T-CELL-MEDIATED SUPPRESSION OF ANTI-TUMOR IMMUNITY

An Explanation for Progressive Growth of an Immunogenic Tumor*

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A central problem in tumor immunology is to explain why immunogenic tumors grow progressively in their immunocompetent syngeneic hosts. Attempts to explain this paradox have included suggestions that (*a*) the weakness of tumor transplantation antigens allows tumors to sneak through immune surveillance (1); (*b*) tumor cells are capable of hiding their surface antigens from immune effector mechanisms by a process known as antigenic modulation (2, 3); (*c*) tumors induce the generation of soluble antibody-dependent blocking factors that specifically block the cytotoxicity of effector lymphocytes (4); and (*d*) tumor growth favors the generation of suppressor T cells (5–13).

The paradox of progressive growth of immunogenic tumors is well illustrated by examples of concomitant anti-tumor immunity, in which a host with a progressive tumor can specifically suppress the growth of cells of the same tumor implanted at a distant site (14). It has been documented, moreover, that concomitant immunity to some tumors undergoes progressive decay after the primary tumors reach a certain critical size (14–20). Indeed, a recent study in this laboratory (21, 22) of the T-cell-mediated nature of endotoxin-induced tumor regression revealed that concomitant immunity generated against one of the tumors under study, the chemically induced Meth A fibrosarcoma, underwent a process of rapid decay very soon after it was generated. It was further shown that the onset of decay of concomitant immunity was coincident with the onset of refractoriness of this tumor to endotoxin-induced regression. The possibility was revealed, therefore, that a suppressor mechanism causes the loss of concomitant immunity to the Meth A fibrosarcoma, and that the same mechanism is responsible for causing this tumor to lose its susceptibility to endotoxin immunotherapy.

The purpose of this paper is to provide evidence consistent with the hypothesis that concomitant immunity to the Meth A fibrosarcoma decays as a result of the generation of a mechanism of T-cell-mediated immunosuppression. Two main findings are presented. First, that it is possible to cause the complete regression of large established tumors by intravenous infusion of sensitized T cells from immune donors, but only if the tumors are growing in thymectomized T-cell-deficient recipients. Second, that the

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adoptive T-cell-mediated regression of established tumors in T-cell-deficient recipients can be inhibited by an infusion of splenic T cells from T-cell-intact, tumor-bearing donors that have lost their concomitant immunity. These and other findings suggest that failure of the immune system to reject this immunogenic tumor is the result of the generation of suppressor T cells.

Materials and Methods

Mice. CB6 (BALB/c × C57BL/6)F_1 mice of either sex were used when they were between 8 and 10 wk of age. They were produced and reared under barrier-sustained conditions in the Trudeau Institute Animal Breeding Facility from caesarean-derived, conventionalized parental BALB/c and C57BL/6 breeding stock originally obtained from The Jackson Laboratory, Bar Harbor, Maine. All mice were shown to be free of known infectious viruses, including lactic dehydrogenase virus.

Tumors. The methylcholanthrene-induced Meth A fibrosarcoma syngeneic in BALB/c mice was originally obtained from Dr. Lloyd J. Old of the Memorial Sloan-Kettering Cancer Center, New York. This tumor possesses a distinct surface transplantation antigen that has been serologically defined (23). It was obtained in the ascites form, and grown in culture in Fischer's medium (Grand Island Biological Co., Grand Island, N. Y.) for several weeks before being grown again in the ascites form in syngeneic BALB/c mice. Tumor cells thus grown were dispensed into a large number of small vials, biofrozen in Fischer's medium that contained 20% fetal bovine serum and 20% dimethylsulfoxide, and cryopreserved over liquid nitrogen. Before each experiment, a vial was thawed and the cells washed in phosphate-buffered saline (PBS),[1] and grown intraperitoneally in semisyngeneic CB6 mice. The cells were harvested from CB6 mice, washed in PBS, and resuspended appropriately in PBS for implantation, either intradermally in the belly region or subcutaneously in the plantar region of the right-hind footpad. Intradermal tumor growth was measured by excising and weighing the tumors of five mice at the times indicated. Footpad tumor growth was monitored by measuring changes against time in the dorsoventral thickness of the footpad with dial calipers.

