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Immune Regulation Towards Immunomodulation for Neuroprotection in Glaucoma

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Abstract

Although the immune system functions to preserve and restore tissue homeostasis, accumulating risk factors, prolonged glial activation, and sustained release of pro-inflammatory mediators in glaucoma may lead to a failure in the regulation of stress-induced immune response, and innate immune cells, autoreactive T cells, autoantibodies, and excess complement attack may exhibit potent stimuli that harm retinal ganglion cell somas, axons, and synapses. Identification of the cellular and molecular components of immune response pathways can provide immunomodulatory treatment strategies to attenuate neuroinflammation, protect neural tissue from collateral injury, and enhance endogenous recovery processes. This review highlights the current knowledge of molecular mechanisms regulating neuroinflammation in glaucoma.

Introduction

Glaucoma is a complex neurodegenerative disease leading to blindness. Glaucomatous neurodegeneration involves specific combinations of genetic predispositions, epigenetic risk factors, and environmental stressors that increase the aging-related stress in retinal ganglion cells (RGCs) and optic nerve axons. It has become clear over years that besides elevated intraocular pressure (IOP), multiple stressors affect the cellular homeostasis in glaucoma, and a stressor-threshold determines the intrinsic vulnerability of neuronal subpopulations for injury. Present evidence indicates highly interconnected downstream pathways of cellular processes in RGCs exposed to glaucomatous stress, which include mitochondrial dysfunction, proteolytic caspase cascade, endoplasmic reticulum stress, and oxidative stress. The precise molecular events initiating the neuronal injury and the time course of glaucomatous neurodegeneration in different neuronal compartments are under intensive investigation and great debate [1,2].

Recent research expanding towards the impacts of cellular interactions has recognized important roles of immune system regulation in cell fate decisions in glaucoma. Neurodegenerative insults and activation responses of neighboring glia initiate an immune response to restore tissue homeostasis. However, an autoimmune component resulting from a failure to properly control stress-induced immune response has the capacity to propagate neuronal injury [3–5]. Despite increasing interest in immune system involvement in

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glaucoma, arguing aspects of neuroinflammation preclude potential therapeutic implications. Ongoing research is expected to provide a much greater understanding of the immune regulatory mechanisms in glaucoma to thereby effectively and safely modulate the immune response for the gain of neuronal survival and tissue repair, while avoiding neurodegenerative inflammation [6]. This review focuses on the immunogenic aspects of glaucomatous neurodegeneration and highlights the current knowledge of molecular mechanisms regulating neuroinflammation.

Immune System Activation in Glaucoma

Initial observations suggesting the immune system involvement in glaucoma have included increased titers of serum autoantibodies to a variety of retina and optic nerve proteins in patients with glaucoma [7–12]. Following analysis of the blood samples collected from patients with glaucoma has also indicated abnormal T cell subsets [13] and increased serum cytokines [14]. Consistent with serum alterations, aqueous humor levels of antibodies [15] and pro-inflammatory cytokines have been found increased in glaucoma compared to non-glaucomatous controls [16–19]. Findings in human glaucoma have been followed by similar findings in experimental models that exhibited a complex profile of serum antibodies [20] and stimulated proliferative activity of isolated T cells in ocular hypertensive animals (Yang et al, 2007 ARVO Abstract 3285; and Tezel et al, 2008 ARVO Abstract 3699). These observations have motivated further research and led the accumulation of considerable information about innate and adaptive immune responses in glaucoma.

Glial cells serve as well-equipped resident immune cells in the retina and optic nerve. As discussed later below, these cells appear to be key players of innate immune responses and also the innate/adaptive immune interplay in glaucoma. Dysfunctional cross talk between neurons and glia represents an immune stimulatory signal. Neurons constitutively express glial inhibitors, and the neuronal injury in glaucoma may remove this suppression. A prominent stimulation of pro-inflammatory signaling is evident from protein and gene expression studies of the retina and optic nerve in human glaucoma and animal models [21–26]. Specific components of immune activity include increased cytokine production [27,28], and increased expression of MHC class II molecules [29,30], toll-like receptors (TLRs) [31], and different complement components [32–34]. Many additional factors present in glaucomatous tissues, including increased antigenicity/exposure (due to increased protein expression/modification [35–37] or epitope spreading [38]), and increased expression of highly antigenic and immune stimulatory stress proteins (HSPs) [39], may also help create a proper environment for innate immunity and antigen presentation for adaptive immunity [40].

