Quantitative Transplantation Assays of Spontaneous Tumors of the C3H Mouse as Allografts in Athymic NCr/Sed-ntu/nu Nude Mice and Isografts in C3Hf/Sed Mice

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ABSTRACT

Three spontaneous tumors of the C3H mouse have been used in a comparison of their transplantability and radiation response (local control) in syngeneic C3H/Sed mice and in allogeneic athymic NCr/Sed-ntu/nu nude mice. The tumors were: MCalV, a moderately well-differentiated mammary carcinoma; FSAll, a poorly differentiated fibrosarcoma; and SCCVII, a moderately well-differentiated squamous cell carcinoma. The tumors were studied as fourth to seventh generation transplants. Assays to determine the number of tumor cells that, on the average, transplant the tumor to half of the recipients or transplant sites (TDM) demonstrated that these 3 tumors transplanted into the s.c. tissue of the NCr/Sed-ntu/nu as readily as of C3Hf/Sed mice. The TDM for MCalV was slightly but significantly lower in 4-week-old NCr/Sed-ntu/nu mice which had received 6 Gy whole body irradiation (WBI) 24 h before transplantation, namely, 5.8 x 10^4 (95% confidence limits, 4.5-7.6) versus 7.8 x 10^4 (6.0-10.0). The 6-Gy WBI did not affect the TDM for 8-10-week-old mice. Similarly, the TDM for SCCVII was lower in 6-Gy WBI NCr/Sed-ntu/nu recipients (1.5 x 10^4 versus 3.9 x 10^4). The TDM for FSAll was not affected by 6-Gy WBI. Further, the TDM for FSAll following i.v. injection of tumor cells (transplant to lung) was the same for C3Hf/Sed and NCr/Sed-ntu/nu mice (this obtained for normal or 6-Gy WBI-treated subjects).

The radiation doses which on the average achieve control of half of the MCAlV, FSAll, and SCCVII tumors were lower, higher, and the same in NCr/Sed-ntu/nu than in C3Hf/Sed mice, respectively. The radiation doses which achieve control of half of the MCAlV and SCCVII tumors were not affected by 6-Gy WBI before transplantation.

INTRODUCTION

Xenografts of human tumors growing in athymic nude mice are used extensively in studies of the pathophysiology of human tumors and their response to various therapeutic strategies (1, 2). In investigations of the response of xenografts to localized radiation, concern has been raised as to the confounding effect of residual immune reactivity by the nude mouse against the xenograft (3). This constitutes a potential difficulty in analysis of results where the radiation dose is sufficient to effect local control of tumor. In that circumstance only a few cells survive the radiation treatment in some of the subjects, and a low level immune reaction against the tumor could affect the result to a significant degree. Experimental studies have shown that the radiation dose required to achieve complete and permanent regression of strongly immunogenic tumors is much lower for tumors growing in normal than in immunosuppressed hosts (4, 5). Further, the required dose increases with the severity of the immune suppression.

One of our research goals is to assess the relative radiation response of the reputedly highly radiation resistant human glioblastoma (6) versus the known radiation responsive human squamous cell carcinoma by using xenografts in nude mice. The experimental aim is to characterize radiobiologically these human tumor xenografts when treated at a constant size (and presumably clonogen number) and anatomic site by a standard radiation technique in one laboratory. Concurrently, cell lines from these tumors are to be evaluated radiobiologically in vitro with the use of single cells and spheroids. The end points for the in vivo studies are to be growth delay and local control. Before initiating the more complex and protracted studies on human tumor xenografts, we planned to evaluate the extent to which immune suppressive procedures could render the nude mouse immunologically blank. Namely, could the perturbing effect of the residual immune capacity of the nude mouse be abrogated and the response of the xenografted tumor be analyzed with minimal allowance for an antitumor immune reaction. For this part of the project, a series of assays have been performed of tumor transplantability and radiation response (local control), using 3 spontaneous tumors as syngeneic transplants in C3Hf/Sed mice or allogeneic transplants into normal or immune modified athymic nude mice.

MATERIALS AND METHODS

Experimental Assays. These experiments used assays which yield quantitative descriptions of the tumor transplantability, the TDM, and the response (local control) to radiation, the TCD50. The TCD50 is the number of tumor cells which would be expected on the average to transplant the tumor to half of the recipients or transplant sites (in assays where 4 sites were used per recipient). Similarly, the TCD50 is the radiation dose which on the average would be expected to achieve control of half of the tumors irradiated.

