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Ocular inflammation in age-related eye diseases

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Citation
Vu, T. H. K. (2019, June 27). *Ocular inflammation in age-related eye diseases*. Retrieved from https://hdl.handle.net/1887/74440

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Author: Vu, T.H.K.
Title: Ocular inflammation in age-related eye diseases
Issue Date: 2019-06-27

THE IMMUNOLOGY OF GLAUCOMA

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Asia-Pacific Journal of Ophthalmology 2013 May-Jun;2(3):187-98.

ABSTRACT

The presence of specific antibodies and T cells that are specific in patients with glaucoma supports the idea that the immune system may play an important role in the initiation and/or sustainment of glaucomatous optic neuropathy, at least in some patients. At present, our understanding regarding immunological mechanisms associated with glaucomatous optic neuropathy is far from satisfactory. In this review, we examined evidence suggesting involvement of autoimmune responses in the pathogenesis of glaucoma. These include detection of auto-antibodies and -T cells and expression of cytokines and stress proteins in patients with glaucoma. While immune responses are thought to be detrimental, some responses may exert a protective effect against neurodegenerative damage. Likely, the balance between positive and negative regulators determines the survival or demise of cells. It is vital that research continues to elucidate the roles of the immune system in glaucomatous neurodegeneration and the possibility of alternative modalities of treatment. These studies may also provide valuable molecular biomarkers for the diagnosis and identification of a specific cohort of patients with glaucoma, i.e. those with normal tension glaucoma.

Glaucoma is a global unmet medical challenge because of its prevalence, debilitating consequences and lack of effective treatment. Affecting 70 million people worldwide, it is a group of ocular diseases characterized by damage to the optic nerve and degeneration of retinal ganglion cells (RGCs) that leads to progressive and permanent loss of vision. Although elevation of intraocular pressure (IOP) is considered a major risk factor associated with optic nerve damage, glaucoma is no longer viewed simply as a neurodegenerative condition caused by elevated IOP. A conservative estimation is that 20% – 30% of patients with glaucoma exhibit a normal IOP range, known as normal tension glaucoma.[1]

To date, the precise mechanisms of the pathogenesis of glaucoma are not fully resolved. Clinical theories attribute optic nerve damage from elevated IOP either to mechanical trauma at the cribriform plate or to alterations in vascular perfusion and subsequent ischemia.[2,3] Evidence is rapidly accumulating that damage to the optic nerve may be initiated or sustained not only by a high IOP, but by a number of factors, including ischemia, glutamate excitotoxicity, a specific genetic background, and immunological factors that have not yet been properly defined.[3-5] Recently, it has been suggested that autoimmune responses directed against retinal proteins may be related to the development of glaucomatous optic neuropathy.[5] These insults likely act through common final pathways that eventually activate cellular proteases and neuronal programmed cell death. The current prevailing view is that glaucoma pathogenesis is multifactorial, with a complex interplay of elevated IOP-induced events and genetic/epigenetic/ageing-related susceptibility factors contributing to neurodegeneration.[4] At present, most therapeutic approaches aim towards lowering IOP, which slows down the disease progress but does not cure the disease. Therefore, more insights into the pathogenesis might lead to earlier treatment and new therapeutic options.

An association of autoimmunity with glaucoma

The eye is an immune-privileged site so that its delicate structures are protected from dangerous immune reactions and pathogens. The immune-privilege of the eye is anatomically established through the blood-aqueous barrier and the blood-retina barrier and partially maintained by local production and release of immune-suppressive cytokines and neuropeptides.[6] The eye's own system blocks activated immune cells that might invade the eye and destroy vision by reacting with important structures such as the

retina.[7] However, disease or injury may interfere with the eye's immune privilege due to the breakdown of the blood-retina barrier or changes in cytokine production.