In addition to resident glial responses, a recent gene expression study has indicated early activation of the leukocyte transendothelial migration pathway resulting in pro-inflammatory monocytes entering the optic nerve prior to detectable neuronal damage in DBA/2J mice with hereditary glaucoma [41]. Although DBA/2J mice exhibit complex inflammatory characteristics different from primary open-angle glaucoma in human, recruitment of blood-borne cells appears to be a shared component of inflammatory responses during neurodegeneration with controversial consequences in a context- and timing-dependent manner [41,42].

Despite the lack of clear evidence supporting parenchymal T cell invasion in glaucomatous human tissues, which is a temporary event, peripapillary chorioretinal atrophy zones, optic disc hemorrhages, and alterations in perivascular barriers may facilitate the access of serum autoantibodies into retina and optic nerve tissues in glaucoma [6]. Recent evidence [43–45] documenting lymphatic drainage from the mouse eye may also support a facilitated immune

system access. Furthermore, histopathological evidence indicates immunoglobulin deposition in the glaucomatous human retina [46].

Although the present evidence supports the immune system activation in glaucoma, its causative importance remains poorly understood. The immune system is a critical component of the body's own neuroprotective potential. However, it is commonly recognized that the immune system plays a pivotal role in both physiological and pathological conditions, such as the restoration of neuronal tissue integrity and the progression of neurodegeneration by autoimmunity. Inflammation-mediated benefits include mechanisms, such as tissue cleaning by phagocytosis of debris, neuroprotection through release of trophic/survival factors, mobilization of neural precursors for repair, remyelination, and axonal regeneration [47]. A properly directed and limited inflammatory response to local tissue stress or injury may similarly be a natural healing process in glaucoma. However, prolonged exposure to glaucomatous stress and increasing risk factors may shift the balance between pro-inflammatory and anti-inflammatory responses and switch the initially protective response to chronic and damaging inflammation [6]. Emerging research findings summarized below illustrate detrimental consequences of uncontrolled immune activity.

Neurodegenerative Consequences of Immune Responses and Treatment Approaches

The knowledge gained from clinical and experimental studies collectively suggests that innate immune cells, autoreactive T cells, autoantibodies, and excess complement attack exhibit neurodegenerative potential in glaucoma [5,6]. It is commonly viewed that co-existing risk factors, such as aging, sustained tissue stress and injury, and the activity status of resident and systemic immune cells, determine the risk of developing autoimmune injury.

Despite numerous protective and restorative outcomes, neuroinflammatory responses of glial cells may result in a more severe and chronic inflammatory cycle promoting bystander tissue injury. As best exemplified by TNF- α /TNFR signaling, increased glial production of pro-apoptotic cytokines may contribute to neuronal injury in glaucoma [48,49]. Autoreactive T cells are also able to induce RGC apoptosis in culture, mainly through cytokine production and receptor-mediated signaling [50]. Regarding autoantibodies, ex vivo studies of human donor retinas have supported that HSP antibodies, when exogenously applied at concentrations similar to detected in the glaucomatous patient serum, can be internalized by retinal neurons, co-localize with the native protein, and facilitate neuronal cell death [51].

Recent studies exploring the immunogenic aspects of glaucomatous neurodegeneration have included the work to produce immune-mediated animal models. Immunization of rats with HSPs has induced RGC loss in a topographically-specific pattern resembling human glaucoma [50]. More recent immunization studies of rats using retina or optic nerve antigens have suggested antibody-mediated RGC injury [52,53]. In another study, adoptive transfer of T cells isolated from ocular hypertensive rats has resulted in increased injury to optic nerve axons in ocular hypertensive animals, but not in naïve animals (Tezel et al, 2008 ARVO Abstract 3699). An immune-mediated component of the neurodegenerative injury has also been supported by observations in experimental mouse glaucoma which indicated neuroprotection in Rag1 knockout mice lacking mature lymphocytes compared with wild-type controls (McKinnon et al, 2010 ARVO Abstract 2523). However, a recent study has not detected a significant difference in the rate of axonal damage or RGC loss between Rag1 knockout mice and wild-type controls with experimental glaucoma that exhibited a relatively mild injury over four-weeks of IOP elevation [54].