Experimental Animals. The mice used in this study were bred and maintained in our defined flora, pathogen-free mouse colony. The C3Hf/Sed mouse has been maintained in this colony for 16 years under continuous brother-sister mating. The history and designation of this line of mice has been described (7). The athymic NCr/Sed-ntu/nu nude mouse is a line of outbred Swiss mice which had the BALB/c nude gene inserted by backcross breeding technique. Our breeding stock of the NCr-ntu/nu and NCr-ntu/+ mice were generously provided by Dr. Carl Hansen of the National Cancer Institute and have been maintained in our colony for more than 25 generations. The athymic NCr/Sed-ntu/nu nude mouse has proven to be very healthy in this colony. We achieve a production index of 1.00 with nearly all the nude pups surviving. At age 4-10 weeks they are placed on experiment. The gross mortality incidences among the NCr/Sed-ntu/nu mice over 120 days in experiment, for causes other than tumors, were 1.5% and 11.6% in control and 6-Gy WBI mice (pooled data from 8 sets of experiments). For the C3Hf/Sed mice the losses were 1%. Further, the required dose increases with the severity of the immune suppression.

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2 The abbreviations used are: TDM, number of tumor cells on the average expected to transplant the tumor to half of the recipients or transplant sites; TCD50, radiation dose on the average expected to achieve control of half of the tumors irradiated; WBI, whole body irradiation.
suspensions of single cells. Suspensions of cells were prepared by a mechanical method. Cell viability was determined by trypan blue dye exclusion. For the T}_50 values, from one cell suspension, 2- to 4-fold dilutions were made and 4-10 animals were given injections of 0.1 ml suspension at each of 5-8 cell dose levels. This was performed at one session on both the C3Hf/Sed and NCr/Sed-nw/nu mice. Unless otherwise noted, equal numbers of male and female mice were used in an assay. For the T}_50 values, tumors were transplanted into the s.c. tissues of the right flank and more recently the right axilla, one site per animal. In the first assays, transplantation was made into the right and left axilla and flank (4 sites per animal, the same cell dose at each site in an individual mouse). The results from these assays were indicated in Tables 1-3. In these few assays, for any one animal, tumors were excised as they reached 8 mm until transplant take had been scored for 3 sites at the end of the experiment. In the T}_50 assays, transplantation was made in the right leg.

Radiation. Local radiation was administered on the day of the mean diameter of the tumor was 6 mm by using a specially designed 137Cs irradiator which features parallel opposed 3-cm diameter fields (9). The mice were anesthetized by an i.p. injection of sodium pentobarbital, 0.05 mg/g body weight. To avoid differences with respect to the comparative blood flow and tissue oxygen status between isografts and allografts, all irradiations of tumors were performed under conditions of clamp hypoxia (10). This assured that all of the cells in all of the tumors were hypoxic during the irradiation. The dose rate during the period of these assays was 7.5 Gy/min. Whole body irradiation was performed by using an standard AECL Gamma Cell Irradiator with parallel opposed 137Cs sources. Animals were irradiated in groups of 5. The dose rate was 0.9 Gy/min.

Immunization. Specific immunization against tumor was attempted by one of two procedures. First, 2 x 10^6 lethally irradiated cells (120 Gy) were injected at days 21, 14, and 7 before challenge with viable cells (11). For the first injection, the cells were admixed with complete Freund’s adjuvant and injected into each groin and axilla. On days -14 and -7, simple suspensions of 2 x 10^6 cells were injected i.p. This procedure was used unless otherwise indicated. Secondly, a transplanted tumor was allowed to grow to 6 mm in the leg; the leg was amputated and the T}_50 assay performed 7-10 days later.

End Points and Analysis of Results. For the T}_50 values, transplant take was scored when the tumor reached 10 mm. Tumor transplant take results were tabulated as a function of cell dose and a log regression line was fitted through the data (10); the T}_50 and its 95% confidence limits were then computed. The end point in the T}_50 assays was local control at 120 days (absence of palpable tumor). Mice with recurrent tumors were sacrificed at tumor size of 12 mm. All mice surviving at 120 days were sacrificed and subjected to necropsy examination for residual or metastatic tumor. Animals dying before day 120 with local control (e.g., distant metastases, lymphoma) were excluded from the analysis. The tumor control results at 120 days were tabulated, a log regression line was fitted, and the T}_50 value with 95% confidence limits was computed (10).

Statistical Methods. Ninety-five % confidence intervals were used to compare separate T}_50 or T}_50 data. When these overlapped, a standard Z test was used to discriminate statistically significant differences that may still exist.

