T Cell-Mediated Autoimmunity in Glaucoma Neurodegeneration

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Glaucoma as the leading neurodegenerative disease leads to blindness in 3.6 million people aged 50 years and older worldwide. For many decades, glaucoma therapy has primarily focused on controlling intraocular pressure (IOP) and sound evidence supports its role in delaying the progress of retinal ganglial cell (RGC) damage and protecting patients from vision loss. Meanwhile, accumulating data point to the immune-mediated attack of the neural retina as the underlying pathological process behind glaucoma that may come independent of raised IOP. Recently, some scholars have suggested autoimmune aspects in glaucoma, with autoreactive T cells mediating the chief pathogenic process. This autoimmune process, as well as the pathological features of glaucoma, largely overlaps with other neurodegenerative diseases in the central nervous system (CNS), including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. In addition, immune modulation therapy, which is regarded as a potential solution for glaucoma, has been boosted in trials in some CNS neurodegenerative diseases. Thus, novel insights into the T cell-mediated immunity and treatment in CNS neurodegenerative diseases may serve as valuable inspirations for ophthalmologists. This review focuses on the role of T cell-mediated immunity in the pathogenesis of glaucoma and discusses potential applications of relevant findings of CNS neurodegenerative diseases in future glaucoma research.

Keywords: glaucoma, T cell, autoimmune, neurodegenerative disease, immune modulation therapy

INTRODUCTION

The retina is an extension of the central nervous system (CNS) in the eye. Retinal ganglial cells (RGCs) are the primary sites of pathology in glaucoma (1). Their cell bodies reside in the inner retina, while their axes extend a long way through the optic nerve into the brain. Thus, glaucoma is considered a leading neurodegenerative disease that is estimated to affect 79.6 million people worldwide in 2020 (2). The pathogenic mechanisms of RGC loss in glaucoma are multifactorial, including elevated intraocular pressure (IOP), aging, oxidative stress, excitotoxicity, and mitochondrial dysfunction, but the full picture of glaucoma remains elusive due to its nature of high complexity and chronicity (3, 4). The role of immune-mediated neurodegeneration in glaucoma has been established in recent decades and is regarded as an important component in the pathogenesis of glaucoma.
Activation of residential immunocompetent cells in the retina (microglia and macroglia) and infiltration of peripheral immune cells (T cells, B cells, macrophages, monocytes, etc.) are found to be pathogenic and associated with the RGC loss (5, 6). Based on the discovery of autoantigens and self-reactive T cells, some scholars have proposed glaucoma to be an autoimmune disease with T cells playing a central role (7–9). Meanwhile, the essential roles of autoreactive T cells in the maintenance of tissue homeostasis and restriction of inflammation in the retina and CNS have also been elucidated in animal studies (10, 11). Evidence of either neurotoxic or neuroprotective roles of autoreactive T cells indicates the complexity of neuroinflammation in the progression of glaucoma. The role of autoreactive T cells is multifaceted, and an imbalance in T cell/microglia interactions is considered to be the culprit of glaucoma. Based on this, immunomodulation therapy has been proposed as a potential strategy for glaucoma (12).

As a representative of neurodegenerative disease in the eye, glaucoma shares many common pathological features with other CNS neurodegenerative disorders, including Alzheimer’s disease (AD), Parkinson’s disease (PD), and multiple sclerosis (MS) (13–15). Most importantly, they are all characterized by compromised barrier function and chronic neuroinflammation toward self-antigens (16–18). As the strategy to harness the immune response is most extensively explored in AD, it may provide valuable insights and experience for the development of a possible immune modulation therapy for glaucoma. In this review, we focus on the role of autoreactive T cells in glaucoma pathology and treatment options and systematically review publications in PubMed, Embase, and the Cochrane Library based on the topics of “glaucoma”, “T cell”, and “neurodegeneration”.

**STRESS RESPONSE AND GUT DYSBIOSIS ACTIVATE PERIPHERAL T CELLS WITH AUTOIMMUNE BEHAVIORS IN GLAUCOMA PATIENTS**

**Heat Shock Proteins in Stress Response**

In glaucoma eyes, chronic stress challenges such as elevated IOP, oxidative stress, glutamate excitotoxicity, deprivation of neurotrophic factors, and ionic imbalance are considered to be primary triggers for neuroinflammation and RGC loss (19, 20). These stress stimuli can be sensed by multiple mechanical and nonmechanical stress receptors expressed on RGCs, including pannexin-1 (Panx1), P2X7 receptor (P2X7R), and transient receptor potential vanilloid isoform 4 (TRPV4), which leads to the production of danger signals (21). Heat shock proteins (HSPs) are one of such signal and have been recognized as principal autoantigens involved in the pathogenesis of glaucoma in both animal disease models and patients (22–25). HSPs are a group of highly conserved proteins that are ubiquitous in cellular organisms and are classified based on their molecular weights into 7 major families (small HSPs, HSP40, HSP60, HSP70, HSP90, HSP100, and HSP110) (26). Under physiologic and stressful conditions, HSPs can serve as molecular chaperones to help refold misfolded proteins, enhance the survival of cells, and resist apoptosis (27, 28). Thus, HSPs are innate protectors of cells in the stress response. In addition, although most HSPs are constitutively intracellular components, under stress challenges, their expression is upregulated, and some HSPs can be released into the extracellular space to provoke immune reactions (29). Complex autoantibody patterns, including antibodies for small HSPs (HSP27, B-crystallin, and vimentin) and HSP70 in the aqueous humor have been detected in patients with various subtypes of glaucoma (30, 31). HSPs can induce both innate and adaptive immunity (32). In addition, a high local level of HSP27 itself is also found to be sufficiently pathogenic for glaucoma neural damage (33). However, it should be noted that HSPs should not be solely considered as proinflammatory factors but may induce immune suppression at suitable concentrations (34). Some HSPs also have neuroprotective effects. For example, induction of endogenous HSP72 in rats protects against neurodegeneration in acute IOP elevation (35, 36). Ongoing clinical trials are even applying HSPs to suppress the overactivation of the immune system in patients with rheumatoid arthritis and COVID-19 (37, 38). Thus, in patients with glaucoma, it is generally believed that aberrant production of HSPs under stress conditions and dysregulated autoimmune response in the long term, such as in the case of gut dysbiosis, may tilt the balance and result in uncontrolled neuroinflammation (39).