In the past years, growing evidence obtained from clinical and experimental studies supports a prominent immune response in the pathogenesis of glaucoma, at least in a subset of patients.[8] While glaucoma typically is associated with chronic elevation in intraocular pressure, in many individuals, glaucomatous damage occurs without the eye pressure exceeding the normal range, namely normal tension glaucoma (NTG). While current glaucoma therapy is directed specifically at lowering the IOP, it does not always stop the progression of the disease. The actual mechanisms causing RGC death are still unclear. It has been evident that glaucomatous pathology in some of these cases arises from an autoimmune response and thus comprises autoimmune neuropathy.[8-10] This may partly be associated with an increased expression and exposure of neuronal and stress antigens as a result of neuronal injury.[5] Oxidative stress caused by an increased generation of reactive oxygen species (ROS) and nitric oxide (NO)-induced damage has been implicated as a major force causing antigen-specific immune activation.[4,11] In addition, an increased prevalence of monoclonal gammopathy and elevated serum antibodies to retinal antigens has been reported in patients with NTG.[5]

It emerges that glaucoma could be a disease with an autoimmune component;[12-14] however, there is an opposing view that immune responses in glaucoma may be neuroprotective or neural destructive. For example, T-cell mediated immune responses may initially be beneficial to limit neurodegeneration.[15-17] The recruitment of T cells allows early communication of the immune system with cellular debris, destruction of damaged cells, and removal of pathogenic agents.[18] Subsequently, T cells mediate the protection of neurons against degenerative conditions, which is referred as 'protective immunity'.[15,16,18] This response is suggested to reduce the secondary degeneration of RGCs when exposed to various noxious stimuli. Schwartz and her colleagues reported that T-cell mediated autoimmunity plays an important role in the progression of glaucomatous optic neuropathy, as they induce protective effects in rodents by active or passive immunization with self-antigens.[18-20]

Although an initial immune response may be beneficial and necessary to limit neurodegeneration, expansion and secondary recruitment of circulating T cells through

an antigen-mediated process is known to shift the protective immunity into chronic autoimmune neurodegeneration. This is usually associated with a failure to control aberrant and stress-induced immune-response.[18] The premise that neurodegeneration in glaucoma contains an autoimmune component is supported by the presence of abnormal T-cell subsets[21,22] and increased production of serum autoantibodies to optic nerve and retina antigens in many glaucoma patients.[13,23,24] An increased glial production of neurotoxic cytokines,[25] T cell[26] and autoantibody-mediated cytotoxicity,[27] and uncontrolled complement attacks[28] may all cause destruction of RGCs and other neurodegenerative consequences. Thus, a failure to properly control aberrant, stress-induced immune responses likely converts the protective immunity to an autoimmune neurodegenerative process that can facilitate the progression of neurodegeneration in some, if not all, glaucoma patients.

Association between glaucoma prevalence and autoimmune disease

Cartwright and colleagues reported that 30% of patients with NTG showed evidence of immune-related disease.[29] Individuals with a tendency toward the development of autoimmune disease, may develop a cross reaction between the antigenic stimuli related to a systemic autoimmune disorder and antigens in the optic nerve or its vessels. For example anti-myelin basic protein antibodies, which can also be detected in patients with multiple sclerosis, can be found in the sera of glaucoma patients.[30]

Thyrotoxicosis (Graves' disease) is an autoimmune disorder and patients with this disorder are known to have several kinds of autoantibodies.[31] It might be possible that some of these antibodies are associated in the development of glaucoma associated Graves's disease. Thyroid eye disease (TED) is an organ-specific autoimmune reaction affecting extraocular muscles and intra-orbital content and occurs in 25-50% of patients with Graves' disease.[31] Visual field loss in patients with Graves' disease can be caused by glaucoma as well as compressive optic neuropathy.[32] In TED, a humoral agent (IgG) induces cellular inflammation with production of glycosaminoglycans and edema in both extraocular muscles and intra-orbital content.[33] The extraocular muscles may be so enlarged that they compress the optic nerve and eventually lead to blindness. In addition, the intraorbital content volume may be so increased that it can lead to a secondary elevation of the intraocular pressure. In TED, the short-term IOP increase observed when looking up is caused by eyeball compression due to enlarged and infiltrated extra-ocular muscles. The

long-term IOP increase seen in TED is caused by episcleral venous pressure elevation secondary to the increase in intra-orbital content and pressure.[31] Ohtsuka et al. showed that the prevalence of primary open angle glaucoma (POAG) and NTG was higher among patients with Graves' disease than in the normal population.[32] However, other studies did not find a significant increase in glaucoma prevalence in patients with TED, and from a pathophysiological standpoint, the long-term IOP increase is essentially due to episcleral venous pressure elevation.[31] Still the importance of these mechanical findings does not exclude a contribution of autoimmune disease to RGC and optic nerve damage.

