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Glaucoma

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Abstract

Glaucoma is a chronic neurodegenerative disease of the optic nerve, in which apoptosis of retinal ganglion cells (RGCs) and progressive loss of optic nerve axons result in structural and functional deficits in glaucoma patients. This neurodegenerative disease is indeed a leading cause of blindness in the world. The glaucomatous neurodegenerative environment has been associated with the activation of multiple pathogenic mechanisms for RGC death and axon degeneration. Growing evidence obtained from clinical and experimental studies over the last decade also strongly suggests the involvement of the immune system in this neurodegenerative process. Paradoxically, the roles of the immune system in glaucoma have been described as either neuroprotective or neurodestructive. A balance between beneficial immunity and harmful autoimmune neurodegeneration may ultimately determine the fate of RGCs in response to various stressors in glaucomatous eyes. Based on clinical data in humans, it has been proposed that one form of glaucoma may be an autoimmune neuropathy, in which an individual's immune response facilitates a somatic and/or axonal degeneration of RGCs by the very system which normally serves to protect it against tissue stress.

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Aberrant T Cell Immunity

Growing evidence supports an aberrant activity of the immune system in glaucoma patients [1–3]. In fact, glaucomatous injury sites, namely the retina and the optic nerve, are 'immune privileged' as are other tissues in the central nervous system (CNS). This requires the deletion and active regulation of immune responses for the control of potentially damaging and sight-threatening autoimmune diseases [4, 5]. Similar to the anterior segment of the eye [6], apoptotic elimination of T cells is likely an essential protective mechanism to prevent inflammation and antigen encounter in the retina and optic nerve.

Despite immune privilege, however, autoreactive T cells are able to enter normal, uninjured brain with an intact blood-brain barrier [7] as part of the constitutive immune surveillance [8]. Although there is no evidence of T cell accumulation in the retina or optic nerve head tissues of glaucomatous eyes, which may be due to the transitory nature of sentinel T cells, episodic disruptions of the blood-eye barrier may facilitate their access into these tissues. The site-specific stromal recruitment of T cells may initially play an important role as a protective mechanism, since it allows early contact of the immune system with cellular debris, destruction of damaged cells, and the removal of pathogenic agents from the CNS. This elicits what has been called 'protective immunity', in which the recruited T cells mediate the protection of neurons from degenerative conditions by providing a source of cytokines, including IFN- γ and possibly neurotrophins [9–11]. Protective immunity has been suggested to occur as a homeostatic response to injury to reduce the secondary degeneration of retinal ganglion cells (RGCs). This has been induced experimentally in rodents by active or passive immunization with self-antigens [12, 13].

While T cell-mediated immune responses may initially be beneficial and even necessary to optimally limit neurodegeneration as evidenced in rodents, compelling evidence in humans obtained during the past decade suggests the conversion of protective immunity or self-limited inflammatory responses into the chronic autoimmune neurodegeneration seen in glaucoma. Despite the neuroprotective features of the immune system, an autoimmune component, resulting from a failure to properly control an aberrant, stress-induced immune response, likely accompanies the progression of neurodegeneration in a cohort of glaucoma patients. This occurs primarily in glaucoma patients in whom the intraocular pressure is in the 'normal' range (i.e. so-called 'normal pressure' or 'low tension' glaucoma). The presentation of neuronal antigens to the immune system may initiate further immune responses followed by the expansion and secondary recruitment of circulating, pathogenic T cells that may lead to antigen-mediated neurotoxicity through an 'autoimmune neurodegenerative disease'.

Support for such a T cell-mediated component of the neurodegenerative immune response in glaucoma is evidenced by abnormal T cell subsets in many glaucoma patients [14]. Recent experimental studies have also provided evidence that antigen-stimulated T cells may directly be cytotoxic to RGCs, mostly through the Fas/Fas ligand-dependent pathway. Although retinal microglia are involved in the apoptotic elimination of T cells from the retina and optic nerve head, similarly via Fas/Fas ligand interactions, RGCs progressively undergo apoptosis in antigen-immunized animals, which results in a pattern of neuronal damage similar to human glaucoma [Tezel and Wax, unpublished data]. These data suggest that T cell-mediated neurodegeneration not only depends on aberrant activation of autoreactive T cells but may also reflect a dysfunction in the

apoptotic termination of the T cell response in the retina and a loss of immune privilege in this site.

