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Myeloid cells in retinal and brain degeneration

Michelle Guo, **Turner D. Schwartz**, **Joshua L. Dunaief**, **Qi N. Cui**

302–303 Stellar Chance Laboratories, 422 Curie Blvd., Philadelphia, PA 19103

Abstract

Retinal inflammation underlies multiple prevalent ocular and neurological diseases. Similar inflammatory processes are observed in glaucomatous optic neuropathy, age-related macular degeneration, retinitis pigmentosa, posterior uveitis, Alzheimer's disease, and Parkinson's disease. In particular, human and animal studies have demonstrated the important role microglia/macrophages play in initiating and maintaining a pro-inflammatory environment in degenerative processes impacting vision. On the other hand, microglia have also been shown to have a protective role in multiple central nervous system diseases. Identifying the mechanisms underlying cell dysfunction and death is the first step towards developing novel therapeutics for these diseases impacting the central nervous system. In addition to reviewing recent key studies defining important mediators of retinal inflammation, with an emphasis on translational studies that bridge this research from bench to bedside, we also highlight a promising therapeutic class of medications, the glucagon-like peptide-1 receptor agonists. Finally, we propose areas where additional research is necessary to identify mechanisms that can be modulated to shift the balance from a neurotoxic to a neuroprotective retinal environment.

Keywords

retina; glaucoma; age-related macular degeneration; retinitis pigmentosa; Alzheimer's disease; Parkinson's disease; inflammation; microglia; monocytes; macrophages

Introduction

A number of recent publications have illuminated the relationship between retinal inflammation and diseases impacting the visual pathway. The central nervous system (CNS) is a site of immune privilege that is relatively shielded from the systemic circulation and is

Corresponding Author: Qi N. Cui, Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA 19104, Qi.Cui@pennmedicine.upenn.edu, Twitter: @CuiLab, qicuilab.org.

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where microglia function as the resident myeloid cells. Like macrophages in the periphery, microglia play many important roles in both health and disease, and they may be either neuroprotective or neurotoxic.

Studies in both humans and animal models have highlighted the roles macrophage infiltration and microglia activation play in ophthalmic diseases. In particular, the contribution of myeloid cells to pathogenesis in glaucoma, retinal degenerative processes such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP), and inflammatory conditions like posterior uveitis, are increasingly well-characterized. As a direct extension of the CNS, the retina provides a window through which neurodegenerative diseases impacting the brain, such as Parkinson's and Alzheimer's diseases, may be imaged and studied *in vivo*.

This review provides an updated perspective on the roles myeloid cells play in retinal inflammation, both in ocular diseases and brain neurodegenerations with ocular extensions. An abbreviated overview of ocular anatomy provides the introductory background upon which these diseases are then discussed in detail. Particular attention will be given to the posterior segment including the retina and the optic nerve. We highlight conditions where myeloid cells have been suggested to be a significant driver in the disease process. Finally, we propose that a class of medications, glucagon-like peptide-1 receptor (GLP-1R) agonists, demonstrates potential as a novel treatment modality for neurodegenerative processes impacting the eye and the brain.

Anatomy of the Eye

The eye is most often conceptualized as two separate compartments (Figure 1). The posterior segment denotes the area lying behind the crystalline lens, while the anterior segment consists of structures in front of, and including, the lens. The anterior segment can be further divided into an anterior and a posterior chamber by the iris, which has a central pupillary opening that connects the two chambers, allowing aqueous humor to flow into the anterior chamber from behind the iris [1].

Externally, the sclera is the white-appearing collagenous shell that maintains the rounded shape of the eye. Covering the sclera and continuous with the inner surface of the eyelids is the conjunctiva, a mucous membrane that provides immune protection from the outside environment and lubricates the eye. The cornea is the clear, avascular window of the eye that provides approximately 80% of its refractive power. It consists of a collagenous stroma sandwiched between an epithelial and an endothelial layer and their respective basement membranes [2]. Posterior to the cornea lies the iris, a heavily pigmented structure that contains both longitudinal and circular smooth muscles that adjust the size of the pupil in response to light intensity. The crystalline lens sits behind the pupil and is suspended from the ciliary body by zonular ligaments [3]. These zonular suspensory ligaments allow the muscular contractions within the ciliary body to modify the shape of the lens, and the eye to focus on images at various distances [4]. Behind the lens, the gel-like vitreous humor fills the posterior chamber [5, 6]. The retina surrounds this vitreous cavity and is the site of the

transduction of light to neural impulses [7]. Lying beneath the retina and within the sclera is the choroid, a layer of blood vessels that nourishes the outer layers of the retina [8].

In addition to adjusting the shape of the lens, the ciliary body also secretes aqueous humor [9]. The aqueous fluid flows through the pupillary opening to circulate within the anterior chamber, where it provides nutrients to ocular structures, after which it drains through the trabecular meshwork in the iridocorneal angle to remove metabolic waste [10]. From the trabecular meshwork, aqueous humor continues into the Canal of Schlemm, which is a modified capillary that drains into the episcleral venous system surrounding the eye [1]. Should aqueous drainage become obstructed as during angle closure, intraocular pressure (IOP) can increase dramatically within the eye. Elevated IOP, which can happen even with open iridocorneal angles, is a major risk factor for the development of glaucomatous neurodegeneration. All currently available glaucoma treatments focus on IOP lowering [11, 12].

