Histopathologic Analysis of Intraocular Allogeneic Tumors in Mice

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The authors have studied histopathologically the growth, invasion, and regression of allogeneic P815 mastocytoma cells placed in the anterior chambers of eyes of three different strains of inbred mice. Previous clinical observations had suggested that the degree of immunogenetic disparity between tumor and recipient governed the intensity and specificity of the host's immune response to the intraocular neoplasm. Our histopathologic studies confirm this conclusion. BALB/c mice, which are H-2 syngeneic with P815 cells, develop progressively growing tumors around which no evidence of host immune or inflammatory response can be found. P815 cells confront A/J mice with a single class I MHC disparity; early intraocular tumor growth is vigorous in this strain, and when the tumor rejection takes place, it is followed by marked fibrovascular scar tissue formation which destroys intraocular structures, resulting in atrophia bulbi. C57BL/6 mice recognize immunologically three categories of allogeneic class I antigens on P815 cells. In these hosts, early tumor growth within the anterior chamber is feeble and rejection is attended by only minimal inflammation; as a consequence, scar formation is trivial and the eye remains anatomically intact. Based on certain histopathologic features, the authors suggest that two distinctly different immune effector mechanisms are involved in intraocular tumor rejection in A/J and C57BL/6 hosts. One immune rejection process results in extensive innocent bystander destruction of normal host tissues (A/J mice) while the other immune mechanism is more precise and does not damage host ocular structures (C57BL/6 mice). Invest Ophthalmol Vis Sci 26:1368–1376, 1985

For the past several years this laboratory has examined extensively the immune responses in mice following inoculation of allogeneic tumor cells into the anterior chamber of their eyes.1–7 In the best defined model, P815 mastocytoma cells (derived originally from a DBA/2 mouse) grow progressively following inoculation into the anterior chamber of BALB/c mice.¹ This latter strain differs from the DBA/2 strain at multiple minor histocompatibility loci; however, both strains share the H-2d major histocompatibility complex (MHC) haplotype. While progressive growth of the P815 tumor within the globe of BALB/c mice is an expression of immunologic privilege within the anterior chamber of the eye, privilege is not always absolute. We have previously shown that tumor cells differing from their recipients at one or more regions of the H-2 complex do not secure permanent tenure within the eye and are eventually rejected.2 The vigor of the rejection mounted by the host against allogeneic intracameral neoplasms is directly proportional to the degree of immunogenetic disparity between the tumor and the host. When tumor and recipient mice differ across the entire H-2 complex, the tumor grows within the anterior chamber for a brief period of time, and then resolves with little or no attendant inflammation—the ocular structures and their anatomic arrangements appear to be spared. By contrast, when the tumor and its recipient differ only by a portion of the major histocompatibility complex (ie, at a single class I locus), the tumor is destroyed by a vigorous process that also damages the structural integrity of the globe.

These gross observations made us wonder about the nature of the pathogenic processes responsible for these different patterns of tumor rejection. In an effort to gain insight into these processes, a histopathologic analysis was conducted to characterize tumor growth and rejection patterns in hosts in whom transplanted intraocular tumors would afford different degrees of immunogenetic disparities. The results of these studies form the basis of this report.

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Supported in part by BRSG S07RR-05426-22 awarded by the biomedical research support grant program division of research resources, NIH, by NIH grant EY-03119 and an unrestricted development grant from the Research to Prevent Blindness, Inc.

Submitted for publication: July 24, 1984.

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Materials and Methods

Experimental Animals

Adult female BALB/c (H-2^d), A/J (H-2^a), and C57BL/6 (H-2^b) mice were purchased from Jackson Laboratories (Bar Harbor, ME) and were used as experimental subjects when 6-10 wk of age. The present investigations conform to the ARVO Resolution on the Use of Animals in Research. All surgical procedures were performed under ketamine hydrochloride anesthesia.