Another disease where an autoimmune component might play a role is diabetes.[34,35] Diabetes and glaucoma are two of the leading causes of blindness worldwide.[36] The possible interaction between diabetes and glaucoma is not well established and up till now evidence regarding a clinical or an epidemiological association between the two diseases remains contradictive.[36,37] Several population-based studies have shown weak associations between occurrence of diabetes and an increased risk for development and severity of glaucoma, for example in the Beaver Dam Study[38] and in the Blue Mountain Eye Study.[39] However, in large-scale epidemiological studies such as the Framingham study,[40] the Barbados[41] and the Baltimore Eye studies,[42] no relationship was found. Both glaucoma and diabetes are diseases with vascular components, which may be the common denominator to ocular damage in patients with both conditions.[36] Abnormalities in blood flow in the retrobulbar and retinal microcirculation have been identified in both diabetes and glaucoma.[36,43,44] There is increasing evidence that hyperglycemia causes crosslinking and is associated with increased central corneal thickness, which results in augmented stiffness of the cornea, leading to overestimation of the actual IOP.[37,45,46] On the contrary, one study even showed that the optic nerve and RGCs are partially protected by short-term hyperglycemia in a rat model of experimental glaucoma.[37] As yet, no evidence has yet been established of one similar immune response underlying both diseases.

However, an association between the presence of Alzheimer's disease and glaucoma was seen.[47] Considerable evidence supports the presence of the characteristic pathological mechanisms of Alzheimer's disease, of amyloid accumulation, neuronal apoptosis and cell loss, in glaucoma.[48]

One might think that when increased serum immunoreactivity to retinal proteins may play a role in glaucomatous damage, immunosuppressive treatment might have a protective effect. A case report described a patient with NTG and rheumatoid disease whose serum immunoreactivity (antibodies) to retinal proteins regressed following methotrexate treatment for rheumatoid disease. During a three-year treatment, the patients' visual fields appeared to have improved, while during a period without treatment, signs of clinical deterioration occurred. Although this is only a report of one case, it suggests a potential role for immune-based intervention.[49]

Association of autoantibodies with glaucomatous neural damage

Autoantibody-based immune processes have long been suspected to be involved in the pathogenesis of glaucoma. Studies reported an increase in autoantibodies against ocular and optic nerve head (ONH) antigens in patients with glaucoma. These included antibodies directed against rhodopsin,[50] γ-enolase, heat shock proteins,[13,51,52] gluthatione-S-transferase,[24] α-fodrin[53], and glycosaminoglycans.[51] Using an antibody-profiling technique based on western blot and digital image analysis combined with multivariate statistics and artificial neural networks, Grus' group were able to analyze complex antibody patterns and demonstrated selective up-regulation of autoantibody repertoires against ocular antigens, including cellular retinaldehyde-binding protein, retinal S-antigen, in the sera of patients with POAG or NTG.[52,54-56]

Many glaucoma patients typically reveal a prominent and progressive atrophy of the retinal pigment epithelium close to the ONH in these eyes that is associated with disease progression. Wax et al. proposed that these parapapillary defects of the outer blood-retina barrier permit communication and access of circulating reactive antibodies to the retina, thereby binding to specific antigens in retinal neural tissue and retinal vasculature leading to injury.[14] Furthermore, Maruyama et al. studied the pathogenic role of serum autoantibodies against RGC in patients with glaucoma.[57] Immunohistochemical labeling revealed that most of the glaucoma patients' sera specifically reacted with the ganglion cell layer, possibly causing apoptosis of the RGCs, in the presence of additional unknown factors that breakdown the blood-retinal barrier to facilitate the antibody to access to the target antigens.

