Deviant immune responses to allogeneic tumors injected intracameraly and subcutaneously in mice

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The ability to introduce carefully controlled numbers of viable cells into the anterior chamber of mouse eyes made it possible to examine the interrelationship between presentation of antigens intracamerally and into conventional body sites and their synergistic/antagonistic effects on the immune system. P815 mastocytoma (DBA/2; H-2$^b$) cells are syngeneic with BALB/c hosts at the major histocompatibility complex but differ at numerous minor histocompatibility loci. When these cells are injected intracamerally into BALB/c mice, they subvert the host's immune response; that is, tumor cells injected subcutaneously developed into tumors. The dynamics of this anterior chamber–associated immune deviation was manipulable. When subcutaneous (SC) inoculations preceded intracameral (IC) inoculations by 5 days or more, systemic anti-DBA 12 immunity elicited by SC inoculation prevented successful engraftment of P815 tumors in the anterior chamber. As the time interval between SC and IC inoculations of P815 cells decreased, the balance between destruction or survival of intracocular tumors was tipped in favor of tumor growth. Intraocular tumor growth increased when IC inoculations preceded SC inoculations and was most impressive when this interval was 7 days. In these mice the tumors grew briskly and aggressively in a fashion comparable to that seen in hosts not receiving prior SC inoculations. The apparent capacity of the immune system to prevent or enhance the growth of tumors can be successfully manipulated in ways that suggest the possibility of therapeutic benefit in ophthalmologic disease.

Key words: anterior chamber, immune response, allogeneic tumors, keratoconjunctivitis, minor histocompatibility antigens

Transplantation antigens placed into the anterior chamber of the eye impact upon the immune system in a manner quite different from that after their introduction into other body sites. The time-honored example of this difference is the observation that allogeneic tissues grafted into the anterior chamber enjoy prolonged, sometimes indefinite survival whereas comparable tissues grafted to other body sites are rejected with dispatch.1-3 The label often applied to the anterior chamber in this context is "immunologically privileged site." Until recently, the "privilege" afforded to allogeneic tissues in the anterior chamber was thought to result from the anatomical observation that the anterior chamber lacks a lymphatic drainage route by which antigen can escape into the systemic circulation. The resultant afferent blockade was thought to prevent alloantigens placed in the anterior
Fig. 1. Growth patterns of anterior chamber tumors following IC inoculation of $10^5$ P815 mastocytoma cells. No keratoconjunctivitis was observed. A, DBA/2 mice. B, BALB/c mice. Asterisk, Ocular phthisis; parentheses, number of eyes.

Fig. 2. Anterior chamber of BALB/c mouse filled with growing mastocytoma 10 days after IC inoculation of $10^5$ P815 cells.

The experiments reported in this paper describe the adaptation of the technique of intracameral (IC) inoculation of cellular suspensions to adult mice. The results reveal that the phenomenon of F1,LI-ID first demonstrated in rats apparently applies as well to mice and may in fact be a general phenomenon.

Materials and methods

Experimental animals. Adult female BALB/c (H-2a), DBA/2 (H-2b) and C57BL/6 (H-2b) mice were purchased from Jackson Laboratories, Bar Harbor, Maine, and used as experimental subjects when they were between 3 and 5 months of age. BALB/c and DBA/2 mice share similar H-2 haplotypes but differ at multiple minor histocompatibility loci.

Tumor cells. P815 mastocytoma (DBA/2) cells were cultivated in suspension cultures in Falcon 75 cm² tissue culture flasks (Falcon Plastics, Oxnard, Calif.) with Dulbecco's modified Eagle's minimal essential medium supplemented with 10% heat-inactivated fetal calf serum and gentamicin (0.05 mg/ml; Schering Corp., Kenilworth, N.J.). EL-4 lymphoma (C57BL/6) was maintained by serial passage as ascites in C57BL/6 mice. Monocellular suspensions of P815 cells and EL-4 cells were washed in Hanks' balanced salt solution (HBSS) and resuspended in HBSS for subcutaneous (SC) and IC inoculations.