Tumor Cells

P815 mastocytoma cells (DBA/2 origin; H-2^d) were cultivated in suspension cultures in Falcon 75-cm^2 tissue culture flasks (Falcon Plastics; Oxnard, CA) using Dulbecco's modified Eagle's minimal essential medium (MEM) supplemented with 10% heat-inactivated fetal calf serum and gentamycin (0.05 mg/ml; Schering Corp; Kenilworth, NJ). Monocellular suspensions of P815 mastocytoma cells were washed in Hank's balanced salt solution and resuspended to a concentration of 2 X 10^7 cells/ml for intracameral (IC) injections.

Anterior Chamber Injections

A modified quantitative technique for depositing a specific number of tumor cells into the anterior chamber of the mouse eye is described elsewhere. Briefly, mice were deeply anesthetized with 0.66 mg of ketamine hydrochloride (Vetalar, Parke, Davis and Co; Detroit, MI) given intramuscularly. The eye was viewed under the low power (8X) 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. A microglass pipet was fitted into a sterile infant feeding tube (No. 5 French, Cutter Laboratories; Berkeley, CA) which was mounted onto a sterile 0.1-ml Hamilton syringe (Hamilton; Whittier, CA). A Hamilton automatic dispensing apparatus was fitted onto the loaded syringe and used to dispense P815 mastocytoma cell suspensions. The pipet was introduced through the puncture site of the cornea and 5 μl of the P815 cell suspension (containing 1 X 10^5 cells) were delivered into the anterior chamber.

Histopathologic Studies

P815 mastocytoma cells, at a concentration of 10^5 cells/5 μl, were injected IC into panels of BALB/c, A/J, and C57BL/6 mice. The eyes were examined thrice weekly under a dissecting microscope (8X) and tumor growth scored according to the percent of the anterior chamber occupied by the tumor cells. Eyes were also observed for tumor perforation of the globe, tumor invasion of the globe, and development of phthisis bulbi. At days 3, 7, 10, 13, and 20, post IC mastocytoma injection, the mice were killed, and the eyes were enucleated, fixed in 10% buffered formalin, progressively dehydrated to 100% ethanol, cleared in chloroform and embedded in paraffin. Numerous 4-μ thick step sections were taken throughout the globes, stained with hematoxylin and eosin (H and E), periodic acid-Schiff (PAS), and toluidine blue, and examined by light microscopy. Three to six eyes were examined from each group at each of the five time periods chosen. On histopathologic examination, particular attention was paid to: tumor growth and extension; viability of tumor cells; evidence of a mononuclear cell infiltrate within the tumor; and reparative inflammation and anatomical integrity of all ocular structures. The ocular tissues examined individually were: cornea, limbus, sclera, anterior chamber, iris, choroid, and vitreous. Using a scale of 0-4+, these areas were scored on tumor invasion, necrosis of tumor, and inflammation. Scores for each time period were arithmetically averaged and displayed graphically for each group of mice. In addition, three to five eyes from normal BALB/c, A/J, and C57BL/6 mice were examined which did not receive IC injections. These eyes were used as normal controls.

Results

The histopathologic results are summarized in Figures 1 and 2. The reader is referred to Figure 1 for schematic representation of the gross tumor growth and invasion of ocular structures in the respective mouse strains. Figure 1a is a labeled schematic drawing of a normal mouse eye for comparison with the tumor-containing eyes depicted in Figure 1. Host inflammatory responses and the patterns of tumor invasion and resolution of individual ocular tissues are summarized in graphic form in Figure 2. Detailed descriptions of these findings are given below and are presented according to the number of days following intraocular tumor inoculation.