Immunogenic mechanisms have also been attractive targets for studies searching new treatment possibilities for glaucoma. In an early case study, methotrexate treatment for a rheumatoid disease has exhibited beneficial effects on serum immunoreactivity and visual function in a patient with glaucoma [55]. An intensive area of research has focused on the enhancement of the native protective potential of the immune system. For example, vaccination with self-antigenic peptides or T cells activated against self-antigens has been proposed to boost protective immune response and provide neuroprotection in glaucoma [56,57]. However, boosting the immune activity is a double-edged sword that awaits well-controlled protocols to avoid autoimmune injury. Since serum antibodies are also present in healthy people [58] and may counteract destructive autoimmune processes by suppressing cross-reactions with self-antigens [59], transfer of natural antibodies has also been suggested as a potential immune modulatory strategy to maintain immune homeostasis in glaucoma [60].

Present evidence also implicates complement activation in glaucomatous neurodegeneration. Studies of human donor eyes with glaucoma and different animal models have provided a list of molecules involved in the complement activation cascade, including the classical and lectin pathways that lead to opsonin-mediated phagocytosis and membrane attack complex-mediated cell lysis [32,33]. In addition, a study of mice deficient in complement components C1q or C3 has suggested the involvement of the classical complement cascade in early elimination of dendritic synapses that occur in glaucoma [61]. Using genome-wide expression profiling of the optic nerve head and retina, complement gene induction has also been found to be one of the earliest events in DBA/2J mice, and a mutation in complement component C1qa has greatly reduced RGC and axon loss in these animals [62].

Glial Cells in Immune Regulation

Highly specialized innate immune cells in the CNS uniquely involve microglia [63,64]. Besides these resident macrophages, the most abundant glial cell population of the CNS, namely astrocytes, also participate in immune responses triggered by a variety of insults [65]. These major classes of glia similarly constitute resident immune cells in the retina and optic nerve, while the retina also possesses Müller cells, specialized astroglia. In addition to many other neurosupportive roles, these innate immune cells engage in several inflammatory processes that defend the neural tissue from pathogens and help recover from stress and injury. Glial cells participating in innate immune reactions are the principal sources of inflammatory mediators, cytokines, chemokines, and several complement components. Cytokines and chemokines expressed by glial cells can also promote the recruitment of systemic immune cells and provide informational input for adaptive immunity [63–65]. Glial cells in the retina and optic nerve become reactive in human glaucoma [66–69] and animal models [70–75]. Interestingly, recent studies of rats and mice with experimentally induced IOP elevation have detected retinal glial responses also in the contralateral eyes with normal IOP [76,77].

Over the past two decades, experimental studies using in vitro and in vivo models, along with the studies of human donor eyes, have contributed to the view of reactive glia-originated neurodegenerative effects in glaucoma. It is widely accepted that after transformation into reactive phenotype, which includes the activation of immune regulatory functions, glial cells may be insufficient in their normal neurosupport functions, and the withdrawal of glial support (and initiation of glia-originated damaging effects) may increase the vulnerability of RGCs and their axons to injury [6,78–81]. A recent morphological study of optic nerve head alterations in experimental rat glaucoma has proposed that astrocyte-originated damaging effects are due to localized loss of metabolic support rather than distorting mechanical forces [82]. A recent study of mouse glaucoma has focused on a

subset of optic nerve head astrocytes within the myelination transition zone and indicated their phagocytic ability that might contribute to glaucomatous neurodegeneration [83].

Similar to other aging-related neurodegenerative diseases [84,85], continuous glial activation is recognized as a sufficient indicator of ongoing neuroinflammatory process in the glaucomatous retina and optic nerve head [6]. Activated glial cells in the human retina and optic nerve produce increased amounts of cytokines, including a major pro-inflammatory cytokine, TNF- α [27,28,48]. Glaucomatous human retina also exhibit up-regulation of various other inflammatory molecules, which include TLR signaling molecules stimulating innate and adaptive immune responses [31], NF- κ B activation involved in the transcriptional regulation of inflammation, and inflammasome components leading to interleukin secretion [86]. A recent study using a cell-specific proteomic approach has evaluated astrocyte responses in experimental rat glaucoma and highlighted TNF- α /TNFR signaling, TLR signaling, NF- κ B activation, and inflammasome assembly as major components of astroglial inflammatory responses [87]. Additionally, up-regulated expression of MHC class II molecules indicates increased antigen-presenting ability of glial cells in human glaucoma [29] and animal models [30]. Furthermore, there is in vitro data indicating that exposure to a variety of stressors, including oxidative stress evident in human glaucoma [34,88], can stimulate retina and optic nerve astrocytes and microglia to expose MHC class II molecules, secrete pro-inflammatory cytokines, and become inducers of T cell activation [40].

