Specific Non-Immunoglobulin G Antibodies and Cell-mediated Response to Herpes Simplex Virus Antigens in Women with Cervical Carcinoma

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SUMMARY

Non-immunoglobulin G-neutralizing antibodies to herpes simplex virus (HSV) type 2 were assayed in sera adsorbed with Staphylococcus aureus Cowan I. They were present in 8% of women with normal cervical smear and in 20, 41, and 74% of women with atypia, dysplasia, and cervical carcinoma, respectively. Lymphocytes of the patients were tested for in vitro transformation by killed HSV type 1 and HSV type 2 (HSV-2), as well as by mitomycin C-treated hamster cells transformed by HSV or other viruses or not transformed. Specific stimulation by the HSV-transformed cells occurred in 2, 22, and 40% of women with normal cervical smear, dysplasia, and carcinoma of the cervix, respectively. This frequency rose to 82% during treatment with irradiation and decreased to 0% after surgery. When HSV-2 virions were used as antigens to stimulate the lymphocytes, similar differences were found between the various groups, but they were less clear-cut, since 16% of the control women had lymphocytes responding to HSV. Non-immunoglobulin G antibodies to HSV-2 were not present in blood at the same time as cell response to HSV-2-transformed cells. There was also a negative correlation between neutralizing activities of the sera and the indices of lymphocyte stimulation, indicating a regulation between humoral and cell-mediated responses.

INTRODUCTION

The presence of HSV\(^2\) antigens in cells of cervical carcinoma has been demonstrated (10, 16). Also, the presence of a specific HSV polypeptide called Ag4 has been demonstrated in living cells from biopsies of the same tumors (3). The latter polypeptides elicit immune responses, such as antibodies that fix complement in the presence of Ag4 (4). These antibodies are present only in patients with precanerous and cancerous lesions, while antibodies that neutralize the virions persist in any patient who has experienced a previous herpes genitalis infection. However, other HSV proteins expressed in the cervical carcinoma probably act as booster antigens, since neutralizing antibody activity increases in patients with prolonged dysplasia or carcinoma and decreases after treatment (18). On the other hand, some HSV antigens of the cancer cells probably adsorb cytotoxic antibodies in the presence of complement, since these antibodies decrease with time in patients with prolonged dysplasia or carcinoma (19). Decreasing antibody titers to membrane antigens of HSV-infected cells also run parallel to the severity of the lesions (6).

We have tried to characterize further the specific immune status of these patients by studying the cell-mediated response of their lymphocytes to stimulation by killed HSV virions and cells transformed with these viruses. Also, we have investigated whether, in the cancer and control groups, neutralizing antibodies to HSV are of an IgG nature only or whether IgM and/or IgA are also present. For this purpose, sera from the patients were adsorbed with suspensions of S. aureus Cowan I, a procedure that removes IgG1, IgG2, and IgG4 (1).

MATERIALS AND METHODS

Patients. Women attending a center for the screening of cancer were entered in the study when atypia, dysplasia, or carcinoma in situ was diagnosed; controls with normal cervical smear were matched for age (±5 years). Five women with a previous diagnosis of in situ cervical carcinoma who had been treated by surgery 6 to 12 months earlier were also entered in the study. All the women belonged to a broadly similar middle-class socioeconomic group. Diagnosis of dysplasia corresponded to the presence in smears of squamous cells showing abnormally large, hyperchromatic nuclei and premature keratinization of cytoplasm. Atypia included all of the cellular reactions to infections, inflammation, repair or regeneration, and benign proliferation such as squamous metaplasia and reserve-cell hyperplasia. Another group of women was studied; they entered 2 university hospitals with the diagnosis of squamous-cell cervical carcinoma of various documented stages; only 10% had an invasive carcinoma, and they were not assigned to a special group. These women were not matched with controls, but their immune response to HSV antigens was followed at 2- to 6-month intervals before and after treatment with irradiation.
tion or surgery, and during irradiation, about 2 weeks after the beginning of this treatment. In all, the following patients with carcinoma of the cervix were studied: 11 before, during, and after irradiation; 8 before and after irradiation (6 to 12 months after beginning treatment); 23 before and after surgery; 5 before treatment; and 5 after treatment.