Anterior chamber inoculations. A modified quantitative technique for depositing a definite number of tumor cells into the anterior chamber of the mouse eye was employed. The technique is as follows. Mice were deeply anesthetized with 0.66 mg of ketamine hydrochloride (Vetalar; Parke, Davis & Co., Detroit, Mich.) given intramuscularly. The eye was viewed under the low power (8×) of a dissecting microscope, and a sterile 30-gauge needle was used to puncture the cornea at the corneoscleral junction, parallel and anterior to the iris. The aqueous humor was expressed by compressing the cornea with the back of a scalpel for extended intervals. Experimental dissection of this phenomenon, termed $F_1$, lymphocyte-induced immune deviation ($F_1$,LI-ID), proved to be difficult in rats because of the lack of appropriate immunologic reagents able to identify functionally distinct lymphocyte subsets and because of the lack of MHC congenic and recombinant rat strains comparable to those available in mice.

Studies recently reported from this laboratory and corroborated by others have demonstrated conclusively that antigen introduced into the anterior chamber of rat eyes does, in fact, make itself known to the systemic immune apparatus. Semiallogeneic ($F_1$, hybrid) lymphoid cells placed in the anterior chambers of parental strain rats, disparate at the rat major histocompatibility complex (MHC) $Rt$-1, evoke the appearance in the host's serum of specific anti-$Rt$-1 alloantibodies. Moreover, the allograft immune response of intracameraly inoculated rats is transiently suppressed, so that orthotopic allografts of skin survive on these animals for extended intervals. Experimental dissection of this phenomenon, termed $F_1$, lymphocyte-induced immune deviation ($F_1$,LI-ID), proved to be difficult in rats because of the lack of appropriate immunologic reagents able to identify functionally distinct lymphocyte subsets and because of the lack of MHC congenic and recombinant rat strains comparable to those available in mice.

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Table I. Ability of P815 tumor cells to immunize BALB/c mice to DBA/2 alloantigens

<table>
<thead>
<tr>
<th>Primary exposure</th>
<th>No. of mice</th>
<th>Secondary exposure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBA/2 skin graft</td>
<td>19</td>
<td>None (first set)</td>
<td>MST = 10.8 days (10.2 - 11.8)*</td>
</tr>
<tr>
<td>DBA/2 skin graft</td>
<td>8</td>
<td>DBA/2 skin graft (second set)</td>
<td>MST = 7.0 ± 0.0 days</td>
</tr>
<tr>
<td>P815 injected SC</td>
<td>8</td>
<td>DBA/2 skin graft</td>
<td>MST = &gt; 20 days</td>
</tr>
<tr>
<td>P815 injected IC</td>
<td>11</td>
<td>DBA/2 skin graft</td>
<td>0/10 Tumors developed</td>
</tr>
<tr>
<td>DBA/2 skin graft</td>
<td>10</td>
<td>P815 injected IC</td>
<td>10/10 Tumors developed</td>
</tr>
<tr>
<td>None</td>
<td>10</td>
<td>P815 injected IC</td>
<td></td>
</tr>
</tbody>
</table>

BALB/c mice were exposed to DBA/2 alloantigens as indicated as a primary exposure (day 0) and secondary exposure (day 14).

*95% confidence limits.

blade, and the evacuated fluid was blotted with sterile 4 by 4 gauze pads. A glass micropipet (approximately 80 µm in diameter) was fitted into a sterile infant feeding tube (No. 5 French; Cutter Laboratories, Inc., Berkeley, Calif.), which was mounted onto a sterile 0.1 ml Hamilton syringe (Hamilton Co., Inc., Whittier, Calif.). A Hamilton automatic dispensing apparatus was fitted onto the loaded syringe and was used to dispense 5 µl quantities of P815 cell suspensions. The pipet loaded with P815 cell suspension (2 x 10⁷ cells/ml = 1 x 10⁵ cells/5 µl) was introduced through the puncture site of the cornea, and 5 µl of the P815 cell suspension were delivered into the anterior chamber. As the needle was withdrawn, the iris prolapsed and plugged the perforated cornea, thereby minimizing leakage of the inoculum.

