

Immunologic Considerations in Glaucoma Care

Innate and adaptive immune responses represent elusive but important components of the human glaucomatous process.

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When evaluating the optic nerve of a glaucoma patient, clinicians see pathological cupping consistent with a loss of retinal ganglion cell (RGC) axons. They intuitively grasp that elevated IOP, ischemia, or possibly even a high translaminal cribrosa pressure gradient contributes to this loss of neural tissue. It is more difficult to conceptualize that immune responses play a role in mediating optic nerve damage in glaucoma. The traditional function of the immune system is to respond to infectious organisms, and mainstream thinking does not suggest that age-related open-angle glaucoma is caused by infection. Regardless of the trigger for optic nerve damage in glaucoma, animal model systems clearly show that both innate and adaptive immune responses are called into action. The question is whether or not these findings from animal models translate into the clinic for humans. This article briefly explores the components of the innate and adaptive immune systems in the optic nerve and how they may respond in human glaucoma.

THE INNATE IMMUNE SYSTEM IN GLAUCOMA

Innate immune system refers to the local neighborhood of defense mechanisms that respond to glaucomatous injury. The innate immune system in the optic nerve and neurosensory retina consists of Müller cells that span the retina, displaced astrocytes that reside adjacent to RGCs, and microglia. The complement cascade is also a part of the innate immune response against injury.

What evidence is there that innate immunity is active in glaucoma patients? Lee et al reported that peripapillary

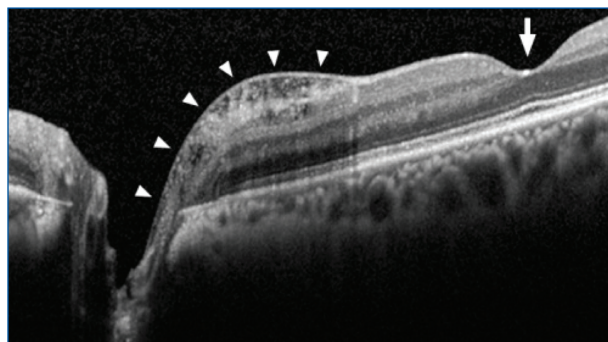


Figure. Spectral domain optical coherence tomography of the eye of a patient with glaucoma illustrates peripapillary retinal NFL schisis without evidence of vitreous traction. The arrowheads delineate the area of schisis that spares the macula (arrow). Note that the entire neurosensory retina has a reduced signal, with fine linear striations extending from the photoreceptor level to the NFL, implicating Müller cell activation in the formation of schisis. Reprinted with permission from Lee et al.¹

nerve fiber layer (NFL) schisis occurred in 5% of glaucoma patients versus 0.5% of controls in the Investigating Glaucoma Progression Study.¹ Peripapillary NFL schisis often occurred without concomitant pit-like lesions in the optic nerve, obvious evidence of vitreous traction, or splitting of the peripheral neuroretinal tissue, but it was associated with elevated IOP. We suspect that the retinal involvement detected on optical coherence tomography (Figure) is indicative of Müller cell activation by the glaucomatous process. These “schisis cavities,” which have been observed by numerous investigators,²⁻⁵ occasionally

extend into the macula to produce profound visual loss. Each time, the researchers seem unable to muster any explanation for these neuroretinal changes aside from uncontrolled IOP.⁶⁻¹⁰

If NFL schisis represents a response of the resident retinal immune cells to IOP, why are retinal gliotic changes not observed more often? Interestingly, Graf et al reported patchy alterations to the retinal surface in Bjerrum's area in 86% of patients with progressive glaucoma but not in age-matched controls. The investigators felt these lesions represented a superficial form of epiretinal gliosis.¹¹ A very clinically relevant point is that glial cell activation could mask considerable NFL dropout in glaucoma, thus serving as a space-occupying lesion when there should otherwise be atrophic change.

THE ADAPTIVE IMMUNE SYSTEM IN GLAUCOMA

Damage to the optic nerve in glaucoma also triggers an adaptive immune response that has humoral and cellular (lymphocytic) arms. A key feature of the adaptive immune response is the development of immunological memory, which allows the immune response to continue even after IOP normalizes. This may have profound clinical implications. Furthermore, the adaptive immune response plays a complex, modulatory role rather than a purely injurious or protective role in glaucoma's pathogenesis. Antibodies involved in the humoral response can be directly cytotoxic,¹² although whether cytotoxic autoantibodies cause RGC loss in human glaucoma is not clear. Nevertheless, numerous investigators have reported elevated immunoglobulin G to various retinal and nonretinal antigens in open-angle glaucoma across the spectrum of IOP.¹³⁻¹⁶ Interestingly, Fellman et al reported a case of a patient with normal-tension glaucoma who demonstrated serum antibodies to retinal proteins that regressed after treatment with methotrexate for her rheumatoid arthritis¹⁷; the visual fields also improved after this treatment.

With respect to the cellular arm of the adaptive immune response, activated lymphocytes can migrate across the blood-brain barrier to secrete cytokines such as tumor necrosis factor (TNF), which has been implicated in human glaucomatous optic neuropathy.¹⁸ Cells of the innate immune system may also produce this proapoptotic cytokine in the retina. Further support for the role activated lymphocytes play in glaucoma comes from a murine glaucoma model where external radiation, which blocked cellular migration into the optic nerve, was neuroprotective.¹⁹ Interestingly, in a primary open-angle glaucoma case control group nested within two population-based cohorts where serum was collected before the diagnosis of glaucoma was made, higher-soluble TNF receptor 2 was

associated with a reduced risk of primary open-angle glaucoma, especially in women.²⁰ The investigators postulated that higher-soluble TNF receptor 2 served to bind TNF and prevented it from inducing RGC loss. Roh et al found that intraperitoneal etanercept injections, which also block TNF's effect on RGCs, were neuroprotective in a rodent model of elevated IOP. This finding suggests that blocking TNF may be a viable therapeutic target in glaucoma.²¹

CONCLUSION

Overall, the immune system seems to be important in glaucomatous optic neuropathy. Understanding its role may lead to novel treatments for the disease. ■

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