Resistance of Retinal Ganglion Cells to an Increase in Intraocular Pressure Is Immune-Dependent

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PURPOSE. Glaucoma is widely accepted as a neurodegenerative disease in which retinal ganglion cell (RGC) loss is initiated by a primary insult to the optic nerve head, caused, for example, by increased intraocular pressure (IOP). In some cases, the surviving RGCs, despite adequate IOP control, may continue to degenerate as a result of their heightened susceptibility to self-destructive processes evoked by the initial damage. In animal models of mechanical or biochemical injury to the optic nerve or retina, a T-cell–mediated immune response evoked by the insult helps to reduce this ongoing loss. The current study was conducted to find out whether the ability to resist the IOP-induced loss of RGCs in a rat model is affected by the immune system.

METHODS. The ocular veins and limbal plexus of rats of two strains differing in their resistance to experimental autoimmune encephalomyelitis (EAE) and in their ability to manifest a beneficial autoimmune response were laser irradiated twice to induce an increase in IOP. The pressure was measured weekly, and RGC losses were assessed 3 and 6 weeks after the first irradiation. To verify the existence of a relationship between the immune system and RGC survival, we assessed neuronal survival in Sprague-Dawley (SPD) rats deprived of mature T cells as well as after transferring splenocytes from Fisher rats, an EAE-resistant rat strain capable of manifesting T-cell–mediated neuroprotection, to rats of a major histocompatibility complex (MHC)–matched EAE-susceptible strain (Lewis), in which the ability to manifest such protective immunity is limited.

RESULTS. Both 3 and 6 weeks after the increase in IOP was initiated, the number of surviving RGCs in SPD rats, a strain in which a beneficial autoimmune response can be evoked spontaneously, was significantly higher than in Lewis rats. Moreover, in SPD rats that were thymectomized at birth, the number of surviving RGCs after an increase in IOP as adults was significantly diminished. Passive transfer of splenocytes from Fisher rats to Lewis rats significantly reduced the IOP-induced loss of RGCs in the latter.

CONCLUSIONS. In rats of different strains, a similar increase in IOP results in differing amounts of RGC loss. This disparity was found to correlate with immune potency. These findings may explain why patients with glaucoma experience different degrees of visual loss after pressure reduction, even when the severity of the disease at the time of diagnosis is similar. The results have far-reaching prognostic and therapeutic implications. (Invest Ophthalmol Vis Sci. 2002;43:2648–2653)

Glaucoma is now recognized as belonging to a group of neurodegenerative diseases characterized by the slow, progressive degeneration of retinal ganglion cells (RGCs) that causes a gradual loss of visual field and eventually leads to blindness. The primary cause of the disease is not yet known, and the factors contributing to its progression are not yet fully characterized. The current treatment of patients with glaucoma is limited to reduction of intraocular pressure (IOP), known to be one of the major risk factors for the disease. It is clear, however, that the lowering of IOP, although significantly reducing the extent of neuronal loss, does not ensure cessation of the disease process, because the loss of RGCs may continue, even after the IOP has been reduced. Recent studies of the association between IOP regulation and visual field loss after medical or surgical intervention showed that ongoing neuronal loss reflected in visual field tests can be diminished if the IOP is low (defined as below 14 mm Hg). Experience has shown, however, that neuronal loss may continue to occur after reduction of IOP to a level that, although above 14 mm Hg, is below the patient’s hypertensive level and even below the normal level. Such IOPs may be difficult to reach, and therefore degeneration may continue.

