

THEORETICAL ARTICLE

Is glaucoma an autoimmune disease?

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Abstract

There is increasing evidence from animal and human studies that glaucoma is an autoimmune disease. Evidence for this hypothesis includes the fact that antibodies as well as T-cell responses to heat-shock proteins (HSPs) are detectable in some patients with glaucoma and in an animal model of the disease. As in the human disease, experimental animal models of glaucoma have been found to demonstrate neurodegenerative changes in the optic nerve associated with immunoglobulin and T-cell infiltration. Although there is still insufficient evidence in humans to classify all cases of glaucoma as autoimmune diseases, the implications of this hypothesis have major impact on the diagnosis and treatment of glaucoma.

Keywords: autoimmunity, glaucoma, immunology, immunotherapy

Glaucoma is a common neurodegenerative disease involving the optic nerve with progressive degeneration of retinal ganglion cells and axons. Elevated intraocular pressure is the major risk factor for the development of glaucoma, although such neural damage may occur in individuals who have normal intraocular pressure (normal-tension glaucoma, NTG). Recent evidence indicates that autoimmune mechanisms may be involved in such neural cell damage.^{1,2} The crucial question remains: 'is there sufficient evidence in man to classify all or most types of glaucoma as an autoimmune disease?'

Autoimmune diseases are a group of harmful immune processes that affect approximately 5% of the adult population. Such diseases are characterised by antibody, immune complex and/or cell-mediated immune reactions that are directed towards self-antigens. The mechanisms underlying these diseases represent an exaggerated immune response to normal constituents of cells and tissues often with evidence of abnormal immune regulation,

resulting in dysfunction, damage or destruction of the target tissue. The pathogenesis of autoimmune diseases involves genetic factors, infections and other environmental factors causing antigenic mimicry that induce an immune response resulting in inflammation and tissue damage. Often the inciting environmental and microbial factors are unrecognised. Genetic factors have mainly involved MHC (HLA in man) and immune-related genes.³

Criteria have been proposed to facilitate the diagnosis of a condition as being an autoimmune disease. These include the demonstration of an antigen-specific immune response to self-antigens, which may involve antibodies or T-cell responses to such antigens, evidence that the response is not due to tissue damage or the result of another pathological mechanism and the absence of another well-defined cause. The development of an animal model of the disease supports the diagnosis of autoimmunity (Table 1).

Antibodies to heat-shock protein (HSP) have been detected in patients with glaucoma and

Table 1. Evidence of autoimmunity in glaucoma

	Animal model	Human studies
Immune response to self antigens	Demonstrated for HSP27 and HSP60-immunization with antigens induce neuro-inflammatory changes ^{5,7}	Demonstrated for antibodies to alpha B-Crystallin, Vimentin, Heat Shock Protein HSP70 and retinal antigens ⁴
Genetic factors	Not described	Multiple genetic associations described but not for a specific "autoimmune" subtype ³
Transfer of disease by antibodies	No	No placental transfer described in humans
Transfer of disease by T cells	Demonstrated in murine model ⁶	Not described in humans
Microbial trigger	Not described	Not described except for infection-induced inflammatory eye disease ¹⁷
Associated with other autoimmune diseases	Not described	Yes ¹²
Breakdown in blood retinal barrier	Not demonstrated prior to Ab or T cell infiltration in murine model	Not demonstrated except for raised IOP associated with uveitis
Response to immunosuppressive therapy	Not demonstrated	Not demonstrated except for associated inflammatory eye diseases
Microbiome changes	Demonstrated: HSP-specific CD4 T cells are abolished in mice in a germ-free environment ⁸	Demonstrated changes are non-specific ¹⁵

animal models with this disease.⁴ Furthermore, immunoglobulins have been detected in neural and optic nerves of such animals and in patients with glaucoma.⁵ The issue remains to be resolved as to whether these antibodies are pathogenic. Experimental studies in animals support the concept that a disease is autoimmune usually by demonstrating that immunisation with a relevant antigen leads to a disease similar to human condition. For example, immunisation of rats with optic nerve antigen homogenate leads to elevated antibody responses and retinal ganglion cell loss.⁶