Pattern of Early Tumor Growth (Days 3 and 7): BALB/c, A/J and C57BL/6 Mice

Day 3: The patterns of tumor growth in all three mouse strains were similar at day 3 (Figs. 1b, 2). All eyes contained viable tumor cells which comprised less than 25% of the volume of the anterior chamber. Rather than growing as a solid mass, the tumor cells were cohesive, clustered in the periphery, and were observed to cling to the angle structures, peripheral cornea, and anterior iris surface (Fig. 3). Incarcerated iris marked...
Day 3:

The site of tumor inoculation and prevented apposition of the corneal wound margins (Fig. 3). As a consequence, tumor grew locally into the corneal stroma at the injection site. Tumor cells also spread from the limbus into the corneal stroma and dissected between the stromal lamellae. The sclera, choroid, and vitreous were minimally invaded by tumor; but the retina, optic nerve, and lens were never invaded. At 3 days, there was no histologic evidence of inflammation at any site within the eyes of any of the three mouse strains.

Day 7:

Once again there were no significant differences in the patterns of tumor growth among all three groups of mice examined at day 7 (Figs. 1c, 2). From their eccentric position in the cornea on day 3, tumor cells now appeared to have migrated centripetally to involve all fields and portions of the cornea, although they remained localized in rows between stromal lamellae (Fig. 4). The majority of tumor cells within the cornea were necrotic with extensive pyknosis and karyorrhexis. The tumor occupied approximately 30% of the anterior chamber; however, the center of this mass was necrotic and contained only ghost tumor cells. Near the periphery, viable tumor cells were observed to cling in clusters onto the posterior corneal surface, the angle structures, and the anterior iris (Fig. 4). At this point, tumor cells found in the vitreous were scattered, rather than clumped, and exhibited signs of necrosis.

At day 7, viable tumor cells filled the limbal area, obliterated the scleral structure, and by infiltration, resulted in a marked expansion of the tissues, which in turn created a bulge under the conjunctiva (Fig. 4). Viable tumor cells extended posteriorly from the limbus and caused thickening of the anterior choroid, ciliary body, and iris. Thus, the enlarging globe and the thickening of intraocular structures were largely due to extensive tumor infiltration.

Up until this time, tumor was not found in the retina, optic nerve, or lens, nor was inflammation observed in these or any other intraocular structure.

Beyond day 7, the patterns of tumor growth diverged in the three mouse strains. Consequently, the histopathologic findings in the three different groups of mice will be described separately in the following sections.

Patterns of Late Tumor Progression (Days 10, 13, and 20): BALB/c Mice

Day 10: By day 10, the tumor cells, which had infiltrated between the lamellae of the cornea, had be-
come necrotic (Figs. 1d, 2). Similarly, the anterior chamber was filled with tumor, but the vast majority of the cells were dead—only a thin rim of viable cells was observed to cling to the posterior surface of the cornea and iris. An increased number of tumor cells was scattered in the vitreous, but these cells were also necrotic. The limbus was also greatly thickened by tumor cells, but in contrast to the previously described sites, only rare cells were necrotic. A similar finding characterized the anterior sclera. Tumor was observed to have spread from these areas to the extraocular muscles and adnexa. Large numbers of viable tumor cells increased the thickness of the iris and choroid as the flow of aggressive tumor cells migrated posteriorly. The lens was cataractous and the lens epithelium was completely absent.

Day 13: Three days later (day 13), the tumor growth pattern resembled that seen on day 10 except that all vascularized intraocular structures were even more thickened by progressive tumor growth (Figs. 1e, 2). The anterior chamber had become enlarged, and necrotic tumor cells appeared to force the cornea to bulge anteriorly. Necrotic tumor cells in the vitreous were further increased in number, but remained scattered. Tumor was never observed to invade the retina, optic nerve, or lens at days 10 or 13, but this was not true subsequently.

