Alteration of Immunogenicity of Xenogenized Tumor Cells in Syngeneic Rats by the Immune Responses to Virus-associated Antigens Produced on Immunizing Cells

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ABSTRACT

A strong transplantation resistance to a fibrosarcoma (KMT-17) is induced in syngeneic Wistar King Aptekman/Hok rats after a single s.c. immunization with Friend virus-infected (xenogenized) viable KMT-17 cells. The resistance induced by the repeated immunizations with irradiated Friend virus-infected KMT-17 cells, however, was unexpectedly weaker when compared with that induced by irradiated KMT-17 cells. The immunogenicity of tumor-associated antigen on xenogenized Friend virus-infected KMT-17 cells was correlated with their shortened survival time in the peritoneal cavity after i.p. inoculation, especially in rats pretreated with xenogenized tumor cells. Furthermore, xenogenized tumor cells producing a medium amount of virus-associated antigen (VAA) but not those producing a large amount of VAA showed an augmented immunogenicity even in normal rats. On the other hand, the tumor-associated antigen immunogenicity was augmented by immunization with xenogenized tumor cells which expressed a relatively small amount of VAA in rats presensitized with VAA. These findings indicate that the immunogenicity of xenogenized tumor cells is augmented by the middle-grade immune responses to VAA produced on xenogenized tumor cells.

INTRODUCTION

For augmentation of antitumor resistance by immunization with tumor cells, many attempts at modification of such cells with viruses (2, 3, 11-15, 17, 22, 23, 26, 27), chemicals (5, 7, 8, 10, 20), and enzymes (1, 4, 24) have been reported. We have reported that rat tumor cells can be modified by infection especially with murine leukemia viruses (6, 9, 11-13). This modification with virus is referred to as "xenogenization of tumor cells" and is characterized by spontaneous regression of a murine leukemia virus-infected rat tumor in normal syngeneic hosts. In rats which rejected xenogenized tumor cells, a transplantation resistance to noninfected identical tumor was induced. However, xenogenized tumor cells have not always shown any strong immunogenicity of TAA.

It is necessary for augmentation of the immunogenicity that xenogenized tumor cells should produce an appropriate amount of VAA on their cell surface. When they produce an excess amount of VAA, the immunogenicity of TAA is reduced. In this report, we discuss the conditions in which xenogenized tumor cells induce a strong resistance against xenogenized tumor cells; we refer especially to the anti-VAA response in the hosts and to the changes of the survival time of tumor cells at the site of immunization.

MATERIALS AND METHODS

Rat. An inbred strain of WKA rats was supplied from the Experimental Animal Institute, Hokkaido University School of Medicine, Sapporo, Japan. The rats were used at 2 to 4 months of age. WKA rats which were given inoculations of FLV within 48 hr of birth were used as FLV-tolerant rats for the passage of the virus-infected tumors.

Tumors. A fibrosarcoma (KMT-17) induced by methylcholanthrene in a WKA rat was used. The tumor was maintained by i.p. transplantation in syngeneic WKA rats as an ascites form. The growth of the tumor was rapid and killed the host within 20 days of this s.c. transplantation of 1 x 10⁶ cells. The minimum number required for a 100% take of tumor was 5 x 10⁴ cells. An FLV-KMT-17 was obtained by infection with FLV through passages in FLV-tolerant rats. The FLV-KMT-17 cells acquired FLV-associated antigens (VAA) and were lysed by anti-VAA serum and complement. The WLFT-6 used was a lymphoma established by the transplantation of spleen cells obtained from a WKA rat which had been given an inoculation of Friend lymphatic leukemia virus at birth. The lymphoma carries VAA and grows in virus-tolerant rats but not in normal syngeneic rats (15).

Estimation of Relative Amount of VAA on Xenogenized Tumor Cells. In order to estimate relative amounts of VAA on xenogenized tumor cells after serial passage in FLV-tolerant rats, cytotoxic sensitivity of xenogenized tumor cells was examined with anti-VAAs serum and complement as reported previously (27). The cytotoxic index with anti-VAA serum has been found to indicate the relative amount of VAA by a comparative examination with an absorbing test (27). The amount of VAA increased by passage generations and reached its maximum at the sixth or seventh generation. The majority of the experiments reported here were carried out with xenogenized tumor cells which expressed the maximum amount of VAA unless otherwise indicated.

