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Review article

# The gut-retina axis: Uncovering the role of autoimmunity in glaucoma development

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ABSTRACT

Glaucoma, a leading cause of irreversible blindness worldwide, is characterized by progressive loss of retinal ganglion cells (RGCs) and optic nerve damage. While elevated intraocular pressure (IOP) is the only known modifiable risk factor, normal-tension glaucoma (NTG) challenges this notion, suggesting other mechanisms beyond IOP may contribute to its development. Emerging evidence support the hypothesis that glaucoma may be an autoimmune disease. This review summarizes evidence for this hypothesis, focusing on the gut-retina axis. We discuss how antigens of gut bacterial prime peripheral T cells to breach the blood-retina barrier (BRB) and initiate cross-reactivity with ocular tissues via molecular mimicry, resulting in autoimmune RGC damage. Understanding these mechanisms may uncover new diagnostic biomarkers and therapeutic strategies targeting immune pathways alongside conventional IOP-lowering treatments.

## 1. Introduction

Glaucoma, a neurodegenerative disease, is characterized by the progressive loss of retinal ganglion cells (RGCs) and injury of the optic nerve [1–3]. Clinically, it presents as gradually expanding visual field defects, ultimately leading to irreversible blindness. Currently, glaucoma has become the leading cause of irreversible blindness worldwide. According to data from 2023, nearly 95 million people worldwide have glaucoma, with approximately 10 million experiencing blindness in at least one eye due to this condition [1].

Glaucoma is primarily classified into several categories, including primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG), congenital glaucoma, and normal-tension glaucoma (NTG) [1]. Typically, POAG, PAGG, and congenital glaucoma are associated with elevated intraocular pressure (IOP), which can lead to optic nerve damage and progressive vision loss, and is the only known modifiable risk factor for glaucoma [1]. However, the pathophysiology of NTG remains unclear, as optic nerve damage

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occurs despite IOP levels within the normal range. Approximately half of glaucoma patients have normal IOP [4,5]. Moreover, some patients with elevated IOP continue to experience ongoing loss of RGCs and optic nerve injury even after their IOP returns to normal [6,7]. This suggests that alternative mechanisms other than IOP may contribute to the development of glaucoma.

Recent research into the immunological mechanisms underlying neurodegenerative diseases has provided significant insights, advancing our understanding of central nervous system (CNS) autoimmunity. In parallel, investigations into the immunological mechanisms related to glaucoma are also progressing rapidly. Increasing evidence suggests that glaucoma may be an autoimmune disease. This article aims to summarize the evidence supporting this hypothesis. The proposal of this perspective holds significant implications for understanding the pathogenesis of glaucoma, developing novel therapeutic strategies, and potentially altering the clinical management of the disease.

## 2. Evidence supporting glaucoma as an autoimmune disease

### 2.1. Gut-retina axis

The gut-brain axis is increasingly recognized as a critical pathway underlying the mechanisms of many CNS diseases. This concept emphasizes that alterations in gut microbiota and gut-derived inflammation can influence CNS conditions. For instance, in Parkinson's disease (PD), changes in gut microbiota often precede the onset of motor symptoms by several years, suggesting that gut dysbiosis may play a role in the etiology of PD [8].

The molecular mimicry hypothesis provides a framework for understanding the connection between the gut and the brain. According to this hypothesis, immunological cross-reactivity between host and microbial antigens can trigger an autoimmune response against the host's tissues [9]. A well-documented example is Campylobacter jejuni-induced Guillain–Barré syndrome, where antibodies generated in response to the infection target gangliosides present in both the bacteria and human neurons, leading to autoimmune-mediated neurological symptoms [10–12]. As such, what the gut-brain axis reveals are the autoimmune mechanisms implicated in CNS diseases.

