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Autoimmune Basis of Glaucoma

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ABSTRACT

Glaucoma is one of the leading causes of blindness worldwide. The current view of glaucoma is that it is a multifactorial disease. Elevated IOP is a recognized etiologic factor which can trigger initial damage through biomechanical and ischemic injury to the retinal ganglion cells. However, elevated intraocular pressure cannot be entirely responsible for the development of glaucoma. Accumulating evidence suggests that abnormal immunity may be contributing to the glaucomatous optic neuropathy. Autoimmunity may be responsible for initiating or exacerbating glaucoma. This review provides an evaluation of the potential role of autoimmunity in some patients with glaucoma.

Keywords: glaucoma, retinal ganglion cell, glia, oxidative stress, immune system, aging

INTRODUCTION

Glaucoma is a heterogeneous group of ocular disorders characterized by progressive loss of retinal ganglion cells (RGCs) and their axons, optic nerve degeneration, and gradual loss of visual field, which may eventually lead to irreversible blindness.[1] More than two million people suffer from glaucoma in the United States.[2] Currently, glaucoma screening is based on tonometry, fundoscopy, and perimetry. The pathogenesis of glaucoma is still only partly understood. It is certain that elevated intraocular pressure (IOP) cannot be entirely responsible for the development of glaucoma.[3]

The current view of glaucoma is that it is a multifactorial disease. Many of the proposed mechanisms traditionally linked to elevated intraocular pressure (IOP)-related factors may facilitate disease progression independently from IOP elevation.

Elevated IOP is a recognized etiologic factor which can trigger initial damage through biomechanical and ischemic injury. However, a complex interplay of cellular events triggered by IOP-related or -unrelated stimuli may also contribute to the primary injury process and disease progression. [3,4]

Is Glaucoma a Neurodegenerative Disease?

Until recently, glaucoma was only seen primarily as a neurodegenerative disease and the actual mechanisms underlying RGC loss are still unclear. Several studies indicate a possible autoimmune involvement in the pathogenesis of glaucoma.[3-8]

Traditionally, elevation in intraocular pressure (IOP) has been considered to be the main cause of glaucoma.[9] Optic nerve damage in glaucoma is classically considered as a result of mechanical,[10,11] hypoxic,[12] and oxidative tissue stress.[13]

Glaucoma research has been focused on lowering the IOP as a primary therapeutic goal, trying to diminish this measurable and only modifiable risk factor.[14-18] Consequently, currently approved glaucoma medications and surgical therapies are directed at lowering IOP, and indeed there is substantial evidence from several clinical trials for a significant attenuation of progressive visual field loss among the patients at risk.[14-16, 19]

However, this view is actually challenged by a number of common observations, such as:

1. A subset of patients continue to suffer from progressive visual field loss even after their IOP was effectively controlled.[12-14]
2. Normal tension glaucoma (NTG) is another challenge to this theory based on IOP for explaining glaucoma. In NTG progressive retinal ganglion cell death and subsequent glaucomatous damage occurs in the absence of any elevated IOP.
3. Furthermore, about 10% of people at the age of 40 have elevated intraocular pressure (IOP). Only a small percentage of them will convert to glaucoma

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and will therefore need treatment. The "Ocular Hypertension Treatment Study" could show that within a five-year period about 10% of the people with OHT will develop glaucoma.[10,11]

4. Some studies have reported a negligible relationship between mean IOP and vision loss in glaucoma.[15-17] These observations indicate the possible contribution of IOP-independent mechanisms to disease progression.

All these findings suggest that some patients may have conditions that facilitate non-pressure-related stress to the retina and optic nerve that might directly contribute to their glaucomatous neuropathy.

Glaucoma is a disease with complex etiology, initiated by several risk factors, whose individual contributions to glaucomatous optic neuropathy have not yet been fully explored.

Immunoregulation and Retinal Ganglion Cell (RGC) Survival and Glaucoma

The central hypothesis is that immunoregulation ultimately determines whether RGCs survive or undergo apoptosis in patients with glaucoma. The immunoregulatory mechanisms that determine RGC fate are influenced at least in part by elevated IOP. Furthermore, other factors such as aging, oxidative stress, altered vascular perfusion, and structural composition of the neuronal tissue, autoimmunity, and other unidentified factors influence the immunoregulatory mechanisms.

Cytotoxic autoantibodies and oxidative stress secondary to increased production of reactive oxygen species (ROS) are also critical factors for the initiation and dysregulation of immune response.[20,21] Two or more stressors that may have additive or even synergistic effects can contribute to RGC fate.