SC inoculations. Tumor cells, 1 x 10⁵, (P815 or EL-4) suspended in 0.1 ml of HBSS were inoculated subcutaneously into the right rear flanks at various times relative to anterior chamber inoculations.

Skin grafting. Full thickness skin grafts were prepared as described elsewhere. Grafts were applied orthotopically and wrapped in plaster of paris bandages. Casts were removed 7 days later, and the grafts were inspected for evidence of rejection. Destruction was judged complete when all remnants of surface epidermis were gone. Median survival times (MSTs) were calculated.

Experiments and results

Our experimental approach was, first, to establish that successful inoculation of reproducible numbers of viable cells into the anterior chamber of murine eyes was feasible and, second, to determine whether allogeneic cells injected intracamerally could make an impact on the systemic immune apparatus of recipient allogeneic mice. The mastocytoma, P815, which originated in DBA/2 mice, was selected because of its ease of maintenance in vitro and its faithful induction of tumors when inoculated into syngeneic DBA/2 adult mice and because this particular tumor cell line has been used extensively by cellular immunologists as a target of in vitro assays of T cell-mediated immunity.

Growth patterns of P815 tumor cells inoculated into the anterior chamber of syngeneic and allogeneic eyes. P815 cells, at a concentration of 10⁵/5 µl, were inoculated into the anterior chambers of eyes of two panels of adult animals: DBA/2 and BALB/c mice. The pattern of tumor growth in both panels was similar (Fig. 1). During the first 4 days after inoculation, no evidence of tumor could be seen with aid of a dissecting microscope. However, between 5 and 6 days white tufts of tumor cells were detected anterior to the iris. These masses grew rapidly, and by 8 to 12 days after inoculation they completely filled the anterior chamber (Fig. 2). Characteristically, at this point a cone-shaped wedge of tumor tissue extended toward the cornea, resulting in corneal perforation between days 12 and 14. Within the next 2 to 4 days, the affected eyes rapidly regressed in size and were replaced by organizing fibrous tissue.

Thus, despite the fact that P815 cells express minor histocompatibility antigens alien to the BALB/c strain of mice, no evidence of transplantation immunity was observed; the growth of P815 cells in the eyes of both
Fig. 3. Influence of P815 mastocytoma cells inoculated subcutaneously on growth patterns of intracamerally inoculated P815 cells. Label in upper left corner of each panel represents time interval between SC and IC inoculations of P815 cells. Minus sign indicates that SC inoculation preceded IC inoculation by (N) days.

panels of animals was indistinguishable.

Corneal perforation, regression of the tumor, and, finally, resorption of the eyes in syngeneic recipients were probably a consequence of the uncontrolled local growth of the tumor. It is presumed, although there is no direct proof, that the tumor brings about its own destruction by progressively compromising the blood supply to the orbit until infarction takes place. As a consequence, the tumor and the eye are both destroyed and resorbed, i.e., ocular phthisis.