Adsorption of Sera with *S. aureus* Cowan A. The bacterial strain was kept lyophilized and grown on solid Tryptose soja agar for the 1st passage. It was then passed once in casein yeast broth (2) for 18 hr with agitation. The final suspension was grown in the same medium in a fermentor with a constant pH of 7 and killed by formaldehyde and heat, as described (2), except that heating was performed for 10 min at 80° in sealed 150-ml vials. A 15% suspension was kept at 4° for 1 to 2 months.

Sera were adsorbed with freshly washed staphylococci; 1 volume of 10% staphylococci suspension was mixed with 1 volume of serum diluted 1:10 and left for 20 min at room temperature before centrifugation. This procedure was repeated once.

Assay for Neutralizing Antibodies. HSV-2 was mixed with the patient’s sera and assayed for residual infectivity after 2 min of contact at 37°. The constant K of inactivation was calculated as previously described (18).

For the assay of non-IgG antibodies, 50 μl of serum adsorbed with *S. aureus* Cowan A were mixed with 50 μl of tissue culture medium containing 2500 plaque-forming units of HSV-2, and similar mixtures were made with nonadsorbed serum.

After 20 min of contact at 37°, residual infectivity of HSV-2 was assayed by plating the mixtures at dilutions of 1:40, 1:60, and 1:120 on primary cultures of chick embryo fibroblasts in Sterilin 306 V plastic dishes. The plaques were read after 3 days at 37°. With most of the sera from normal individuals and with hyperimmune rabbit antisera to HSV-2, all neutralizing activity was removed after a double adsorption with the staphylococci; these sera were considered to possess only IgG-neutralizing antibodies to HSV-2. With other sera, neutralizing activity remained after *Staphylococcus* adsorption and amounted to 50 to 100% of the activity of the nonadsorbed sera; these were counted as non-IgG-containing sera. Only a small percentage of the sera showed intermediate results; it was not included in the statistical evaluation.

Lymphocyte Transformation Test. As previously described (17), cells from heparinized blood were washed twice in Roswell Park Memorial Institute Tissue Culture Medium 1640 with 10% fetal calf serum and resuspended in this medium at the original volume. One hundred μl of this suspension were added to 2 ml of medium containing PHA (10 μg/ml), mitomycin C-treated cells (2 × 10³/ml), or a preparation of HSV containing plaque-forming units (5 × 10⁶/ml) and inactivated by heat. Cells had been treated with mitomycin C (50 μg/ml) for 30 min at 37°, and the virus preparations were heated for 30 min at 60° and used at final dilutions of 1:20 and 1:200 for HSV-2 and of 1:20 for HSV-1. Two μCi of [³²P]thymidine were added 3 days after the addition of PHA or medium alone and 6 days after addition of cells, viruses, or medium alone. The amount of radioactivity incorporated into acid-insoluble material was evaluated after 4 hr of incubation with tritiated thymidine. Each test was performed in quintuplicate. Indices of stimulation are expressed as ratios of cpm after treatment with PHA or virus antigens to those obtained at similar intervals in culture medium alone; specific stimulation by transformed cells was evaluated as the ratio of cpm in the presence of transformed cells to those in the presence of untransformed hamster cell lines. Many other cell lines were used as controls (see below).

Viral Antigens. The KOS strain of HSV-2, provided by Dr. Melnick, was grown in primary cultures of rabbit kidney cells. After 48 hr of growth at 37°, the cells were scraped off the glass, suspended in the growth medium, and spun down for 60 min at 100,000 × g. The pellet was suspended in 0.9% NaCl solution at one-tenth the original volume and frozen and thawed. The suspension was centrifuged for 10 min at 2000 × g, and the pellet was discarded. Virus plaque-forming units present in the supernatant were titrated in monolayers of rabbit kidney cells. The HSV-1 antigen was the French vaccine "Diamant."

