends on point fluorescence, not absolute concentration, which is a feature not distinguished by the IAT used (25). These results also have demonstrated that the detected antibodies bind specifically to xenogeneic murine as well as allogeneic human FLC, but they do not react with adult mouse spleen or liver cells, suggesting that human anti-mouse species antibodies are not involved in this reaction. Further supporting evidences were obtained when a selected panel of sera reactive to fetal and tumor antigens failed to demonstrate immunofluorescence reactivity on adult mouse liver cells, regardless of their origins. These serological reactions could be reduced by specific adsorption procedures with either human or mouse FLC. Since the level of specific binding to both target cells was similar, strong evidence is provided that indicates that the same immunoglobulin being removed is reactive with both species of cells. Further testing for specificity demonstrated specific removal of serum reactivity by mouse FLC adsorptions when tested simultaneously either on human tumor or FLC targets. Moreover, adsorption of selected breast carcinoma sera with human FLC and subsequent testing for residual reactivity on mouse FLC by IAT provided further direct support of cross-reactivity between tumor-associated fetal antigens of human and mouse origins. Tests for residual reactivity after serial adsorptions of the sera of 2 breast carcinoma patients revealed increasing concentration of mouse FLC in the sera and clearly indicated a 10-fold FLC differential removal capacity (Chart 2). Assuming a constant antigenic density on the mouse FLC surface, we observed limited cross-reactivity in the serum of such a patient (N. D.), which was perhaps due to the expression of different fetal antigen specificities in the breast tumor cells. Analogous observations have been recently reported in experimental systems (39, 40).

When compared with control sera, titration of anti-FLC antibodies in the sera of cancer patients showed a maximum reactivity at 1:100 (Chart 1). This increased sensitivity

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**Table 5**

Specificity of immunofluorescence reactions on tumor and fetal cells

<table>
<thead>
<tr>
<th>Sera used</th>
<th>Human breast tumor cells</th>
<th>Mouse FLC</th>
<th>Mouse adult liver cells (unadsorbed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadsorbed</td>
<td>Adsorbed</td>
<td>Unadsorbed</td>
</tr>
<tr>
<td>Patient sera</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. B. (carcinoma of the breast)</td>
<td>±</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>B. A. (carcinoma of the breast)</td>
<td>+</td>
<td>±</td>
<td>+++</td>
</tr>
<tr>
<td>N. D. (carcinoma of the breast)</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>C. W. (benign)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>K. M. (control)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mouse sera</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal liver immunized</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Multiparous Pregnant Control</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>

*a Adsorption of each sera was done with 5 x 10⁷ FLC and was tested simultaneously.

- ±, negative, less than 25%; ±, 25 to 30%; +, 30 to 40%; ++, 40 to 60%; ++++, 75% or more, positive-reacting cells, as compared to control sera.
observed with decreasing concentration of normal sera agrees with previously reported observations (31).

Mouse sera reacting positively to FLC were tested on a variety of human tumor cells by immunofluorescence. In spite of the fact that human colon carcinoma cells are known to express carcinoembryonic antigen (13), they did not react with the mouse FLC-positive sera. Thus, no direct evidence of relationship between carcinoembryonic antigen and our reported FLC antigen was suggested.

The following considerations can be formulated in interpreting our data: (a) Our previous reports (32, 34, 35) describing cross-reactivity of fetal and tumor antigens were confirmed. Similar cross-reactivity has also been described by several investigators in both animal models (3, 18, 37, 39) and humans (9, 12, 20, 41); (b) our data support and extend our previous observations (32, 33) and those of others (1, 15) that these tumor-associated fetal antigens do cross-react across species barriers; and (c) our data tend to confirm reported studies that have demonstrated naturally occurring antibodies to fetal antigens in the sera of cancer patients (9, 11, 27).

These results also indicate that the reacting antibody detected may not be the same as that reported to be host responsive to tissue-specific or organ-specific antigen as described by Kumar and Taylor (24) and others (6, 23, 37). The reactivity detected may correspond either to the widespread fetal antigen reported by Steele et al. (37) or to the non-organ-specific type described by Kumar and Taylor (24), type et al. (22), Dickinson et al. (10), and Avis and Lewis (2). These detectable antibodies are not restricted to sera from patients with tumors of a particular type; they seem to be universally present in cancers, a situation similar to that reported by Dickinson et al. (10) and Bendich et al. (5) in humans and animals, respectively.

REFERENCES

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