Despite essential homeostatic functions of the glia, persistent alterations in glial behavior may play a critical role in the overall phenotype driving innate and adaptive immune responses towards neuronal injury and regenerative failure. Interactions between resident and infiltrating innate immune cells (namely resident glia and infiltrating monocytes) and adaptive immune cells (namely lymphocytes) are also crucial to determine the outcome of an immune response. Better understanding of glial alterations at the molecular level may offer innovative treatment options to selectively inhibit neurodestructive consequences of the glial activation response in glaucoma. There is no doubt that targeting the specific molecules involved in the sequence of neuroinflammatory events is a logical strategy for immunomodulation [6]. The next section discusses the outcomes of recent studies that provide molecular links to inflammatory responses in human glaucoma and animal models.

Immune Mediators/Regulators Linked to Immune Responses

Based on global proteomic analysis of the glaucomatous human retina and cell-specific proteomic analysis of ocular hypertensive astrocytes, various pathways, including pro-inflammatory TNF- α /TNFR signaling [86,87], TLR signaling [31], NF- κ B activation, inflammasome assembly [86,87], and complement activation [34], are co-players of inflammatory responses and represent key treatment targets for immunomodulation.

TNF- α is a well-studied pro-inflammatory cytokine increasingly produced by activated glial cells in the glaucomatous retina and optic nerve [27,28,48]. This multifunctional cytokine with beneficial and detrimental effects on neurons exhibits important links to glial activation responses, mediation of RGC death, and inflammatory processes during the neurodegenerative injury in glaucoma [48,49,86,87]. Another cytokine, IL-6, has also been shown to increase in expression by retinal microglia in DBA/2J mice [89] and optic nerve head astrocytes in ocular hypertensive rats [90].

TLRs serve as innate immune receptors for extrinsic and intrinsic danger signals [91,92] and stimulate T cell-mediated [93,94] and autoantibody-mediated [95,96] adaptive immunity in different disease models. In vitro evidence supports that glaucomatous stress-related intrinsic ligands, such as HSPs and oxidation products, can activate glial TLRs, and

stimulate co-cultured T cells [31]. After recognizing specific molecular patterns, TLRs recruit adaptor proteins, such as MyD88, and activate NF- κ B, a major transcription factor for the expression of pro-inflammatory cytokines [97]. Proteomic data from human glaucoma and animal models, along with the findings of in vitro treatment experiments, support that the glial TLR signaling initiated by glaucomatous stress-related ligands includes MyD88-dependent pathways and activates NF- κ B [31,86,87].

An important outcome of recent proteomic studies of human glaucoma has indeed included up-regulation of the NF- κ B activation pathway through TNF- α /TNFR signaling [86,87] and TLR signaling [31]. Based on cell-specific proteomic analysis of retinal astrocytes, NF- κ B activation has also been linked to regulation of astrocyte-driven pro-inflammatory processes in experimental rat glaucoma [87]. Glaucomatous retina has exhibited increased glial expression of specific kinases involved in the NF- κ B activation pathway, such as RIPK, NIK, and I κ K, including a master regulator, I κ Kgamma (NF- κ B essential modulator, NEMO), and phosphorylation of NF- κ B subunits, NF- κ B1-p105/p50 and p65 (RelA). NF- κ B regulates neuronal survival programs, including in the retina and optic nerve [98]. However, this important transcription factor also functions as a master regulator of the innate and adaptive immune response implicated in neuroinflammation and secondary injury processes in the CNS [97,99]. In the retina, inactivation of astroglial NF- κ B has reduced the inflammatory environment and promoted RGC survival after ischemia [100].

