

Glaucoma and the Immune System

Is glaucoma a systemic disease curable by therapeutic vaccination?

BY MICHAL SCHWARTZ, PhD

Although glaucoma has often been linked etiologically to high IOP, it is now evident that pressure is only the most common of several risk factors. In an effort to halt disease progression, investigators have expanded their research to the areas of neuroprotection and the restoration of the optic nerve. My group showed that the body's immune system helps fight off the causes of progressive neurodegeneration. After a primary insult, lymphocytes (specifically, T cells) home in on their specific eye-resident antigens, where they render the local immune cells (ie, microglia) protective in a way that the eye can tolerate. To prevent, or at least retard, glaucomatous progression, we developed a vaccination that boosts the T-cell response. The antigens of choice are synthetic peptides that cross-react weakly with retinal and optic nerve antigens; they evoke a response that allows the relevant specific T cells to reach the lesion site and become weakly activated there in a way that leads to neuroprotection without a risk of autoimmune disease.

NEUROPROTECTION: BACKGROUND AND AIMS

During the last decade, scientists and clinicians have begun to categorize glaucoma as a part of the large group of neurodegenerative disorders of the central nervous system that are characterized by a primary loss of neurons and a subsequent, ongoing process of secondary degeneration.¹ This view of glaucoma has significantly altered the nature of glaucoma research, the way in which clinicians perceive the disease, and their approach to therapy. Instead of focusing on primary risk factors and their effect on optic neurons, today's researchers emphasize the hostile environment created by the primary insult and the consequential progression of degeneration (even if that particular etiological factor is adequately neutralized). Most current study targets neuroprotection; it involves identifying the compounds and factors responsible for mediating the self-perpetu-

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ating degeneration and seeking ways to circumvent or block them.

My colleagues and I, as well as other investigators, have postulated that factors contributing to the ongoing cell death in glaucoma include the emission of physiological compounds in toxic quantities from the injured fibers, their cell bodies, and neighboring supportive cells.²⁻⁶ Some of the compounds identified in the pathogenesis of glaucoma are also known to be active in other neurodegenerative diseases.⁷⁻¹¹ Our studies¹²⁻¹⁷ of acute and chronic injuries of the rodent's optic nerve led us to the unexpected discovery that the immune system plays a key role in the ability of the optic nerve and retina to withstand injurious conditions.

IS GLAUCOMA A SYSTEMIC DISEASE?

Our first observations that the immune system (in the form of T cells directed to specific antigens of the central nervous system [ie, "autoimmune" T cells]) can protect injured neurons from death came from our studies in rodents. We found that the passive transfer of T cells specific to myelin basic protein reduced the loss of retinal ganglion cells after trauma to the optic nerve.¹⁵ The myelin-specific T cells were also effective when directed (1) to either cryptic or pathogenic epi-

topes of myelin basic protein and (2) to other myelin antigens or their epitopes.^{18,19}

Our findings raised some fundamental questions. First, are myelin antigens capable of protecting the visual system from all types of acute and chronic insult? Second, is the observed neuroprotective activity by immune cells merely an experimental artifact? Alternatively, does it reflect the critical participation of the immune system in fighting off injurious conditions in the central nervous system in general and in the visual system in particular? Third, if the immune system combats injury to the visual system, is glaucoma a systemic disease? If so, can this finding be translated into a systemic therapy that will protect the eye?

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From our research over the last few years, we have learned that an insult to the central nervous system physiologically evokes a protective T-cell response, but we found that reaction may not be sufficiently effective when the insult is severe and that it may not always be optimally controlled. Moreover, the specificity of the protective T cells depends on the site of the insult. For example, the protective effect of vaccination with myelin-associated antigens is restricted to injuries of the white matter (ie, myelinated axons).^{16,19,20} These antigens would have no effect on an injury to the retina, which contains no myelin.

