Differences in the Effects of Host Suppression on the Adoptive Immunotherapy of Subcutaneous and Visceral Tumors

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ABSTRACT

A syngeneic transplantable sarcoma induced in C57BL/6 mice, MCA 105, was used in studies to examine host suppression on the adoptive immunotherapy of established intradermal and experimentally induced pulmonary and hepatic metastases. Fresh immune splenocytes were generated from mice immunized to the MCA 105 tumor by a mixture of viable tumor cells and Corynebacterium parvum. The adoptive immunotherapy of intradermal MCA 105 tumor with immune cells required prior immunosuppression of the recipient by sublethal irradiation with 500 R or T-cell depletion. The effect of whole-body sublethal irradiation appeared to eliminate a systemic host suppression mechanism, since partial-body irradiation involving the tumor-bearing area did not permit successful immunotherapy. Host irradiation was not required to achieve successful immunotherapy of experimentally induced pulmonary or hepatic metastases. In nonirradiated recipients bearing both intradermal and pulmonary tumors, host suppression did not affect the function of transferred immune cells to induce regression of pulmonary metastases. Thus, suppression of adoptive immunotherapy appears to be relevant to tumors confined to the skin and subcutaneous tissue but not to tumors in visceral sites, such as the lung and liver.

INTRODUCTION

Experimental data accumulated in several independent laboratories support the concept that one of the major obstacles for successful cellular immunotherapy is the occurrence of host suppression (1-4). Regression of established tumor by the systemic transfer of immune cells requires the elimination of suppressor cells in the recipient by T-cell depletion, treatment with cyclophosphamide, or sublethal irradiation (5, 6). The presence of host suppressor T-cells was elegantly demonstrated by the transfer of T-cells from tumor-bearing animals which abrogated the antitumor effects of specifically sensitized cells (5). Mice exposed to UV light have been shown to generate suppressor T-cells which interfere with the rejection of highly antigenic UV-induced skin tumors (7, 8). However, these reports of host suppression include only tumors inoculated s.c. or i.d.

The function of host suppression has not been examined in animals with visceral tumors that do not involve skin. In this paper we confirmed that there was a suppression mechanism generated in a host bearing a weakly immunogenic intradermal tumor newly established in our laboratory. This suppression mechanism can be overcome by host T-cell depletion or sublethal irradiation, and it allowed successful therapy with sensitized T-cells. However, with the same tumor, adoptive immunotherapy of experimentally induced pulmonary or hepatic metastases with immune cells was not subject to this radiosensitive suppression mechanism. Furthermore, the presence of an intradermal tumor in a nonirradiated recipient did not interfere with the regression of pulmonary metastases following the transfer of immune cells. Concomitantly, the intradermal tumor was refractory to the immunotherapy. These observations suggest that the function of host-derived suppression to adoptive immunotherapy is not a systemic phenomenon; rather, it is confined to tumors growing at selected histological locations.

MATERIALS AND METHODS

Mice. Female C57BL/6 mice, 8 to 12 wk old, obtained from the Jackson Laboratory, Bar Harbor, ME, or the Animal Production Colonies of the NIH, Bethesda, MD, were used for all experiments. Caged in groups of 6 or fewer, the animals were fed NIH laboratory chow and given water ad libitum.

Immunization. MCA 105 and 106 are methylcholanthrene-induced sarcomas of C57BL/6 origin (9). They were maintained in vivo in syngeneic animals by serial subcutaneous transplantations of cryopreserved tumor samples. The MCA 105 and 106 tumors used for the current study were in the second to the fifth transplantation generation.

Single cell suspensions were prepared from solid tumors by digestion with a mixture of DNase, collagenase, and hyaluronidase as previously described (9). Mice were immunized against the MCA 105 and MCA 106 sarcomas by giving them injections i.d. of 1.5 x 10⁶ tumor cells admixed with 100 μg of formalin-killed Corynebacterium parvum (Burroughs Wellcome Co., Research Triangle Park, NC). This procedure resulted in a brief period of tumor growth and then complete regression in about 70 to 80% of animals. Mice free of tumor at 3 to 4 wk were challenged i.d. with 2 x 10⁵ and 10⁶ viable tumor cells consecutively within 3 wk. Immune spleens were obtained from animals 2 to 4 wk after the last challenge.