X-irradiation of Tumor Cells. Tumor cells were collected aseptically from the peritoneal cavity of rats 3 days after the passage. After washing 3 times with Eagle’s minimum essential medium, tumor cells were suspended in cold Eagle’s minimum essential medium at a concentration of 5 x 10⁶ cells/ml. The tumor cells were treated with 8000 rads using a Toshiba KXC-18-2 X-ray unit which delivers 440 rads/min at 180 kVp with a 0.5-mm copper and a 0.5-mm aluminum filter. This treatment did not alter the viability of the cells as measured by the exclusion of trypan blue immediately thereafter.

Immunization and Challenge with Tumor Cells. WKA rats were immunized s.c. with 1 x 10⁷ cells of viable FLV-KMT-17 into the left back. The tumor grew temporarily to a peak of 15 to 20 mm in diameter for 7 days and eventually regressed within 2 weeks after immunization. Three weeks after immunization, KMT-17 cells were challenged s.c. to the right back of rats. Fifty million cells of X-irradiated tumor cells were inoculated s.c. for immunization with irradiated cells. The other method of immunization, i.e. inoculation of irradiated tumor cells, was performed...
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at biweekly intervals. In order to confirm the role of preimmunization with VAA, the rats were immunized with WLFT-6 cells, which were carrying the VAA but not the TAA of KMT-17 cells, followed by immunization with xenogenized and nonxenogenized tumor cells. KMT-17 cells were challenged s.c. 2 weeks after the last immunization.

Examination of the Existence of Tumor Cells in the Peritoneal Cavity. After i.p. inoculation of irradiated tumor cells into rats, a small amount of peritoneal fluid was sampled every 12 hr, and tumor cells were examined under a light microscope after instantaneous staining with acetocarmine.

Observation of Tumor Growth. After challenge of the tumor, 2 tumor diameters were measured with a caliper every third day. The observation was terminated on the 50th day after the transplantation of the tumor, at which time all the surviving rats were tumor free.

Calculation of LTD50. The number of tumor cells required for a 50% lethal growth was estimated by the method of Read and Muench (21) and indicated as a LTD50. Preliminary experiments estimated that the LTD50 of KMT-17 cells in normal WKA rats was 1 x 106 cells.

Statistical Analysis. The statistical difference in the lethal rate between the 2 indicated groups was calculated by the x2 test, and the difference in the mean days for survival time of irradiated tumor cells in the peritoneal cavity was analyzed by the Student's t test.

RESULTS

Immunogenicity of Viable Xenogenized Tumor Cells. As shown in Table 1, when viable xenogenized tumor (FLV-KMT-17) cells were given to rats challenged 2 weeks later with 107 cells of KMT-17, only 5 of 19 rats (26%) were killed by tumor growth. This result was compared to the lethal growth in rats immunized 3 times with irradiated nonxenogenized KMT-17 cells; 12 of 19 rats (63%) were killed by tumor growth. The results indicate that the immunizing effect of viable xenogenized tumor cells on the growth of identical nonxenogenized tumor was stronger than that of irradiated nonxenogenized tumor cells. The augmented immunogenicity of viable xenogenized tumor cells might be partially due to an increased amount of immunogen, since xenogenized tumor cells can grow temporarily in syngeneic rats.

Immunogenicity of Irradiated Xenogenized and Nonxenogenized Tumor Cells. In order to compare the immunogenicity of xenogenized and nonxenogenized tumor cells under the same conditions, WKA rats were immunized with irradiated tumor cells at weekly intervals, and various doses of KMT-17 cells were challenged 1 week after the third immunization. All nonimmunized rats were killed by challenges with 105, 106, and 107 cells of KMT-17 as shown in Table 2. On the basis of the lethal growth rates indicated in Table 2, LTD50 was calculated as 56 x 104 in rats immunized with xenogenized tumor cells and 200 x 104 in rats immunized with nonxenogenized tumor cells. This result—that the immunogenicity of xenogenized FLV-KMT-17 cells was weaker than that of nonxenogenized KMT-17 cells when an immunization was performed with irradiated cells—was unexpected.