Cell Antigens. The hamster cells transformed by HSV, kindly provided by Dr. F. Rapp, had been obtained (7, 8, 13) by treating hamster embryo fibroblasts with HSV-2 inactivated with UV (cell line 333-B-9), HSV-2 inactivated with neutral red plus light (cell line HSV-2-26), or UV-inactivated HSV-1 (cell line 14-012-8-1). Nil cells are a cell line derived from hamster embryo fibroblasts and were obtained from Dr. Zur Hauzen, together with the same cell line (Nil Tr) transformed by adenovirus type 12. The SV40-transformed hamster cells (Flow Laboratories, Rockville, Md.) originated from a hamster tumor. The BHK-21 line (baby hamster kidney cells, clone 21; Flow Laboratories) was also used as a control line, together with primary cultures of rabbit kidneys and mouse embryo fibroblasts. Human cells were Hep-2 cell line (Flow Laboratories), HeLa Saarbrück (Hela S, obtained from Dr. Gelderblom), and HeLa 229 (American-type culture collection).

RESULTS

Evaluation of Tests. In all patients and control individuals, serum antibodies to HSV-2 were assayed by kinetics of neutralization. The constant K evaluated neutralizing activities of the sera to HSV-2 after a 2-min contact with the virus. This short contact period ensured a fairly good specificity to the test, since sera from children with primary HSV-1 infection reacted only with HSV-1 by this procedure. However, the situation may be different in adults with viral reactivations and possibly even reinfections. Most but possibly not all of the positive tests with HSV-2 were indicative of a previous herpes genitalis infection.

For determination of the presence of specific non-IgG antibodies in these groups of patients, their sera were adsorbed with *S. aureus* Cowan A; no neutralizing activities were left in the supernatants when sera were assayed after 2 min of contact with HSV-2. Since IgM antibodies react more slowly than IgG, the tests were repeated using a 20-min and a 60-min contact of virus with adsorbed sera. Under these conditions some of the adsorbed sera conserved their
neutralizing activity on HSV-2, and this activity was similar after 20- or 60-min contacts. Three of these adsorbed sera were centrifuged at 114,000 x g for 14 hr in a 10 to 40% sucrose gradient, and the neutralizing activity was found in the 19S region, indicating that at least part of the activity of some of the adsorbed sera was due to IgM antibodies.

Heparinized blood was obtained from more than half of the patients. Table 1 shows examples of specific stimulation of the lymphocytes by mitomycin C-treated hamster HSV-transformed cells in 3 patients with cervical carcinoma. Thymidine incorporation was significantly greater (p < 0.01) in the presence of 2 or 3 HSV-transformed cells than in the presence of other hamster, rabbit, mouse, or human cells. Indices of stimulation were calculated as the ratios of cpm in the presence of each HSV-transformed cell line to cpm in the presence of Nil or BHK-21 cells. Ratios ranged from 1.5 to 4.2, indicating that the stimulation indices were significantly positive but much lower than those obtained with PHA. There was also a significant association (p < 0.01) between tests that were positive with 1 HSV-transformed cell line (333-8-9) as well as with another (HSV-2-26), since, of 17 positive blood samples, 13 were positive with both cell lines. The assay with the 3rd HSV-transformed cell line (14-012-8-1) was only recently performed in a few patients.

**Humoral and Cell-mediated Responses in 8 Patient Groups.** We first analyzed the differences between women with normal cervical smears and those with precancerous and cancerous lesions (Table 2; Chart 1). Antibodies to HSV-2, as measured by kinetics of neutralization, were found in 21% of the women with normal cervical smears and in 41, 70, and 75% of those with atypia, dysplasia, or cervical carcinoma, respectively (p < 0.001). Graded differences between the groups were even greater when neutralizing antibodies were assayed in sera adsorbed with *S. aureus* Cowan, since only 8% of the women with normal cervical smears still possessed antibodies to HSV-2 after removal of the IgG.