It is possible that autoantibodies are the result of a stress response of the RGCs.[24,58] This stress may be caused by ischemia, mechanical stress from high IOP, a high level of amino acids, or toxic products from high nitric oxide synthethase production in neurons.[54,59] Epitope mapping of anti-rhodopsin antibodies from patients with NTG revealed epitopic specificity of the patients' antibody profile, which suggests that a common mechanism underlies their generation.[60] A potential explanation is molecular mimicry, in that immune responses to infectious agents may generalize to native cellular proteins with similar epitope homology, resulting in serum antibodies that recognize these proteins.[60,61] An infection may thus initiate aberrant autoimmune tissue-specific responses due to cross-reactions between the infectious agent and native tissue proteins.[62,63] This mechanism has been implicated in the development of several organ-specific autoimmune diseases.[64] It has been shown that the C terminus of rhodopsin shares sequence identical to the C termini of numerous proteins from pathogenic bacteria and viruses.[60]

Apart from the serum, abnormalities in antibody patterns have also been detected in the aqueous humor of glaucoma patients.[65,66] Despite the immune privilege of the eye, autoantibody reactivity in the aqueous humor is nearly similar to those in serum of the same patients.[67] This concordance underlines the specificity and utilization of detected changes in sera of glaucoma patients, and suggests changes in systemic immunity in at least some patients. While these findings are consistent with the possibility that aberrant autoimmunity directed toward antigens in the retina or optic nerve is present in some patients with glaucoma, specific roles of these autoantibodies in the pathogenesis of the disease remains to be determined. It is not known whether these antibody profiles are an epiphenomenon of the disease, causative for the development of the disease, or if they occur as a result of glaucoma.

Accumulating evidence supports that the autoimmune mechanisms play a role in NTG, and it points to new approaches to the investigation, diagnosis, and treatment of this devastating disorder. In the future, it is important to compare autoantibody concentrations with optic nerve and RGC damage to establish the relevance of autoantibodies in the pathogenesis of NTG. There is also the possibility that the stage of glaucoma plays a role in the antibody profile composition.[30] However, we should remember that antibodies not only can be destructive, but can also be regulatory as they may help to modulate the activity of target molecules and influence their physiological functions, as natural autoantibodies

even occur in the sera of healthy subjects.[68-71] Loss of endogenous naturally-occurring and maybe protective autoantibodies in glaucoma may lead to a loss of immune protection, or to an increased risk to develop the disease.[30]

If autoantibodies detected in the sera of glaucoma patients are not directly responsible for the manifestation of glaucoma, they may still serve as diagnostic markers.[72] Finding a specific antigen or antibody repertoire may also provide a possibility to evaluate progression of the disease and treatment efficacy in a glaucoma patient. Glaucoma is sometimes called the "silent blinder" because the patients have no noticeable symptoms before they lose their central vision.[73] A screening method in which glaucoma can be detected prior to vision loss is therefore needed. In clinical practice, screening for specific autoantibodies or antibody patterns is performed for neurological disease screening or diagnosis.[74] This might also be possible for glaucoma. However, looking at only one specific marker may not be sufficient; a complex pattern of biomarkers is probably needed, as is seen by the complex antibodies patterns in glaucoma patients. [53,56,66,75,76] In fact, complex IgG antibody patterns against optic nerve and retinal antigens can be reproducibly identified in the serum of a study population from the United States and Germany, and autoantibodies to α-fodrin found in other neurodegenerative diseases such as Alzheimer's, further imply a role for autoimmunity and the neurodegenerative processes in glaucoma.[53] The high correspondence of autoantibody patterns found in the study populations from different continents supports the idea that serum autoantibody patterns may be useful as biomarkers for glaucoma detection or for determining prognosis.[53,77]

T cell participation in glaucomatous neural damage

Despite the assumption that the CNS is an immune-privileged site, T cells are able to enter normal, uninjured brain[78] as part of constitutive immune surveillance.[78,79] The site-specific parenchymal recruitment of T cells may initially play a beneficial role, as mentioned above.

According to Schwartz and colleagues, 'protective autoimmunity' refers to the situation in which immune cells recognize self-antigens and act as the body's defense mechanism against various injury, including high elevated IOP as seen in glaucoma.[80] They also suggest the existence of a mechanism, called secondary degeneration, that may explain why glaucomatous neuropathy continues to progress even after the primary cause (e.g. high IOP), has been removed. Secondary degeneration refers to the spread of degeneration