Humoral Immune Response

The evidence that the humoral immune response also favors the onset and/or progression of neurodegeneration in some glaucoma patients is found in studies of autoantibodies in glaucoma patient sera or tissues and studies of autoantibody-mediated toxicity to RGCs in experimental models. For example, there is an increased prevalence of monoclonal gammopathy [15] and elevated serum titers of autoantibodies to many optic nerve [16] and retinal antigens [17–20] in patients with glaucoma. There is also evidence of immune globulin deposition in the glaucomatous retina [21]. It has been proposed that peripapillary chorioretinal atrophy, commonly present in glaucomatous eyes [22], may be the site for a facilitated access of serum antibodies to the retina [21], since the blood-retina barrier is disrupted in these areas. Increased autoantibodies in the serum of glaucoma patients include those to heat shock proteins, e.g. hsp60, hsp27, and α -crystallins [18, 19]. The increased titers of serum autoantibodies may reflect a response to tissue stress and/or injury in glaucomatous eyes. However, direct application of antibodies against small heat shock proteins to retinal neurons, at similar concentrations to that found in the serum of many glaucoma patients, has resulted in the apoptotic death of these neurons, *in vitro* and *ex vivo* [19, 23, 24]. This apoptotic effect has been found to be associated with the diminished protective abilities of native heat shock proteins, including the attenuation of the ability of native hsp27 to stabilize retinal actin cytoskeleton [24]. These findings suggest that heat shock protein autoantibodies have direct pathogenic potential to facilitate RGC death in glaucoma and that their presence is not just an epiphenomenon. This is further supported by a clinical study in which serum titers of autoantibodies to heat shock proteins did not differ depending on the degree of glaucomatous damage in either American or Japanese patients [25]. On the other hand, antibody-mediated neuronal damage in glaucoma may also occur indirectly by way of a ‘mimicked’ autoimmune response to a sensitizing antigen [17, 18, 26]. Molecular mimicry as a potential causal mechanism of glaucomatous neurodegeneration is supported by findings of elevated autoantibodies to bacterial heat shock proteins, including hsp60 [18], as well as the increased expression of HLA-DR/CD8 on circulating T cells of normal pressure glaucoma patients [14]. In addition, epitope mapping revealed that the immunogenicity of rhodopsin antibodies in these patients is shared by epitopes of proteins found in common bacterial and viral pathogens [26].

Additional recent reports from several laboratories of elevated serum antibodies against neuron-specific enolase [27] or phosphatidylserine [28], and complex patterns of serum antibodies against retina and optic nerve antigens [29] in glaucoma patients also support the association of serum autoantibodies with glaucomatous neurodegeneration.

Tissue Stress in Glaucoma

What seems to be the most important parameter for the modulation of the immune system in glaucoma is that the retina and optic nerve head are under widespread and long-term tissue stress in glaucomatous eyes. In addition to the clinical evidence of elevated intraocular pressure in glaucoma patients, there is also evidence of hypoxic [30] and oxidative tissue stress [31] in glaucomatous eyes. The tissue stress in glaucoma is best represented by increased expression of stress proteins, including heat shock proteins, in the retina and optic nerve head [32]. While heat shock proteins function as endogenous protectants of retinal neurons in response to a variety of stressors, including those associated with glaucoma [24, 33], they also have the ability to elicit an activated immune response. For example, heat shock proteins are known to be highly antigenic, and immune responses to heat shock proteins are implicated in the development of a number of human autoimmune diseases as a consequence of molecular mimicry [34, 35].

Tissue stress is probably a major force that drives a resting immune system over the threshold of antigen-specific activation, since several stress-associated costimulatory factors are required for the activation of resting antigen-presenting cells, including glial cells [35–37]. Glial major histocompatibility complex class II expression is indeed induced under stress conditions [38, 39]. Similarly, optic nerve head and retinal glia, including both macroglia and microglia, prominently respond to glaucomatous tissue stress by exhibiting an activated phenotype [40], which includes the activation of their antigen-presenting ability. Major histocompatibility complex class II molecules on glial cells are upregulated in glaucomatous eyes [41]. Microglial cells [42], and also glial fibrillary acidic protein-positive astrocytes, exhibit HLA-DR immunolabeling in glaucomatous human donor eyes [41]. Thus, glial cells not only function in the innate immune response (by clearing the debris and the deleterious breakdown products from degenerating RGCs and their axons), but are also involved in adaptive immunity through antigen presentation. In addition, despite their many neuroprotective functions, glial cells may also be directly cytotoxic to RGCs through the increased production of neurotoxic cytokines [43]. Due to their diverse functions, glial cells have been implicated in traumatic injuries and

chronic neurodegenerative diseases of the CNS [44–47]. The prominent and persistent activation of glial cells in glaucomatous eyes, including the activation of their antigen-presenting ability, point out a similar role of these cells in the activation of an autoimmune neurodegenerative process in glaucoma.

Conclusion

The onset, progression, and termination of tissue-specific immune responses are largely determined by the interactions between the tissue-infiltrating T cells, stromal cells of the CNS (in the case of glaucoma, RGCs, astrocytes, and Müller cells), and tissue macrophages (microglia). Whether the outcome of immune system activity is deleterious or beneficial for tissue integrity and function depends on complex interactions between these cells [48]. Although protective autoimmunity may govern the retina and optic nerve environment under homeostatic conditions, it is proposed that an adverse neurodegenerative component resulting from a failure to properly rectify the initial injury-induced immune response, accompanies neurodegeneration in some glaucoma patients. Tissue stress present in glaucomatous eyes seems to be decisive for the balance between protective immunity and the progression of neurodegeneration by autoimmunity. Alterations in neuron-glia-T cell interactions under glaucomatous stress conditions, along with the increased antigenicity in the damaged tissue and the increased antigen-presenting ability of resident glial cells, appear to be important factors determining the role of the immune system in glaucoma. Continued efforts to better understand the role of the immune system in glaucoma should allow for both the identification of biomarkers that may signal the most advantageous time to intervene in order to minimize disease progression, as well as the development of immunomodulatory strategies that could be utilized for such therapeutic gain.

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