Survival Time of Xenogenized Tumor Cells from the Peritoneal Cavity after i.p. Inoculation. Xenogenized FLV-KMT-17 cells possess VAA which is especially highly antigenic in rats. It is therefore possible that the xenogenized tumor cells in rats were eliminated faster than were the nonxenogenized tumor cells owing to recognition not of TAA but of VAA. An exploration of the survival time of xenogenized tumor cells was performed by examination of the tumor cells in peritoneal fluids after i.p. inoculation of irradiated tumor cells. The summarized results are indicated in Table 3. After the first inoculation of 5 x 107 tumor cells, the mean survival time of xenogenized tumor cells was 6.4 ± 0.6 days, and that of nonxenogenized tumor cells was 7.4 ± 0.9 days. Although the difference between them was only 1 day, it was statistically significant (p < 0.001). The difference in the existence was distinct after the secondary inoculation (p < 0.001) when it was 1.3 ± 0.6 days for xenogenized tumor cells and 3.1 ± 0.6 days for nonxenogenized tumor cells. This might be the result of secondary response to VAA in rats presensitized with VAA on xenogenized tumor cells. The validity of the explanation given above—that xenogenized tumor cells were eliminated faster than were nonxenogenized tumor cells—is therefore evident.

Transplantation Resistance to Nonxenogenized KMT-17 in WKA Rats after i.p. Immunization with Irradiated Tumor Cells. The rats used in the experiment indicated in Table 3 were s.c. challenged with KMT-17 cells 2 weeks after the first or second immunization (Table 4). Present in rats immunized with xenogenized tumor cells LTD50 after single and repeated immunization were 10 x 106 and 120 x 106 cells, respectively. In the rats immunized with nonxenogenized tumor cells, LTD50 was 38 x 106 and >1600 x 106 cells after repeated immunization. The immunizing effects with irradiated tumor cells therefore closely correlated with the survival time of immunogen at the peritoneal cavity.

### Table 1

Comparison of immunogenicity between viable xenogenized and irradiated nonxenogenized KMT-17 cells against transplantation of nonxenogenized KMT-17 in WKA rats

<table>
<thead>
<tr>
<th>Immunization</th>
<th>Times used</th>
<th>No. of rat deaths/No. of rats immunized</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>12/12</td>
<td>(100)†</td>
</tr>
<tr>
<td>Viable xenogenized FLV-KMT-17</td>
<td>1</td>
<td>5/19† (26.3)</td>
</tr>
<tr>
<td>Irradiated xenogenized KMT-17</td>
<td>3</td>
<td>12/19† (63.2)</td>
</tr>
</tbody>
</table>

† Numbers in parentheses, percentage.

### Table 2

Comparison of immunogenicity between irradiated xenogenized and nonxenogenized KMT-17 cells against transplantation of xenogenized KMT-17 in WKA rats

<table>
<thead>
<tr>
<th>Immunization</th>
<th>No. of rat deaths/No. of rats immunized</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8/8 (100) 8/8 (100) 7/7 (100) 1</td>
</tr>
<tr>
<td>Xenogenized</td>
<td>7/14 (50) 16/29 (62) 4/7 (57) 56</td>
</tr>
<tr>
<td>Nonxenogenized KMT-17</td>
<td>1/12 (8) 12/27 (44) 2/7 (29) 200</td>
</tr>
</tbody>
</table>

§ Irradiated tumor cells (1 x 107) were inoculated s.c. for immunization 3 times at weekly intervals, and xenogenized KMT-17 cells were challenged 1 week after the final immunization.

§ Numbers in parentheses, percentage.

§ Statistical difference was significant by x2 test (p < 0.05).
cavity of the hosts. It can be considered that, since xenogenized tumor cells are easily recognized and rejected in the host by VAA, secondary immunization with TAA on xenogenized tumor cells is less effective for induction of resistance against nonxenogenized tumor which does not possess VAA.