The SA-1 fibrosarcoma syngeneic in A/J mice was used as an allograft. It was grown in vitro and passaged in A/J mice in the same way as described for the Meth A.

T-Cell-deficient Mice. Mice were made T-cell deficient by thymectomy (THXB) at 3 wk of age followed 7 d later by 900 rads of whole-body gamma irradiation delivered from a cesium-137 irradiator at a midphantom dose rate of 35.5 rads/min. They were infused with 10^6 syngeneic bone marrow cells within 2 h of irradiation and employed in experiments after a further 4–5 wk.

Adoptive Immunization. The donors of tumor-sensitized T cells were mice that had been made specifically immune to a Meth A challenge implant by causing their 6-d intradermal tumors to completely regress by intravenous infusion of 50 μg of endotoxin (21). Their spleens were removed 10 d after tumor regression, diced into small pieces, and gently pushed through a 200-mesh stainless steel screen into PBS that contained 1% heat-inactivated fetal bovine serum. The suspension was triturated with a Pasteur pipette to break up clumps, and passed through six layers of sterilized surgical gauze. The cells were washed and resuspended at an appropriate concentration in PBS for intravenous infusion. Spleen cells from tumor-bearing donors and from normal donors were prepared in the same way.

The recipients of tumor-sensitized spleen cells were T-cell-deficient mice and age-matched, control mice carrying either intradermal or footpad tumors initiated 4 or 6 d earlier by the implantation of 1×10^6 or 2×10^6 tumor cells.

Antiserum. Anti-Thy-1.2 serum was produced in AKR mice immunized with C3H thymocytes. The serum was absorbed with AKR thymocytes and its specificity tested by adsorption with brain tissue as described previously (24). Spleen cells were incubated at 5×10^7/ml in a 1:5 dilution of the antiserum for 30 min on ice. The cells were then washed in PBS and incubated for 30 min at 37°C in the same volume of a 1:5 dilution of agarose-absorbed, noneytotoxic guinea pig serum. They were then washed in PBS and prepared for intravenous infusion.

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[1] *Abbreviations used in this paper:* PBS, phosphate-buffered saline; THXB, T-cell deficient by thymectomy.

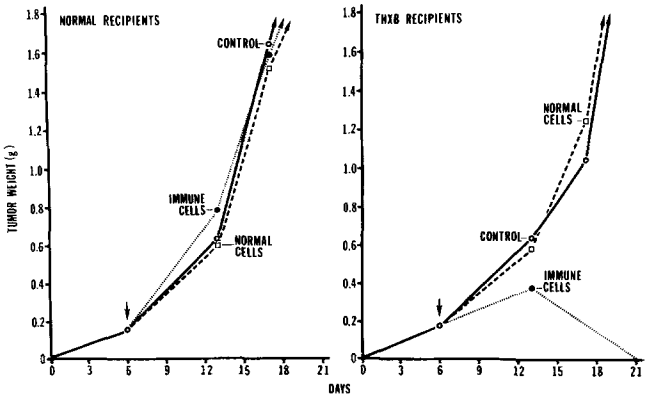


FIG. 1. Evidence that it is not possible to cause regression of an established intradermal Meth A tumor by intravenous infusion (arrow) of sensitized T cells from immune donors, unless the tumors are growing in THXB recipients. Infusion of 1.5×10^8 sensitized spleen cells into THXB recipients resulted in the onset of tumor regression after an ~ 7-d delay and caused complete rejection of the tumors after a further 7 d. Means of five mice per time interval.