**Gut Microbiota Shapes the Immune System**

Recently, researchers have revealed a potential link between gut dysbiosis and glaucoma, with the immune system as the connecting bridge. The gut microbiota is a critical factor that shapes the peripheral immune system and has been found to contribute to the activation of autoimmune T cells in glaucoma and other neurodegenerative diseases (40–42). The gut microbiota serves as the major source of bacterial HSPs in the human body, which cross-react with the highly conserved human HSPs to provoke autoimmunity and RGC damage (40, 43).

The pathological roles of gut dysbiosis in glaucoma are found to be chiefly mediated by T cells rather than autoantibodies or humoral immunity. In a mouse ocular hypertension (OHT) model induced by microbead injection, transient elevation of IOP resulted in a prolonged activation and infiltration of interferon-γ-secreting CD4-positive T cells in the RGC layer and subsequent neurodegeneration. The activated T cells were reactive to HSP27, which, along with its autoantibody, were found to increase in the serum after the OHT challenge. This prolonged autoimmune to the retina, however, was absent in TCRβ−/− mice with deficient T cell immunity but not in IgH6−/− mice with deficient B cell immunity (40). On the other hand, although the infiltration of plasma cells in the retina and deposition of autoantibodies are also evident in the retina of glaucoma animal models, their causative roles in glaucoma remain elusive based on the finding that inhibition of B cells or autoantibody deprivation brings no significant benefits of RGC protection (44–46). Moreover, mice raised in a germ-free environment were found to be resistant to chronic OHT challenge and did not result in similar T cell infiltration in the...
retina, indicating the fundamental role of preexisting gut microbiota modulation of the immune system in the trigger of glaucomatous retinal damage (40).

The exact mechanisms of how gut microbiota shapes the host systemic immune system remain to be further elucidated, and the local gut mucosal immune system, as well as the compromised gut vascular barrier (GVB), have been suggested to play a role. Studies have found that primary open-angle glaucoma (POAG) patients have different compositions of gut microbiota compared to healthy individuals, with a higher abundance of *Prevotellaceae, Enterobacteriaceae, Escherichia coli*, and decreased number of *Megamonas* and *Bacteroides plebeius* (47). *Helicobacter pylori* infection was also linked to POAG and normal-tension glaucoma (NTG) in a recent meta-analysis (48). The opening of the GVB and dislocation of bacteria and bacterial elements not only affects autoimmune T cells, but may initially result in an overall chronic shift from the anti-inflammatory microenvironment to the pro-inflammatory one locally, systemically, and even at far target sites such as the brain and retina by activating the innate immune system (49). In a mouse experiment, a single peripheral administration of the bacterial element lipopolysaccharide (LPS) resulted in prolonged activation of brain resident microglial cells for over 10 months, resulting in progressive neurodegeneration (50). In the retina, resident microglia can recognize microbial pathogen-associated molecular pattern (PAMP) molecules via Toll-like receptors (TLRs), and upregulate the secretion of proinflammatory cytokines, including interleukin (IL)-6, IL-1β, and tumor necrosis factor-α (TNF-α), as well as major histocompatibility complex (MHC) II, an essential element for antigen presentation to T cells during peripheral bacterial infection (51, 52). The chronic activation of innate immunity in the retina, in turn, can facilitate the homing and infiltration of peripheral primed T cells into the retina. Studies have found that peripheral T cells responsive to microbial antigens in the intestine through autoreactive T cell receptors (TCRs) can break the blood-retinal barrier (BRB) and infiltrate the retina, which has previously been considered an immune-privileged site (53). This so-called “dual-hit hypothesis” (first hit in GVB and second hit in BRB) proposed by Braak et al. was first used to describe the potential role of gut dysbiosis in the pathogenesis of PD but is also supposed to be suitable for glaucoma and other neurodegenerative disorders (Figure 1). Interestingly, in patients with POAG, dislocation of gut *Helicobacter pylori* is even found in the trabecular meshwork (54). However, it is not clear whether the dislocation of gut bacteria itself is pathogenic or essential for glaucoma or is just an epiphenomenon of GVB impairment. In addition, recent evidence also suggests that an imbalance in the oral microbiota may also contribute to the pathogenesis of glaucoma, which needs further investigation (55, 56). Above all, emerging evidence suggests that gut dysbiosis may result in the activation of both innate and adaptive immune systems. Through the cross-reaction of human and bacterial HSPs, peripherally-activated T cells may break the BRB and result in RGC damage under stressful conditions.

Recently, modulation of the gut microbiota to reshape the systemic immune response has become an emerging therapy for glaucoma. A study found the beneficial roles of fermented maize slurry and its supernatant rich in probiotic bacteria to reshape gut microbiota in rats in the modulation of retinal immune reaction and protection of RGCs (57). Further studies, especially clinical trials, to illuminate the crosstalk between the retina and gut may provide more valuable information on the pathogenesis of glaucoma and explore the possible intervention methods.