In parallel, the existence of a gut-retina axis has been proposed to explain the autoimmune responses in the eye [13]. Retina is an immunologically privileged site, located within the physical isolation of the blood-retinal barrier (BRB) and an immunosuppressive microenvironment [14]. Normally, peripheral immune cells cannot encounter antigens within the retina and thus will not generate a response. However, bacterial antigens, derived mainly from the intestinal microbiota, can activate peripheral T cells. Primed peripheral T cells can cross the BRB and infiltrate the retina [15]. Given the high conservation of the antigens, such as heat shock proteins (HSPs) [16], T cells primed by bacterial antigens can cross-react with human ocular tissues, leading to autoimmune responses [13,17,18]. Evidence supporting the existence of a gut-retina axis includes: in a mouse model of spontaneous uveitis, peripheral retina-specific T cells can be activated even in the absence of ocular antigens [15]. In mouse models where IOP is elevated and gut microbiota is depleted, prolonged damage to RGCs does not occur after IOP normalization [18]. These findings suggest that the peripheral T cells are primarily activated by bacterial antigens and lead to RGC damage presumably through immunological cross-reaction.

### 2.2. Alterations of gut microbiota in glaucoma

As changes in the gut microbiota are involved in the pathogenesis of glaucoma through the gut-retina axis, it is necessary to investigate the specific changes in the gut microbiota under glaucomatous conditions. After normalization of IOP following elevated IOP, germ-free mice no longer suffer RGC damage, while mice with eight specific gut microbiota species continue to experience RGC, although to a lesser extent than those with normal gut microbiota. This indicates that peripheral T cells are not activated by a single microbial species [18]. Studies have found that glaucoma patients have increased quantities of Firmicutes, Bacteroidetes, Proteobacteria, Prevotellaceae [19], Enterobacteriaceae, Dysgonamonadaceae, Lactobacillus, and *Escherichia coli*, and decreased quantities of Baresiellaceae, Megamonas, Mollicutes, and Bacteroides plebeius in their gut [19–23]. Furthermore, a meta-analysis reveals that *Helicobacter pylori* infection is associated with POAG and NTG [24]. The alterations in gut microbiota in glaucoma patients and mouse models have been extensively summarized in a review published in 2023 [25]. Also, the alterations of microbiota at other sites, which may also contribute to glaucoma through molecular mimicry, were summarized in another review published in 2023 [26].

### 2.3. Peripheral T-cell activation enables BRB crossing

In normal physiological states, the BRB effectively prevents the infiltration of peripheral immune cells into the retina, maintaining retinal immune privilege [14]. Acute IOP elevation can compromise BRB integrity, allowing immune cell infiltration [27]. However, in cases of NTG, the BRB is thought to remain intact [27]. This presents an intriguing question: how are peripheral T cells enabled to cross an intact BRB in NTG conditions?

Peripheral activation is essential for peripheral T cells to acquire the ability to cross the BRB. In a glaucoma mouse model induced by elevated intraocular pressure (EIOP), he et al. demonstrated that peripheral β7+ $CD4^+$ T cells undergo a gut-homing process and transcriptional reprogramming before infiltrating the retina [13]. β7+ $CD4^+$ T cells extracted from the intestine 20 days before their peak presence in the gut cannot cross the BRB, indicating that intestinal activation is necessary for this capability.

The transmigration of immune cells across the BRB involves four steps: initial adhesion, activation, tight adhesion, and diapedesis [28]. This process requires interactions between adhesion molecules on immune cells and those on the retinal vascular endothelium. Gut-primed β7+ $CD4^+$ T cells can induce MAdCAM-1 expression on retinal microvessels. The interaction between MAdCAM-1 and its

ligand β7 on T cells is critical for their transmigration across the BRB. Neutralizing MAdCAM-1 with an antibody reduces retinal T-cell infiltration and alleviates RGC damage. Thus, He et al. suggest that treatments targeting the α4β7 integrin-MAdCAM-1 interaction, such as vedolizumab (an anti-α4β7 monoclonal antibody), could be potential interventions for glaucoma [13]. These findings were derived from the EIOP-induced glaucoma mouse model. In glaucoma patients, researchers also observed an increased percentage of circulating β7+ $CD4^+$ T cells in the peripheral blood [13], supporting the relevance of these mechanisms in human glaucoma.