Animal Irradiation. Mice were given 500 R of whole-body irradiation from a 137Cs source (Gammacell 40; Atomic Energy of Canada, Limited). Partial-body irradiation required anesthetizing mice with pentobarbital i.p. (Somnifer; Richmond Veterinary Supply Co., Richmond, VA) and shielding the upper or lower half of the body with lead. X-irradiation of 500 R was then given (RT 250; Philips Medical Systems, Inc., Alexandria, VA); mice requiring whole-body irradiation in these experiments received it from the same source.

Preparation of ATXBMMice. Adult C57BL/6 mice were converted to ATXBM mice by thymectomy at 8 wk of age followed, 1 to 2 wk later, with lethal (900 R) whole-body irradiation. Within 1 h of irradiation, mice were infused with 3 x 10⁶ syngeneic bone marrow cells that had been treated with Thy-1.2 monoclonal antibody (New England Nuclear, Boston, MA) and complement (Low-tox-M rabbit complement; Accurate Chemical and Scientific Corporation, Westbury, NY). Mice were used as recipients for adoptive immunotherapy within 4 wk after irradiation.

Adoptive Immunotherapy of Intradermal Tumor. C57BL/6 mice were sublethally irradiated (500 R), and 2 to 4 h later, 2 x 10⁵ viable MCA 105 tumor cells in 0.05 ml of HBSS were given i.d. to each animal in the ventral skin. On Day 3, when tumors were palpable, freshly prepared spleen cells were transferred i.v. through the tail vein to each mouse. Tumor size was monitored by measuring perpendicular diameters with a vernier caliper every 3 to 4 days for up to 4 wk. Size was recorded as the average of perpendicular measurements and presented in mm as the mean of a group. Animals cured of tumor were observed for up to 3 mo for evidence of recurrent disease and recorded as the fraction of mice that showed progressively growing tumors.

Adoptive Immunotherapy of Experimentally Induced Pulmonary and Hepatic Metastases. C57BL/6 mice were inoculated with 3 x 10⁶ MCA 105 or 4 x 10⁶ MCA 106 i.v. to establish pulmonary metastases. On Day 3, when growing tumor metastases were evident on histological...
sections of lung, mice were treated by the i.v. injection of immune splenocytes. On Day 15 mice were sacrificed, and the lungs were insufflated with a 15% India ink solution (Higgins Black 4417; A. W. Faber-Castell, Newark, NJ) and bleached in Fekete’s solution (10). Pulmonary nodules on the lung surface were then counted. Lungs with nodules that were too numerous to count were scored as 250.

Hepatic metastases were induced as described previously (11). Briefly, C57BL/6 mice were anesthetized with an i.p. injection of pentobarbital. The spleen was exposed, and its short gastric vessels along with the gastrosplenic ligament were cut allowing the spleen to be flushed into the portal circulation. The splenic pedicle was then clipped and the spleen removed. The abdominal wall musculature and skin were then closed in one layer. By Day 3 after the tumor injection, micrometastases were apparent histologically, and splenocytes were transferred i.v. On Day 14, the mice were given a tail vein injection of 15% India ink solution, and isolated livers were bleached in Fekete’s solution. Hepatic nodules were then counted. Livers with nodules that were too numerous to count were scored as 250.

In all adoptive immunotherapy experiments reported in this study, the mice were ear tagged and randomized following the last treatment. All tumor measurements and tumor nodule enumerations were made by investigators who had no knowledge of the experimental protocol.