RESULTS

MCAIV transplanted as readily into the allogeneic 4-week-old NCr/Sed-nu/nu mice as into the syngeneic C3Hf/Sed mice as shown by the data given in Table 1. For the 8-week-old mice the T}_50 was marginally higher in the NCr/Sed-nu/nu recipients. The T}_50 values in both the C3Hf/Sed and the NCr/Sed-nu/nu mice tended to be higher for transplantation into MCAIV immunized recipients (achieving significance in experiment 1 for the C3Hf/Sed mice) and lower in 6-Gy WBI recipients. We have examined further for an effect of 6-Gy WBI or immunization to modify the T}_50 in separate experiments (experiments 2 and 3). For transplantation of MCAIV into C3Hf/Sed mice, the T}_50 was significantly higher in preimmunized than in 6-Gy WBI animals (Z test; P < 0.05). However, neither of those T}_50 values differed from the T}_50 for control mice. In comparable, but separate, assays in NCr/Sed-nu/nu mice, there was no effect of 6-Gy WBI or preimmunization on acceptance of MCAIV transplants. In experiments performed in the mid-1960s, the T}_50 for MCAIV transplanted into C3Hf/He mice were modestly but significantly increased by prior immunization (5.0 x 10^4 to 13.3 x 10^4) (11). However, 4.7-Gy WBI did not affect transplantability into F_1 hybrid mice (12).

The T}_50 values for SCCVII were the same for syngeneic and allogeneic transplantation into normal recipients (Table 1). The T}_50 was marginally but significantly lower in 6-Gy WBI NCr/Sed-nu/nu mice.

The T}_50 for transplantation of FSAll into the s.c. tissue are also shown in Table 1; comparable values were obtained for syngeneic and allogeneic transplantation for the various experiments. The T}_50 in NCr/Sed-nu/nu mice was not modified by 6-Gy WBI or immunization.

In addition, for FSAll, T}_50 assays were performed by using i.v. (essentially transplantation to lung) injection of viable tumor cells. As shown by Table 2, the T}_50 were the same for i.v. injection of tumor cells (transplant to lung) into C3Hf/Sed and NCr/Sed-nu/nu mice. Whole body irradiation caused a significant (Z test, P < 0.05), lowering of T}_50 for both syngeneic and allogeneic transplantation. The numbers of tumor nodules at 13–14 days after i.v. injection of FSAll cells were the same in NCr/Sed-nu/nu and C3Hf/Sed mice at all cell doses used in both normal and 6-Gy WBI recipients in 2 of 3 experiments. In one experiment, the numbers of tumor nodules were lower in the NCr/Sed-nu/nu mice. In each of the 3 assays, the numbers of nodules in lungs were higher in the mice which had received 6-Gy WBI. The mean survival times after i.v. injection of FSAll cells were the same for the NCr/Sed-nu/nu and the C3H mice. The observed lower T}_50 values and higher number of tumor nodules in the 6-Gy WBI recipients is not proof that an immune rejection reaction had been suppressed. The phenomenon of greater transplantability in irradiated lung is well known and obtains with nonimmunogenic tumor systems (13).

The final group of experiments were assays of local control of 6-mm tumors as a function of radiation dose. The resultant T}_50 values are shown in Table 3. The T}_50 values were significantly lower for MCAIV when growing in normal or 6-Gy WBI NCr/Sed-nu/nu mice than in normal C3Hf/Sed mice as shown in two independent experiments. There was, however, no significant effect of the 6-Gy WBI to increase the T}_50. Local control of FSAll required significantly higher doses for allografts in the NCr/Sed-nu/nu mice than transplants in the syngeneic C3Hf/Sed mice. For SCCVII, the T}_50 values were the same for tumors in C3Hf/Sed and NCr/Sed-nu/nu mice. For both MCAIV and SCCVII, the T}_50 was unaffected by 6-Gy WBI 24 h before transplantation. This does not support an immune rejection reaction as responsible for T}_50 MCAIV transplants. In experiments performed in the mid-1960s, the T}_50 for MCAIV transplanted into C3Hf/He mice were modestly but significantly increased by prior immunization (5.0 x 10^4 to 13.3 x 10^4) (11). However, 4.7-Gy WBI did not affect transplantability into F_1 hybrid mice (12).