Lymphocytes were specifically stimulated by mitomycin C-treated HSV-2-transformed hamster cells, as compared to stimulation by normal hamster cells, in 40% of the patients with cervical carcinoma, in contrast with 2% of the women with normal cervical smear. The frequency of responses was intermediate in the cases of atypia and dysplasia. Significant differences (p < 0.001) were also found between normal and dysplasia or carcinoma groups when lymphocytes were stimulated by killed HSV-2 virions; this test was, however, less discriminating because in the normal group the frequency of stimulation by the virions was higher (16%) than the frequency of responses to HSV-2-transformed cells (2%).

The responses to HSV-1 virions were even less discriminating, because the cancer and the dysplasia patients responded less frequently to HSV-1 than to HSV-2, indicating that this test was at least partly specific for the HSV serotypes.

We now turn to the differences between treated and nontreated cancer patients. Cell-mediated responses were studied in 11 women during and after irradiation treatment and in 17 women who were treated by surgery without irradiation. During irradiation, the number of women with lymphocytes that responded to HSV-2-transformed cells increased greatly, since 82% now responded in this test, as compared to 40% in the group of nontreated cases of carcinoma. In contrast, many of these women lost their non-IgG antibodies to HSV-2 during irradiation, while this treatment did not modify the proportion of women with IgG antibodies.

### Table 1

<table>
<thead>
<tr>
<th>Lymphocyte stimulators</th>
<th>Patient 112</th>
<th>Patient 115</th>
<th>Patient 107</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-transformed hamster cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>333-8-9</td>
<td>1,540 ± 153*</td>
<td>1,353 ± 223</td>
<td>2,120 ± 490</td>
</tr>
<tr>
<td>HSV-2/26</td>
<td>1,512 ± 203</td>
<td>1,553 ± 141</td>
<td>1,794 ± 301</td>
</tr>
<tr>
<td>Ham HSV-1</td>
<td>1,922 ± 344</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus-transformed hamster cells</td>
<td>459 ± 129</td>
<td>543 ± 80</td>
<td></td>
</tr>
<tr>
<td>SV40-transformed hamster cells</td>
<td></td>
<td>499 ± 64</td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>460 ± 90</td>
<td>540 ± 242</td>
<td>867 ± 216</td>
</tr>
<tr>
<td>BHK-21</td>
<td>498 ± 82</td>
<td>540 ± 78</td>
<td>1,154 ± 471</td>
</tr>
<tr>
<td>Mouse cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary embryo fibroblasts</td>
<td></td>
<td>620 ± 67</td>
<td></td>
</tr>
<tr>
<td>Rabbit cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary kidney fibroblasts</td>
<td>463 ± 109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HeLa Sarrebrück</td>
<td>537 ± 76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HeLa 229</td>
<td>370 ± 149</td>
<td>628 ± 176</td>
<td></td>
</tr>
<tr>
<td>Hep-2</td>
<td>699 ± 72</td>
<td>1,113 ± 123</td>
<td></td>
</tr>
<tr>
<td>PHA</td>
<td>18,961 ± 1,278</td>
<td>16,056 ± 2,763</td>
<td>25,036 ± 2,300</td>
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<tr>
<td>Medium alone</td>
<td>694 ± 163</td>
<td>480 ± 162</td>
<td>527 ± 122</td>
</tr>
</tbody>
</table>

* Mean ± S.D.
Neutralizing antibodies to HSV-2 and lymphocyte response to HSV virions and HSV-2-transformed cells in various groups of patients

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. tested</th>
<th>Adsorbed sera</th>
<th>% positive</th>
<th>Lytic cells HSV-2</th>
<th>Lytic cells HSV-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cervix</td>
<td>51</td>
<td>21</td>
<td>8</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Atypia</td>
<td>34</td>
<td>41</td>
<td>20</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>54</td>
<td>70</td>
<td>41</td>
<td>41</td>
<td>22</td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>47</td>
<td>75</td>
<td>74</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>During irradiation</td>
<td>11</td>
<td>70</td>
<td>20</td>
<td>11</td>
<td>82</td>
</tr>
<tr>
<td>After irradiation</td>
<td>19</td>
<td>66</td>
<td>16</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>After surgery</td>
<td>28</td>
<td>54</td>
<td>8</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Other carcinoma</td>
<td>12</td>
<td>8</td>
<td>8</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

* Index of stimulation determined by [3H]thymidine incorporation into acid-insoluble material (see "Materials and Methods").

b Constant of the kinetics of neutralization.

c Presence of neutralizing antibodies in sera adsorbed with S. aureus Cowan I.