**COMPROMISED BRB IS ESSENTIAL FOR T CELL INFILTRATION IN GLAUCOMA EYES**

The neural retina is a delicate visual transmission system and is firmly protected from the BRB, which controls the entrance of peripheral immune cells under normal conditions (58). Recently, some scholars have proposed the breakdown of BRB as an essential pathogenic step in glaucoma (59). This theory, although lacks definite evidence, is primarily supported by the observations of retinal T cell infiltration in different animal models of glaucoma (40, 60–62). In addition, the breakdown of blood-brain barrier (BBB) has been observed in some other CNS neurodegenerative diseases. Their common pathogenic features with glaucoma and the similar structures of the BBB and BRB also suggest the potential role of BRB breakdown in glaucoma development (13, 63–65).

The neural retina is isolated from the systemic circulation by the inner BRB (iBRB, formed with nonfenestrated retinal capillary endothelium, vascular basement membrane, pericytes, astrocytes end-feet, and microglial cells) and from the leaky choroidal vessels by the outer BRB (oBRB, formed with tightly connected RPE that stands on the Bruch’s membrane) (66). Acute IOP elevation is sufficient to alter the protein levels of tight junctions and adherens junctions of the RPE and subsequently affect the integrity of the BRB in glaucoma animal models (67). In dogs with primary glaucoma, disruption of PRE and extravasation of T cells and plasma proteins suggest the breakdown of both iBRB and oBRB (60). Acute induction of OHT in rats results in a significant reduction in pericyte coverage after 7-10 days, but the extent of vascular leakage remains unchanged (68). However, in patients with POAG and NTG, neurodegeneration is a slowly progressive event, and the breakdown of the BRB is likely associated with the long-standing retinal parainflammation otherwise. For example, aging as a contributing factor of glaucoma is associated with the progressive loss of BRB integrity and a low level of retinal inflammation (69). Some degenerative proteins such as amyloid-beta (Aβ) and hyperphosphorylated tau (p-tau), which are hallmarks of CNS neurodegenerative diseases are also found in the retina of glaucoma patients (14). These degenerative proteins contribute to the local inflammatory response and compromise BRB function by damaging tight junctions of the RPE and activating retinal microglial cells (70–72). The parainflammation state makes the retina vulnerable to the attack by adaptive autoimmune cells of peripheral origin.

The infiltration of T cells into retinal parenchyma includes 2 major steps: first, the extravasation from retinal vessels and then the breaching of glia limitans formed by astrocyte end-feet. The whole process is a continuous action that relies on the close interaction of T cells with multiple local factors and cells, as discussed in detail below.
T Cell Extravasation

As retinal capillaries are nonfenestrated, T cells have to escape through the tightly-connected vascular endothelium to reach the paravascular space in the retina (Figure 2). The extravasation of T cells into the retina is decided by the state of T lymphocyte activation, the state of retinal vascular endothelium, the microenvironment of the neuroretina, and local blood flow, which all affect the lymphocyte-endothelium interaction (73, 74). A study of T cell subsets in glaucoma patients revealed a significant shift in the T cell population and a greater stimulation response (75). When the BRB is intact and vascular endothelial cells are nonactive, peripherally-activated T lymphocytes can also cross the BRB and scan the retina for immune surveillance. Nevertheless, intravenous infusion of $5 \times 10^6$ activated ovalbumin-specific T cells in rats only results in the transient opening of the BRB and activation of resident microglial cells that subsides within 3 days (76). This indicates that intact and quiescent BRB can endure the challenge of systemic inflammation. However, when the retina is inflamed, activated vascular endothelium becomes highly adhesive for circulating

**Figure 1** | “Dual-hit hypothesis” for the association of peripherally-activated T cells during gut dysbiosis with glaucoma. In gut dysbiosis, the alteration of the components of gut microbiota, compromised mucin and gut epithelium, and dislocation of bacteria result in chronic local inflammation. Autoreactive T cells primed by microbial HSPs are generated and enter the systemic circulation (first hit). In the retina, the chronic stress response results in the release of HSPs and activation of resident microglia. Autoreactive T cells breach the compromised BRB and become reactivated in the retinal parenchyma (second hit). T cells can further induce the apoptosis of RGCs via the interaction of Fas/FasL.
lymphocytes by the upregulation of the expression of surface adhesion molecules, and a higher level of T cell extravasation is expected. The whole process of T cell trafficking across the retinal vascular endothelium is a complex action and includes 4 steps: tethering and rolling on the luminal surface, activation, firm adhesion on the vascular endothelium, and diapedesis (Figure 2) (74). In the initial step, the interaction of selectins and integrins on the surface of lymphocytes and endothelial cells helps capture circulating immune cells to roll slowly and finally become arrested at the luminal surface (77). This initial attachment is not firm enough, and subsequent activation via chemokines presented by endothelial cells is needed to induce clustering and conformational changes of integrins to improve their affinity and avidity (78). T lymphocytes, now tightly

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**FIGURE 2** | Infiltration of peripheral T cells into the retinal parenchyma during the pathogenesis of glaucoma. The BRB is tightly protected with nonfenestrated vascular endothelium, basement membrane, pericytes, and glia limitans formed by astrocyte end-feet. T cells need to first reach the perivascular space and then breach the glia limitans to finally infiltrate the retinal parenchyma. T cell extravasation includes steps of initial tethering and rolling, activation, firm adhesion, and final diapedesis. In the perivascular space, T cells need to be reactivated by antigen-presenting cells and secrete cytokines and MMPs to breach the glia limitans. Otherwise, T cells have to travel back to the vessel. In glaucoma, the local proinflammatory microenvironment favors the infiltration of T cells due to the higher abundance of molecules (cytokines, selectins, and chemokines) and cells (microglia, dendritic cells) involved in these processes.
grasped by endothelial cells, can break tight junctions and crawl out of blood vessels via transcellular or paracellular pathways (79–81).