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3 Radiations were 250 kVp X-rays. Dose is expressed here in terms of 60Co Gy equivalent units, namely, doses in 250 kVp rads were multiplied by relative biological effectiveness factor of 1/0.85.
**DISCUSSION**

MCalV, FSaII, and SCCVII transplanted virtually as readily into the s.c. tissue of normal allogeneic athymic NCr/Sed-nu/nu nude mice as into syngeneic C3H mice. This was also true for transplantation to the lung for FSaII, using i.v. injection of tumor cells, using TCD50 values following i.v. injection of FSaII cells into C3Hf/Sed and NCr/Sed-nu/nu mice.

In conclusion, these results from quantitative tumor cell transplantation and radiation response (local control) assays using MCalV, FSaII, and SCCVII indicate only very small

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Table 1 TCD50 values for syngeneic and allogeneic transplantation of MCalV, FSaII, and SCCVII into the s.c. tissues of control, 6-Gy whole-body irradiated, or "immunized" recipients

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Recipient age (wk)</th>
<th>Status</th>
<th>C3Hf/Sed</th>
<th>NCr/Sed-nu/nu</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCalV</td>
<td>4</td>
<td>Control</td>
<td>11.0 x 10^6 (8.6-14.0)</td>
<td>7.8 x 10^6 (6.0-10.0)</td>
</tr>
<tr>
<td></td>
<td>6-Gy WBI</td>
<td>7.4 x 10^6 (4.7-12.0)</td>
<td>5.8 x 10^6 (4.5-7.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Control</td>
<td>7.1 x 10^6 (5.6-8.9)</td>
<td>10.1 x 10^6 (6.9-15.0)</td>
</tr>
<tr>
<td></td>
<td>Immune</td>
<td>24.0 x 10^6 (11.0-51.0)</td>
<td>14.0 x 10^6 (1.8-10.0)</td>
<td></td>
</tr>
<tr>
<td>2 and 3</td>
<td>8-10</td>
<td>Control</td>
<td>14.3 x 10^6 (8.4-24.4)</td>
<td>9.0 x 10^6 (4.2-19.3)</td>
</tr>
<tr>
<td></td>
<td>6-Gy WBI</td>
<td>11.8 x 10^6 (8.3-16.8)</td>
<td>11.2 x 10^6 (5.8-21.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immune</td>
<td>18.7 x 10^6 (13.3-26.2)</td>
<td>7.0 x 10^6 (2.9-16.7)</td>
<td></td>
</tr>
<tr>
<td>FSaII</td>
<td>4</td>
<td>Control</td>
<td>12.3 (5.3-28.5)</td>
<td>1.0 (0.5-2.0)</td>
</tr>
<tr>
<td></td>
<td>6-Gy WBI</td>
<td>2.6 (1.6-4.3)</td>
<td>2.0 (1.4-2.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immune</td>
<td>3.8 (2.1-6.8)</td>
<td>1.2 (0.8-1.6)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>Control</td>
<td>2.0 (1.4-2.8)</td>
<td>1.2 (0.8-1.6)</td>
</tr>
<tr>
<td></td>
<td>6-Gy WBI</td>
<td>1.3 (1.0-1.8)</td>
<td>1.5 (1.1-2.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCCVII 4</td>
<td>Control</td>
<td>3.0 x 10^6 (1.3-11.0)</td>
<td>3.9 x 10^6 (1.3-11.0)</td>
</tr>
<tr>
<td></td>
<td>6-Gy WBI</td>
<td>&gt;10^6 (10^-6)</td>
<td>1.5 x 10^6 (0.6-3.6)</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses, 95% confidence limits.

Table 2 FSaII tumor nodules in lung at 13–14 days, mean survival times, and TCD50 values following i.v. injection of FSaII cells into C3Hf/Sed and NCr/Sed-nu/nu mice

<table>
<thead>
<tr>
<th>No. of FSaII cells</th>
<th>C3Hf/Sed</th>
<th>NCr/Sed-nu/nu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>6-Gy WBI</td>
</tr>
<tr>
<td>Mean no. of tumor nodules in lungs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experiment 1 4 x 10^4</td>
<td>50.4 ± 18.8</td>
<td>67.5 ± 37.6</td>
</tr>
<tr>
<td>16 x 10^4</td>
<td>98.2 ± 65.5</td>
<td>127 ± 31.0</td>
</tr>
<tr>
<td>Experiment 2 4 x 10^4</td>
<td>1.8 ± 1.3</td>
<td>3.4 ± 1.4</td>
</tr>
<tr>
<td>16 x 10^4</td>
<td>5.0 ± 3.8</td>
<td>12.9 ± 8.0</td>
</tr>
<tr>
<td>Experiment 3 16 x 10^4</td>
<td>35.3 ± 12.7</td>
<td>47.5 ± 12.5</td>
</tr>
</tbody>
</table>