Day 20: By day 20, tumor had so expanded the ocular tissues in BALB/c mice that the globe was twice its normal diameter (Figs. 1f, 2, 5A). Neoplastic cells extensively invaded the limbus, sclera, iris, choroid, retina, and optic nerve such that these individual structures were unrecognizable (Fig. 5A). Tumor cells also filled the vitreous and anterior chamber spaces, but the cells were necrotic and formed a sterile abscess. The central cornea appeared to have perforated as there was a large gap in Descemet’s membrane through which necrotic tumor protruded. Tumor involvement
Fig. 3. Photomicrographs of typical histologic features of tumor at day 3. A/J mouse strain is illustrated. Iris is thickened peripherally by mastocytoma cells. Paracentrally, iris is incarcerated in the perforation at the site of previous IC injection (asterisk). Tumor cells are present in the: anterior chamber; cornea, both in the periphery and at the site of IC injection (asterisk); limbus; and sclera. BALB/c and C57BL/6 mouse strains show similar features at day 3 (H and E).

Fig. 4. Photomicrograph of the typical histologic features of tumor at day 7. A/J mouse strain is illustrated. Choroid (arrows) is now involved. Changes are representative of those present in BALB/c and C57BL/6 mouse strains at day 7. (Outer retinal degeneration with loss of the outer nuclear and photoreceptor cell layers [arrowheads] with normal retinal pigment epithelium and choroid of A/J mouse eye is illustrated.) Similar retinal degeneration was noted in normal control A/J mice over 5 mo of age and is thus unrelated to the presence of tumor (H and E).

of adnexal structures destroyed their normal anatomic integrity. Despite massive evidence of tumor necrosis in poorly vascularized intraocular compartments, inflammation was never observed in the eyes of BALB/c mice. No distant metastases were noted at necropsy.

Summary: In BALB/c mice, P815 tumor cells appeared to grow aggressively throughout the ocular structures within the globe and into the adnexa (Fig. 1f). The absence of an attendant inflammatory response suggests that little, if any, host antitumor response operated in these animals. Tumor necrosis appeared to occur only in those ocular compartments where a tenuous blood supply is likely to be a limiting factor (ie, cornea, anterior chamber, and vitreous). Where the vasculature is abundant (ie, iris, choroid, sclera, and limbus) the tumor grew progressively with little evidence of necrosis.

At this point we would like to affirm that the pattern of P815 tumor growth, which has been described in the eyes of BALB/c mice, is identical to that observed when P815 cells were injected into the anterior chambers of eyes of DBA/2 mice. Since DBA/2 mice are syngeneic with the P815 tumor cells, this finding further underscores the lack of an antitumor response in the allogeneic BALB/c hosts.

Pattern of Late Tumor Growth and Resolution (Days 10, 13, and 20): A/J Mice

Day 10: In many ways, the appearance of P815 tumor involvement of A/J eyes was very similar to that in BALB/c eyes at day 10 (Figs. 1g, 2), with the important exception that a severe mononuclear cell infiltrate was observed to cuff the veins (periphlebitis) within the retina and optic nerve. Curiously, there was no evidence to suggest that tumor cells had invaded these ocular structures at this point.

Day 13: Dramatic changes occurred over the next three days. By day 13, the extent of tumor within the eye had obviously receded—tumor was no longer present within the iris and choroid of A/J mice (Figs. 1h, 2). The only viable mastocytoma cells to be found on day 13 were located in extraocular, adnexal structures. A vigorous fibrovascular inflammatory response was present within the globe at this time and was characterized by proliferation of capillary vascular channels,
Fig. 5. Photomicrograph depicting differing end results of tumor invasion, inflammation, and/or resolution in (A) BALB/c, (B) A/J, and (C) C57BL/6 eyes on day 20. A, BALB/c mouse strain at day 20. The globe is enlarged by tumor. The anterior segment (brackets) is necrotic and tumor invasion obliterates all ocular structures except collapsed lens capsule (arrows) (PAS). B, A/J mouse strain at day 20. The globe is shrunken from contraction of scar tissue. Descemet's membrane is thrown into folds (arrows) and the anterior chamber is obliterated by fibrovascular scar tissue. A fibrovascular preretinal membrane is causing traction folds in the retina (arrowheads) (PAS). C, C57BL/6 mouse strain at day 20. Pigment-laden macrophages in the angle are the only sequelae of mastocytoma invasion and regression. Artifactiously, only small, peripheral portions of lens and retina are shown (PAS).
activated fibroblasts, macrophages, and scattered lymphocytes and plasma cells which were typically found in sites which tumor had previously occupied (ie, cornea, limbus, sclera, iris, and choroid). The intensity of the fibrovascular reactions was greatest in the anterior segment.