to healthy neurons that survived the primary insult.[81] Likely, cells undergoing secondary degeneration are adjacent to the damaged neurons and therefore are exposed to the degenerative environment. The degenerating neurons create a hostile milieu due to physiological factors that emerge in toxic amounts from the injured neurons, such as excessive glutamate and NO.[80,82] The first observation of 'protective autoimmunity' was seen in rodents where passive transfer of T cells specific to myelin basic protein (MBP) reduces the loss of RGC after traumatic optic nerve injury in rodents.[4] The spontaneous protective T-cell response may not be sufficient in its natural state or in case of severe insult, and may not be properly controlled, leading to chronic glaucomatous neurodegeneration.[80,82] For this reason Schwartz and colleagues suggested boosting of this protective autoimmune response by either passive transfer of self-reactive T cells or active immunization using self-antigens.[16,82-84] Once activated by self-reactive antigens, the protective T cells create a neuroprotective milieu that prevents or attenuates the secondary degeneration by affecting the local innate immune response. T cells facilitate recruitment of monocytes from the blood to the site of injury and properly activate resident microglia, which contribute in the regulation of the local inflammation and restoration of the homeostasis.[82] However, careful use of self-antigens is recommended, as the antigen should not induce an autoimmune response leading to further destruction.[15,80,85] Interestingly, in rats with different strains, the same IOP leads to different quantities of RGC loss, due to their difference in immune potency. The number of surviving RGCs in Sprague-Dawley (SPD) rats, a strain in which a beneficial autoimmune can be evoked spontaneously, was higher than in Lewis rats. In addition, in thymectomized SPD rats, the number of surviving RGCs after IOP increase was decreased.[16]

T cells can also initiate an immune response leading to chronic autoimmune neurodegeneration, particularly if they are presented with retinal or ONH antigens, due to failure to control an aberrant, stress-induced immune-response. Co-cultures of RGC-5 cell line with T cells isolated from immunized rats revealed that T cells activated by heat shock protein (HSP) 27 and HSP60 immunization in rats induced RGC degeneration and axon loss via the release of the inflammatory cytokine Fas-Ligand (FasL), accompanied by an up-regulation of the FasL receptor in RGCs. ***In vivo***, this resulted in a transient infiltration of T cells into the retina of HSP-immunized rats.[26] T-cell mediated neurodegeneration does not depend only on aberrant activation of autoreactive T cells, but maybe also reflect a dysfunction in the termination of T cell responses in this immune-privileged site by

apoptosis.[18,26] It is widely accepted that chronic activation of glial cells and accompanying increases in the production of proinflammatory cytokines, primarily TNF-α, are hallmarks of inflammation or parainflammation in the glaucomatous eyes. TNF-α through binding to TNFR1, a death receptor, elicits RGC death and inflammation during neurodegenerative injury in glaucoma.[86,87]

Activation of an adaptive immune response, which requires antigen presentation, is also evident in glaucoma patients.[8] For example, abnormal T-cell subsets[22] as well as elevated titers of serum autoantibodies to ONH and retina antigens are detected in glaucoma patients.[58] In order to examine whether the cellular immune system may play a role in the initiation/and or sustainment of glaucomatous optic neuropathy, T lymphocyte subsets in peripheral blood from patients with NTG or POAG were assessed and compared to age-matched control subjects.[22] In this study, the frequency of CD8+HLA-DR+ lymphocytes were seen to increase in NTG patients, and CD3+CD8+ lymphocytes in both patients with NTG and POAG, as compared to healthy subjects. An increased expression of HLA-DR molecules on lymphocytes has also been found in several other organ-specific autoimmune diseases, such as autoimmune thyroid disease, rheumatoid arthritis and in newly manifested type I diabetes.[88-92] This might suggest that autoantigens originating from the retina or optic nerve may be present in glaucoma patients in a similar way as in the aforementioned autoimmune-related diseases.[22]

Heat shock proteins

Heat shock proteins, also called stress proteins, are among the most highly-conserved and abundant proteins found in nature that are constitutively expressed in most cells under normal physiological condition.[93,94] They are thought to play a vital role in the cell in the presence of stress. One of the main roles that HSPs play is that of molecular chaperones. Particularly, they have been shown to function in protein maturation events, such as protein folding, unfolding, and translocation. In response to environmental stresses, such as heat, anoxia, and mechanical stress, HSPs accumulate to very high levels in stressed cells. Increased expression of HSPs is involved in protecting cells from the deleterious effects of heat and other stresses and helps them survive or promotes recovery from stress.[93,95,96] The expression of HSPs in neuronal cells suggests that they may require constitutive levels of these proteins for survival against various stresses. Furthermore, the accumulation

of HSPs in these cells during acute toxic states and in a variety of degenerative and inflammatory neurological diseases suggests their role for neuronal survival.[97-99]