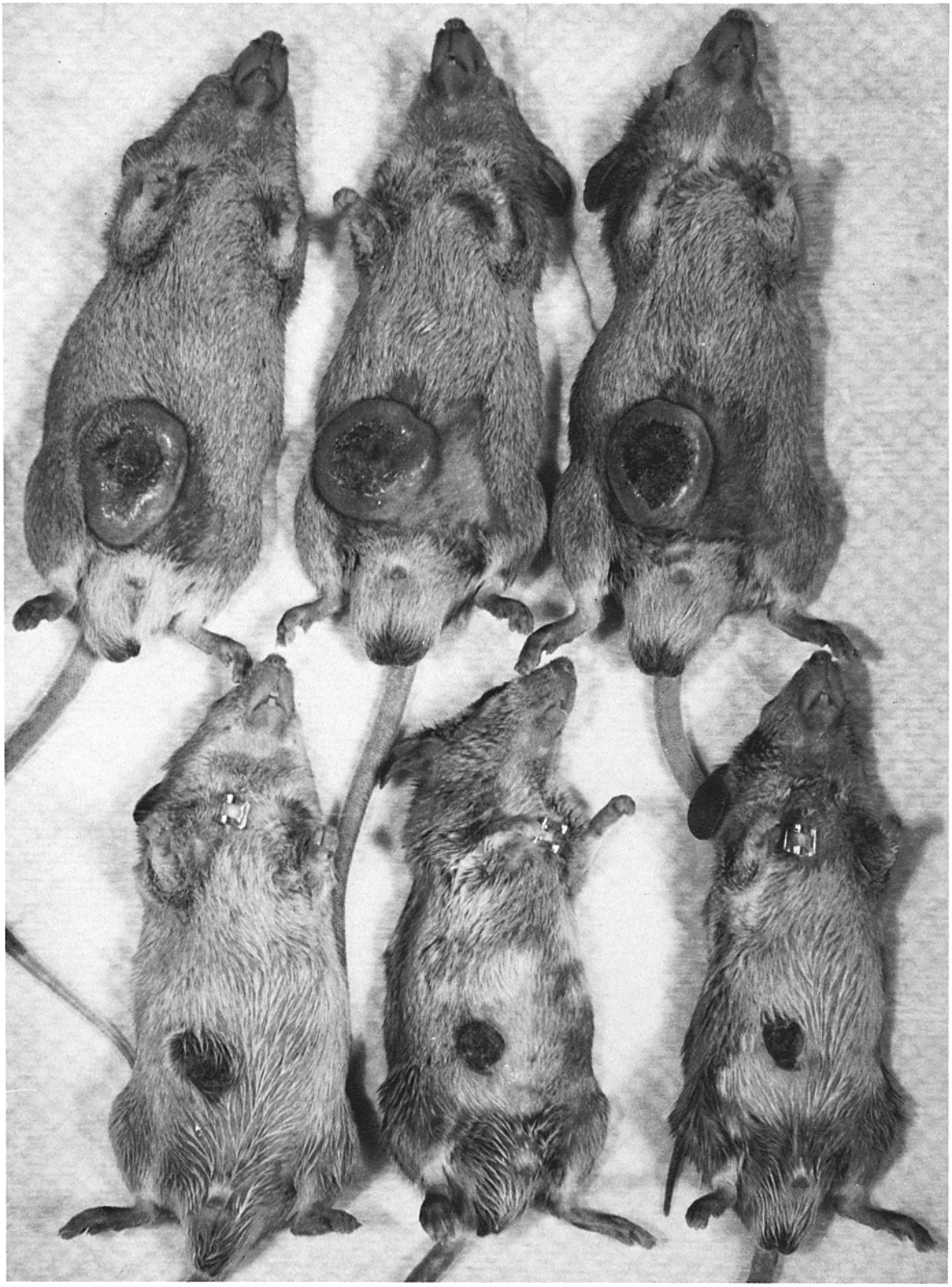
Concomitant Immunity. Mice carrying intradermal or footpad tumors were tested against time of tumor growth for the acquisition of resistance to growth of a standard 1×10^6 tumor cell challenge implant given in the left-hind footpad. Growth of the challenge implant was measured against time with dial calipers. Immunity is expressed as the difference between the size of the implant in control mice and tumor-bearing mice 8 d after challenge.