In patients with glaucoma, the alterations of both T cell states and induced expression of local cytokines/chemokines may collectively contribute to the elevated extravasation of T cells. Some proinflammatory cytokines, particularly interferon-γ (IFN-γ), tumor necrotizing factor-α (TNF-α), and interleukin-1 (IL-1), are elevated in the aqueous humor or tears of glaucoma patients, indicating a globally proinflammatory state (82–84). These cytokines help T cell tethering and rolling by inducing the expression of integrins on the cell surface (85). Under resting conditions, only approximately 5% of lymphocytes derived from peripheral lymph nodes adhere to the retinal vascular endothelium, which doubles when the endothelium is activated by IFN-γ or IL-1 (86). In addition, peripherally activated T lymphocytes are also able to upregulate the expression of intercellular adhesion molecule-1 (ICAM-1) on the retina, a key integrin molecule for T cell rolling (87). In addition, RGCs of glaucomatous eyes demonstrate significantly enhanced expression of genes involved in chemokine signaling (88). In the murine retina, the β chemokine and its receptor C-C chemokine ligand 5/C-C chemokine receptor type 5 (CCL5/CCR5) are constitutively expressed and can respond to IOP challenge (89). CCR5, which is inducible on activation, is found to be involved in the recruitment of T-helper 1 (Th1) cells into the mouse retina (90). Another pair of chemokines (C-X-C motif) ligand 10/(C-X-C motif) receptor 3 (CXCL10/CXCR3) are found to be induced by acute IOP elevation and subsequently contribute to the release of proinflammatory cytokines, elevated expression of E-selectin, and infiltration of inflammatory cells (91). In patients with glaucoma, the levels of chemokines of macrophage chemoattractant protein-1 (MCP-1), CXCR3, CCL2, and CCL7 show prognostic value and are correlated with disease progression (92–94). On the other hand, the induced expression of corresponding chemokines and receptors on the T cell surface under inflamed conditions favors their interplay with the vascular endothelium (90, 95). Overall, the activation of both T cells and the vascular endothelium are two arms of inflammatory episodes in glaucoma that promote T cell extravasation.

The Breaching of Glia Limitans and Roles of Antigen-Presenting Cells

The retinal vessels are tightly wrapped with end-feet of astroglial cells that serve as a double barrier for T cell infiltration into the retinal parenchyma after extravasation (Figure 2). This physical barrier, named glia limitans, is concentric to the retinal vessels and creates a paravascular space. Tightening glia limitans with induced matrix metalloproteinase-3 attenuates lymphocyte infiltration after optic nerve injury (96). To cross the glia limitans, primed T cells need to be reactivated by the cognate antigen presented by antigen-presenting cells (APCs) or otherwise have to re-enter the retinal circulation. Thus, such APCs serve as major gatekeepers of the BRB, as they decide the fate of extravasated T cells. Compared with the CNS, the retina lacks meningeal layers and choroidal plexus which harbor numerous MHC-II+ APCs such as marginal dendritic cells and meningeal macrophages (97). In the pathogenesis of glaucoma, it is still under debate whether the APCs that initiate retinal inflammation are exogenous or activated resident cells. To serve as initial APCs, candidate cells need to distribute in the paravascular region and constitutively express MHC-II and costimulatory molecules. In a canine model of acute primary angle-closure glaucoma (PACG), infiltration of MHC-II+ phagocytes in the optic nerve and retina is observed within the first 24 hours, along with the infiltration of circulatory immune cells and RGC loss (98). However, it is controversial whether the infiltration of systemic phagocytes precedes the infiltration of T cells or vice versa. Some researchers also identified some innate players that may serve as initial APCs in the retina. A specific group of microglial cells that are located in the paravascular space instead of retinal parenchyma are found to constitutively express high levels of CD45, MHC-I, and MHC-II (99). However, these CD45+ microglial cells demonstrate only a weak activation effect on primed T cells (100). Thus, the player (s) of initial antigen presentation and associated antigen in glaucoma remain to be determined, and their dynamic change and interplay with T cells during the disease course need to be further investigated. The initial antigen presentation process may serve as a novel therapeutic target to halt the initiation of neuroinflammation in glaucoma.

Currently, the study of BRB breakdown and the pathogenesis of glaucoma is still an emerging research field, and many detailed aspects remain to be determined. As suggested by studies of AD, the breakdown of the BBB seems to be one of the initiating events that contribute to the subsequent tissue deposition of degenerated proteins and immune cell infiltration (101). Acute animal glaucoma models suggest the temporary breakdown of the BRB in response to elevated IOP and a globally proinflammatory state that facilitates T cell infiltration. However, whether BRB breakdown only serves as the initial trigger of glaucoma neuroinflammation or is essential during the full term of disease progression remains to be determined by appropriate animal models and clinical studies. In addition, the spatial-temporal pattern of T infiltration in the glaucoma retina remains largely unknown.