Day 20: By day 20, tumor had receded from all intraocular and extraocular structures in the A/J hosts (Figs. 1i, 2). Only scattered necrotic cells remained in the vitreous (Fig. 5B). The retinal and optic nerve periphlebitis had resolved. There was vascularization and scarring of the cornea with dense fibrovascular retrocorneal tissue firmly binding the entire iris to the posterior corneal surface, thus obliterating angle filtration structures at the limbus (Fig. 5B). Fibrovascular inflammatory scar tissue was also present in the sclera, choroid, and vitreous (Fig. 5B). Retraction of the extensive intraocular scar tissue reduced the size of the globe by approximately 30% in overall diameter (compared to normal A/J eyes) resulting in atrophia bulbi. No distant metastases were noted at necropsy.

Summary: In A/J mice, tumor resolution, which is undoubtedly achieved by immunologic means, is followed by a vigorous, intense fibrovascular inflammatory reaction which invades and disrupts the architecture of the eye, especially the anterior segment. As this reaction subsides, scar formation and contraction further distort the anatomy of the eye, rendering it atrophic, thus accounting for the clinical observation of phthisis bulbi.2

Pattern of Late Tumor Growth and Resolution (Days 10, 13, and 20): C57BL/6 Mice

Day 10: The ocular tumor load and its pattern of distribution was different by day 10 in C57BL/6 mice, compared to that described in A/J and BALB/c mice (Figs. 1j, 2). The amount of tumor in the eyes of the C57BL/6 mice was significantly less than that observed in the eyes of the other mice (Fig. 1j); nonetheless, it did invade extraocular structures. Within the tumor itself, no mononuclear cells were seen. However, these inflammatory cells were especially abundant in the cornea, limbus, and sclera. Surprisingly, there was only minimal evidence of a fibrovascular inflammatory response. The periphlebitis of the retinal and optic nerve vessels observed in A/J mice was also evident in C57BL/6 mice.

Day 13: By day 13, a dramatic change had taken place in the C57BL/6 hosts. Tumor had virtually disappeared from the adnexa, iris, limbus, and choroid (Figs. 1k, 2). The small numbers of tumor cells remaining within the cornea, anterior chamber, and vitreous were completely necrotic. An intense inflammatory response, characterized chiefly by a mononuclear clear cell infiltrate, was evident in the cornea and limbus; yet, the fibrovascular response was insignificant.

Day 20: The eyes of C57BL/6 mice examined on day 20 (Figs. 11, 2) showed no evidence of tumor (Fig. 5C). Punctate evidence of fibrovascular inflammatory tissue was occasionally found in the anterior segment, but the majority of eyes had returned to a relatively normal anatomic appearance with the exception that the lens was catacteous (Fig. 5C). Pigment-laden macrophages were present in the angle as the only residue of tumor resolution (Fig. 5C). No distant metastases were noted at necropsy.

Summary: Tumor destruction, which is also accomplished by immune processes in C57BL/6 mice, is achieved with only modest damage to intraocular structures. The virtual absence of a fibrovascular inflammatory response permitted the eye to retain its anatomic integrity without the distortions that scar formation and retraction imposed upon ocular structures in A/J mice.