HUMORAL CELLULAR RESPONSES

Chart 1. Illustration of the results shown in Table 1 for the following groups of women: N, normal cervical smears; A, atypia; D, dysplasia; C, cervical carcinoma; CX, irradiated carcinoma; TX and TS, carcinoma 6 to 12 months after irradiation and surgery, respectively. Tr, transformed.

The differences were less clear-cut when coexistence of non-Ig antibodies and lymphocyte responses to the virions to the same virus. Later on, 6 months after treatment with irradiation or surgery, the immune status of the treated women was similar to that of the control group with no cervical lesion. The reason that irradiation of the tumor resulted in increased frequency of cell-mediated response to HSV-transformed cells, but not concomitantly to HSV-2 antigen, is unclear. The responses to HSV-transformed cells were probably induced by HSV antigens, since hamster cells transformed by SV40 or by adenovirus type 12 did not stimulate the lymphocytes of these patients. Analysis of the association of lymphocyte response to HSV-2 with that of HSV-2-transformed cells (Table 3) shows that most of the lymphocyte samples that responded to 2 different HSV-transformed cell lines also responded to HSV-2 virions, while none of these samples reacted with SV40- or adenovirus-transformed cells. Conversely, among all the tests that were positive with HSV-2, 53% were also positive with HSV-transformed cells in cancer and dysplasia patients and 15% responded to these cells in normal and cured patients.

Chart 1 illustrates that 2 tests discriminated more clearly than the others between diseased and nondiseased patients: these were the assay for non-IgG antibodies and the lymphocyte stimulations by HSV-2-transformed cells. We then calculated how often these 2 tests were simultaneously positive in a given blood sample: it was striking that this only occurred exceptionally (Chart 2). Only 2% of the patients with carcinoma or dysplasia possessed non-IgG antibodies to HSV-2 in the serum together with lymphocytes responding to HSV-2-transformed cells; in this group, a majority of the samples (68%) were positive in 1 of the 2 tests, while most samples of the normal group (79%) were negative in both tests.

The differences were less clear-cut when coexistence of non-Ig antibodies and lymphocyte responses to the virions

<table>
<thead>
<tr>
<th>Lymphocyte stimulators</th>
<th>Cancer and dysplasia</th>
<th>Normal and cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2 and HSV-Tr cells</td>
<td>53</td>
<td>15</td>
</tr>
<tr>
<td>Other Tr cells</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HSV-Tr cells and HSV-2</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>Other Tr cells</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Tested 6 months after irradiation or surgery. Data for the tests performed during irradiation were not entered into this table.

b HSV-Tr cells, HSV-2-transformed cell line 333-6-9; Tr, transformed.
were studied. The latter responses were, however, also significantly rarely associated with non-IgG antibodies, since they were found in 6 to 8% of the blood samples of the normal and cancer groups.

A negative correlation between humoral and cell-mediated responses is also demonstrated in Chart 3, where only the cancer patients with combined positive lymphocyte response to HSV-2 and positive constant of neutralizing antibodies to this virus were taken into account. High constants of neutralization were associated with the lowest positive indices of lymphocyte stimulation \((r = -0.6\) with a confidence limit of 95\%). When results were similarly plotted for the other groups of patients without current cervical carcinoma, the points were scattered, with no positive or negative correlations (results not shown). These results clearly indicate some regulation between humoral and cell-mediated responses.