RETINAL GLIOSIS AND INTERPLAY WITH T CELLS

The retinal parenchyma harbors a group of endogenous immunocompetent cells including microglial cells, astrocytes, and Müller cells, and the latter two are also called macroglial cells. Under physical conditions, retinal glial cells closely interact with neurons and are highly versatile, participating in functions of mechanical support, metabolite transport, nourishment, tissue remodeling, and immunosurveillance (102). As key players of the retinal immune system, glial cells are distinct from conventional immune cells in the systemic circulation, as they are sequestered by the BRB and have no access to lymph nodes for lymphocyte
priming. Nevertheless, the compromised BRB of glaucoma enables their contact with myeloid-derived peripheral immune cells that infiltrate the retina. These glial cells serve as sensors, mediators, and effectors of the immune response and are found to be early responders in the pathogenesis of glaucoma (103, 104).

Different States of Retinal Glial Cells
In glaucoma eyes, resident glial cells undergo a dynamic change with close coordination of each other in a time-dependent manner during the disease course (105, 106). This process, so-called "retinal gliosis" contributes to both neurodegeneration and neuroprotection, depending on the severity and chronicity of the reaction. Retinal microglial cells and astrocytes are highly heterogeneous and can be chiefly divided into 2 states after activation, i.e., the neurotoxic/form (M1 and A1 phenotype, respectively) and neurotrophic form (M2 and A2 phenotype) (107, 108). For example, retinal microglial cells, as the major effector and APCs, assume an M1 phenotype with amoeboid morphology when stimulated by the proinflammatory cytokine interferon-γ (IFN-γ), and are able to release TNF-α, IL1-β, superoxides, proteases, and reactive oxygen species (ROS). On the other hand, when stimulated by IL-4, microglial cells turn into the M2 phenotype characterized by thin cell bodies with ramified processes. The M2 phenotype is associated with immunomodulatory cytokines such as IL-4, IL-10, IL-13, and TGF-β (Figure 3) (5, 109). Animal models of acute OHT suggest that a predominant M1/A1 type of microglial cells and astrocytes in the acute phase contributes to the early proinflammatory state, which may subside thereafter. The dynamic turnover and interplay between microglial and macroglial cells in glaucoma set the background of retinal inflammation, which is reviewed in detail by Zhao et al. (110).

T Cell-Microglial Interplay for Neurotoxicity
In the acute phase, infiltrated T cells interact with neurotoxic glial cells to induce the escalation of inflammation. This process can result in neurotoxicity and damage to RGCs if not properly controlled. Once breaching the BRB, peripherally activated T cells can interact with microglial cells, which serve as the bridge between innate immunity and adaptive immunity. The roles of microglia are versatile. First, microglial cells act as early sensors of the retinal stress response via inherent Toll-like receptors (TLRs) on their surfaces (111). They are found to rapidly respond to extrinsic danger signals such as HSPs and oxidative stress and assume a predominant M1 phenotype within 24 hours after the induction of OHT (112–114). For example, extracellular HSP27 can activate TLRs and their downstream nuclear factor-kappa-light-chain-enhancer (NFκB) pathway in microglial cells, which subsequently promotes the release of proinflammatory cytokines (TNF-α, IL-6, and IL-1β) and chemokines (MCP-1, MCP-3, MIP-1α, MIP-1β) to facilitate the recruitment and activation of T cells (115–117). Knockout of TIR-domain-containing adapter-inducing interferon-β (TRIF), an adaptor molecule downstream of the TLR3 pathway, results in reduced microglial activation and preserves RGCs following damage (118). Recently, studies found that microglial cells can also propagate inflammatory signals in a paracrine way through the release of exosomes and activate remote microglial cells (119, 120). Another important function of retinal microglial cells is their role as APCs. In the retinal parenchyma, APCs are responsible for the reactivation of T cells with cognate antigens by the expression of MHC class II molecules and costimulatory molecules (CD40, CD86, B7, etc.), which can subsequently result in the clonal proliferation of T cells (121). In glaucoma eyes, activated microglial cells gain a stronger ability of antigen presentation and secretion of proinflammatory immune mediators, which further escalate retinal inflammation (122, 123). Conversely, T helper cells are also able to differentially modify the phenotypes of microglial cells via the secretion of proinflammatory or suppressive cytokines (124, 125). CD4+ Th1 cells secrete IFN-γ for M1 conversion, while the Th2 interferon IL-4 is associated with the M2 phenotype. Adoptive transfer of primed T cells from hereditary glaucoma mice leads to focal activation of Iba1+ microglial cells with amoeboid morphology that stand in close proximity to infiltrated T cells (126). In tyrosinase T cell receptor (TCR) transgenic mice that spontaneously develop glaucoma, marked infiltration of T cells is observed. T cells, through induction of effector cytokines, lead to a robust increase in glial fibrillary acidic protein (GFAP) glial cells that colocalize to T cells in the nerve fiber layer (61). Above all, as demonstrated in Figure 3, the interactions of T cells and retinal microglia are reciprocal and collectively shape the inflammatory background in glaucoma.

Both T cells and microglia can directly contribute to RGC loss, but there are also some distinctions in their mechanisms of action, and their relative contributions remain elusive. Histological studies reveal that the neuroinflammation characterized by retinal gliosis and T cell infiltration parallel ongoing neural degeneration spatially and temporally (68, 127, 128). Primed T cells after immunization with HSP27 and HSP60 can induce the apoptosis of retinal ganglion cells by secretion of fas-ligand (FasL) and upregulation of its receptor on RGCs (129). On the other hand, microglial cells can also contribute to RGC loss in other distinct ways such as pyroptosis and complement-mediated synaptic pruning (130). In glaucomatous eyes, both intrinsic and extrinsic pruning pathways of RGCs are involved in cell death (116).