NF- κ B activation after engagement of TNFRs or TLRs leads to increased transcription of genes encoding IL-1 family cytokines. Pro-forms of resulting peptides, for example pro-IL-1 β , remain cytoplasmic until enzymatically cleaved by activated caspase-1. Activation of caspase-1 is initiated by signaling from a second set of innate immune receptor, nucleotide-binding domain leucine-rich repeat-containing receptors (NLRs). These cytoplasmic proteins are involved in the assembly of protein complexes termed inflammasomes that promote caspase-1-mediated proteolytic activation of pro-interleukins and secretion of mature cytokines. The largest NLR subfamily and the one most pertinent for neuroinflammation is designated the NACHT domain-, LRR domain-, and pyrin domain-containing protein (NALP) family [101,102]. Recent data indicate NALP expression and caspase-1 activation in the glaucomatous human [86] and rat retina [87]. Inflammasomes can be activated not only by the cytoplasmic presence of specific microbial components, but also by tissue-injury products as evident in glaucoma. For example, inflammasome activation has been linked to oxidative stress [103–105]. In addition, the ATP released from damaged RGCs can activate purinergic receptor-regulated channels to cause cytosolic ion fluxes [106] that can be detected by NLRs. Moreover, pannexins expressed in RGCs have been implicated in inflammasome formation after ischemic injury [107]. Thus, similar to TLRs, NLRs are highly effective at sensing intrinsic danger signals and responding to non-infectious sterile tissue injury. The interplay of TLRs and NLRs participates in innate immune responses in the CNS, through which secretion of biologically active interleukins elicits production of a secondary inflammatory cytokine cascade by both microglia and astrocytes [108].

Complement activation is another key component of immune responses in glaucoma. Histopathological studies of human tissues and in vivo studies using different animal models have demonstrated the deposition of various complement components in the glaucomatous retina and optic nerve [32,33]. A recent proteomic study of human glaucoma has expanded the list of complement components expressed in the glaucomatous retina, including the proteins involved in the classical and the lectin pathways of complement activation [34]. Identified molecules have included C1q that is the first element in the classical complement activation pathway, several proteases that initiate opsonization and anaphylactic reactions attracting phagocytic cells, components of the membrane attack complex that leads to cell

lysis, and also complement receptors, and regulatory molecules. The more recent study of Rag1 knockout mice has indicated that immunoglobulins are not required for C1q binding and complement activation in experimental glaucoma, suggesting alternative binding partners [54]. Regarding complement regulation, complement regulators identified in human glaucoma have included complement factor H (CFH), and the experimental data have showed that the oxidative stress-related epigenetic factors may alter the regulation of CFH expression [34].

Further studies are needed to determine the potential of pro-inflammatory TNF- α /TNFR signaling, TLR signaling, NF- κ B activation, inflammasome assembly, and complement activation, as well as their oxidative stress-mediated regulation[5], as treatment targets to provide immunomodulation in glaucoma.

Conclusions

Immune system-mediated events are emerging as a major contributor in glaucomatous neurodegeneration. Present research findings collectively suggest that accumulating risk factors, prolonged glial activation, and sustained release of pro-inflammatory mediators may shift the physiological equilibrium of immune response pathways toward an inflammatory neurodegenerative process in glaucoma. If uncontrolled, innate immune cells, autoreactive T cells, autoantibodies, and complement activation may exhibit potent stimuli to harm RGC somas, axons, and synapses, and increase the susceptibility for disease progression in glaucoma (Figure 1). With respect to various damaging consequences of aberrant immune activity, efficient control of immune responses can attenuate neuroinflammation, protect neural tissue from collateral injury, and enhance endogenous recovery processes. Ongoing studies evaluating the molecular interactions between resident/systemic immune cells and neurons are proceeding rapidly with the hope to provide translational applications for immunomodulation as a neuroprotective strategy in glaucoma.

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Highlights

- Immune system is activated in human glaucoma and experimental models.
- Glia play key roles in innate immune responses and the innate/adaptive interplay
- Cytokines, TLRs, NF- κ B, inflammasome, and complement are co-players.
- Homeostasis of immune response pathways determines neurodegenerative potential
- Immunomodulation may serve as a neuroprotective treatment strategy.

Figure 1. Immune regulation in glaucoma. Various pathways, such as pro-inflammatory cytokine signaling (including TNF- α /TNFR signaling), TLR signaling, NF- κ B activation, NLRs and inflammasome assembly, and complement activation are co-players of inflammatory responses in glaucomatous tissues. A failure in the regulation of immune response pathways may shift the physiological equilibrium toward an inflammatory neurodegenerative process.