Stress proteins have been shown to be among the dominant antigens recognized in immune responses. On the one hand, immune responses against HSPs can be highly cross-reactive and can even evolve anti-self antibody; at the other hand, they may lead to elimination of the bodies' own cells when the cells are affected, transformed, or otherwise stressed.[93] By serving as a danger signal, up-regulation of HSP27 may facilitate detection and elimination of stressed RGCs by the immune system. Uncontrolled immune-mediated cytotoxicity to RGCs and their axons may eventually facilitate the progression of neurodegeneration.

HSPs have been involved in the innate immune response and in the anti-apoptosis process.[100] They can bind to the CD14-toll like receptor 4 (TLR4) complex of the APCs and produce an inflammatory effect.[101] Furthermore, HSPs are highly antigenic, and immune responses to HSPs are implicated in the development of a number of human autoimmune diseases.[64] An activated immune response, such as increased autoantibodies to HSP27, 60 and 70 have been found in many patients with glaucoma.[51,61,66,75,77] The elevated titers of HSP27 autoantibodies in glaucoma patients are thought to induce neuronal apoptosis through attenuation of the ability to stabilize retinal actin cytoskeleton and activation of caspases.[27] Tezel et al. observed that exogenously applied anti-HSP27 antibodies enter neuronal cells in the human retina by an endocytotic mechanism. Subsequent to internalization, the anti-HSP27 antibodies facilitate apoptotic cell death. Anti-HSP27-antibody binding to actin results in depolymerization and proteolytic cleavage of actin, which leads to a decreased ability of endogenous HSP27 to stabilize actin cytoskeleton, thereby facilitating neuronal cell death. This may clarify why anti-HSP27 autoantibodies underlie glaucomatous optic neuropathy. [27]

Anti-HSPs may be generated through molecular mimicry, as described above: immune responses to infectious agents may generalize to native tissue proteins that share similar protein sequences, resulting in serum antibodies that recognize both HSP of infectious agents as well as native tissue proteins.[61,77] Mycobacterial stress proteins are recognized by human antibodies and T lymphocytes, and the evidence suggests that these proteins are among the major targets of the human cell-mediated immune response. The major stress protein antigen recognized by antibodies in bacterial infection is HSP60.[93] Therefore,

invasion of a host by a pathogenic organism such as a bacteria or virus is misinterpreted by the immune system in such a way that a response is mounted not only to the invading agent, but to other body proteins that share the same protein sequence to the invading agent.[77]

Increased expression of HSP27 and HSP60 was seen in postmortem eyes from glaucoma patients. Retinal immunostaining showed that HSP60 was prominent in RGCs and photoreceptors, whereas HSP27 was prominent in the nerve fiber layer and the RGCs as well as in the retinal vessels.[94] Although increased expression of HSPs in glaucomatous eyes may serve initially to protect cells from further destruction and facilitate repair,[94] they subsequently may recruit immune responses that contribute to the progression of disease.[64]

Glial cell contribution to immune responses associated with glaucoma

During the development and maintenance of the central nervous system (CNS), there exists a complex partnership between neurons and glial cells. Glial cells maintain the normal function of the CNS both by controlling the extracellular environment and by supplying metabolites and growth factors.[102] In addition, glial cells play an important role in maintaining perivascular barriers and securing immune privilege to protect neurons from potentially damaging effects of an inflammatory immune response.[4,102] Both microglial and macroglial cells exhibit important immunoregulatory functions in the brain as well as in the ONH and retina.[103-105] The immune privilege nature of the CNS makes it crucial that glial cells are capable of responding rapidly to any injurious condition or damage. Activation of glial cells can be brought about either through mechanical or ischemic stress or any other type of injury.[3]