Likewise, another study by He et al. observed that $CD4^+$ T cells from glaucoma patients showed increased activation and a Th1-biased response. In EIOP-induced glaucoma mouse models, $CD4^+$ Th1 cells upregulate the expression of adhesion molecule VCAM-1 on retinal vascular endothelium [29], facilitating their entry into the retina.

The above pathways focus on how peripheral T cells cross the BRB through molecular interactions. However, these conclusions are derived from EIOP-induced glaucoma mouse models, and the potential direct damaging effects of EIOP on the retina cannot be excluded. Consequently, these findings may not be entirely applicable to situations with normal IOP. Nonetheless, activated peripheral T cells may still directly cause minor disruptions to the BRB [30]. Therefore, even in NTG, the peripheral activation of T cells still facilitates their crossing of the BRB.

### 2.4. Continuous ocular inflammation enables persistent T-cell transmigration across the BRB

The ability of peripheral T cells to cross the BRB does not necessarily result in glaucoma. In non-pathological states, peripherally primed T cells can also cross the BRB and play a role in immune surveillance within the retina, which is only transient [30]. However, glaucoma is characterized by a gradual and chronic progression, suggesting a cumulative effect of immune-mediated damage over an extended timeframe. Therefore, long-term infiltration is required to cause RGC damage. It is inferred that continuous ocular inflammation may be necessary to enable the persistent transmigration of T cells across the BRB [31]. In the inflamed state of the eye, inflammatory factors promote the expression of integrins on the surface of immune cells [32] and adhesion receptors on retinal vascular endothelium [33]. This upregulation promotes stronger adhesion between immune cells and the vascular endothelium, facilitating the transmigration of immune cells across the BRB.

Indeed, elevated levels of pro-inflammatory cytokines, such as certain Interferons (IFN-α, IFN-γ), tumor necrosis factor-α (TNF-α), certain Interleukins (IL-1, IL-9, IL-10, IL-12), and CXCL9, have been documented in the aqueous humor and tears of glaucoma patients [34,35]. This increase in pro-inflammatory cytokines potentially correlates with the activation of retinal glial cells, a topic that will be more thoroughly examined in the subsequent section dedicated to glial cells.

### 2.5. T cell mediates RGC damage

There is a documented increase in T cell infiltration within the retinas of both human glaucoma patients and mouse models of the disease [36,37], suggesting a spatial correlation between T cell presence and RGC damage. In an EIOP-induced glaucoma mouse model, researchers found that the disease process can be divided into two distinct stages. The first stage involves direct RGC damage caused by EIOP, without the involvement of immune cells [18,27,38]. The second stage, which occurs after IOP normalization, involves RGC damage mediated by immune cells. T cells are believed to play a major role in this latter stage [13,18].

The role of T cells in mediating RGC damage in the second stage is supported by compelling evidence: Experiments with T cell-deficient mouse models have demonstrated a lack of RGC damage following IOP normalization, thereby implicating T cells as necessary mediators in the progression of RGC loss [18,36]; Transfer of T cells from mice with EIOP-induced glaucoma to healthy mice results in RGC damage, suggesting that T cells can directly contribute to RGC pathology [27]; Furthermore, T cells specific for heat shock proteins (HSP27 or HSP60) can release Fas ligand (FasL), which upregulates Fas expression on RGCs, leading to apoptosis through the FasL/Fas pathway, thereby providing a potential mechanism for T cell-mediated RGC loss [22].