Effect of Secondary Immunization with Xenogenized Tumor Cells. Further investigation of secondary immunization with xenogenized tumor cells was performed in the rats presensitized with FLV-KMT-17 or KMT-17 cells. As indicated in Table 5, the survival time of the xenogenized tumor cells (FLV-KMT-17, 1.4 days) was shorter than that of nonxenogenized tumor cells (KMT-17, 2.5 days) in rats presensitized with xenogenized tumor cells (p < 0.01). This difference might have been due to presensitization with VAA, since the survival times of both tumor cells were similar in rats presensitized with nonxenogenized tumor cells; 3.0 and 3.2 days, respectively (p > 0.05). The immunizing effects of the secondary inoculum are also shown in Table 5. As a result of 2 challenging doses, LTD<sub>50</sub> was 62 × 10<sup>4</sup> in rats immunized with FLV-KMT-17 and FLV-KMT-17, >1780 × 10<sup>4</sup> in rats immunized with FLV-KMT-17 and KMT-17, 240 × 10<sup>4</sup> in rats immunized with KMT-17 and FLV-KMT-17, and >1340 × 10<sup>4</sup> in rats immunized with KMT-17 and KMT-17. These results indicate that, nevertheless, the secondary immunization with xenogenized tumor cells was less effective, while presensitization with xenogenized tumor cells and the booster with xenogenized tumor cells induced a strong resistance.

Effects of Immunization with Xenogenized Tumor Cells Carrying Various Amounts of VAA in WKA Rats Presensitized with VAA. As immunization with xenogenized tumor cells produces anti-TAA response as well as anti-VAA response, the first immunization was performed with WLFT-6 cells, which carry VAA but not TAA of KMT-17 cells, in order to observe an influence of anti-VAA response, following immunization with xenogenized and nonxenogenized tumor cells. The survival time of xenogenized tumor cells was also observed to be shortened.

### Table 3
Comparison of survival time between xenogenized and nonxenogenized KMT-17 cells inoculated i.p. after irradiation (8000 rads) in WKA rats.

<table>
<thead>
<tr>
<th>Tumor cells&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1st inoculation</th>
<th>2nd inoculation&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenogenized FLV-KMT-17</td>
<td>6.4 ± 0.9&lt;sup&gt;c&lt;/sup&gt; (n = 32)</td>
<td>1.3 ± 0.8 (n = 16)</td>
</tr>
<tr>
<td>Nonxenogenized KMT-17</td>
<td>7.4 ± 0.9&lt;sup&gt;c&lt;/sup&gt; (n = 31)</td>
<td>3.1 ± 0.6 (n = 15)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Irradiated tumor cells (5 × 10<sup>7</sup>) were inoculated i.p. in normal WKA rats.  
<sup>b</sup> Days for survival of tumor cells in ascites fluid (see "Materials and Methods").  
<sup>c</sup> Mean ± S.D. Statistical difference was significant by Student's t test (p < 0.001).

### Table 4
Transplantation resistance to nonxenogenized KMT-17 in WKA rats after i.p. immunization with irradiated xenogenized and nonxenogenized KMT-17 cells.

<table>
<thead>
<tr>
<th>Immunization&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Times used</th>
<th>10&lt;sup&gt;4&lt;/sup&gt; cells challenged</th>
<th>10&lt;sup&gt;5&lt;/sup&gt; cells challenged</th>
<th>10&lt;sup&gt;6&lt;/sup&gt; cells challenged</th>
<th>LTD&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
<td>6/6 (100)</td>
<td>17/17 (100)</td>
<td>5/5 (100)</td>
<td>1 × 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Xenogenized FLV-</td>
<td>5/9 (56)</td>
<td>4/5 (80)</td>
<td>ND&lt;sup&gt;e&lt;/sup&gt;</td>
<td>10 × 10&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>KMT-17</td>
<td>2</td>
<td>ND</td>
<td>6/13&lt;sup&gt;c,e&lt;/sup&gt; (48)</td>
<td>4/4&lt;sup&gt;c,e&lt;/sup&gt; (100)</td>
<td>120 × 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nonxenogenized KMT-17</td>
<td>2</td>
<td>2/10 (20)</td>
<td>3/5 (60)</td>
<td>ND</td>
<td>38 × 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>d</sup> Irradiated (8000 rads) tumor cells (5 × 10<sup>7</sup>) were inoculated i.p. once or twice at biweekly intervals, and KMT-17 was challenged 2 weeks after the test immunization.  
<sup>e</sup> ND, not done.  
<sup>f</sup> Statistical difference was significant by χ<sup>2</sup> test.  
<sup>g</sup> p < 0.05;  
<sup>h</sup> 0.01 < p < 0.02.

### Table 5
Effects of secondary immunization with xenogenized and nonxenogenized KMT-17 cells against xenogenized KMT-17 in WKA rats.