Results

Need for T-Cell-deficient Recipients to Demonstrate Adoptive Immunity against Established Tumors. Whereas published descriptions of the adoptive transfer of immunity against growth of implanted tumor cells are relatively numerous, descriptions of the expression of adoptive immunity against already established tumors are almost nonexistent (25). The purpose of the results described in this section is to show that failure of passively transferred, sensitized T cells to cause regression of established Meth A fibrosarcomas is caused by the presence in the tumor-bearing recipients of a thymus-dependent mechanism of immunosuppression.

Fig. 1 shows the results of an experiment in which an attempt was made to regress established 6-d intradermal tumors growing in T-cell-intact and T-cell-deficient recipients by the intravenous infusion of spleen cells from immune donors. The donors were made specifically immune to growth of a tumor implant by causing their tumors to completely regress by endotoxin therapy 10 d earlier (21). It can be seen that whereas an infusion of immune spleen cells had no effect on established tumors growing in T-cell-intact recipients, the same number of immune spleen cells caused dramatic regression of large established tumors growing in T-cell-deficient recipients. It will be noted, moreover, that there was an ~ 7-d delay before the onset of regression, but that once the regression process commenced it was rapid and complete. An idea of the size of the established tumors that were caused to regress in T-cell-deficient recipients by passive transfer of immune spleen cells can be gauged from an examination of Fig. 2.

Direct Evidence that Tumor-bearing Mice Possess Suppressor Cells. The foregoing results show that mice bearing established Meth A tumors acquire a thymus-dependent mechanism that prevents their tumors from being regressed by an infusion of sensitized



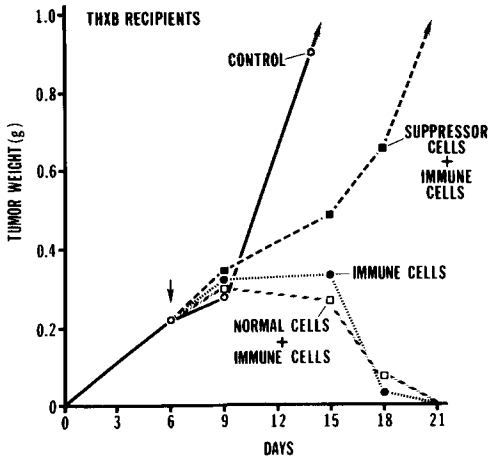


FIG. 3. Evidence that T-cell-intact, tumor-bearing mice contain spleen cells that can prevent the expression of adoptive cell-mediated regression of established tumors in THXB recipients. On day 6 of tumor growth (arrow) THXB tumor bearers were infused intravenously with 1.5×10^8 spleen cells from donor mice bearing 15-d tumors, and infused 4 h later with the same number of spleen cells from immune donors. It is obvious that prior infusion of spleen cells from tumor-bearing donors prevented immune spleen cells from causing tumor regression. Means of five mice per time interval.

lymphocytes from immune donors. The purpose of the experiments in this section is to show that this thymus-dependent suppressor mechanism can be passively transferred to T-cell-deficient recipients with spleen cells from tumor-bearing donors.

It can be seen in Fig. 3 that prior (4 h) intravenous infusion of spleen cells from T-cell-intact donors bearing 15-d intradermal tumors prevented an infusion of spleen cells from immune donors from regressing established intradermal tumors in T-cell-deficient test recipients. Fig. 4 shows the results of an identical experiment, except that in this case, the test tumors were growing subcutaneously in the right-hind footpad. It can be seen, in both experiments, that normal spleen cells possessed no detectable suppressor activity according to this assay. Suppressor cells alone had no effect on tumors growing in either T-cell-intact or T-cell-deficient recipients (evidence not shown).