### 2.6. Ocular HSPs induce T-cell response

The mechanism by which EIOP in the first stage leads to an immune response in the second stage can be explained by the involvement of HSPs. Under conditions such as EIOP and oxidative damage, RGCs sense stress and release danger signals, including HSPs [39,40]. These proteins, acting as molecular chaperones, assist in the refolding of misfolded proteins and protect against apoptosis [41,42]. Normally, HSPs are intracellular, but their expression is upregulated and they can be released extracellularly under stress [31]. Consequently, the released HSPs can elicit both innate and adaptive immune responses [43]. In EIOP mouse models, transient elevation of IOP leads to prolonged activation of peripheral HSP27-specific $CD4^+$ T cells, which in turn infiltrate the RGC layer and cause RGC damage [18]. Concurrently, serum levels of HSP antibodies are elevated, and there is plasma cell infiltration and HSP antibody deposition in the retina. However, in *Igh6*$^{-/-}$ mice with deficient B cell immunity or mice deprived of HSP autoantibodies, the degree of nerve damage is not diminished [18,44–46]. Thus, the role of humoral immunity in glaucomatous optic nerve damage remains elusive, which is further examined in the following section.

### 2.7. Role of humoral immunity

In the serum of glaucoma patients, elevated levels of various autoantibodies can be detected. In-depth research has been conducted on HSP antibodies, including α-crystalline antibodies [47,48], HSP27 antibodies [47,48], and HSP60 antibodies [48,49]. Additionally, there is an increase in autoantibodies targeting other ocular antigens, including glycosaminoglycans [50], myelin basic protein (MBP)

[51], a-fodrin [52], phosphatidylserine [53], γ-enolase [54], retinaldehyde-binding protein [55], retinal S-antigen [55], neuron-specific enolase [56], and glutathione S-transferase [57]. Furthermore, the presence of Immunoglobulin G (IgG) deposition and plasma cells in the retina of glaucoma patients [44], along with elevated levels of autoantibodies in the aqueous humor (including HSP27 [58], αB-crystalline protein, vimentin, and HSP70 antibodies [59]), highlights the involvement of antibodies in the ocular environment and further supports the autoimmune nature of glaucoma.

However, it is still unclear whether these changes in antibody levels are a cause or a consequence of the disease [60]. Experimental studies have shown that immunization of rats with optic nerve antigens or retinal homogenates results in the deposition of corresponding antibodies and subsequent nerve damage [61,62], indicating a correlation between antibody presence and nerve damage. Moreover, direct treatment of the human retina with specific autoantibodies (αA-crystalline, αB-crystalline, and HSP27) has been shown to induce apoptosis of RGCs [47], suggesting a potential causal role of these antibodies in optic nerve damage.

Despite these findings, the prolonged onset of glaucoma contrasts with the acute nerve damage observed in antibody-induced models [60], indicating a need for further research to elucidate this discrepancy. Additionally, studies on mice with deficient B cell immunity or deprived of HSP antibodies still show nerve damage after normalization of elevated IOP [18,44–46], suggesting that humoral immunity is not the primary mechanism of glaucomatous nerve damage.

### *2.8. Glial cells contribute to an ocular inflammatory state*

The maintenance of an ocular inflammatory state depends on the activation of glial cells and the release of inflammatory factors. In response to elevated IOP, Müller cells are activated through a cascade involving the activation of metabotropic glutamate receptors (mGluR) I and inhibition of inwardly rectifying potassium (Kir) 4.1 channels [63–65]. This activation triggers a series of responses, including proliferation and the release of inflammatory and growth factors, collectively known as gliosis. Activated Müller cells release cytokines and chemokines that contribute to the recruitment and activation of microglia [66].

Microglia, once activated, undergo morphological and functional changes, enhancing the release of pro-inflammatory factors like TNF-α and interleukins (e.g., IL-1β, IL-6) [67,68]. Even after IOP is normalized, microglial cells can remain activated, which may explain why some glaucoma patients continue to experience optic nerve damage even after controlling their IOP [69].

Astrocytes, particularly in the optic nerve head, are activated by elevated IOP and the pro-inflammatory milieu created by Müller cells and microglia. This activation, known as astrogliosis, involves significant changes in morphology, gene expression, and function. Activated astrocytes release pro-inflammatory cytokines and growth factors, further altering the extracellular matrix and exacerbating the inflammatory environment [66].