Progressive degeneration of RGCs and their axons in human glaucoma and in animal models is accompanied by a chronic activation of glial cells,[3,4] which is usually displayed by a change in cell morphology and gene expression profile and upregulation of glial fibrillary acidic protein (GFAP).[3,4,102] After becoming reactive in glaucoma, stressed glial cells may be insufficient and/or dysfunctional in their ability to support neurons, which may facilitate RGC and axonal injury.[4,102] Recent evidence supports the view that glial cells may not be purely neuroprotective but may participate in the pathological process of neuronal damage.[4,102] Glial cells in the glaucomatous human retina and ONH rapidly respond to

tissue disturbance by exhibiting a reactivate phenotype.[106,107] This may lead to increased production of cytokines, immunomediators, cell death inducers (e.g. Tumor necrosis factor-α (TNF-α) and NO) and complement components, extracellular matrix remodeling of the ONH, and increased antigen-presenting ability of glial cells.[4,102] In agreement with this notion, a study by Tezel et al. demonstrated that following exposure to different stress conditions, such as ischemia and elevated hydrostatic pressure, glial cells secreted TNF-α and other noxious agents, such as NO, into the culture media and facilitated the apoptotic death of RGCs. Moreover, RGC apoptosis was attenuated by a neutralizing antibody against TNF-α and by a selective inhibitor of inducible NO synthase.[108]

Microglia, which are derived from the monocyte/macrophage lineage, play a crucial role in the regulation of the immune response.[109] As in other types of neurodegeneration,[110,111] resident microglial cells with increased MHC expression in glaucomatous eyes[112] likely participate in the immune-mediated process by functioning as antigen-presenting cells (APCs) in innate immune responses. Resident microglia also regulate the initiation and perpetuation of adaptive immune responses mediated by both T cells (the cellular immune response) and B cells (the humoral immune response).[109,113-115] It has been shown that following exposure to ROS/oxygen stress, microglial cells derived from the rat retina and ONH upregulated MHC class II molecules and became potent inducers of T cell activation as assessed by T-cell proliferation and TNF-α secretion, when were compared with non-treated microglial cells.[11]

Considerable evidence indicates that astrocytes, the most numerous glial cells in the CNS, are also capable of regulating immune responses. Similar to microglia, human lamina cribrosa astrocytes can be induced to express MHC molecules and acquire the ability of APCs. Yang et al. studied the expression of HLA-DR (a human MHC class II molecule) in astrocytes and found an increased expression of HLA-DR in ONH astrocytes of glaucomatous eyes secondary to exposure with elevated serum cytokines (IFN-γ, IL-10) or ischemia as compared to those of age-matched normal donors.[106] As a result, human lamina cribrosa astrocytes acquire the potential of APCs and may contribute to immunoregulatory events participating in the neurodegeneration process in glaucoma.

The finding that both microglial cells[112] and GFAP-positive astrocytes exhibit increased HLA-DR expression in glaucomatous human eyes suggests the presence of auto-immunity.

The fundamental basis of cellular immune recognition demands that T cells recognize antigens in the form of small peptides bound to MHC class II molecules displayed on the surfaces of APCs.[116] Consequently, upregulation of MHC class II molecules may help stimulate detrimental adaptive immune responses and lead to T cell activation and expansion.[107] These observations further support the likelihood of autoimmune injury in glaucoma.