It has been suggested by our group that the ongoing loss of neurons in glaucoma may be explained, at least in part, by secondary factors resulting from the degeneration of neurons (RGCs and their fibers) that were involved in the primary insult caused, for example, by the increase in IOP. According to this view, although the primary insult does not directly affect all fibers and RGCs, it causes alterations in the neuronal environment (including changes in neurotransmitters, depletion of growth factors, influx of calcium into the cells, and formation of free radicals), which in turn increase the vulnerability of spared neurons. Such alterations (e.g., the abnormally high concentrations of glutamate and nitric oxide) have been demonstrated in patients with glaucoma, as well as in monkeys with abnormally high IOP. Similar changes have been observed in a rat model of partial optic nerve injury, often used for studies of secondary degeneration and neuroprotection. Evidence of the presence of deleterious factors that may be associated with secondary degeneration of the optic nerve also was recently demonstrated in monkeys. This view of the pathogenesis of glaucoma has prompted attempts to identify additional compounds that make the extracellular environment hostile to neurons and to find ways of inhibiting the activity of these compounds or circumventing their effects.

Using the simplified rat model of a single acute trauma to the optic nerve, our group discovered that mechanical (e.g., crush injury) or biochemical (e.g., glutamate-induced) insults to the optic nerve or retina stimulate a physiological protective mechanism that is mediated by T cells. It was postulated that this T-cell–mediated immune response is designed to help the body cope with the self-destructive processes induced by trauma and to term it “protective autoimmune.” Rats or mice devoid of mature T cells showed a worse recovery from axonal injury or glutamate toxicity than...
matched control animals with normal immune systems.\textsuperscript{17,18,24} Moreover, not all animals or strains are equally endowed with the ability to sustain an autoimmune response with beneficial outcome.\textsuperscript{17} Animals that are inherently resistant (when challenged with myelin-associated antigens emulsified in adjuvant) to the development of a transient monochromat central nervous system (CNS) autoimmune disease, known as experimental autoimmune encephalomyelitis (EAE), recover better from optic nerve injury than EAE-susceptible animals.\textsuperscript{17} Differences in recovery appear to be attributable to differences in the ability of a particular animal or strain to manifest a spontaneously well-controlled autoimmune response with a beneficial outcome. In the present study, using a rat model, we showed that the ability to cope with a chronic condition of the visual system, such as increased IOP, is also immune dependent.

\section*{Materials and Methods}

\subsection*{Animals}

Inbred adult male Lewis, Fisher, and Sprague-Dawley (SPD) rats (average weight, 300 g) were supplied by the Animal Breeding Center at The Weizmann Institute of Science. The rats were raised in a light- and temperature-controlled room and were matched for age and weight before each experiment. All animals were handled according to the regulations formulated by International Animal Care and Use Committee (IACUC) and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

\subsection*{Induction of High IOP}

Rats were deeply anesthetized by intramuscular injection of ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (0.5 mg/kg). A slit lamp emitting blue-green argon laser irradiation (Haag-Streit, K"oniz, Switzerland) was used to treat the right eye of the anesthetized rat with 80 to 120 applications directed toward three of the four episcleral veins and toward 270° of the limbal plexus. The laser beam was applied with a power of 1 W for 0.2 seconds, producing a spot size of 100 mm at the episcleral veins and 50 mm at the limbal plexus. At a second laser session 1 week later, the same parameters were used, except that the spot size was 100 mm in all applications. Irradiation was directed toward all four episcleral veins and 360° of the limbal plexus.\textsuperscript{24}

\subsection*{Measurement of Intraocular Pressure}

Most anesthetic agents cause a reduction in IOP,\textsuperscript{25} thus precluding a reliable measurement. To obtain accurate pressure measurements while the rat was in a tranquil state, we injected the rat intraperitoneally with 10 mg/mL acepromazine, a sedative drug that does not reduce IOP, and measured the pressure in both eyes 5 minutes later with a tonometer (Tono-Pen XL, Automated Ophthalmics, Ellicott City, MD). after applying Localin to the cornea. Pressure was always measured at the same time after injection if acepromazine, and the average of 10 measurements taken from each eye was recorded. Measurements were taken on five different occasions, all at the same time of day: before laser treatment, 1 day later, 1 week after treatment just before the second laser session, 2 weeks after the first laser session, and 1 day before the retina was excised (3 or 6 weeks after the first laser session). The untreated contralateral eye served as the control.

