INTRODUCTION

It is commonly accepted that glaucomatous neuropathy, like other neurodegenerative diseases, is a multidimensional disease in which several molecular and cellular factors contribute to the pathological process, beyond the primary cause of the disease. These factors, while not initially causative, are key players in disease progression, and may continue to contribute even after the primary pathology is alleviated. As part of the search for additional approaches to slow disease progression, an entire field of research has been opened up, the field of neuroprotection and restoration. We have proposed, based on experimental evidence, that the immune system may be recruited to help eliminate many of the causes of glaucoma-associated neurodegeneration. This defense involves lymphocytes specific for antigens expressed in the CNS and in the eye, as well as resident and infiltrating innate immune cells, the microglia and macrophages. In an attempt to boost such a beneficial immune response, we proposed a vaccination, to be administered as a means of preventing disease progression, though not its onset. This vaccine induces an immune response and recruits immune effector cells that counteract or neutralize many of the compounds and factors that contribute to ongoing destruction, and in addition supports cell renewal and repair.

NEUROPROTECTION

During the past decade, scientists and clinicians began to recognize that glaucoma is a neurodegenerative disorder in which the primary loss of retinal ganglion cells (RGC) and axons (optic nerve fibers), caused by elevated intraocular pressure (IOP) or other risk factors (mechanical, genetic, vascular, metabolic, immunological), is followed by an ongoing process of secondary degeneration. This view of glaucoma has led to major changes in the nature of glaucoma research, the way in which clinicians perceive the disease, and the approach to therapy. The emphasis, instead of being mainly on the primary risk factors and their effect on the optic neurons, has shifted toward reducing the damage/pathology created by the primary insult, and mitigating the consequent progression of degeneration even if the triggering factor is adequately neutralized.

The factors contributing to ongoing cell death are physiological compounds emerging in toxic quantities from the injured fibers or their cell bodies. Studies along these lines have revealed that some of the compounds identified in the pathogenesis of glaucoma are already known to be active in other neurodegenerative diseases. Among these self-destructive compounds and cells are those that, at physiological levels, are pivotal for maintenance, but at concentrations exceeding physiological levels, are destructive. These compounds include glutamate, NO and others. The cells mediating secondary destruction are microglia, the innate immune cells of the CNS, infiltrating macrophages, and adaptive immune cells. In addition an association was made in many neurodegenerative diseases between the degeneration of neural tissue and the local immune response. As a result, it has been commonly accepted for a while, that any local cellular immune infiltration to the damaged CNS is detrimental, leading to an unwanted inflammatory response and should be eliminated. Our studies over the last decade have provided data suggesting that the picture is more complicated, and that the association of immunity with destruction is an outcome of a failure to recruit effective protective immune responses. Accordingly, we have proposed that in order to contain neurodegenerative conditions there is a need to modulate and boost the relevance immune response rather than deny and suppress it altogether.

Local and Systemic Immune Cells in Protection from Glaucoma

Our first observations that the immune system (in the form of T cells directed to specific self-antigens) can protect injured neurons from death came from studies in rodents showing that passive transfer of T cells specific to myelin basic protein (MBP) reduces the loss of retinal ganglion cells (RGCs) after traumatic optic nerve injury. We found that these T cells are also effective when directed to either cryptic or pathogenic epitopes of MBP, as well as to other myelin-related antigens or their epitopes. These findings raised a number of critical questions. For example, are myelin antigens capable of protecting the visual system from any type of acute or chronic...
insult? Is the observed neuroprotective activity of immune cells merely an anecdotal finding reflecting our experimental conditions, or does it indicate the critical participation of the immune system in fighting off injurious conditions in the visual system and in the CNS in general? Can this finding be translated into a therapy that would protect the eye?

In a series of experiments carried out over the last few years we have learned; firstly, that the protective T cells response is a physiologically evoked response that might not be sufficient in cases of severe insult, and might not always be properly controlled. Moreover, we discovered that the specificity of such protective T cells depends on the site of the insult. Thus, for example, the protective effect of vaccination with myelin-associated antigens is restricted to injuries of the white matter, i.e. to myelinated axons.5-7 If the insult is to the retina, which contains no myelin, immunization with myelin-related antigens would have no effect. We further found that in T cell deficient animals, the number of surviving retinal ganglion cells following an insult causing elevated intraocular pressure (IOP) is significantly lower than in matched controls with an intact immune system. These results suggest that the ability to withstand insult to the optic nerve or to the retina depends on the integrity of the peripheral immune system and specifically on the exact population within the immune system that recognizes the site-specific self-antigen.8

**T cells Specific to Antigens Residing in the Site of Damage Help Clean and Heal**

In order to be protective, the adaptive immune response in the form of T cells should recognize self-antigens residing in the retina or in the damaged optic nerve. Once activated, the T cells provide a source of cytokinins and growth factors that regulate the resident eye sentinel cells, the microglia and the recruited blood-borne monocytes, to endow them with a protective phenotype that the eye can tolerate.9,10 According to our perception, under normal physiological conditions the level of the relevant T cells is sufficient to maintain homeostasis, and to correct small deviations from it. Under pathological conditions, as in the case of glaucoma, a boost is needed. Such a boost can be achieved by an active or passive vaccination.7,11-13

Among the many compounds we tested in the search for a safe and suitable antigen for boosting neuroprotection was glatiramer acetate (GA, also known as Copolymer-1, Cop-1), a synthetic 4-amino acid oligo-peptide, currently used as a treatment for multiple sclerosis. We chose to test this FDA-approved compound because it is known to be safe. Our studies have demonstrated its low-affinity cross-reaction with a wide range of self-antigens.14 In the rat model of chronically high IOP, vaccination with GA significantly reduces RGC loss even if the intraocular pressure remains high. The vaccination does not prevent disease onset, but can limit its progression by controlling the local extracellular environment of the nerve and retina, making it less hostile to neuronal survival and allowing the RGCs to be better able to withstand the stress induced by IOP.14-16

For chronic conditions, occasional boosting is needed (weekly or monthly but not daily).13 We recently established the optimal frequency of boosting, as a step toward translating our animal studies into clinical trials. Moreover, attempts are currently underway to identify additional antigens besides GA that may be more effective and may require even less frequent administration.

**CONCLUSION**

a. Glaucoma, a slow progressive neurodegenerative disorder associated with death or retinal ganglion cells and degeneration of their connected optic nerve fibers has often been linked to high intraocular pressure.

b. Neuroprotection, a general name given to interventions aiming for halting at disease progression.

c. Protective autoimmunity, a general name given by us to the immune cells recognizing self-antigen(s), acting as the body’s defense mechanisms against internal intruders.

d. T cell-based neuroprotective vaccination, a vaccination, given as a way of preventing disease progression. The antigens of choice are synthetic antigens that weakly cross-reacts with self-antigens residing in the retina and optic nerves and thereby evokes a T cell response with a specificity that allows the corresponding T cells to home to the lesion site and to be activated locally in a way that benefit without imposition of the risk of autoimmune disease.

**REFERENCES**