T Cell-Microglial Interplay for Neuroprotection
The role of the bidirectional interplay between T cells and microglial cells is multifaceted. Apart from neurotoxicity, it also enhances the clearance of dead neurons via phagocytosis, prevents escalation of inflammation, and sets the chance for subsequent tissue remodeling and neural repair, which may benefit the survival of remaining RGCs (131). Damaged neurons can release intracellular components after necrosis, such as DNA and nucleotides, which are highly proinflammatory and trigger the spread of inflammation. Activated microglial cells gain stronger mobility and phagocytic power and quickly move to the damaged site to isolate damaged
neurons. As found in other CNS neurodegenerative diseases, tissue deposition of Aβ and p-tau is evident in glaucoma eyes (132, 133). These degenerative proteins are pathogenic and involved in progressive neuron death. In the CNS, Aβ can be taken up by activated microglial cells via phagocytosis and contribute to T cell activation (134, 135). In turn, primed T cells with Aβ immunization can also enhance the uptake and removal of Aβ in the brain and demonstrate beneficial effects (136, 137). IL-4 and IL-10 secreted mainly by Th2 cells are beneficial for the clearance of tissue deposition and debris by accelerating microglial phagocytic activities (138). In addition, activated retinal microglial cells and infiltrating macrophages secrete proinflammatory IL-6 and TNF-α to stimulate CD4⁺CD25⁺ T cells and suppress T cell-mediated cytotoxicity (139). Following the phase of intense attack, microglial cells, macroglial cells, and T cells coordinate to resolve immune reactions in the retina. In this phase, microglial cells convert from the proinflammatory M1 phenotype to the neuroprotective M2 phenotype and are able to secrete neurotrophic factors to promote neuronal survival. The retina, as an immune-privileged tissue, also possesses multiple negative regulatory circuits to restrict inflammation. For example, retinal microglial cells, as well as neurons and endothelial cells, were found to constitutively express CD200. Through interaction with the CD200 receptor, it attenuates the activation of myeloid cells (140). Microglial cells upregulate the expression of programmed death ligand-1 (PD-L1) at the peak phase of activation and suppress Th1 function via interaction with PD1 on their surfaces (141, 142).

Above all, it is generally accepted that the T cell-microglia interaction has both protective and destructive consequences and is related to the disease course. However, it is still under debate how to appropriately modify the immune process and benefit the survival of RGCs in glaucoma patients. Some animal studies in acute OHT explicitly support the beneficial role of neurons by suppressing microglial functions in different ways (143–146). However, this
may not mimic the true chronic nature of glaucoma in most patients. It seems that this prompt immune reaction elicited by the stress response is at least beneficial in the restriction of neuroinflammation, but the longstanding insults of IOP fluctuation may lead to chronic activation of the microglia-T cell axis that exceeds the normal immunomodulation. As suggested by animal models of glaucoma, retinal gliosis is not only an early response but also persists in the chronic phase. Microglial cells remain activated after IOP returns to the normal level, which may potentially explain the ongoing neurodegeneration in patients after IOP has been controlled (147). Autopsy studies in postmortem glaucoma eyes may serve as direct evidence for marked retinal gliosis and infiltration of activated microglial cells in the optic nerve head (111, 148, 149). Glaucomatous eyes of humans also assume a chronic environment of neuroinflammation characterized by IgG autoantibody accumulation and increased levels of proinflammatory cytokines (45). In addition, from the point of view of T cells, there is a lasting imbalance of Th1/Th2 cells that tilts to the proinflammatory side in glaucoma patients (150, 151). These findings support the theory that chronic insults from endogenous (IOP, oxidative stress, etc.) and exogenous sources (gut dysbiosis, aging, etc.) lead to overactivation and disorder in immune regulation that turns the T cell-microglial axis into a predominant neurotoxic mode in the long term. Above all, this suggests the validity of immune modulation therapy in the treatment of glaucoma, as discussed in more detail in the section below.

THE EMERGING ROLE OF T CELL-BASED IMMUNE MODULATION THERAPY IN THE TREATMENT OF GLAUCOMA - A LESSON FROM CNS NEURODEGENERATIVE DISEASES

As discussed earlier, the immune reactions of T cells and microglia have both beneficial and detrimental effects on RGC survival, depending on whether they are properly evoked and regulated. In glaucoma, the chronic local proinflammatory microenvironment unfavorably shapes the immune reaction to the neurotoxic form and leads to progressive RGC loss. Considering the essential role of immune cells in tissue repair and maintenance of homeostasis, it is generally accepted that immune modulation, instead of simple immune suppression, is a valid option for glaucoma. The term “protective autoimmunity”, which refers to the beneficial roles of autoreactive T cells in the protection of neurons in the CNS, has been recognized for more than 2 decades (152, 153). This subsequently leads to the active exploration of T cell-based immune modulation therapy in glaucoma and other CNS neurodegenerative diseases.