\subsection*{Anatomic Assessment of Retinal Damage Caused by the Increase in IOP}

The hydrophilic neurotracer dye dextran tetramethylrhodamine (Rhodamine Dextran, Molecular Probes, Eugene, OR) was applied directly into the intravitreal portion of the optic nerve. Only axons that survive an incomplete optic nerve crush injury remain functional with live cell bodies can take up the dye and demonstrate labeled RGCs. The rats were killed 24 hours later, and their retinas were excised, whole mounted, and preserved in 4% paraformaldehyde. The RGCs were counted under magnification of ×800 in a fluorescence microscope (Carl Zeiss, Oberkochern, Germany). From each retina four fields were counted, all with the same diameter (0.076 mm²) and at the same distance from the optic disc.\textsuperscript{17–21} Eyes from untreated rats were used as the control. RGCs were counted by an observer blinded to the identity of the retinas.

\section*{Partial Crush of the Rat Optic Nerve}

The optic nerve was crushed as previously described in detail.\textsuperscript{14} Using a binocular operating microscope, we exposed the right optic nerves of the anesthetized rats. Calibrated cross-action forceps were used to inflict a moderate or severe crush injury on the optic nerve, 1 to 2 mm from the eye. To assess systemic and local inflammatory effects, we inflicted a severe crush in both strains. The contralateral nerve was left undisturbed.

\subsection*{Measurement of Secondary Neuronal Degeneration}

Two weeks after crush injury, survival of cell bodies with intact fibers was assessed by application of the fluorescent lipophilic dye 4-(dicyanomethylene)-2-methyl-6(3-dimetlyaminostyril)tetra-1,4-pyrindinium iodide (4-DiI-Asp; Molecular Probes Europe BV, Leiden, The Netherlands) distally to the site of lesion, as previously described.\textsuperscript{24}

\subsection*{Examination of Immune System Involvement in IOP-Induced Neuronal Loss after Partial Crush Injury}

To examine the role of the immune system in determining the extent of neuronal loss, we transferred splenocytes from Fisher rats, which are moderately resistant to EAE, to the EAE-susceptible Lewis rats. Splenocytes obtained from Fisher rats were injected intravenously into Lewis rats (3.5 × 10⁸ per rat) immediately after the first laser session. Three weeks later, the retinas were retrogradely labeled with dextran tetramethylrhodamine and excised. As a control group, we used Lewis rats that underwent the same procedure but were injected intravenously either with PBS or with splenocytes derived from other Lewis rats.

\section*{Results}

\subsection*{Achievement of High IOP}

Studies in our laboratory have shown that in EAE-resistant strains, such as SPD or Fisher rats, the numbers of fibers and cell bodies that survive an incomplete optic nerve crush injury are larger than in the EAE-susceptible Lewis strain and that these differences are diminished when SPD rats, as a result of neonatal thymectomy, are devoid of mature T cells.\textsuperscript{17} In the present study we examined whether these strains also differ in their resistance to the effects of high IOP. An increase in IOP was induced in SPD (n = 13) and Lewis (n = 10) rats. Throughout this experiment, IOPs were recorded weekly. In each rat, 10 measurements were taken at each time point to ensure that the recorded value represented the real IOP and not a momentary fluctuation. The validity of the measurements in the tested rats is further supported by our finding that measurements in normal eyes did not vary significantly. For each strain, we produced a graph depicting fluctuations in mean IOP (± SD) in both eyes over time (Fig. 1). In most cases we observed a sharp increase in IOP to a mean of 30 mm Hg 1 day after the first laser session. At the next measurement, 1 week after the first session and just before the second one, a decrease of 2 to 3 mm Hg was observed. After the second laser session the mean IOP remained stable at approximately 26 mm Hg. Fluctuations in IOP in the untreated contralateral eye over the period of measurements were not significant (Fig. 1). Table 1 records the average IOPs in all rats examined in each group in the study, demon-
stratifying the reproducibility of both the IOP increase and its measurement (see Table 5).26