Growth patterns of P815 tumor cells inoculated subcutaneously into syngeneic and allogeneic mice. Inoculations of 10^5 P815 cells were placed subcutaneously into panels of adult DBA/2 and BALB/c mice. In DBA/2 recipients palpable tumor nodules appeared at inoculation sites within 5 days. These masses grew rapidly, reaching approximately 4 cm in diameter within 19 days after inoculation. Unrestrained growth of these tumors eventually proved fatal for the recipients, death occurring within 3 weeks of original implantation. By contrast, no evidence of SC tumors was seen in BALB/c recipients. The failure of subcutaneously injected P815 cells to grow in BALB/c hosts was found, as expected, to be due to the ability of these cells to elicit allograft immunity directed at the minor histocompatibility antigens expressed on the tumor cells. This was proved to be the case as follows. Panels of BALB/c mice that received 10^5 P815 tumor cells subcutaneously on day 0 were grafted with DBA/2 skin orthotopically on day 14. Accelerated rejection of these grafts (MST = 7.0 ± 0.0 days) compared to the speed of rejection of DBA/2 skin grafts placed on immunologically virgin BALB/c recipients (MST = 10.8, 95% confidence limits of 10.2 to 11.8) indicates that the initial SC encounter with P815 cells elicited allograft immunity in BALB/c hosts (see Table I). Taken together with the P815 tumor cell growth patterns in the anterior chambers described above, these data support the hypothesis that a histoincompatible tumor graft placed subcutaneously elicits a specific immune response that prevents malignant cells from establishing a viable tumor in situ; by contrast, the immunologically privileged status of the anterior chamber of the eye "protects" locally injected allogeneic tumor cells from immune recognition and/or de-
struction, and as a consequence the malignant cells are able to develop into a progressively growing tumor that leads to ocular destruction with a tempo and vigor indistinguishable from those seen in syngeneic hosts.

A considerable body of evidence indicates that the P815 tumor cell line expresses both transplantation alloantigens and tumor-specific antigens. In order to determine whether the failure of P815 cells to grow in the SC tissues of BALB/c mice was due to an immune response directed at minor histocompatibility differences between DBA/2 and BALB/c strains, BALB/c recipients of subcutaneously injected P815 cells were grafted 2 weeks thereafter with DBA/2 skin. In a related experiment, BALB/c mice were grafted orthotopically with DBA/2 skin. Two weeks later, they received 10⁵ P815 cells injected into the anterior chamber. This latter experiment examined formally the hypothesis that pre-existent systemic anti-DBA/2 alloimmunity can prevent the development of DBA/2 tumor in the anterior chamber. The results of these experiments are presented in Table I. For the sake of comparison conventional first- and second-set graft survival times are included in the table. It can be seen that an SC inoculation of P815 tumor cells effectively immunized BALB/c mice to DBA/2 alloantigens; these animals rejected subsequent DBA/2 skin grafts in an accelerated fashion, i.e., 7.0 ± 0.0 days (compare with MSTs of first- and second-set grafts). Moreover, active immunization of BALB/c mice with DBA/2 skin prevented P815 cells from establishing a successful graft in the anterior chamber. These results offer strong circumstantial evidence in support of the hypothesis that subcutaneously injected P815 cells immunize BALB/c mice to DBA/2 minor histocompatibility antigens and that this immunization can express itself in the anterior chamber.

The data do not address directly, however, the question of whether P815 tumor cells also can immunize BALB/c mice to the tumor-specific antigen(s). Experiments are under way to test this possibility. At present we are willing to conclude that, at the very least, the tumor cells express DBA/2 minor antigens and elicit allograft immunity in BALB/c mice. With this in mind and with the observations that there is a marked disparity in growth patterns of P815 cells injected into the SC tissue compared to that following inoculation into the anterior chamber of BALB/c mice, we recognized an opportunity to examine the putative relationship between alloantigens implanted as tumor cells at both sites.

Influence of SC inoculation of P815 cells on growth pattern of intracameral inoculated P815 cells. The next series of experiments was designed to determine whether flank inoculation of DBA/2 alloantigens (expressed on P815 cells) before, after, or simultaneously with IC inoculation of P815 cells might influence the growth of the latter in the anterior chamber. These data are summarized in Fig. 3 and Table I. Evidence supporting the conclusion that SC injections of P815 cells induced anti-DBA/2 transplantation immunity was found in panels where SC injection of 10⁵ P815 cells preceded IC injection by 7 or 5 days. In neither group of BALB/c mice were SC or anterior chamber tumors observed. This finding corroborates previously published reports that a state of pre-existing specific immunity can rob the anterior chamber of its ability to confer immunologic privilege.