Protective Autoimmunity in the CNS and Retina

Under physical conditions, peripherally primed T cells that recognize self-antigens can patrol the retina and brain parenchyma over time. This immunosurveillance is not only helpful for immune detection but also plays a role in maintaining neural homeostasis by actively engaging in multiple physiological activities, including neurogenesis, regulating spatial learning and memory, and assisting neuron survival with neurotrophic factors (154). Deprivation of CNS-specific autoreactive T cells halts the normal development of the CNS system and is involved in cognitive impairment in animal models and exacerbation of CNS injury (155). On the other hand, accumulating evidence suggests that the T cell-mediated immune response may also provide beneficial effects in neuroprotection in the case of acute neural damage. In a rat model of optic nerve crush and contusive spinal cord injury, single low-dose γ-irradiation treatment induces the activation of proinflammatory T cells that ultimately leads to spontaneous recovery, which is absent in mice with T cell deficiency or transferred with regulatory T cells (Tregs) (11). A prior traumatic brain injury evoked protective autoimmunity that was found to prevent RGC loss when the contralateral optic nerve was crushed later in a rat model (10). These protective effects are chiefly dependent on neuron-specific autoimmune T cells, as evidenced by the finding that only transgenic T cells overexpressing the T cell receptor for the CNS-specific antigen of myelin basic protein (MBP) rather than the nonself antigen of ovalbumin demonstrate protective effects on RGC survival after optic nerve injury (156). Thus, the involvement of autoimmune T cells in the protection of neurons during acute CNS insult indicates the validity of the immune modulation approach for the treatment of glaucoma.

Cop-1 Therapy

One investigated approach of immune modulation therapy in glaucoma is active immunization with a weak self-antigen that stimulates a moderate autoreactive T cell response. Autoimmune T cells are expected to regulate the immune response in a beneficial way and coordinate with local and other circulatory immune cells to boost faster tissue repair. Copolymer-1 (Cop-1, or glatiramer acetate), a synthesized analog of MBP, is a suitable candidate because it serves as a weak agonist of numerous self-antigens in the CNS. Immunization with Cop-1 has been tested in many CNS neurodegenerative diseases, and its commercial product Copaxone® has been approved by the US Food and Drug Administration (FDA) for the treatment of MS (157). Glaucoma shares common aspects of pathogenesis with MS, including generation and tissue deposition of common autoantibodies (anti-MBP) and activation of local microglial cells (45, 158). Clinical examination with optical coherence tomography (OCT) also indicates a close relationship between retinal RGC damage and MS neuropathy (15). Thus, Cop-1 as an approved therapy for MS is also explored in glaucoma treatment. Coculture of Cop-1-stimulated T cells and retinal microglia results in their reciprocal activation and the release of insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF), TNF-α, and IL-10 in vitro, which favors RGC survival in vitro (159). Immunization with Cop-1 by subcutaneous injection in a rat glaucoma model results in elevated intraretinal T cell infiltration and prevention of RGC loss, which indicates that the induced T cell response is more
protective than destructive (160). In addition, Cop-1 immunization has been delivered in combination with stem cell transplantation to rescue and replenish RGCs in animal glaucoma models. Cop-1 immunization induces a local favorable environment by balancing the levels of proinflammatory (IFN-γ) and anti-inflammatory (IL-4) cytokines and the secretion of neurotrophic factors (161). Activated T cells also release chemoattractants (such as MCP-1) to facilitate the recruitment of stem cells and progenitor cells to damaged sites (162, 163). The synergic action results in improved landing and survival of transplanted stem cells and alleviates nerve damage in glaucoma animal models (164, 165). Recently, the interim results of an ongoing double-masked clinical trial investigating Cop-1 immunization for the treatment of acute primary angle-closure glaucoma (PACG) have been disclosed (trial No. 01936129). Thirty-eight patients with PACG received either 2 subcutaneous injections of Cop-1 or the placebo without adjuvant, one within 24 hours of onset, and the other one week later. The patients in the Cop-1 group demonstrated improved mean deviation and a trend of a lower mean number of progressing points, but the retinal nerve fiber layer thickness showed no difference after 16 weeks. Due to the small sample sizes in both arms and high interindividual variation, the researchers could not confirm the protective role of Cop-1 in PACG based on the current evidence (166). In addition, no serum or immune examination test results were reported, whether the 2 subcutaneous injections of Cop-1 without adjuvant elicit an adequately strong and long-lasting immune response cannot be determined.

Concerns and Further Considerations on Immune Modulation Therapy for Glaucoma

Although immune modulation therapy seems to be a reasonable treatment option for glaucoma and has been well explored in CNS neurodegenerative diseases, in clinical practice, many conditions need to be optimized. Safety is a chief concern. Immunization with R16, a self-peptide from interphotoreceptor retinoid-binding protein, in a mouse model of acute OHT led to neuron protection but induced monophasic autoimmune uveitis in a susceptible mouse strain (167). More experience from CNS clinical trials warns that the stimulation of unwanted detrimental immune responses could lead to adverse events. In a phase II clinical trial investigating the tolerability and efficacy of intramuscular injection of self-antigen Aβ42 with QS-21 as the adjuvant in patients with mild to moderate AD, subacute meningoencephalitis occurred in 6% of patients in the test arm, which led to the termination of the study (168). An aberrant Th1 cell response is speculated to be responsible for the adverse inflammatory response, as QS-21 is a strong inducer of Th1 and infiltration of active T cells was found in an autopsy study (169). Similar meningoencephalitis has been reported in amyloid precursor protein-transgenic (APP/Tg) mice that express limited IFN-γ, but not in other strains. The activation of Th1 cells in a proinflammatory environment and their interplay with microglial cells are causative of neuroinflammation (170). Moreover, the adoptive transfer of Aβ-activated Th1 cells, but not Th2 cells, in mice results in local microglial activation and exacerbation of AD in a mouse model (171). As the patients with CNS neurodegenerative diseases such as AD and glaucoma assume a generally proinflammatory state, the immune response with self-antigen vaccination should be carefully modified, as the induction of proinflammatory Th1 cells may further tilt the balance of immunity. In turn, a vaccination that induces a predominant Th2 response is preferred and helps restore Th1/Th2 imbalance (151, 172). In the study of AD, a dominant Th2-type response has been achieved by multiple means, such as applying Th2-inducing adjuvants (alum) (173), modifying the structures of the self-antigen (174), liposome coating (175), DNA vaccination (176), intranasal immunization (177), and transcutaneous delivery (178), but activation of Th1 cells cannot be fully eradicated and may still be considered a potential risk. Currently, the only safety data of immune modulation therapy in glaucoma patients come from the pilot clinical trial of the Cop-1 vaccine, which shows no other adverse events other than injection site pain (166). In a rat glaucoma model, systemic administration of Cop-1 with complete Freud’s adjuvant evokes a strong Th2 response and IL-4 secretion that peaks at 7 days and lasts for more than 31 days, with no obvious Th1 activation (179). In addition, as an old drug in MS that has been monitored for more than 2 decades, subcutaneous injection of Copaxone® daily or three times per week is well tolerated, which is also suitable for children and pregnant women (180, 181). These results support the Cop-1 vaccine as a relatively safe therapy, but its long-term safety in glaucoma should be further elucidated.