Loss of RGCs Caused by Increase in IOP
As a baseline, we compared the number of RGCs in five SPD and five Lewis rats by applying a dye to the optic nerve and counting the retrogradely labeled RGCs in the excised, whole-mounted retinas 24 hours later. The average number of RGCs per square millimeter (±SD) was 2657 ± 368 in the SPD rats and 2525 ± 368 in the Lewis rats (Table 2). The difference, according to a two-tailed t-test, was not significant (P = 0.7).

To examine whether the two strains differ in their ability to resist the damaging effect of the increased pressure on their RGCs, we compared the number of surviving RGCs in the two strains 3 weeks (n = 10 and n = 12 in Lewis and SPD rats, respectively) and 6 weeks (n = 7 and n = 21, respectively) after the first laser treatment. At both times, the mean numbers of surviving RGCs were significantly higher in the SPD rats than in the Lewis rats (Table 2). At both time points no significant differences were observed in the IOPs between the two strains. In both strains, the extent of neuronal loss was far greater during the first 3 weeks after the laser-induced increase in IOP than later on.

Because the two strains selected for this experiment differ in their ability to manifest a beneficial autoimmune response (protective autoimmunity), it was important to determine whether their differences in RGC loss are also immune-related—that is, whether the better survival of RGCs in SPD rats is T cell-dependent and whether the greater loss of RGCs in the Lewis rats might be a reflection of the lower ability of their cellular immunity to sustain a protective response.

Absence of T Cells in Resistant Strains Leads to a Larger Loss of RGCs after an Increase in IOP
Three weeks after the IOP was increased, we compared RGC survival in adult SPD rats that had been thymectomized at birth (and therefore lack mature T cells) to that in normal adult rats. Table 3 shows that the number of surviving RGCs in the thymectomized rats was significantly lower than that in the non-thymectomized controls.

Effect of Splenocyte Transfer from Resistant Donors to Susceptible Recipients
To determine whether the relatively poor ability of Lewis rats to resist the IOP-induced damage to their RGCs is related to the ability of their lymphocytes to mediate a protective response, we injected these rats with splenocytes transferred from a strain known to be capable of manifesting protective autoimmunity and examined the effect of the transfer on the survival of RGCs after the IOP was increased. To obtain valid results from this immune manipulation, it was necessary to ensure matching of the donor and recipient major histocompatibility complexes (MHCs). We therefore had to choose a rat strain other than SPD as a donor, while making sure that the selected strain was endowed, like SPD, with the endogenous ability to manifest a beneficial autoimmune response. The strain chosen was Fisher, because Lewis and Fisher rats possess identical alleles of the rat MHC RT1.B except for a single allele in the nonclassic region corresponding to the mouse Qa-Tia.17,27

We examined whether the RGC loss caused by high IOP in Lewis rats can be reduced by the transfer of splenocytes from Fisher rats (Table 4). The splenocyte transfer was intended to provide the recipients with the equivalent of the total number of splenocytes in the adult rat. In Lewis rats with high IOP, the mean number of surviving RGCs was found to be significantly higher after intravenous injection of Fisher splenocytes than after intravenous injection of PBS. To verify that this increase in RGC survival resulted from the introduction of splenocytes from Fisher rats and not just from an increase in the total number of lymphocytes, we injected Lewis rats with homologous splenocytes from other Lewis rats. This injection had no effect on RGC survival. To further verify that the transfer of