Immunisation of mice with HSP27 and HSP60 was found to induce an optic neuropathy, similar to that observed in glaucomatous neural damage.^{5,7} Recent elegant studies by Chen *et al.*⁸ have provided evidence that a transient elevation of intraocular pressure (IOP) induces the expression of HSP by retinal ganglion cells and axons, and the subsequent CD4⁺ T-cell infiltration with specificity for HSPs into the retina leads to the development of aggressive glaucomatous neurodegeneration. It is hypothesised that a single transient increase in intraocular pressure is enough to induce the expression of heat-shock proteins in the ocular tissue and that the auto-aggressive CD4⁺ T cells have previously been activated by HSP derived from the gut microbiota.⁸ Antigenic mimicry of bacterial and eukaryotic HSPs expressed in the eye as a stress reaction to elevated intraocular pressure may cause the tissue damage observed in glaucoma. Ocular autoimmunity initiated by antigenic

mimicry of antigens provided in the gut and in the retina has been previously shown for uveitis; however, those antigens were derived from a pathogen (rotavirus) or a nutritional protein (bovine milk protein).⁹ The presence of autoantibodies and antigen-specific T cells infiltrating tissue does not prove that such antibodies or T cells have a role in pathogenesis of disease as they may result secondarily from tissue damage. Passive transfer of antibodies or lymphocytes (T cells) from disease-affected animals should cause a similar disease in other healthy experimental animals. This was successfully demonstrated by adoptive transfer of T cells from HSP27-immunised mice to normal mice that induced loss of retinal ganglion cells and axons, a major problem of patients with NTG.⁶ Furthermore, Jiang *et al.*¹⁰ have recently shown that administration of multiple low doses of bacterial HSP60 induced immune tolerance and attenuated RGC loss and function in their murine model of glaucoma, as indicated by an increase in T regulatory cells and reduced DTH responses.

The pathogenic role of antibodies in glaucoma still remains to be proven. As a proof of concept, the phenomenon of pathogenic antibody transfer is seen in humans in whom the placental transfer of antibodies (IgG) between mother and child may lead to the child developing autoimmune symptoms. Women who have lupus, for example, may have SSA (anti-Ro) antibodies that cross the placenta and produce congenital heart block and other features of SLE in the offspring. Similarly,

passive transfer of anti-TSH (thyroid-stimulating hormone) receptor antibodies from a mother with thyrotoxicosis may lead to similar but transient clinical manifestations in her newborn child.¹¹ This so-called 'experiment of nature' has not been observed in the case of glaucoma. The reason could be that in a healthy eye, the blood–retina barrier would prevent the influx of antibodies from the circulation, only if the tight junctions of the barrier are damaged; for example, by infiltration of activated lymphocytes or leucocytes, antibodies and other serum proteins would gain access to the retina.¹² This argues strongly for autoantibodies as an epiphenomenon in glaucoma, unless the elevation of the intraocular pressure was sufficient to abolish the blood–retina barrier and override the immune privilege of the eye.

Autoimmune diseases tend to occur in clusters, and subjects with one autoimmune disease are at increased risk of developing another autoimmune disease. This occurs, for example, in patients who have autoimmune thyroid disease. Such individuals have an increased risk of developing other autoimmune diseases involving the stomach, such as pernicious anaemia and the adrenal glands manifesting as Addison's disease.¹³ There are reports of such AID clustering in patients with glaucoma in association with thyroid disease.¹⁴

While a large number of genes have been shown to be associated with autoimmune diseases and glaucoma, it remains to be proven whether a specific genetic phenotype is associated with a subset of patients with 'autoimmune glaucoma'. Autoimmune diseases also occur with increased frequency in patients with an underlying immune deficiency, for example the increased prevalence of coeliac disease in patients with IgA deficiency.¹⁴ This has not been reported in patients with glaucoma.

A characteristic feature of autoimmune diseases is that they usually respond to immunosuppressive therapy. This has been demonstrated in a large number of autoimmune diseases, such as MS, SLE and RA, but is yet to be tested in patients with glaucoma. Unfortunately, corticosteroids, which are the most commonly used anti-inflammatory and immunosuppressive drugs, may cause raised IOP¹⁵ as well as other effects on the retina, including central serous retinopathy, cystoid macular oedema and RGC loss in some patients treated with aldosterone.¹⁶

Numerous recent studies have explored the role of the gut microbiome in the pathogenesis of a

large number of autoimmune and inflammatory diseases.¹⁷ This was also shown in a mouse model of retina-specific transgenic T cells where autoimmune uveitis is only initiated if the animals have gut microbiota to trigger a presumed cross-reactive T-cell response.¹⁸ The role of the microbiome in the induction of immune responses to heat-shock proteins has been explored in experimental animal models of glaucoma.⁸ Showing that HSP-specific CD4⁺ T cells are abolished in mice in a germ-free environment does not constitute proof of a pathogenic role for such T cells in causing an optic neuropathy; however, Chen *et al.*⁸ have additionally shown the increased loss of retinal ganglion cells and axons after adoptive transfer of HSP-specific T cells and IOP-induced intraocular HSP expression, demonstrating that HSP-specific T cells are responsible for destructive immune responses in glaucoma. Here, the pressure-induced stress response of the cells ought to protect them from damage is unfortunately triggering a destructive immune response. Although patients with glaucoma show increased T-cell responses to the respective HSPs, the final proof of glaucoma being a T-cell-mediated autoimmune disease in humans is still pending.