HSPs play a significant role in the activation of glial cells. HSPs are upregulated in response to stress and injury and function as molecular chaperones. HSPs released from damaged or stressed cells act as danger-associated molecular patterns (DAMPs). They can bind to Toll-like receptors (TLRs) on glial cells, particularly TLR2 and TLR4, initiating signaling pathways that lead to glial activation [70–72].

The interactions among these glial cells create a feedback loop that sustains and amplifies ocular inflammation, which is crucial in creating a local inflammatory environment in the eye and facilitating infiltration of peripheral immune cells [31].

## 3. Discussion

The immunological mechanisms underlying glaucoma have emerged as a pivotal area of research interest. In this review, we provide a detailed exploration of the mechanisms supporting the autoimmune nature of glaucoma.

The concept of the gut-retina axis is central to glaucoma autoimmunity. It suggests that bacterial antigens from the gut can prime peripheral T cells, which then cross the BRB and cross-react with ocular tissues due to molecular mimicry, leading to autoimmune damage in the retina. We provide a detailed description of each step involved in this process. Glaucoma patients exhibit significant changes in their gut microbiota, with increases in certain bacterial families and associations with *Helicobacter pylori* infection. These alterations are implicated in the activation of peripheral immune responses. Gut-derived antigens can prime peripheral T cells, enabling them to cross the BRB through interactions with adhesion molecules like MAdCAM-1. T cells play a critical role in mediating RGC damage during the later stages of glaucoma, contributing to apoptosis of RGCs through mechanisms such as the FasL/Fas pathway. Chronic inflammation in the eye, driven by activated glial cells (Müller cells, microglia, and astrocytes), facilitates continuous T cell infiltration and ongoing RGC damage, even after IOP normalization. Elevated levels of autoantibodies against various ocular antigens are observed in glaucoma patients. While the exact role of these antibodies—whether causative or secondary—is still debated, they represent a significant aspect of the autoimmune landscape in glaucoma.

The concept of “gut-retina axis” provides a potential explanation for glaucoma autoimmunity [18], where peripheral immune cells activated by gut microbial antigens cross-react with heterophilic retinal self-antigens. Current studies mostly use HSP as heterophilic antigens, studying the peripheral activation of HSP-specific immune cells and their attack against retinal antigens [18,73]. However, besides HSP, there are many homologous molecules between the commensal microbiota and humans, which may also act as antigens to cause similar cross-immune reactions. Future research may explore more heterophilic antigens and investigate their potential as therapeutic targets or diagnostic markers.

In terms of the activation of peripheral immune cells, several questions remain to be answered. In the EIOP-induced glaucoma mouse model, elevated IOP causes the release of HSPs, which then leads to the activation of peripheral HSP27-specific $CD4^+$ T cells through a “gut detour” [13]. However, it remains unclear how ocular HSPs facilitate the entry of these peripheral HSP27-specific $CD4^+$ T cells into the “gut detour”. Additionally, in cases of NTG, it is important to explore what other factors are responsible for the

activation of peripheral T cells in the absence of elevated IOP. Future research can utilize mouse glaucoma models with normal IOP [74] to investigate these mechanisms.

While the presence of autoantibodies in glaucoma patients highlights the involvement of humoral immunity in the disease, defined autoantibodies are lacking, and their exact role remains to be fully understood. Determining whether these antibodies are initiators of pathology or merely a consequence of tissue damage will be essential in understanding their role in the autoimmune landscape of glaucoma. Based on current evidence, it is plausible that these autoantibodies are generated as a secondary response to initial damage caused by other factors, such as elevated IOP or oxidative stress, and then contribute to the progression of the disease. Humoral immunity may contribute to glaucoma progression through a combination of direct and indirect effects. Direct effects may include antibody-mediated damage to RGCs, while indirect effects could involve the modulation of immune cell behavior and the inflammatory environment within the eye. Future research should aim to explore whether there are defined autoantibodies, delineate the causal relationships between autoantibodies and glaucomatous damage, identify the triggers for autoantibody production, and elucidate the specific pathways they activate.