Table 1. Mean IOP in All Animals

<table>
<thead>
<tr>
<th>Strain</th>
<th>Normal</th>
<th>1 Week</th>
<th>2 Weeks</th>
<th>3 Weeks</th>
<th>6 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis (Right Eye)</td>
<td>17.10 ± 1.20</td>
<td>28.32 ± 1.99</td>
<td>29.24 ± 2.58</td>
<td>28.42 ± 2.81</td>
<td>26 ± 2.72</td>
</tr>
<tr>
<td>(n = 31)</td>
<td>(n = 24)</td>
<td>(n = 17)</td>
<td>(n = 21)</td>
<td>(n = 10)</td>
<td></td>
</tr>
<tr>
<td>Lewis (Left Eye)</td>
<td>16.49 ± 1.09</td>
<td>17.55 ± 2.01</td>
<td>17.22 ± 1.155</td>
<td>18.21 ± 1.26</td>
<td>20.23 ± 1.48</td>
</tr>
<tr>
<td>(n = 31)</td>
<td>(n = 24)</td>
<td>(n = 17)</td>
<td>(n = 21)</td>
<td>(n = 10)</td>
<td></td>
</tr>
<tr>
<td>SPD (Right Eye)</td>
<td>17.37 ± 2.19</td>
<td>27.54 ± 3.79</td>
<td>27.32 ± 2.84</td>
<td>28.36 ± 3.01</td>
<td>24.10 ± 3.44</td>
</tr>
<tr>
<td>(n = 23)</td>
<td>(n = 23)</td>
<td>(n = 13)</td>
<td>(n = 23)</td>
<td>(n = 13)</td>
<td></td>
</tr>
<tr>
<td>SPD (Left Eye)</td>
<td>19.41 ± 1.68</td>
<td>19.78 ± 1.82</td>
<td>19.28 ± 2.08</td>
<td>19.30 ± 2.18</td>
<td>19.83 ± 2.53</td>
</tr>
<tr>
<td>(n = 23)</td>
<td>(n = 23)</td>
<td>(n = 13)</td>
<td>(n = 23)</td>
<td>(n = 13)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean IOP (mm Hg) in each group in which measurements were taken at the indicated time points after laser irradiation. IOPs in laser-irradiated (right) eyes and contralateral (left) eyes of both strains are shown.
Immune Neuroprotection in Glaucoma

**TABLE 2.** Number of Viable RGCs 3 and 6 Weeks after Induction of High IOP in Laser-Treated and Untreated Lewis and SPD Rats

<table>
<thead>
<tr>
<th>Strain</th>
<th>Mean RGCs ± SD (per mm²)</th>
<th>Mean IOP ± SD (mm Hg)</th>
<th>Mean RGCs ± SD (per mm²)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>3 Weeks after Laser</td>
<td>6 Weeks after Laser</td>
<td></td>
</tr>
<tr>
<td>Lewis</td>
<td>2525 ± 372 (n = 5)</td>
<td>29.92 ± 2.38 (n = 10)</td>
<td>1420 ± 272 (n = 12)</td>
<td>53.9</td>
</tr>
<tr>
<td>SPD</td>
<td>2661 ± 372 (n = 6)</td>
<td>27.86 ± 2.91 (n = 12)</td>
<td>1994 ± 161 (n = 21)</td>
<td>74.2</td>
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<tr>
<td></td>
<td></td>
<td>25.62 ± 2.58 (n = 7)</td>
<td>1267 ± 215 (n = 21)</td>
<td>47.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.8 ± 3.77 (n = 21)</td>
<td>1838 ± 326 (n = 21)</td>
<td>69.8</td>
</tr>
</tbody>
</table>

SPD and Lewis rats were subjected to laser irradiation. Surviving RGCs in rats with normal IOP and in rats with a laser-induced increase in IOP were counted after being retrogradely labeled. Three weeks after the first laser irradiation, 10 SPD rats and 12 Lewis rats were examined. Six weeks after the first laser irradiation, 21 SPD rats and 7 Lewis rats were examined. Results are expressed as the mean ± SD of RGCs per square millimeter. Statistical analyses were performed with a two-tailed t-test. *P* values for the differences in RGCs between the two strains were 0.001 and 0.0001 at 3 and 6 weeks, respectively, after laser irradiation. No significant differences in IOPs between the two strains were found 3 weeks or 6 weeks after initiation of laser treatment (*P* = 0.104 and *P* = 0.64, respectively).