Studies in glaucoma are similar to those in uveitis where there are several relevant animal models of disease and evidence of immune responses to retinal and uveal antigens in humans, but recent studies indicate that only 5% of patients with uveitis have other autoimmune diseases.¹⁹ It may be that there is a small group of patients with glaucoma who have evidence of autoimmunity. In a recent study of 108 patients with NTG from the University Hospital of LMU Munich, only two had additional autoimmune diseases, one had thyroiditis and the other giant cell arteritis, so there was no (significant) association with autoimmune diseases and NTG (unpublished observation by Gerhild Wildner). A higher percentage of NTG cases associated with autoimmune diseases would provide the opportunity to ascertain whether immunosuppressive therapy for treatment of autoimmunity would also have an ameliorating effect on the progressive tissue damage in the eye.

Nevertheless, immune-mediated damage of RGC and axons during NTG is a chronic disease with slow progression. Those patients with faster progression would need a therapy targeting T cells, according to the data of Chen and

colleagues.⁸ To avoid systemic immunosuppression, a local, intraocular therapy would be desirable. The only available intraocular therapies today are blockers of VEGF, which are irrelevant for NTG, and corticosteroid-releasing devices, which are contraindicated because of the IOP-increasing effect of steroids in susceptible patients (steroid-induced glaucoma). Intravitreal methotrexate has been used for treating autoimmunity and lymphoma but is burdened with several side effects while the efficiency for uveitis was moderate.²⁰⁻²²

A new small-molecule inhibitor of DHODH (dihydroorotate dehydrogenase), PP-001, has been proven to very efficiently suppress autoimmune T-cell responses in two rat models of experimental autoimmune uveitis.²³ In addition to systemic application, a single intravitreal injection of PP-001 significantly suppressed relapses of intraocular inflammation in rats without inducing any adverse effects on intraocular tissues.²⁴ Therefore, a clinical phase 1b/2a study in patients with uveitis receiving a single intraocular injection of PP-001 was performed to demonstrate safety and tolerability (ClinicalTrials.gov identifier NCT03634475, accessed 31 May 2020). The results of this trial are due to be published soon.

The application of such therapy might open up a new therapeutic approach for patients with NTG suffering from progressive immune-mediated destruction of RGC and axons. A slow-release formulation for intraocular application is under development and would revolutionise the treatment of this disease for which there is no good therapy available at present.

CONCLUSION

There is increasing evidence that a subtype of glaucoma may be an autoimmune disease. Evidence for this hypothesis includes the fact that antibodies as well as T-cell responses to HSP are detected in some patients with glaucoma and in an animal model associated with neurodegenerative changes and immunoglobulin and T-cell infiltration, discussed for normal-tension glaucoma with the lack of constant elevated intraocular pressure as a trigger for cell damage.⁸ However, there is still insufficient evidence in humans to classify all cases of glaucoma as an autoimmune disease.

The mechanism by which an autoimmune disease could lead to the characteristic visual field defects in

glaucoma is unknown. We hypothesise that the inner axons of the papilla might primarily suffer from hypoxia after increased pressure on the optic nerve head compared to outer axons. The inner axons of the optic nerve are from ganglion cells proximal to the papilla, while the outer axons of the optic nerve are coming from peripheral ganglion cells. Pressure on the optic nerve head could primarily disturb the blood supply of the inner nerve fibres, therefore preferentially stressing the proximal ganglion cells in the early phase of the disease. If those ganglion cells are the first to upregulate heat-shock proteins and become T-cell targets, this might explain the typical sectorial axonal injury and early visual field defects in glaucoma.

What is needed to be confident that a subtype of glaucoma is an autoimmune disease is answer to the following questions. What is the sensitivity and specificity of antibody and T-cell responses to relevant antigens (e.g. HSP) in patients with glaucoma? Is there a genetic phenotype or biomarker that helps define autoimmune glaucoma? Does presumed autoimmune glaucoma respond to nonsteroid, T-cell-targeting immunosuppressive therapy or tolerance induction? What is the role of the microbiome in the immunopathogenesis of autoimmune glaucoma? The answer to these questions would dramatically improve our approach to the diagnosis and treatment of at least some patients with glaucoma.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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