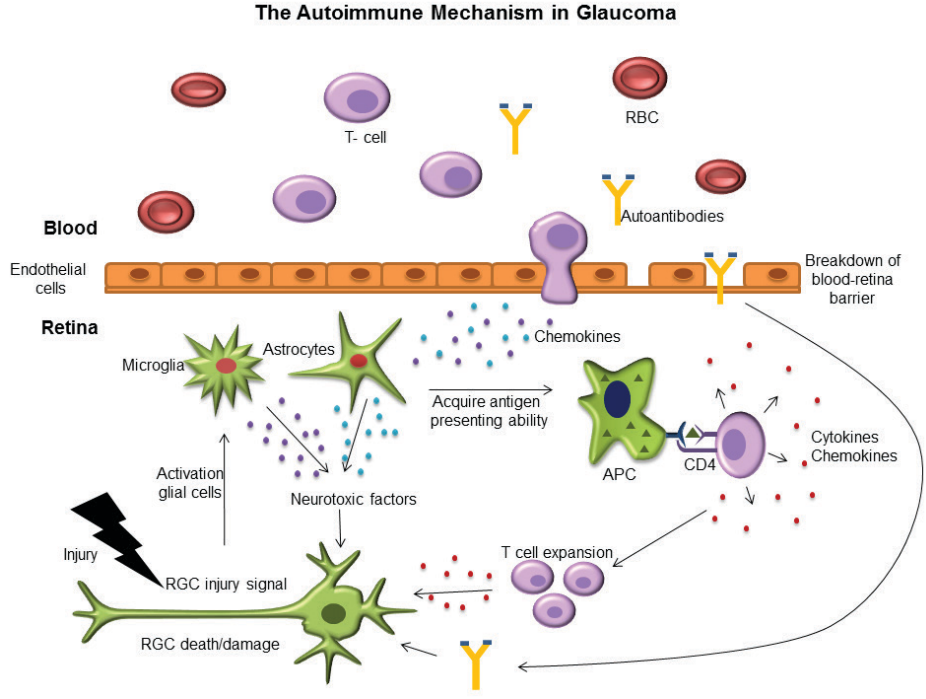

Figure 1. The Autoimmune Mechanism in Glaucoma This figure represents an oversimplified summary of the autoimmune mechanism in glaucoma. Mechanical or ischemic stress injury to RGCs and their axons causes chronic activation of glial cells (microglia and astrocytes), thereby exhibiting a reactivate phenotype. After becoming reactive in glaucoma, stressed glia cells produce cytokines, immunomediators, cell death inducers (e.g. TNF-α, NO) and complement component, resulting in death or damage of the RGCs and their axons. In addition, glial cells acquire and increase their antigen-presenting ability by expressing increased HLA-DR (a human MHC class II molecule) on the surface. Subsequently, the antigen-presenting cells present retinal or optic nerve head antigens to the T cells, which induce T cell activation and expansion. T cells in turn, produce and secrete pro-inflammatory cytokines (e.g. TNF-α, FasL) and chemokines, which results in RGC and axon damage and T cell recruitment into the retina, respectively. In glaucoma, breakdown of the blood-retina barrier facilitate communication and access of circulating autoantibodies and autoreactive T cells to the retina, thereby binding to retinal neural tissue leading to injury.

CONCLUSION

Evidence suggests that glaucoma may (in part) be a consequence of an immunological process. Findings supporting this statement include: 1) Insufficiency and/or dysfunctions of glial neurosupportive abilities in glaucomatous conditions; 2) abnormal T-cell subsets as well as elevated titers of serum autoantibodies to ONH and retinal antigens; 3) elevated serum levels of autoantibodies to small heat shock proteins in animal models and patients with glaucoma; and 4) possible comorbidity of immune-related disease in glaucoma patients.

Alterations of the cellular and humoral immune system in patients with glaucoma support that the immune system may play an important role in the initiation and/or sustainment of glaucomatous optic neuropathy.[22] The outcome of complex interactions between the immune system and retinal resident immune cells appears to be critical for the development of autoimmune RGC degeneration in animals as well as in humans. Preventing migration of activated T cells into the retina could be an important neuroprotective strategy, as these cells can recruit and activate other immune cells and initiate an autoimmune process.[26] On the other hand, it has been suggested that the involvement of T cell-mediated cellular immunity plays a neuroprotective role against glaucomatous optic neuropathy.

Despite the strength of these associations, there is presently no evidence to confirm that RGC loss occurs as the direct result of aberrant cellular and humoral immunity in these patients. Therefore, current understanding of the mechanisms underlying the complex interplay between immune-privilege, protective immunity, and autoimmune neurodegenerative disease is not satisfactory yet. An improved understanding of how tissue stress, neuronal injury, and glial responses during glaucomatous neurodegeneration orchestrate individual components of immunity can help designing immunomodulation-based treatment strategies.[117] It is vital that research continues to elucidate the potential role of the immune system in glaucomatous neurodegeneration and the possibility of alternative treatment. In addition, such studies may lead to valuable molecular biomarkers for the diagnosis and identification of patients in whom we suspect that aberrant immunity is directly relevant to glaucomatous neurodegeneration. To date, more extensive studies are needed to improve our knowledge about the role of autoimmune mechanisms and the autoantibodies in glaucoma.

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