RESULTS

Systemic Immunosuppression of the Host Required for Successful Adoptive Immunotherapy of i.d. Tumor. In 3 independent experiments (Fig. 1), successful adoptive immunotherapy of i.d.-inoculated tumors required immunosuppression of the host by ATXBM (Experiment 1) or sublethal irradiation with 500 R (Experiments 2 and 3). In all 3 experiments, mice received $10^8$ immune cells which are approximately the equivalent of one whole spleen from an immune animal. The requirement for immunosuppression was examined at supraoptimal doses of immune cells in the nonirradiated host (Fig. 2). In this experiment a dose titration of immune cells was performed in irradiated and nonirradiated mice bearing i.d.-inoculated tumors. In irradiated mice a dose as low as $1.25 \times 10^7$ immune cells was capable of causing i.d. tumor to regress. In nonirradiated mice a dose of $3 \times 10^8$ immune cells (3 splenic equivalents) did not induce tumor regression and represented a 24-fold increase of the effective therapeutic dose seen in irradiated animals.

In order to ascertain whether the irradiation had a local influence on the i.d. tumor or if it was a systemic effect on the host, experiments designed to administer irradiation to the upper or lower half of the body were performed (Table 1). In both experiments intradermal tumor was inoculated in the lower half of the body. Whole-body irradiation performed prior to tumor injection was required for tumor rejection after the adoptive transfer of immune cells. However, irradiation confined to the lower or upper half of the host did not result in successful adoptive therapy. Therefore, a systemic immunosuppression achieved with whole-body irradiation of the host was required for the successful therapy of i.d. tumor with immune cells, and local effects of irradiation did not appear to play a role in the therapeutic response.

Whole-Body Irradiation Not Required for the Adoptive Immunotherapy of Experimentally Induced Pulmonary Metastases. Two separate experiments were performed to determine if whole-body irradiation was necessary to obtain successful immunotherapy of established pulmonary metastases. Table 2 demonstrates that the adoptive transfer of immune cells was capable of causing significant regression of established 3-day MCA 105 pulmonary metastases in both nonirradiated and irradiated hosts. A dose-response relationship was generally seen between the number of immune cells transferred and the reduction of pulmonary metastases in the nonirradiated and irradiated recipients. The data in Experiment 1 suggest that host irradiation enhanced the antitumor effect of immune cells at lower doses compared to the nonirradiated host. This finding was not corroborated in Experiment 2. Whole-body irradiation

![Fig. 1. Adaptive immunotherapy of intradermal MCA 105 tumor. Two $10^8$ tumor cells were inoculated i.d. into ATXBM mice (Experiment 1) or 500 R sublethally irradiated (Irrad.) mice (Experiments 2 and 3) on Day 0. One $10^8$ immune or normal cells were transferred i.v. on Day 3. The fraction of mice that had progressively growing tumors is shown for each group. Immunosuppression was required for successful adoptive immunotherapy of i.d. tumor.](image)

![Fig. 2. Dose titration of immune cells in the immunotherapy of i.d. MCA 105 tumor. Two $10^6$ tumor cells were inoculated i.d. into irradiated (right) and nonirradiated (left) mice. Lymphoid cells were transferred i.v. on Day 3. The fraction of mice that had progressively growing tumors is shown for each group. In the nonirradiated host, a supraoptimal dose of immune cells ($3 \times 10^6$) was ineffective and represented a 24-fold increase in the effective therapeutic dose seen in the irradiated host.](image)

### Table 1 Half-body irradiation of intradermal tumor and nonsuccessful tumor regression after adoptive immunotherapy

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Site of irradiation</th>
<th>Tumor progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>6/6</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>Upper body</td>
<td>6/6</td>
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<tr>
<td></td>
<td>Lower body</td>
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<tr>
<td>2</td>
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<td>0/4</td>
</tr>
<tr>
<td></td>
<td>Lower body</td>
<td>6/6</td>
</tr>
</tbody>
</table>

* Two $10^6$ MCA 105 cells i.d. on Day 0 in lower half of abdomen. Adoptive transfer on Day 3 of $7 \times 10^7$ immune cells and $8 \times 10^8$ immune cells in Experiments 1 and 2, respectively.