Evidences Supportive of the Rule of Autoimmunity in Glaucoma

Epidemiological Studies

In 1992, Cartwright et al. reviewed the charts of 67 patients with the diagnosis of NTG. These patients were matched with respect to age, race, and sex with an equal number of patients having ocular hypertension. All medical diagnoses in the charts for both groups were tabulated and classified as either immune-related or non-immune-related. Twenty (30%) patients with normal-tension glaucoma had one or more immune-related disease(s) such as arthritis and hypothyroidism, compared with five (8%) patients in the comparison group ($P = .001$).[22]

Adaptive Immunity and Autoantibodies in Glaucoma

Wax et al. first reported an abnormal antibody reactivity in patients with NTG.[23] They described an increased level of heat shock protein 60 (HSP60) antibodies.[21] Later, this research group and others found several serum autoantibodies that are elevated in glaucoma patients; for example, higher levels of antibodies against small HSPs ([alpha]A-crystalline, [alpha]B-crystalline, and HSP27) in NTG patients.[5] Tezel et al. examined the pathogenetic effects of antibodies against HSPs on isolated human retinae.[13] They could show that direct application of antibodies against [alpha]A-crystalline and [alpha]B-crystalline or HSP27 results in apoptosis of neurons and cells of the retinal vasculature.[5] Increased expression of HSP27 and HSP60 were observed in retina and optic nerve head in human donor eyes with glaucoma.[13]

Several other antibodies were detected in the sera of glaucoma patients such as gamma-enolase,[23] glutathione-S-transferase,[24] antiphosphatidylserine,[25] neuron-specific enolase,[26] and glycosaminoglycans.[27]

It is known that complex natural autoantibody profiles exist even in healthy people,[28,29] hence it can be important not to screen only for one or a few antibodies, but to investigate disease-specific changes in complex profiles of naturally occurring autoantibodies. With antibody profiling techniques, Grus et al. detected changes in complex IgG antibody patterns against ocular antigens in sera of glaucoma patients.[6,8] These studies not only confirmed the known up-regulations of immunoreactivities in glaucoma, but also demonstrated some regions with down-regulated immunoreactivities in glaucoma patients in comparison to healthy subjects.

Innate Immunity and Glaucoma

In addition to the evidence supporting the adaptive immunity, an innate immune response is also evident in glaucoma. Proteomic and immunohistochemical analyses demonstrate findings that are consistent with an early up-regulation of several complement components in experimental glaucoma models as well as in human glaucoma.[30] In addition, a recent study provided evidence that the complement cascade may directly contribute to the neurodegenerative injury in glaucoma.[31] The role of complement in glaucomatous neuropathy has been linked to the putative role of complement proteins in synapse elimination. One feature of many neuropathies is die-back inhibition, or an atrophy of primary neural pathways due to "disconnection" or atrophy at the next order synaptic neuron.[32,33]

Therapeutic Implications

Elevated IOP, decreased neurotrophin support, glutamate-associated excitotoxicity, hypoperfusion, and

vasospasm have been implicated in the pathogenesis of glaucoma.

A major goal of glaucoma research has been to develop neuroprotective treatment approaches to prevent the death of ganglion cells of the retina. Such strategies have been developed for neurologic conditions such as traumatic central nervous system injuries and neurodegenerative diseases such as Parkinson disease.

Schwartz [34,35] postulates that boosting the natural autoimmunity could be a mechanism for protective intervention in the event of central nervous system impairment in animal models. Schwartz suggests that vaccination with self-like antigens may evoke an autoimmune-like response without induction of autoimmune disease. They used Copaxone, a synthetic antigen copolymer, which is already used in multiple sclerosis therapy, to protect rats with high IOP from RGC loss.[34,36] A vaccination can be used not to prevent the disease onset, but might be a way of stopping, halting, or attenuating its progression.[37]

CONCLUSION

The current view of glaucoma is that it is a multifactorial disease. Elevated IOP is a recognized etiologic factor, which can trigger initial damage through biomechanical and ischemic injury to the retinal ganglion cells. However, elevated intraocular pressure cannot be entirely responsible for the development of glaucoma.

Different studies reveal specific changes in the natural autoantibody repertoires in glaucoma patients. These antibody patterns are not only specific for normal pressure glaucoma patients but also for primary open-angle glaucoma.

Even though glaucoma is not considered a classic autoimmune disease, the change in antibody profiles might be used as a screening test for glaucoma. Autoantibodies might not be directly responsible for the manifestation of autoimmune diseases; they can still be a marker for future diseases in presently healthy individuals.

Future studies on the immune mechanism involved in the different stages of the disease and on the identification of autoantigen that triggers the pathogenic response should further support the autoimmune hypothesis. More work is required to develop a neuroprotective treatment approaches to preserve the ganglion cells of the retina to stop, halt, or attenuate glaucoma progression.

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