**DISCUSSION**

For the sake of brevity, we have termed "non-IgG" those antibodies that remained in the sera after adsorption with \(S.\ aureus\) Cowtan A; protein A of this staphylococcus, however, does not bind IgG3, and antibodies of this class may have remained in the serum supernatant. They represent only 5% of the total IgG content of human serum and could probably not account for the high neutralizing activities to HSV-2 that were found in the adsorbed sera of some of the women with cervical carcinoma. The presence of specific IgM in these adsorbed sera was verified in a few cases by ultracentrifugation in sucrose gradients, which showed neutralizing activity in the 19S region, but the presence of IgA was not assayed.

Thus, IgG3 and IgA may have played some part in the positive reactions observed, but the role of IgM was probably predominant. It is now progressively recognized that IgM production is not restricted to primary infections, since IgM antibodies to varicella virus were found in cases of herpes zoster, caused by reactivation of a latent varicella virus (15). Also, the continued presence of an endogenous oncornavirus in mice induces 19S but not 7S neutralizing antibodies (12). Our findings that IgM-neutralizing antibodies to HSV-2 are present almost exclusively in cases of dysplasia and cervical carcinoma, as compared to the healthy and treated groups, fit with other indications that these precancerous and cancerous lesions bear herpesvirus antigens that continuously stimulate immune responses. Complement-fixing antibodies to Ag4, which are also restricted to cases with similar lesions of the cervix, were also shown to be of IgM nature (5).

Cell-mediated response, as assayed by lymphocyte transformation in the presence of HSV virions, was more frequent in the cases of dysplasia or cervical carcinoma than in the control groups. However, 16\% of the healthy women possessed lymphocytes sensitized to some HSV antigens, which were probably common to HSV-1 and HSV-2 since the reactions were most often simultaneously positive with both serotypes. This indicates that latent herpetic infection or unsuspected reactivations may be sufficient to maintain lymphocyte responsiveness. It was striking that only 2\% of the healthy women showed in vitro lymphocyte response to HSV-2-transformed cells, in contrast to a 22 or 40\% response in the dysplasia and carcinoma groups, respectively. The responses were not due to nonspecific antigens present on any type of tumor cells, since they were not paralleled by similar results if SV40- or adenovirus-transformed cells were used as stimulating antigens. There were, in addition, indications of an association between lymphocyte responses to HSV and to HSV-transformed cells, since responses to the latter antigen were almost always accompanied by a positive response to the virion; the reverse was not true, however, since healthy women most often responded only to the virion antigens. HSV antigens that
remained in the transformed cells are ill defined. These cells were not observed in early passages, and they had ceased demonstrating herpesvirus antigens with current immunofluorescent or radioimmunoassay techniques; however, hamsters bearing tumors caused by these cells had serum antibodies that were specifically cytotoxic to HSV-infected cells, in the presence of complement, an indication that the tumors developed in vivo expressed some herpesvirus antigens. It is clear from our results that some in vivo mechanism must exist that modulates the immune reactions in such a way that the simultaneous presence of non-IgG antibodies to HSV-2 and lymphocyte responsiveness to this virus is excluded. T helper cells have indeed been shown to be needed for efficient conversion of 19S to 7S immune response in mice (14), and in vitro studies showed that supraproportional numbers of T helper cells decreased the number of antibody-forming cells (9).

It would be very interesting to know whether regressions of the dysplastic lesions to atypia, which were not rarely observed in this study, were due to the action of non-IgG antibodies or to the appearance of cell-mediated response. On the one hand, IgM may help to reject a tumor, as indicated by the fact that mice inoculated with Moloney sarcoma virus and undergoing regression of the tumor possessed IgM antibodies, and that these could induce specific cytotoxicity against the sarcoma cells by normal thymocytes (11). On the other hand, the cytotoxicity of antibodies in the presence of complement may be efficient only on target cells with high antigen density: in the situation of renal allografts in rats, IgM antibodies were cytotoxic to the donor's lymphocytes, but they enhanced the graft (20). One of the reasons that tumors are not rejected may be their low antigen density.

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