*A total of 500 R delivered to whole, upper, or lower body prior to tumor inoculation.*
SUPPRESSION OF ADOPTIVE IMMUNOTHERAPY

Table 2 Whole-body irradiation unnecessary for the successful adoptive immunotherapy of experimental MCA 105 pulmonary metastases (3 x 10^6 MCA 105 cells administered i.v. on Day 0)

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Source of cells transferred</th>
<th>No. of cells transferred</th>
<th>Pulmonary metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>HBSS</td>
<td>6 x 10^7</td>
<td>49 ± 17 (5)</td>
</tr>
<tr>
<td></td>
<td>Normal spleen</td>
<td>6 x 10^7</td>
<td>21 ± 13 (5)</td>
</tr>
<tr>
<td></td>
<td>Immune</td>
<td>3 x 10^7</td>
<td>14 ± 8 (5)</td>
</tr>
<tr>
<td>2</td>
<td>HBSS</td>
<td>6 x 10^7</td>
<td>21 ± 13 (5)</td>
</tr>
<tr>
<td></td>
<td>Normal spleen</td>
<td>6 x 10^7</td>
<td>14 ± 8 (5)</td>
</tr>
</tbody>
</table>

* Adoptive transfer given i.v. on Day 3.
+ Whole-body irradiation (500 R) administered on Day 0 prior to tumor injection.
' Mean ± SE.
" Numbers in parentheses, number.

Table 3 Specificity of adoptive immunotherapy of experimental MCA 105 and MCA 106 pulmonary metastases

<table>
<thead>
<tr>
<th>Tumor injected</th>
<th>Cells transferred</th>
<th>Pulmonary metastases</th>
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</thead>
<tbody>
<tr>
<td>MCA 105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal spleen</td>
<td>150 ± 14 (6)</td>
<td>162 ± 18 (6)</td>
</tr>
<tr>
<td>Immune</td>
<td>109 ± 14 (6)</td>
<td>119 ± 15 (6)</td>
</tr>
<tr>
<td>MCA 106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal spleen</td>
<td>153 ± 9 (6)</td>
<td>153 ± 21 (6)</td>
</tr>
<tr>
<td>Immune</td>
<td>147 ± 20 (5)</td>
<td>147 ± 20 (5)</td>
</tr>
<tr>
<td>MCA 106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal spleen</td>
<td>36 ± 12 (6)</td>
<td>36 ± 12 (6)</td>
</tr>
</tbody>
</table>

* Normal C57BL/6 mice were given injections i.v. of either 3 x 10^6 MCA 105 or 4 x 10^6 MCA 106 on Day 0.
+ Adoptive transfer of 3 x 10^6 cells was performed on Day 3.
' Mean ± SE.
" Numbers in parentheses, number.

Whole-Body Irradiation Not Required for the Adoptive Immunotherapy of Experimentally Induced Hepatic Metastases. The lung represents the first capillary bed exposed to transferred cells given i.v. In order to examine the efficacy of immune cells in another organ system beyond the first capillary bed of the lung, adoptive immunotherapy of experimentally induced hepatic metastases was performed in 2 separate experiments. Immune cells were transferred into nonirradiated and irradiated mice bearing 3-day-old hepatic metastases (Table 4). In both experiments immune cells were capable of causing significant regression of established hepatic metastases in nonirradiated and irradiated animals. A dose-response relationship was seen between the number of immune cells transferred and the reduction of hepatic metastases. As was observed in the treatment of pulmonary metastases, irradiation appeared to enhance the antitumor effect of immune cells at a lower dose compared to the nonirradiated host (Experiment 1). This finding was not evident in a repeat experiment. Whole-body irradiation was not required for the successful immunotherapy of MCA 105 hepatic metastases.