Discussion

Syngeneic neoplastic cells produce progressively growing intraocular tumors following transplantation into the anterior chamber. However, when tumor cells and their recipients are immunogenetically disparate, several different types of intracameral tumor growth patterns have been observed: (1) a progressive pattern unassociated with inflammatory reaction that resembles in every detail the growth of tumors in syngeneic anterior chambers; (2) transient tumor growth followed by resolution in which an intense inflammatory reaction results in destruction of the tumor, accompanied by anatomic disruption and disintegration of the globe itself; and (3) transient and more limited tumor growth with subsequent resolution, accompanied by a very mild inflammatory reaction in which the anatomic integrity of the eye is preserved. These patterns have been observed in every detail the growth of tumors in syngeneic anterior chambers; (2) transient tumor growth followed by resolution in which an intense inflammatory reaction results in destruction of the tumor, accompanied by anatomic disruption and disintegration of the globe itself; and (3) transient and more limited tumor growth with subsequent resolution, accompanied by a very mild inflammatory reaction in which the anatomic integrity of the eye is preserved.2 The recipient strains in the present studies are representative of these three patterns. The histopathologic changes described here correspond well to our previous clinical observations and provide some insights into the immunopathogenesis of the ocular phenomena. Clinical observations suggest that BALB/c mice offer little resistance to growth of P815 cells injected into the anterior chamber.1 The histologic findings similarly reveal little evidence of host response in or around the intraocular neoplasm. In fact, the tumor appears to infiltrate progressively throughout ocular structures without restraint. Significant evidence of tumor necrosis was observed only in those compartments of the eye in which the blood supply is presumed to be a limiting factor: cornea, anterior chamber, and vitreous. These findings
are consistent with the immunologic findings that BALB/c mice are unable to respond in an effective immunologic fashion to protect themselves against the invading P815 neoplasm. This is of some immunologic interest since mice bearing P815 tumors in their anterior chambers make circulating antibodies and cytotoxic T-cells specific for antigens on the tumor. However, these same mice display significantly suppressed delayed hypersensitivity to the P815 cells. By implication, the protective modality which tumor-bearing BALB/c mice lack is the capacity to develop delayed-type hypersensitivity.

Both A/J and C57BL/6 strains of mice are able to destroy P815 tumors inoculated into the anterior chamber; consequently, they are cured of their malignant disease. In these strains, expansion of donor-host immunogenetic disparity to include one or more strong MHC-encoded transplantation antigens is undoubtedly responsible for the effectiveness with which the immune system achieves tumor graft rejection. However, the patterns with which the tumors are rejected within the eyes of these two strains are considerably different. In C57BL/6 animals, the pace at which the tumor grows is retarded compared to its growth rate in A/J and in BALB/c mice. As a consequence, even at its peak size, the tumor mass occupies less than 50% of the globe. In addition, as the tumor recedes in C57BL/6 mice, there is only a mild mononuclear cell infiltrate. By contrast, in A/J mice the tumor grows to a larger size, invades more deeply within the tissues, and subsequently undergoes necrosis prior to histologic evidence of intrusion of an intense inflammatory reaction. Unlike C57BL/6 mice, the inflammatory reaction in tumor-containing A/J eyes is intense and comprised predominantly of a fibrovascular reparative response. As the reaction subsides, there is gross distortion of the anatomic arrangements, especially the anterior segment of the globe. We have made the clinical observation that the eyes of A/J mice become phthisic following rejection of the P815 tumor whereas C57BL/6 eyes return to an apparently physiologic anatomic appearance following tumor resolution. Our histopathologic studies reveal that retraction and scar formation in the anterior segment of A/J eyes account for the phthisic appearance.