In addition, we found that the observed injury-induced behavior of autoimmune T cells is a spontaneous physiological response.¹⁷ We therefore sought to identify the antigenic specificity and the phenotype of the beneficial autoimmune T cells and to understand what determines the balance between a beneficial (ie, neuroprotective) outcome of the T-cell-mediated response to a central nervous system injury and a destructive effect, which causes autoimmune disease. We also examined ways of translating the beneficial response into a therapy for glaucoma.

We had to address several issues during the course of our research. First, we verified that the loss of retinal

ganglion cells in a rat model of high IOP, simulating some types of hypertensive glaucoma, depends on the immune system's integrity.¹³ Second, we attempted to determine whether the specific T cells that are harnessed in our rat model of chronic glaucoma (and that can be used for therapeutic boosting of the beneficial T-cell-mediated response) are directed to self-antigens that reside in the retina or the optic nerve.¹² Lastly, we searched for an antigen that would safely boost the physiological response without causing an autoimmune disease.

Using a rat model of elevated IOP, we showed that a protective response could be obtained only with an antigen residing in the retina. This finding suggests that, at least in this experimental model, the site at which the self-perpetuating degeneration is initiated—and therefore the site primarily in need of protection—is not the optic nerve but the retina.^{12,16} We further determined that, in T-cell-deficient rats, the number of retinal ganglion cells that survive a high-IOP insult is significantly lower than in matched controls with an intact immune system. The ability to withstand insults to the optic nerve or retina may therefore depend on the integrity of the peripheral immune system—specifically, on immune cells that recognize site-specific self-antigens.

Interestingly, the use of steroids after an IOP-induced injury in rats, as well as in the healthy animals, caused a significant loss of retinal ganglion cells.¹² Moreover, in a model of retinal ganglion cell loss caused by conditions other than IOP (eg, uveitis), steroids that reduced the inflammation not only failed to rescue the retinal ganglion cells, but they actually caused these cells' death. These results led us to suggest that boosting a well-controlled level of T cells might protect retinal ganglion cells in patients with glaucomas associated with high IOPs and in those with normal-tension glaucoma.

NEUROPROTECTIVE ACTIVITIES OF THE ANTI-SELF T CELLS

To be protective, autoimmune T cells must travel to the site of damage and become activated by the encounter with their specific antigens there. For that reason, only antigens located at that site are relevant for the purposes of vaccination. Once activated, the T cells provide a source of cytokines and growth factors that, in turn, activate the microglia to exert defensive activities that the eye can tolerate (eg, an uptake of glutamate, the removal of debris, the production of growth factors). Importantly, these factors do not produce the poorly tolerated toxic agents that are part of their microbe-killing apparatus, such as tumor necrosis factor-alpha.²¹⁻²⁵ Such T cells are constitutively controlled by naturally occurring

regulatory T cells, which are themselves amenable to physiological or therapeutic control.^{26,27}

CHOICE OF ANTIGENS FOR THERAPEUTIC PURPOSES

Among the compounds we tested in our search for a safe, suitable antigen for neuroprotection was glatiramer acetate (also known as Cop-1). This synthetic 4-amino-acid copolymer is currently used in a regimen for multiple sclerosis. We chose to test this FDA-approved compound, because it is known to be safe and because our studies^{16,28} have demonstrated its low-affinity cross-reaction with a wide range of self-antigens. In our rat model of chronically high IOP, vaccination with Cop-1 significantly reduced the loss of retinal ganglion cells even if the IOP remained high. Although the vaccination did not prevent the onset of disease, the therapy can slow its progression by controlling the local extracellular environment of the nerve and retina. In other words, vaccination makes the environment friendlier to neuronal survival and helps the retinal ganglion cells to withstand the stress.^{16,27-29}

Chronic conditions that are not autoimmune diseases occasionally require boosting of T cells directed to or cross-reactive with the relevant self-antigens. Bakalash et al³⁰ established that the frequency of vaccination requires long-lasting neuroprotection in a rat model of elevated IOP. A search by our group is now on for antigens besides Cop-1, some of which are being tested and developed. Because numerous factors participate in self-perpetuating degeneration, it seems likely that a multidimensional therapy based on the immune system will be superior to any treatment involving the use of any single neuroprotective drug. □

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