When SC injections of P815 cells preceded IC injections by only 4 days, tumors devel-

Fig. 4. Intense ocular inflammation of BALB/c mouse inoculated first intracamerally on day 0 and then subcutaneously with 10⁵ cells on day 4.
Table II. Temporal relationships of IC and SC injections of P815: effects on tumor growth

<table>
<thead>
<tr>
<th>Day* of SC inoculation of P815 cells</th>
<th>No. of eyes injected</th>
<th>Eyes with tumors (%)</th>
<th>Eyes with keratoconjunctivitis (%)</th>
<th>Eyes destroyed (%)</th>
<th>Mice developing SC tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/10</td>
</tr>
<tr>
<td>-5</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>-4</td>
<td>10</td>
<td>10</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
</tr>
<tr>
<td>-2</td>
<td>10</td>
<td>9</td>
<td>(90)</td>
<td>(0)</td>
<td>(0)</td>
</tr>
<tr>
<td>+0</td>
<td>18</td>
<td>17</td>
<td>(94)</td>
<td>(11)</td>
<td>(0/10)</td>
</tr>
<tr>
<td>+2</td>
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<td>10</td>
<td>(100)</td>
<td>(100)</td>
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</tr>
<tr>
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<td>(100)</td>
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<td>(0/10)</td>
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<tr>
<td>+7</td>
<td>10</td>
<td>10</td>
<td>(100)</td>
<td>(100)</td>
<td>(0/10)</td>
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</tbody>
</table>

*Day = day of bilateral IC inoculation of P815 cells.

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oped in the anterior chambers. These neoplasms appeared as floccular aggregates 5 to 7 days after inoculation and rapidly increased in size thereafter. Their growth was accompanied by intense signs of inflammation; that is, the conjunctivae became injected and edematous, the cornea developed severe keratitis, the globes swelled to enormous size, and ultimately these eyes were destroyed, becoming desiccated between 21 and 24 days after inoculation.

Tumor also developed in eyes of BALB/c mice that received SC inoculations of P815 2 days prior to IC injections. In these animals, evidence of tumor appeared earlier (within 4 to 5 days of IC inoculation), which grew to fill the anterior chamber by 9 days then rapidly defervesced. Between days 14 and 25 after inoculation gross ocular morphology returned to normal. At no time was keratoconjunctivitis resembling that described above observed in the eyes of these animals. Similarly, if P815 cells were simultaneously inoculated subcutaneously and intracameral, tumors appeared in the anterior chamber by 5 days. These neoplastic collections grew rapidly, filling the anterior chamber between days 9 and 14; a minority of eyes at this time had an accompanying keratoconjunctivitis. However, in every instance the inflammation receded, tumor regression intervened, and the eyes returned toward a normal appearance.

Thus, if SC injections of P815 tumor cells preceded or coincided with IC injections of P815 cells, a host response was elicited (we presume the response to be immunologic in nature) which was capable of controlling IC tumor growth. If the SC injection preceded the IC injection by 5 or more days, the host response absolutely prevented IC tumor development, and there was negligible inflammation. However, as the interval between the two tumor cell injections became progressively shorter, a less efficient host response took charge, a response in which intense inflammation was a significant component. When the two injections were placed at virtually the same time, the inflammation was not sufficient to cause permanent ocular destruction but did rid the eye of the tumorous tissue.