<table>
<thead>
<tr>
<th>Immunization&lt;sup&gt;i&lt;/sup&gt;</th>
<th>1st inoculation</th>
<th>2nd inoculation&lt;sup&gt;j&lt;/sup&gt;</th>
<th>Av. existence of 2nd inoculated tumor cells&lt;sup&gt;k&lt;/sup&gt;</th>
<th>No. of rat deaths/No. of rats immunized (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>1.4 ± 0.9&lt;sup&gt;l&lt;/sup&gt; (n = 12)</td>
<td>10/10</td>
<td>1 × 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>FLV-KMT-17</td>
<td>FLV-KMT-17</td>
<td>2.5 ± 0.8&lt;sup&gt;l&lt;/sup&gt; (n = 14)</td>
<td>5/8 (63)</td>
<td>&lt;62 × 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>KMT-17</td>
<td>FLV-KMT-17</td>
<td>3.0 ± 0.6&lt;sup&gt;l&lt;/sup&gt; (n = 15)</td>
<td>1/9 (11)</td>
<td>&gt;1780 × 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>KMT-17</td>
<td>KMT-17</td>
<td>3.2 ± 0.4&lt;sup&gt;l&lt;/sup&gt; (n = 16)</td>
<td>4/10 (40)</td>
<td>&gt;240 × 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>i</sup> Irradiated tumor cells (5 × 10<sup>7</sup>) were inoculated i.p. for immunization. Two weeks after the first inoculation, the second inoculation was performed and was followed by the challenge of KMT-17 cells 2 weeks later.  
<sup>j</sup> Days for existence of tumor cells in ascites fluid (see "Materials and Methods").  
<sup>k</sup> Mean ± S.D.  
<sup>l</sup> Statistically significant by Student's t test (0.01 > p > 0.001).  
<sup>m</sup> Statistically not significant by Student's t test (0.1 > p > 0.05).
Thus, it may be suspected that the exposure time of TAA is too short for the induction of anti-TAA immunity. Furthermore, xenogenized tumor cells with a medium amount of VAA showed less TAA immunogenicity even in normal rats (Table 6). This is because an excessive amount of VAA may act as a competitive antigen to TAA (27). In VAA-presensitized hosts, the TAA immunogenicity of xenogenized tumor cells producing medium amount of VAA was not augmented. On the other hand, xenogenized tumor cells with a small amount of VAA were able to induce stronger resistance in VAA-presensitized rats (Table 6) as compared to immunization with nonxenogenized tumor cells, although antitumor resistance, in general, was induced more weakly in VAA-presensitized hosts than in normal hosts.

As a result of the above findings, it can be proposed that the middle grade of immune response induced by a medium amount of VAA in normal rats and by a relatively small amount of VAA in VAA-presensitized rats assists the induction of anti-TAA immune resistance. On the other hand, too strong a response to VAA accelerates the elimination of xenogenized tumor cells resulting in decreased immunogenicity of TAA.

The authors would like to emphasize that a newly induced antigen like VAA to xenogenized tumor cells can act either as a helper or as a competitive antigen for the induction of anti-TAA immune resistance. Modification of tumor cells with Con A was observed to augment anti-TAA immune resistance (10, 18, 19). Martin et al. (19) have reported that unmodified EL4 cells stimulate spleen cells more effectively in vitro than do Con A-modified EL4 cells when the responder spleen cells were sensitized with Con A-modified EL4 cells in vivo. Con A reactivity of responder spleen cells might interfere with the generation of effector cells to TAA. With regard to the presensitization of the hosts with modifying antigens, Lachman and Sikora (16) and Takatsu et al. (25) reported that purified protein derivative-modified tumor cells were more immunogenic in a host presensitized with Bacillus Calmette-Guerin. It has also been reported by Hamaoka et al. (7) that TNP-modified myeloma (TNP-X5563) cells were more immunogenic in syngeneic C3H/He mice presensitized with TNP-mouse gamma globulin. It may be considered that PPD or TNP is a haptenic antigen and does not induce immune response by itself. Although these haptenic antigens may not act as competitive antigens to TAA, it is necessary to induce reactive cells to