Currently, Cop-1 vaccination is the only immune modulation therapy that has been tested in animals and patients with glaucoma, and more clinical data are expected to reflect its validity in patients. In CNS neurodegenerative diseases, many forms of passive or active immune modulation therapy have been explored, including self-antigen vaccination (182), DNA vaccination (183, 184), and transfer Treg cells (185, 186). The highly shared pathological and immunological features of glaucoma with other CNS neurodegenerative diseases support these therapies as rational options for glaucoma, which is worth further investigation. In addition, parallel changes in retinal neurons with the CNS have been observed in animals and patients on immune modulation therapy for CNS disorders (187, 188). However, the development and clinical translation of a mature immune modulation therapy for glaucoma are much more challenging than expected. Experience from clinical trials of AD and other CNS neurodegenerative diseases implicates numerous factors that may affect the efficacy and safety of immune modulation therapy, including antigens for immune induction, the time window of injection, frequency and amount of injection, drug delivery route, adjuvants, drug carriers, and individual factors (age, sex, etc.) (153). The development of a suitable regimen for a specific disease should be explored on a case-by-case basis. For example, Cop-1 immunization prior to or on the day of OHT damage significantly prevents RGC loss, while immunization 48 hours later generates no protection (189). In addition, a single Cop-1 immunization with complete Freud’s adjuvant in a mouse acute OHT model is protective, but it dose not work for the optic nerve transection injury or amyotrophic...
lateral sclerosis (ALS) (190, 191). On the other hand, daily subcutaneous injection of Cop-1 is most effective for MS, but this regimen causes negative effects on the female mouse ALS model (191). Thus, a careful selection of regimens based on extensive animal and human studies is essential for an immune modulation therapy for glaucoma. Most importantly, researchers need to keep in mind that chronic neurodegeneration is multifactorial and highly complicated, and the efficacy observed on pathology may not translate into clinical improvement. For example, Aβ42 immunization in Alzheimer's patients showed obvious benefits of prolonged plaque removal. Nevertheless, most of the patients progressed to Braak stage V-VI and developed severe dementia before death (192). Thus, a reliable clinical evaluation of drug efficacy is vital for immune modulation therapy of glaucoma and other neurodegenerative diseases.

Above all, the development of a mature immunomodulation therapy for glaucoma needs many more investigations on its safety and practical conditions. Special attention should be given to avoid unwanted exacerbation of the Th1-mediated response. In addition to Cop-1 immunization, more novel therapies, such as DNA vaccination and cell therapy, are also worthy of investigation in glaucoma.

SUMMARY AND CONCLUSIONS

The perspectives on the pathogenesis of glaucoma are continuously updating, and debates are ongoing as new evidence from animal or clinical studies comes out. Although the research, diagnosis, and treatment focus primarily on IOP, T cell-mediated immune attack and its dynamic interplay with retinal microglial cells have been recognized to be the culprit of glaucoma. Researchers are attempting to shape the immune reaction to take advantage of its favorable neuroprotective effect. However, currently, no clear clinical evidence on the beneficial role of immunomodulation therapy in glaucoma patients has been illuminated on patients. Most importantly, signs of activation of autoimmunity and imbalance of immune reactions, including autoantibodies, a shift in the T cell subpopulation, and activation of retinal innate immunity, are clearly involved in the early phase of glaucoma. However, whether these clinical signs and associated biomarkers can assist the early diagnosis and primary prevention of glaucoma remains elusive. In addition, basic research on the autoimmune aspects of glaucoma is still a fresh field. Many theories of immune reactions in glaucoma basically come from findings from other CNS neurodegenerative diseases. In particular, the spatial-temporal breakdown of the BRB and retinal infiltration of peripheral immune cells during the chronic disease course in glaucoma patients are needed to illuminate the real contribution of T cells. As with other neurodegenerative diseases, a chronic animal disease model that mimics the true complexity and chronicity of glaucoma development in humans is lacking. Thus, findings from the acute OHT model may not reflect the whole picture, and more autopsy studies from human glaucoma samples may provide more valuable information. Moreover, the close overlap of glaucoma with other CNS neurodegenerative diseases indicates the need for a closer follow-up of patients in both ophthalmic and neurologic clinics. Their common pathogenesis in immune-mediated neurodegeneration indicates the possibility of their parallel progression and reaction to common therapies. Therefore, the ophthalmic follow-up of patients with CNS neurodegenerative disease going on trials of immunomodulation therapy may also provide valuable insights for glaucoma treatment.

AUTHOR CONTRIBUTIONS

Conception and design – LW and XW. Manuscript preparation – LW. Critical revisions – XW. All authors contributed to the article and approved the submitted version.

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