SC injections of P815 cells also were made at timed intervals after IC injection of tumor cells: at 2, 4, 5, and 7 days. In every instance injected eyes in every panel of animals developed evidence of anterior chamber tumor within 5 days of injection. These tumors grew rapidly, filled the anterior chamber within 10 days, and were accompanied by intense inflammatory changes especially prominent in the conjunctiva and cornea (Fig. 4). In
animals whose SC injection of P815 cells followed IC injection by 2 days, a minority of eyes resolved both the inflammation and tumor infiltration, returning to normal within 25 days. In the remainder of subjects the eyes were destroyed by the reaction within the globe; two eyes developed corneal perforation. In panels of BALB/c mice whose SC injections of P815 followed the IC injection by 4, 5, and 7 days, phtisis of all injected eyes occurred, and corneal perforation was common; in the last panel (+7-day interval), every eye underwent corneal perforation. It would appear therefore that SC injections of tumor cells that follow IC injection of tumor cells cause progressively less host response able to control the growth of the ocular tumor. That these eyes developed intense keratoconjunctivitis suggests that a host immune response had been initiated; however, the response was inadequate to the task, and the tumors destroyed the eyes as successfully as though no flank injections had been made.

**Influence of IC inoculation of P815 cells on growth pattern of subcutaneously injected tumor cells.** The preceding description focused on the capacity of tumor cells placed subcutaneously in BALB/c mice to influence the growth of tumor cells injected into the anterior chamber of the eye. On the basis of our previous studies, we suspected that tumor cells placed in the anterior chamber might alter the capacity of tumor cells to grow in the SC inoculation site. All the animals described above were examined at regular intervals for the appearance of SC tumors. The summary of these observations are presented in Table II. It should be restated for the sake of comparison that under no circumstance did local tumors appear in BALB/c mice if $10^5$ P815 cells were injected subcutaneously without other experimental manipulation; we took this as evidence of the vigor of allograft immunity elicited by these allogeneic tumor cells placed at this site. To our surprise, SC tumors did appear in certain panels of animals that also received IC injections of P815 cells (Fig. 5). Specifically, SC tumors developed in mice whose IC injections (1) preceded the SC injection by 5 days, (2) followed the SC injection by 2 days, or (3) were given simultaneously with SC injections. No SC tumors were discovered at other time intervals tested. In all instances these unexpected SC tumors appeared approximately 9 days after SC inoculation, irrespective of the timing of the IC tumor cell injection. SC tumors grew and then regressed over the subsequent 2 to 7 days. No progressively growing SC tumor became established or threatened the life of the host.

The power of DBA/2 allogeneic tumor cells placed in the anterior chamber to affect the nature of the BALB/c hosts' response to DBA/2 antigens placed elsewhere was dramatically seen in the following experiment. P815 cells ($1 \times 10^5$) were inoculated into the anterior chamber of BALB/c animals on day 0. Fourteen days later these animals were grafted orthotopically with DBA/2 skins. The grafts enjoyed a surprisingly prolonged tenure on their allogeneic host (see Table I). Not only were they not rejected in second-set fashion; they survived longer than did DBA/2 grafts on normal BALB/c hosts. Thus the IC presentation of alloantigens subverted the allogodestructive host immune response and instead allowed prolonged acceptance of these allodisperate grafts.

These data clearly demonstrate that the presence of tumor cells in the anterior chamber can profoundly affect the capacity of the immune response to deal with tumor cells placed subcutaneously. Tumor growing...
in the anterior chamber seems to blunt, suppress, and/or delay the development of an effective and destructive alloimmune response; as a consequence, for a transient interval the tumor is able to establish itself and grow. Ultimately, however, the host immune response gains ascendance, and tumor regression is procured, presumably by the action of alloimmune T lymphocytes.

Discussion
The ability to introduce carefully controlled numbers of viable cells into the anterior chamber of mouse eyes is an important technologic achievement. Although these experiments are not the first to claim success in this regard (Gallie et al.13 and Boone and DuPree14 reported successful inoculation of human melanoma cells into the anterior chambers of the eyes of nude mice), the use of an allogeneic tumor model makes it possible to examine the interrelationships between presentations of antigens intracamerally and into conventional body sites. We have been rewarded with an illuminating and in many ways surprising array of findings. We feel that the most significant observation is that intraocular allogeneic DBA/2 tumor cells, syngeneic with BALB/c hosts at the MHC but differing at numerous minor histocompatibility loci, can subvert the host's immune response in such a manner that tumor cells injected subcutaneously are able to proliferate transiently. Since P815 tumors never develop in SC tissues of unmanipulated BALB/c hosts, the deviation seen in the host's immune response in these experiments is impressive.