**DISCUSSION**

This study shows that rats of two different strains, when subjected to an identical or near-identical insult induced by IOP, experienced RGC losses of different amounts. This difference was found to be linked to immune system activity. High IOP is considered to be a major risk factor in glaucoma. However, in some patients with glaucoma the loss of RGCs continues despite therapeutic IOP reduction. There are at least three possible reasons for this: (1) insufficient IOP reduction; (2) emergence of additional risk factors during the course of the disease; and (3) increased susceptibility of the remaining neurons to the unfavorable conditions. The ongoing loss of RGCs in glaucoma may be partially attributable to a process of secondary degeneration occurring in an extracellular nerve environment made hostile to spared neurons as a consequence of the primary insult induced by IOP or other risk factors. Research worldwide has been devoted to identifying the compounds and processes that may help explain why the damage continues to spread, even after normal pressure is restored. The mechanisms of damage propagation seen in various acute and chronic degenerative conditions appear to have much in common. As an example, the ubiquitous neurotransmitter glutamate, a major mediator of chronic neurodegenerative disorders, is a potential mediator of toxicity in animal models of acute optic nerve injury, as well as in glaucoma. Attempts have therefore been focused on ways to neutralize or diminish the toxicity of such mediators or at least to increase the ability of the neurons to resist the effects of the unfavorable environment.

Studies in our laboratory have demonstrated that the number of RGCs in rats or mice that survive a partial injury to the optic nerve or exposure to glutamate toxicity is a function of the availability of T-cell-mediated protective immunity; in the absence of mature T cells, more RGCs are lost. Not all individuals or strains are equally capable of recruiting the

**TABLE 3.** Lower RGC Survival after IOP Increase in SPD Rats Devoid of Mature T Cells

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean RGCs ± SD (per mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymectomized SPD</td>
<td>1256 ± 145 (n = 6)</td>
</tr>
<tr>
<td>Normal SPD</td>
<td>1950 ± 148 (n = 6)</td>
</tr>
</tbody>
</table>

Adult SPD rats that were thymectomized at birth and normal adult SPD rats were subjected to an increase in IOP. Three weeks later, the number of surviving RGCs was determined by retrograde labeling. The number of surviving RGCs was significantly higher in the thymectomized SPD rats than in the normal controls (*P* < 10⁻⁶, two-tailed t-test).

**TABLE 4.** IOP-Induced Loss of RGCs in Lewis Rats after Transfer of Splenocytes from Fisher Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean RGCs ± SD (per mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis replenished with Fisher</td>
<td>1955 ± 176 (n = 11)</td>
</tr>
<tr>
<td>Lewis replenished with Lewis</td>
<td>1427 ± 177 (n = 9)</td>
</tr>
<tr>
<td>Lewis injected with PBS</td>
<td>1418 ± 130 (n = 5)</td>
</tr>
<tr>
<td>Fisher injected with PBS</td>
<td>1842 ± 72 (n = 4)</td>
</tr>
</tbody>
</table>