Evidence that the Mechanisms of Regression and Suppression are Mediated by T Cells. The results in Table I show that the spleen cells from immune donor mice, which mediate regression of established tumors in T-cell-deficient test recipients, like the spleen cells from T-cell-intact, tumor-bearing donors, which suppress the mediation of this regression, were destroyed by incubation with anti-Thy-1.2 serum and complement. Table I also shows that intravenous infusion of 0.5 ml of serum from the tumor-bearing donors of suppressor cells had no effect on the expression of adoptive T-cell-

FIG. 2. Photographic demonstration of the model of adoptive T-cell-mediated regression of established tumors used in this study. Both groups of mice received an intravenous infusion of 1.5×10^8 spleen cells from immune donors on day 6 of tumor growth. The mice were photographed 12 d later. Tumors in the three T-cell-intact recipients at the top of the picture continued to grow. In contrast, tumors in the three thymectomized T-cell-deficient mice at the bottom of the picture dramatically regressed. Regression commenced ~ 7 d after passive transfer of spleen cells, by which time the tumors had reached a large size. The remaining scab sloughed off after a further 2–3 d.

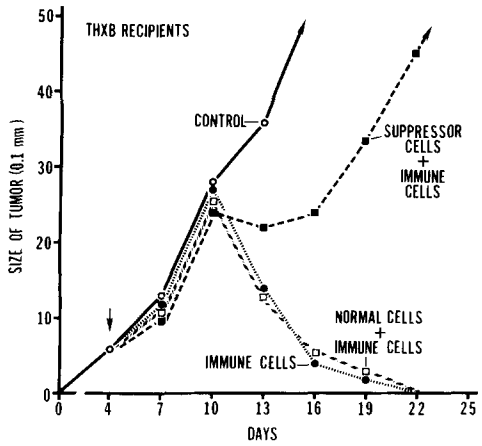


FIG. 4. Additional evidence that spleen cells from tumor-bearing donors cause suppression of adoptive T-cell-mediated regression of established tumors in T-cell-deficient recipients. The experimental design was the same as that described for Fig. 3, except that in this case the test tumors were growing in the right-hind footpad. This avoided the need to sacrifice mice to excise and weigh their tumors, and allowed the same tumors to be measured repeatedly throughout the course of the experiment. Means of five mice per time interval.

TABLE I

Effect of Anti-Thy-1.2 Serum on the Effectors and Suppressors of Adoptive T-Cell-mediated Tumor Regression in THXB Recipients

Spleen cells infused intravenously on day 6	Tumor weight 14 d after cell transfer (mean ± SE)	No. complete regressions at time of excision
	g	
Normal cells	2.41 ± 0.089	0/7
Immune cells	0.095 ± 0.015	3/5*
Thy-1.2-treated immune cells	2.16 ± 0.198	0/5
Immune cells + suppressor cells	1.45 ± 0.156‡	0/7‡
Immune cells + Thy-1.2-treated suppressor cells	0	7/7
Immune cells + 0.5 ml of serum from suppressor donors	0.076	4/5*

1.5×10^8 anti-Thy-1.2-treated spleen cells or untreated spleen cells from immunized donors and/or from donors with progressive 15-d tumors (suppressor donors) were infused intravenously into THXB test recipients with 6-d established intradermal tumors. Tumors were excised and weighed 14 d later when tumor regression in appropriate experimental groups was on the way to completion.

* Previous experiments indicate that all tumors in these regressor groups would have completely regressed over the next 7 d.

‡ At the time of excision, the tumors in recipients that received immune cells plus suppressor cells were growing at the same rate as tumors in recipients of normal spleen cells (Fig. 3).

mediated tumor regression. These results leave little doubt, therefore, that T cells were responsible for mediating regression and for suppressing regression.