Intradermal Tumor and Nonsuppression of the Regression of Pulmonary Metastases by Immune Cells. Lack of suppressive mechanisms in the adoptive immunotherapy of established pulmonary and hepatic metastases could be due to the failure of metastatic tumors in visceral organs to induce host suppression. An experiment was performed to elucidate whether the suppressive mechanism induced by intradermal tumor affected the regression of pulmonary metastases by immune cells (Fig. 3). Nonirradiated and irradiated mice were simultaneously inoculated with i.v. and i.d. MCA 105. On day 3, adoptive therapy was performed, and on Day 15 half of the mice were sacrificed, and pulmonary metastases were enumerated (5 mice/group). The other half of the animals were followed for growth or regression of i.d. tumor (4 to 5 mice/group). This latter half of the experiment confirmed that the immune cells were capable of causing rejection of i.d. tumor in irradiated but not nonirradiated hosts (Fig. 3A). Irradiated mice followed for i.d. tumor growth who received normal or no cells died of progressive tumor after Day 15, prior to the next tumor measurement on Day 18. Despite the presence of progressively growing dermal tumors in nonirradiated animals, mice receiving immune cells demonstrated a statistically significant reduction in numbers of pulmonary metastases compared to animals given normal cells (P<0.05, Wilcoxon rank sum test). The presence of established growing i.d. tumor did not inhibit the ability of the transferred immune cells to mediate a reduction in the number of pulmonary metastases.

DISCUSSION

One of the problems intrinsic to successful antitumor therapy by the adoptive transfer of immune cells has been the adverse host response to the growing tumor that interferes with the function of the transferred cells. Experimental evidence of the generation of a functional suppressor cell population has been reported by several investigators (1-4). The ability of these suppressor cells to inhibit antitumor immunity has been dem-
SUPPRESSION OF ADOPTIVE IMMUNOTHERAPY

Fig. 3. Adoptive immunotherapy of mice inoculated with both i.v. and i.d. tumor. Irradiated and nonirradiated mice were inoculated with $2 \times 10^8$ MCA 105 cells i.d. and $3 \times 10^6$ MCA 105 cells i.v. on Day 0. Adoptive immunotherapy with $6 \times 10^7$ cells per animal was performed on Day 3. In A, tumor growth i.d. was serially measured, and only irradiated mice had regression of tumor after the transfer of immune cells. In B, the number of pulmonary metastases (METS) was enumerated on Day 15. Columns, mean of 5 animals per group; bars, SE. Both irradiated and nonirradiated mice had regression of pulmonary metastases after the transfer of immune cells.

Demonstrated in studies where suppression was transferred to a secondary host. Fujimoto et al. documented that the i.v. transfer of T-cells from tumor-bearing animals abrogated the rejection of a tumor challenge in mice that had been immunized to a methylcholanthrene-induced tumor (2). North and coworkers have reported that suppressor T-cells from tumor-bearing mice will interfere with the regression of established tumor after the passive transfer of immunized T-cells (5). In order to obtain regression of established tumors by transferred immune T-cells, North and coworkers have indicated that immune suppression of the host is necessary to eliminate the generation of suppressor cells (6). Therefore, tumor-induced suppression has been considered a potential problem in the immunotherapeutic approach to cancer. However, in all previously published reports, the tumors that were under the influence of suppression mechanisms were inoculated i.d. or s.c. In this paper we have found that cellular immunotherapy of tumors established at pulmonary and hepatic sites was not subject to the suppression that normally functions with growing dermal or subcutaneous tumors.

We utilized the MCA 105 tumor which is a weakly immunogenic methylcholanthrene-induced tumor induced and characterized in our laboratory (9). The MCA 105 fails to elicit immunity to reject a $10^6$ tumor challenge by the classical immunization protocol of tumor growth and excision. The advantages of using this newly induced tumor have been discussed previously (9, 13). The adoptive transfer of tumor immune splenocytes results in the specific regression of established i.d. tumor, provided the host had been immunosuppressed by whole-body irradiation or made T-cell deficient prior to immune cell transfer. These findings confirm the presence of a radiosensitive suppression mechanism in the recipient mouse which interfered with the function of transferred immune cells (Fig. 1). These findings appear to be in accordance with the hypothesis of North et al. that the growth of immunogenic tumors (i.e., Meth A, P815) induces the generation of suppressor T-cells in the host (5). In 3 experiments, utilizing the same protocol described by North, a transfer of $1.5 \times 10^8$ splenocytes from animals bearing 14- to 28-day subcutaneous tumors failed to inhibit the antitumor activity of transferred immune cells (data not shown). Since the MCA 105 tumor is weakly immunogenic, quantitative differences in the generation or expression of suppressor cell activity compared to highly immunogenic tumors may exist. Alternatively, a different suppression mechanism is operating in the MCA 105 tumor model. The interpretation of the requirement for irradiation may not be confined to immunosuppression of the host. Mule et al. described the selective localization of long-lived lymphocytes to subcutaneous tumor implants only after sublethal irradiation of the host (14).