Our studies have not proceeded far enough to have gained any meaningful insight into the nature of the contributing immunologic factors. In the antecedent rat model of this same (or very similar) phenomenon,6 it was concluded that deviation of the systemic immune response achieved by intracamerally injected allogeneic cells required that (1) the time interval between IC injection and test allograft be confined within narrow limits, (2) the eye containing the alloantigenic cell inoculum must remain anatomically intact for at least 48 hr, and (3) a normally functioning spleen must be present. Adaptation of the model to the murine system will permit a more sophisticated analysis of the cellular basis of immune deviation of this type. The immunologic interrelationship between SC and IC inoculation of the P815 tumor also was revealed in the capacity of flank tumor cells to modulate growth of IC tumors. The most obvious direct effect occurred when SC injections preceded IC injections by 5 or more days: the systemic anti-DBA/2 immunity elicited by SC tumor cell injections prevented successful engraftment of P815 cells in the anterior chamber. More interestingly, however, was the promotion of IC tumor growth by SC injections performed near to or simultaneously with the time of IC injections. The pattern of tumor growth in anterior chambers under these circumstances, the severe keratoconjunctivitis, and the successful destruction of the tumor with preservation of the eye indicate that the two independent injections achieved a state of transient balance in the anterior chamber. By carefully selecting the sequence and time interval between SC and IC injections of P815 tumor cells, it was possible to predict the "winning side"; that is, given one protocol, the tumor would be destroyed and the eye saved from destruction, whereas with another protocol the tumor gained ascendance and proliferated mindlessly until both tumor and eye succumbed. These startling observations suggest that experimental dissection of the cellular and molecular basis of the immune response in this new model might bring important new insights into the physiologic process by which the immune response can be enlisted in a host's effort to contain malignant neoplasms in the anterior chamber of the eye.

It is interesting that the histoincompatible DBA/2 tumor grows so successfully in the anterior chamber of BALB/c eyes without evoking the inflammatory response seen in tumor-injected eyes of animals that also were injected with tumor cells subcutaneously. The presumption is that intracamerally injected P185 cells make a significant impact.
upon the immune system. However, the nature of the resulting immune response is qualitatively different from the response elicited by SC tumors; tumor-bearing eyes in these latter animals develop severe keratoconjunctivitis. It is suspected, but there is no direct proof, that SC tumors elicit T cell-mediated immunity that in the absence of antibody destroys SC tumor cells and tumor cells in the anterior chamber with dispatch. It is further possible that severe inflammatory reactions which take place in anterior chambers of tumor-infested eyes of animals injected at nearly the same time in the flank with P815 cells result from a dynamic in situ interplay of destructive T cells and protective antibodies similar to the phenomenon of immunologic enhancement. 

Alternatively, the inflammatory response seen in these eyes may represent immunostimulation of the tumor, an idea first proposed by Prehn.

Studies to examine these and other possibilities are under way.

Much remains to be investigated in this newly described ocular tumor model. Immunologic and other physiologic aspects of the biology of intracamerally injected murine tumors are essentially unexplored. It might be anticipated that an entire storehouse of interesting and provocative new findings is waiting. Although a weakly histoincompatible tumor has been employed in this first version of the model, there is good reason to expect that some of the lessons learned will be applicable to tumor-specific transplantation antigens. In many ways, minor histocompatibility antigens resemble tumor-specific antigens immunologically, especially in the types of effector immune responses they elicit. Moreover, faint glimpses of therapeutic implications can be seen in the data already collected. Certainly the possibility can be raised that inoculation of tumor cells subcutaneously might be able to direct the host's immune response such that the growth of similar tumor cells in the anterior chamber would be suppressed, the tumor eventually eradicated, and the architecture of the eye preserved.

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REFERENCES