Evidence that Concomitant Immunity to the Meth A Fibrosarcoma Decays Soon after It is Generated. The purpose of this section is to show that although an immune response

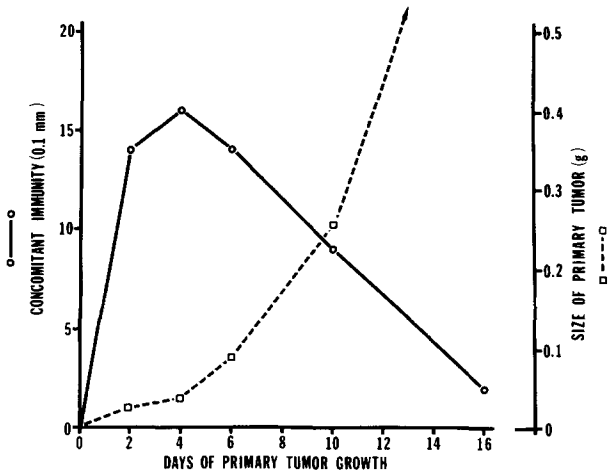


FIG. 5. Evidence that concomitant immunity generated against the Meth A fibrosarcoma undergoes progressive decay at an early stage of tumor growth. Shown are changes in concomitant resistance to growth of a standard challenge of 1×10^6 Meth A tumor cells implanted in the right-hind footpad at progressive stages of growth of an intradermal primary tumor. Concomitant immunity is expressed as the difference between the size of the challenge implant in normal mice and its size in tumor-bearing mice 8 d after challenge. Means of five mice per time point.

to the Meth A fibrosarcoma is generated at an early stage of tumor growth, the immunity is either progressively suppressed or decays soon after.

The kinetics of generation and decay of concomitant immunity during intradermal growth of the Meth A fibrosarcoma is shown in Fig. 5. The results are recorded as changes against time of growth of the primary tumor in the level of resistance to growth of a standard 10^6 challenge implant given in the right-hind footpad. It can be seen that concomitant immunity was generated rapidly, peaked at about day 4, and then underwent progressive decay, until about day 16 when immunity to the challenge implant was no longer expressed. It is evident, therefore, that the donors of suppressor T cells in the foregoing experiments were employed at a stage when their concomitant immunity had been completely suppressed.

Specificity. To properly investigate the specificity of suppression would require the possession of a syngeneic tumor with similar immunogenic properties to the Meth A fibrosarcoma. The possibility that one or more such tumors is present in our tumor bank is being investigated. However, an estimate of whether or not the suppressor T cells generated in response to progressive growth of the Meth A can cause a state of generalized immunosuppression can be obtained by determining whether Meth A tumor bearers are deficient in their capacity to reject a tumor allograft. This was investigated by following the growth of 10^6 allogeneic SA-1 sarcoma cells ($H\text{-}2^a$) implanted in the right-hind footpad of CB6 ($H\text{-}2^d \times H\text{-}2^b$) mice carrying 9-d intradermal Meth A tumors.

It can be seen in Fig. 6 that CB6 mice carrying large progressive Meth A tumors were not deficient in their capacity to reject the SA-1 allograft after it had grown to an appreciable size. In fact, Meth A tumor bearers showed more anti-allograft resistance than control mice, probably because of the presence of a Meth A-induced, activated macrophage system (22). Thus, this evidence shows that the T cells