Based on histopathologic and clinical observation, we believe that two different immunopathologic processes are involved in A/J mice and C57BL/6 mice. In support of this contention are the following points: (1) the end result of graft rejection is different in the two strains: anatomic integrity of the eye is maintained in C57BL/6 mice, while the anterior segment of A/J eyes is destroyed; (2) the tumor mass never reaches the same magnitude in C57BL/6 as it does in A/J eyes unless the former hosts are immunologically suppressed with sublethal, whole-body gamma irradiation (previous unpublished results); and (3) the inflammatory response is mild and coincident with resolution of the tumor in C57BL/6, whereas the more intense inflammatory response in A/J is delayed beyond the time at which tumor necrosis appears, and appears to be predominantly a fibrovascular reparative reaction. We have suggested in the past that the reason for the precision with which tumor grafts are rejected without significant ocular injury in C57BL/6 mice is that immune effector modalities that cause only trivial innocent bystander injury are employed. Specific antibody as well as cytotoxic T-cells can be regarded as effectors capable of this degree of precision. By contrast, delayed hypersensitivity involves release of pharmacologically active lymphokines and the recruitment of nonspecific host defense mechanisms and cells into the site and, thus, carries a high burden of innocent bystander destruction. Our histopathologic findings are consistent with the suggestion that in C57BL/6 mice, antibody and/or cytotoxic T-cells are likely to be the predominant mediators of tumor rejection and not DTH since there was no evidence of nonspecific damage to normal host ocular tissues in these mice. By contrast, the extensive tissue destruction attending tumor rejection in A/J mice suggests that a DTH-like mechanism was involved. Whether this was specifically due to a classical DTH response elicited by Lyt 1 + lymphokine-secreting T-cells cannot be determined definitively by histologic means. An alternate hypothesis is that a significant amount of tumor destruction occurred in A/J mice through direct cytolysis by CTL. According to this hypothesis, the increased damage to the eyes of A/J mice may simply be due to a greater and more prolonged immunologic reaction within these eyes because of the larger tumor burden present in A/J hosts compared to C57BL/6 hosts. Thus, extensive CTL-mediated tumor destruction might in turn culminate in significant nonspecific necrosis of normal host tissues. However, it is difficult to envision direct cytolysis by CTL as the sole explanation of such a process when one considers the exquisite precision and antigen restriction of CTL-mediated cytolysis of allogeneic cells.

These are not the first experimental results to suggest that delayed hypersensitivity is an important mediator of allograft immunity. Dvorak and his colleagues have proposed that delayed hypersensitivity is the dominant effector mechanism operating in the rejection of solid tissue allografts (ie, skin), as well as in rejection of syngeneic tumors that bear tumor-specific antigens to which the host has mounted an immune response. Based on histologic analysis and adoptive cell transfer experiments, other investigators have similarly suggested that extraocular syngeneic tumors are rejected by a DTH mechanism elicited by Lyt 1 +, an-
tigen-specific T-cells. The extensive nonspecific and innocent bystander destruction we have observed in A/J eyes containing the P815 tumor is typical of a response initiated by T-cells of the DTH type. Bulk necrosis of the tumor in well-vascularized compartments of A/J eyes implies that ischemia, presumably due to microvascular damage, has taken place. In addition, the presence of periphlebitis in an intraocular site, distant from the tumor, further supports a DTH mechanism reminiscent of that described by Dvorak et al.9,12

The most common intraocular tumor of childhood is retinoblastoma. In this clinical situation, spontaneous regression is a relatively common event.16 It is pertinent that a significant number of these regressions result in phthisical eyes, while the remainder result in an eye that is anatomically intact.17 While infarction secondary to the tumor’s outstripping its blood supply may account for phthisis in certain instances, we would suggest that a DTH component of the host’s antitumor response may account for the remainder. In that regard, it has recently been reported that unique tumor-specific antigens can be identified on retinoblastoma cells.18 If this thesis is correct, then it might be considered that the eyes in which tumor regression takes place without disruption of the visual axis may have benefitted from an effector modality dominated by cytotoxic T-cells, and/or specific antibody. Perhaps, clinical strategies of ocular tumor immunotherapy that are designed to optimize the production of cytotoxic T-cells and antibodies at the expense of DTH would have important clinical benefits.

Key words: mastocytoma, tumor allografts, anterior chamber, anterior chamber associated immune deviation, immune rejection, major histocompatibility complex

Acknowledgments

The excellent technical assistance of Ellen Johnson, Elizabeth Mayhew, Jessamee Krenek, and Dora Valles is greatly appreciated. The manuscript was carefully prepared by Scott Guthrie and Sara Howard.

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