Mean survival times (days)

| Experiment 2 16 x 10^4 | 27.0 | 20.0 | 25.0 | 24.0 |
| 4 x 10^4 | 21.0 | 16.9 | 16.4 | 18.0 |

TCD50 values

| Experiment 4 | 16.5 | 5.1 | 18.5 | 6.3 |
| (7.9-34.5) | (2.4-10.4) | (61-56.3) | (3.5-11.4) |

* Numbers in parentheses, 95% confidence limits.

* One standard deviation.

Table 3 TCD50 values for 6-mm diameter isotransplants and allotransplants of MCalV, FSaII, and SCCVII treated by single doses under clamp hypoxia

<table>
<thead>
<tr>
<th>Tumor</th>
<th>C3Hf/Sed</th>
<th>NCr/Sed-nu/nu (6-Gy WBI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCalV</td>
<td>70.1 (66.9-73.4)</td>
<td>58.6 (52.2-65.7)</td>
</tr>
<tr>
<td></td>
<td>65.9 (64.5-67.3)</td>
<td>62.5 (59.6-65.4)</td>
</tr>
<tr>
<td></td>
<td>67.6 (66.0-69.2)</td>
<td>61.5 (58.6-64.5)</td>
</tr>
<tr>
<td></td>
<td>70.3 (65.3-75.6)</td>
<td>83.6 (79.2-88.2)</td>
</tr>
<tr>
<td></td>
<td>72.2 (69.4-75.1)</td>
<td>87.0 (75.9-89.0)</td>
</tr>
<tr>
<td></td>
<td>77.6 (74.5-80.4)</td>
<td>82.5 (80.1-84.9)</td>
</tr>
<tr>
<td></td>
<td>66.6 (63.8-69.5)</td>
<td>64.7 (51.1-81.9)</td>
</tr>
<tr>
<td></td>
<td>74.1 (71.6-76.6)</td>
<td>71.3 (66.6-76.3)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, 95% confidence limits.

The TCD50 value would be expected to decrease with effectiveness of the host immune rejection reaction to the tumor. In these experiments, the TCD50 values for MCalV, FSaII, and SCCVII growing in NCr/Sed-nu/nu mice were lower, higher, and the same, respectively, than for these three tumors growing in the syngeneic C3Hf/Sed hosts. There is no basis for expecting a higher TCD50 for a spontaneous tumor growing in allogeneic nude mice than in syngeneic mice as was found for FSaII in repeat experiments. The TCD50 values for MCalV were 10% lower (P < 0.05) when growing in NCr/Sed-nu/nu mice. If that lesser TCD50 reflected an active immune rejection reaction participating in tumor eradication, a higher TCD50 would have been expected for MCalV transplanted into 6-Gy WBI mice. This was not found. Similarly, 6-Gy WBI had no effect on the TCD50 for SCCVII in NCr/Sed-nu/nu mice. As noted earlier, 6-Gy WBI was associated with a lower TCD50 in NCr/Sed-nu/nu mice for SCCVII but not for MCalV. These observed differences in TCD50 values for syngeneic and allogeneic transplantation may reflect limitations in the experimental assays and/or be due in part to unknown differences in number of clonogens in tumors measured to be 6 mm growing in the normal and the nude mice.

In conclusion, these results from quantitative tumor cell transplantation and radiation response (local control) assays using MCalV, FSaII, and SCCVII indicate only very small
differences between the syngeneic C3Hf/Sed and allogeneic NCr/Sed-"nu/"nu mice. Reports from other laboratories have clearly shown that xenografting of human tumor into nude mice is facilitated by whole body irradiation, antiserum to natural killer cells, etc. (14, 15). We interpret our present findings as showing that the histocompatibility differences between tumors of the C3H mouse and the NCr/Sed-"nu/"nu mice are not sufficient for the planned research; namely, to assay for changes in immune reactivity following various immune suppressive procedures designed to render the nude mouse essentially immunologically blank to challenge by human tumor xenografts. This assumes that our nude mice would react immunologically against a human tumor xenograft. To test this, experiments need to be performed that use stronger histocompatibility differences between tumor and nude mouse recipient than obtains for these allografted tumors. Studies are planned using xenografts of rat and human tumors transplanted into normal and immune-modified athymic nude mice.

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