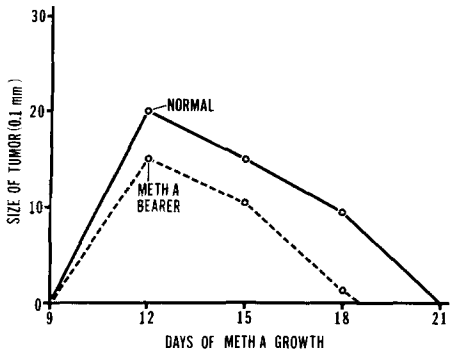


FIG. 6. Evidence that a large progressive intradermal Meth A tumor does not suppress the capacity of the host to reject a tumor allograft. In this experiment intradermal belly tumors were initiated with 2×10^6 Meth A cells, and the hosts injected with 10^6 SA-1 cells in the right-hind footpad on day 9 of Meth A growth. If anything, the Meth A bearers were more capable than controls of generating and expressing immunity to the allograft after it had grown progressively for ~ 6 d. Means of five mice per time interval.

responsible for suppressing anti-Meth A immunity do not suppress the capacity to generate and express cell-mediated immunity in general.

Discussion

The results of this paper provide an explanation for why the highly immunogenic Meth A fibrosarcoma is not rejected by its immunocompetent syngeneic host. The findings are consistent with the hypothesis that progressive growth of this tumor causes the generation of a population of T cells that functions to prevent the host from generating a protective level of anti-tumor immunity. It was shown first, that passively transferred, sensitized T cells from immunized donors fail to cause regression of established tumors, unless the tumors are growing in recipients that have been made T-cell deficient by thymectomy and irradiation, and protected with bone marrow. It was shown next, that adoptive T-cell-mediated regression of established tumors in T-cell-deficient recipients can be prevented by prior infusion of splenic T cells from T-cell-intact, tumor-bearing donors. It follows, therefore, that the tumor-bearing donor mice acquired a tumor-induced state of T-cell-mediated immunosuppression. Hence, the reason for the progressive decay of an earlier acquired state of T-cell-mediated concomitant anti-tumor immunity.

The results also suggest the reason for the paucity of published demonstrations of regression of established tumors by passively transferred sensitized T cells (25). Indeed, it is easy to demonstrate adoptive T-cell-mediated immunity to growth of implants of the Meth A fibrosarcoma in normal recipients (21), provided the passive transfer of sensitized T cells is not delayed more than 3–4 d after tumor cell implantation. After this time the tumor becomes completely refractory to the effects of the infused T cells. It is obvious, therefore, that the generation of suppressor T cells begins at an early stage of tumor growth, but not before the host generates a transitory state of T-cell-mediated immunity, as evidenced by the curve for the generation and decay of concomitant immunity. In fact, the evidence revealed here about the host response to the Meth A fibrosarcoma is in keeping with the prediction (26) that negative T-cell regulation of the immune response is always preceded or accompanied by positive T-

cell regulation, presumably because the generation of the former relies on feedback signals from the latter (27, 28). It is also apparent that the response to this tumor resembles the induction of high-zone tolerance, where it has been shown that a transitory immune response, more often than not, precedes the onset of the state of immunological unresponsiveness (29). There is little doubt, moreover, that this type of immunological tolerance is mediated by suppressor T cells (30, 31).

Presumably, then, the increase in the quantity of tumor-specific transplantation antigen that results from progressive tumor growth resembles the antigen overloading conditions required for the induction of high-zone tolerance. It seems reasonably clear, therefore, that any attempt to cause the regression of an established immunogenic tumor by passively transferring sensitized T cells represents an attempt to abrogate immunological tolerance in a recipient that is receiving tolerance-sustaining doses of antigen. Because attempts to break tolerance to antigens by passive transfer of lymphocytes is difficult to achieve, it is not surprising that published demonstrations of the regression of established tumors by the passive transfer of sensitized T cells are rare (25).