### Table 6

<table>
<thead>
<tr>
<th>Immunization</th>
<th>Lethal growth of KMT-17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cytoxic Normal rats</td>
</tr>
<tr>
<td>Tumor cells</td>
<td>index with anti-VAA serum</td>
</tr>
<tr>
<td>None</td>
<td>8/8</td>
</tr>
<tr>
<td>Xenogenized</td>
<td></td>
</tr>
<tr>
<td>FLV-KMT-17-P₁</td>
<td>0.15</td>
</tr>
<tr>
<td>FLV-KMT-17-P₂</td>
<td>0.40</td>
</tr>
<tr>
<td>FLV-KMT-17-P₃</td>
<td>0.54</td>
</tr>
<tr>
<td>FLV-KMT-17-P₄</td>
<td>0.84</td>
</tr>
<tr>
<td>Nonxenogenized KMT-17</td>
<td>0</td>
</tr>
</tbody>
</table>

* Irradiated (8000 rads) tumor cells (5 x 10⁷) were inoculated s.c., and KMT-17 cells were challenged s.c. 2 weeks after the inoculation.

### DISCUSSION

The results in this report indicate that TAA immunogenicity of xenogenized tumor cells with FLV is probably altered by the host immune responses to VAA produced on their cell surface. A secondary immunization with xenogenized tumor cells is less effective than that with nonxenogenized tumor cells especially in rats preimmunized with xenogenized tumor cells (Table 5). The survival time of xenogenized tumor cells in the peritoneal cavity is shorter in rats preimmunized with xenogenized tumor cells or virus-induced WLFT-6 cells, both of which are carrying VAA. Thus, it may be suspected that the exposure time of TAA is too short for the induction of anti-TAA immunity. Furthermore, xenogenized tumor cells producing a large amount of VAA showed (1.4 + 0.5 days) as compared with that of nonxenogenized tumor cells (7.0 + 0.9 days) in VAA-presensitized rats after i.p. immunization (data not shown). As indicated in Table 6, when normal rats were used, xenogenized tumor cells with a medium amount of VAA induced a stronger resistance to KMT-17, since the LTD₉₀ was >120 x 10⁴ and >270 x 10⁴ in rats immunized with FLV-KMT-17-P₃ and FLV-KMT-17-P₅, respectively. Xenogenized tumor cells with a smaller or larger amount of VAA (FLV-KMT-17-P₁ or FLV-KMT-17-P₄) induced weaker resistance than did nonxenogenized KMT-17. These results support our previous report indicating that only xenogenized tumor cells carrying a medium amount of VAA show augmented immunogenicity of TAA (27). When VAA-presensitized rats were used, however, xenogenized tumor cells with a small amount of VAA (FLV-KMT-17-P₁) produced the strongest resistance, while those with a medium amount of VAA (FLV-KMT-17-P₃ and FLV-KMT-17-P₅) showed a less immunizing effect. The immunogenicity of the line with a large amount of VAA (FLV-KMT-17-P₃) was not detected in VAA-presensitized rats. It was also observed that immunogenicity of KMT-17 cells was weaker in VAA-presensitized rats than in normal rats. These results indicate that immunogenicity of xenogenized tumor cells was affected not only by the amount of VAA but also by the host response to VAA.
them previously in order that the antigen might help the induction of antitumor resistance. On the other hand, strongly immunogenic antigens like VAA and Con A may help TAA-immunogenicity by themselves, while their superiority as antigens over the TAA in the presensitized host results in their being competitive antigens to TAA. This is especially important when considering the induction of a strong antitumor response to TAA by immunization with xenogenized tumor cells. Another consideration of the reason why a large amount of VAA is unable to augment the TAA immunogenicity is that a large amount of VAA might induce immunosuppressor cells which disturb immune responses to VAA on xenogenized tumor cells. This possibility is unlikely however, because xenogenized tumor cells are rejected more rapidly than are nonxenogenized tumor cells in rats presensitized with xenogenized tumor cells possessing a large amount of VAA (Table 3).

The feasibility of viable xenogenized tumor cells may be to prolong the antigen exposure time as a result of their temporary growth in the host. Moreover, VAA can help the host to recognize tumor cells. For the exhibition of the above advantage of xenogenized tumor cells, it is necessary to control the amount of VAA produced on the xenogenized tumor cells in order to avoid the too-strong responses of the host against VAA which shorten the exposure time of TAA.

REFERENCES


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