Data are the number of surviving RGCs after 3 weeks of high IOP of Lewis rats injected intravenously with Fisher splenocytes, or with Lewis splenocytes, or PBS, as well as in untreated Fisher rats. After 3 weeks, the IOP was 27.5 ± 1.96 mm Hg (n = 7) in the Lewis rats injected with Fisher splenocytes, 28.5 ± 1.25 mm Hg (n = 4) in the Lewis rats injected with Lewis splenocytes, and 31.5 ± 1.46 mm Hg (n = 5) in the Lewis rats injected with PBS. IOP between groups did not differ significantly (rats injected with Lewis splenocytes versus rats injected with Fisher splenocytes, *P* = 0.26; rats injected with Lewis splenocytes versus PBS injected rats, *P* = 0.27). In a separate set of experiments, we examined three groups of rats with raised IOP: Lewis rats treated with Fisher splenocytes (n = 4), Lewis rats treated with Lewis splenocytes (n = 5), and untreated Fisher rats. The results of the two experiments with respect to survival of RGCs were pooled. In Lewis rats, differences in the number of surviving RGCs between those injected with Fisher splenocytes and those injected with Lewis splenocytes were significant (*P* < 0.001; two-tailed t-test). The number of surviving RGCs in Lewis rats injected with Lewis splenocytes did not differ from the number in the PBS-injected control group (*P* = 0.27). The difference in the number of surviving RGCs between Lewis and Fisher rats in response to an increase in IOP was significant (*P* < 10⁻⁶, two-tailed t-test).
Lewis rats (n = 17) were subjected to unilateral crush injury. Immediately after the insult, the rats were injected with splenocytes from Fisher rats or from other Lewis rats or were injected with PBS. Two weeks later the numbers of surviving neurons were determined by retrogradely labeling and counting the surviving RGCs after applying a dye distally to the lesion site. The number of surviving neurons in the Lewis rats was significantly higher in recipients of Fisher splenocytes than in recipients of PBS or Lewis splenocytes (P < 0.05 and P < 0.008, respectively). No statistical differences were observed between Lewis rats treated with PBS or replenished with Lewis splenocytes.

The protective aid of the immune system in response to optic nerve insults, and their ability to avoid the loss of RGCs after optic nerve insult correlates with their ability to resist the induction of EAE.17 The T cells evidently exert their protective effect by assisting the microglia/macrophages to remove the sources of self-destruction (Butovsky et al., unpublished data, 2002, and Nevo et al., unpublished data, 2002).

In the present study a similar correlation was found between resistance to autoimmune disease and the ability to withstand an insult induced by an increase in IOP. The lower resistance to the IOP-induced RGC loss (seen in Lewis rats) was evidently attributable to immune system deficiency, as indicated by the beneficial effect in the Lewis rats replenished with splenocytes from Fisher rats, which are capable of manifesting protective T-cell-mediated immunity. Similar results were obtained in a rat model of optic nerve partial crush injury.

The difference in the RGC losses observed here between rats with a similar increase in IOP is in line with the general experience that the ability of individuals to tolerate increased pressure varies. It was not realized, until the present study, that the ability to tolerate pressure is related to immune system activity. This latter finding, however, is in line with the recent suggestion by our group that the immune system plays a pivotal role in protecting the organism, not only against invading pathogens, but also from potentially destructive self-components such as glutamate.3,12,20,21,23 Thus, just as T-cell activity against foreign antigens confers protection from microbes, a T-cell response against self-antigens helps to protect against the threat of self-destruction. Rat strains may of course differ with respect to many other characteristics besides the ability to tolerate increased pressure.

Recent studies in our laboratory have shown that the RGC loss induced by high IOP, such as that induced by glutamate toxicity or acute crush injury, can be reduced by vaccination with the immunomodulatory drug Cop-1.24,45 The results of morphologic analysis suggest that the immune system exerts its effect locally (i.e., within the eye). We suggest that the immune system, known to protect the body against harmful foreign antigens, is also the body’s own maintenance mechanism for protection against destructive self-compounds (such as glutamate). Such maintenance is mediated by a local innate response, which is regulated by an adaptive response in the form of specific T cells directed to self antigens.

By gaining a better understanding of the role of the immune system in glaucoma, and hence of individual differences in the immune response to the insult, we will improve our ability to design and develop treatments leading to better prevention of visual loss and disease progression.

References