Immunological tolerance can be broken, however, by the passive transfer of lymphocytes into recipients that have been x-irradiated (32), and high-zone tolerance in general is known to decay after the antigenic stimulation is discontinued (29). It was not surprising to find, therefore, that T-cell-mediated suppression induced by the Meth A fibrosarcoma resembles high-zone tolerance in both of these respects. It is known, in the first place, that x-irradiated Meth A tumor bearers can substitute for T-cell-deficient tumor bearers for demonstrating that passively transferred sensitized T cells (and, to a lesser extent, normal T cells) can cause regression of established tumors (M. J. Berendt and R. J. North. Manuscript in preparation.). It is also known that removal of the tumor antigen load by surgical excision of established Meth A tumors results, in < 2 wk, in the emergence of specific immunity to the growth of implants of this tumor (21). Because tumor excision and subsequent tumor cell challenge is a classical technique for demonstrating the immunogenicity of transplantable tumors, it seems highly likely that other tumors shown to be immunogenic by this method will be found to resemble the Meth A fibrosarcoma in terms of its capacity to evoke the generation of suppressor T cells.

Direct evidence that immunogenic tumors induce the generation of functionally dominant numbers of suppressor T cells has been published by others (8–13). We believe, however, that the suppressor model revealed by this study is exceptionally convincing, by virtue of the fact that suppression can be measured against a mechanism of T-cell-mediated immunity powerful enough to cause the regression of large, established tumors. We are aware, nevertheless, that the model contains many unknowns. It is not known at this stage, for example, whether the passively transferred T cells that cause tumors to regress in T-cell-deficient recipients are cytolytic T cells or memory T cells. Again, the delay before infused suppressor T cells allow tumors to completely escape from adoptive immunization (Figs. 3 and 4) suggests some interesting mechanistic possibilities.

Perhaps the most important unknown, however, is whether the mechanism of suppression is specific or nonspecific. A proper investigation of this problem will require a syngeneic, immunogenic tumor that gives rise to the same type of host response as the Meth A. This would allow a direct determination of whether the T

cells that suppress adoptive T-cell-mediated regression of the Meth A also suppress adoptive T-cell-mediated regression of an immunogenically similar tumor, and vice versa. We are certain at this stage, however, that growth of the Meth A fibrosarcoma does not cause a generalized state of immunosuppression, as evidenced by the findings that mice bearing this tumor are capable of generating T-cell-mediated immunity against, and of causing regression of, a large tumor allograft. They are also capable of generating and expressing T-cell-mediated immunity against the bacterial pathogen, *Listeria monocytogenes* (M. J. Berendt and R. J. North. Manuscript in preparation.).

It can be suggested in conclusion that the acquisition of a tumor-induced state of T-cell-mediated immunosuppression is almost certainly responsible for the onset of refractoriness of the Meth A fibrosarcoma to endotoxin-induced regression, as described in previous reports (21, 22). Therefore, the possibility that the emergence of functionally dominant numbers of suppressor T cells is responsible for the onset of resistance of this and other tumors to the effects of commonly employed immunotherapeutic agents, such as Bacillus Calmette-Guérin and *Corynebacterium parvum,* should be considered.

Summary

The results of this paper are consistent with the hypothesis that progressive growth of the Meth A fibrosarcoma evokes the generation of a T-cell-mediated mechanism of immunosuppression that prevents this highly immunogenic tumor from being rejected by its immunocompetent host. It was shown that it is possible to cause the regression of large, established Meth A tumors by intravenous infusion of tumor-sensitized T cells from immune donors, but only if the tumors are growing in T-cell-deficient recipients. It was also shown that the adoptive T-cell-mediated regression of tumors in such recipients can be prevented by prior infusion of splenic T cells from T-cell-intact, tumor-bearing donors. The results leave little doubt that the presence of suppressor T cells in T-cell-intact, tumor-bearing mice is responsible for the loss of an earlier generated state of concomitant immunity, and for the inability of intravenously infused, sensitized T cells to cause tumor regression. Because the presence of suppressor T cells generated in response to the Meth A did not suppress the capacity of Meth A-bearing mice to generate and express immunity against a tumor allograft, it is obvious that they were not in a state of generalized immunosuppression.

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