Research into the autoimmune mechanisms underlying CNS diseases provides valuable insights that can guide future studies on glaucoma. Some autoimmune CNS disorders have not been linked to specific autoantibodies as well, with multiple sclerosis (MS) being a prime example [9]. In these conditions, it is important to examine the role of T cells and other immune cells in the pathogenesis of these disorders. Simultaneously, exploring the genetic underpinnings and how they interact with environmental factors to cause disease is essential. MS is found to be a multifactorial disease with genetic, environmental, and infectious contributions. Similarly, glaucoma research can benefit from focusing on triggers that disrupt immune tolerance, such as infections, tumors, and therapies involving immune checkpoint inhibitors.

Recognizing glaucoma as an autoimmune disease has profound implications for its diagnosis and treatment. Autoantibody profiles could serve as biomarkers for early detection and disease monitoring. Furthermore, immunomodulatory therapies targeting specific immune pathways, such as the use of monoclonal antibodies or small molecule inhibitors, could complement existing IOP-lowering treatments. Future research should focus on large-scale clinical trials to validate these therapeutic approaches and explore the potential of combination therapies that address both IOP and autoimmune mechanisms.

## 4. Conclusion

Recent insights increasingly implicate autoimmune processes in the pathogenesis of glaucoma. The gut-retina axis is pivotal in glaucoma autoimmunity. Patients with glaucoma show altered gut microbiota, activating peripheral immune responses. Gut antigens prime T cells to cross the BRB via MAdCAM-1 interactions, mediating RGC apoptosis through the FasL/Fas pathway. Persistent eye inflammation, driven by activated glial cells (Müller cells, microglia, astrocytes), sustains T cell infiltration and ongoing RGC damage even after IOP normalization. Elevated autoantibodies against ocular antigens suggest the involvement of humoral immunity in glaucoma, though their role remains debated. Future research should concentrate on several key areas: identifying new heterophilic antigens beyond HSPs, elucidating the mechanisms of peripheral immune activation in NTG, defining specific autoantibodies associated with glaucoma and determining their role in disease progression, and validating immunomodulatory therapies in conjunction with IOP-lowering treatments.

## Ethics declaration

Review and/or approval by an ethics committee as well as informed consent was not required for this study because this literature review only used existing data from published studies and did not involve any direct experimentation/studies on living beings.

## Data availability statement

No data was used for the research described in the article.

## CRediT authorship contribution statement

**Zuyi Yang:** Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Dianzhe Tian:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xinyu Zhao:** Writing – review & editing, Validation, Supervision. **Yunping Luo:** Writing – review & editing, Validation, Supervision. **Youxin Chen:** Writing – review & editing, Validation, Supervision.

## Declaration of competing interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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## Abbreviations

*Intraocular pressure:* IOP
*Elevated intraocular pressure:* EIOP
*Primary open-angle glaucoma:* POAG
*Primary angle-closure glaucoma:* PACG
*Normal-tension glaucoma:* NTG
*Parkinson's disease:* PD
*Retinal ganglion cells:* RGCs
*Heat shock proteins:* HSPs
*Blood-retinal barrier:* BRB
*danger-associated molecular patterns:* DAMPs
*Toll-like receptors:* TLRs
*multiple sclerosis:* MS
*metabotropic glutamate receptors:* mGluRs
*inwardly rectifying potassium 4.1 channels:* Kir 4.1 channels
*T cell receptor:* TCR

*Myelin basic protein:* MBP
*Central nervous system:* CNS
*Immunoglobulin G:* IgG
*Interferon:* IFN
*Tumor Necrosis Factor:* TNF
*Interleukin:* IL
*Chemokine (C-X-C motif) ligand:* CXCL