Experimentally induced pulmonary and hepatic micrometastases established by i.v. or intrasplenic inoculation of MCA 105 were originally designed for evaluating the antitumor efficacy of LAK cells and IL-2 in our laboratory (11, 15). Immunosuppression of the host is not required to obtain significant regression of pulmonary and hepatic micrometastases with LAK cells and IL-2 therapy. In the present study, we found that, similar to immunotherapy with LAK and IL-2, these tumors will regress with the transfer of specifically sensitized cells in nonirradiated recipients. The data in Tables 2 and 4 suggested that host irradiation resulted in an enhanced reduction of pulmonary and hepatic metastases at lower doses of immune cells compared to nonirradiated hosts. This was a minor quantitative effect which might be attributed to a radiosensitive suppression effect induced by the tumor. However, this effect could not be reliably reproduced. Also, this possibility would be extremely unlikely, since it would indicate that a minor increase in the immune cell dose could overcome a suppression effect. As was demonstrated in the intradermal tumor model, excessively large doses of immune cells did not result in regression of tumor in the nonirradiated host.

Another difference between the i.d. and i.v. tumor models may be tumor size. Adoptive transfer of cells was performed on Day 3 after tumor inoculation when the i.d. tumors were approximately 1 to 3 mm in diameter. By contrast, 3-day-old metastases in the lung and liver were microscopic in size. However, significant regression of 7-day-old multiple, macroscopic pulmonary tumors, whose aggregate size was larger than a 3-mm i.d. tumor, can be obtained in nonirradiated hosts given immune cells (data not shown). Therefore, tumor size does not affect the induction of host-derived suppression to adoptive immunotherapy.

Unlike i.d. tumor, the establishment of pulmonary or hepatic tumor did not lead to the suppression of the action of transferred immune cells. While these observations may reflect the inability of pulmonary or hepatic tumors to induce suppression, it is more likely that these tumors are not subject to host-derived, radiosensitive suppression. To further elucidate this possibility, an experiment utilizing nonirradiated hosts bearing both established intradermal tumor and pulmonary metastases revealed that immune cells were capable of causing pulmonary tumors to regress, while dermal tumor growth in the same mouse was refractory to the transferred cells. In irradiated mice, tumors at both sites were susceptible to therapy with transferred cells. The results of this type of experiment ruled out the
possibility that pulmonary and hepatic metastases did not simply fail to induce suppression, although Malave et al. demonstrated that there are differences in suppressor cell induction between subcutaneous and footpad inoculation of tumor (16). Local factors such as lymphatic drainage, local angiogenesis, temperature, and lymphocyte trapping of the tumor have been postulated to play a role in the immunoregulatory mechanisms activated by a tumor. Our findings may relate to the different homing and migration patterns of immune cells to extravascular i.d. tumor sites compared to tumor sites in vascularized organs. Tumors in well-vascularized organs may not be as restrictive to the migration of immune cells as compared to intradermal/subcutaneous tumors. Indeed, Tilney et al. reported that non-irradiated hosts bearing vascularized cardiac allografts demonstrate preferential localization of immune cells to the allografts (17).

The lack of host suppression in the adoptive immunotherapy of visceral metastases was not confined to the MCA 105 tumor. Experimentally induced pulmonary metastases of another antigenically distinct tumor, MCA 106, were found to regress after the transfer of specifically sensitized cells in nonirradiated hosts. By contrast, we have previously shown that the adoptive cellular therapy of intradermal MCA 106 required host irradiation prior to tumor inoculation (9).

One of the most challenging problems in the treatment of the cancer patient is the control of metastatic disease. The lung and liver are the two most common organ sites where metastases develop (18). Our findings of the lack of suppression of adoptive immunotherapy against established pulmonary and hepatic metastases may have significant clinical implications in developing effective approaches to the immunotherapy of cancer.

REFERENCES

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