Retinal Anatomy and Visual Signal Transduction

The retina and optic nerve are extensions of the CNS that develop from the optic cup, a protrusion of the forebrain [7]. As the retina is an extension of the CNS, the blood-retina barrier (BRB) functions like the blood-brain barrier to offer the retina a degree of immune privilege [7, 13, 14]. In primates, the retina contains an oval-shaped macula lutea, and within the macula the fovea provides for the highest degree of visual acuity [15]. The human retina itself is a complex structure with 10 distinct layers (Figures 1 and 2). The outermost layer is the retinal pigment epithelium (RPE), situated between the choroid and the photoreceptors of the retina. The RPE contains melanin that absorbs light to minimize light reflections off of the sclera, and also forms the BRB [7]. Internal to the RPE lies the photoreceptor layer, containing extensions of rods and cones that respond to incoming light. Internal to this, the external limiting membrane is formed by a layer of cellular connections between Müller cells and the photoreceptors [16]. Moving even closer to the vitreous cavity, the outer nuclear layer (ONL) contains the nuclei of the photoreceptors, followed by the outer plexiform layer (OPL), where the photoreceptors synapse with the dendrites of bipolar and horizontal cells. The inner nuclear layer (INL) contains the nuclei of the bipolar cells, horizontal cells, amacrine cells, and Müller glia. Adjacent to the INL is the inner plexiform layer (IPL), where bipolar and amacrine cells synapse with retinal ganglion cells (RGCs). Ganglion cell bodies reside in the adjacent ganglion cell layer (GCL). Finally, RGC axons traverse the retinal nerve fiber layer (RNFL) and coalesce to form the optic nerve, which primarily transmits to the visual cortex in the occipital lobe of the brain [7]. To form the optic nerve, RGC axons exit the eye through openings in the lamina cribrosa, a multilayered connective tissue comprised of plates of collagen that are a part of the optic nerve head (ONH) [17]. The internal limiting membrane sits adjacent to the vitreous and is formed by the footplates of Müller cells and segregates the vitreous humor from the retina [16].

Within the photoreceptor layer, relative to cones, rods are more abundant in the peripheral retina and are highly sensitive to changes in light and dark. Cones are most densely packed in the fovea and are responsible for color vision in bright light [7]. Mouse and human retinas differ in that mouse retinas lack a macula lutea, and mouse retinas have two cone opsins, one

for UV light and one for green light [18, 19]. In contrast, there are three types of cones in the human retina, with each maximally responsive to different wavelengths of light: red, green and blue [20]. Rods and cones convert light to electrical signals in neurons in a process called phototransduction. While multiple bipolar cells synapse with a single cone, many rods converge onto a single bipolar cell to increase light sensitivity at the cost of acuity. Amacrine cells modulate RGC firing by sending inhibitory signals to the axon terminals of bipolar cells synapsing with RGCs. Horizontal cells receive input from photoreceptors and send inhibitory signals as feedback to rods and cones, thereby inhibiting adjacent photoreceptors to enhance contrast [21]. The retina contains 3 types of glial cells: Müller cells, microglia, and astrocytes. Müller cells modulate the exchange of nutrients from the circulation to neurons in the retina [22]. Like Müller cells, astrocytes associate with blood vessels in the GCL and contribute to the BRB, while also sharing synaptic pruning responsibilities with microglia [13].

Microglia and Macrophages

Microglia serve as important mediators of immune response within the CNS [23]. In healthy eyes, microglia have a highly branched morphology, with cell bodies located in several layers of the inner retina: the RNFL/GCL, IPL, and OPL [24]. Microglia have multiple functions, including immune surveillance, synaptic pruning, modulation of neuronal activity, and regulation of neuronal soma and axon growth [25]. Activated microglia, which exhibit an amoeboid appearance, may serve either neuroprotective or neurotoxic roles depending on their functional states. They have been shown to migrate to the subretinal space and adhere to the RPE in response to photoreceptor damage and aging [26, 27].

In their activated states, microglia remodel neural synapses to facilitate plasticity during development, phagocytose cellular debris, and produce neurotrophic factors to regulate neuron survival and apoptosis [28–36]. Activated microglia can also produce superoxide ions, release pro-inflammatory cytokines, and present self-antigens in autoimmune responses [24, 37, 38]. Neurotoxic microglia may phagocytose stressed but viable neurons during development, inflammation, and in pathological states such as CNS ischemia [39, 40].

Although microglia and macrophages have similar functions, microglia are developmentally and functionally distinct from monocyte-derived macrophages. Microglia arise from myeloid progenitors in the yolk sac early in development whereas peripheral macrophages derive not only from the yolk sac, but from both fetal monocytes and postnatal hematopoietic stem cells [41–44]. Further, microglia are distinct from prenatal-derived tissue-resident macrophages located throughout other organs including the eye [26, 45, 46]. Monocytes travel through the systemic circulation before extravasating into end tissues in response to specific chemoattractant signals, after which they differentiate into tissue-specific macrophages [47, 48]. The population of microglia cells is maintained via self-renewal, largely separate from the influence of blood-derived monocytes [28, 49].

Microglia can occupy the IPL, OPL and subretinal spaces, and monocyte-derived macrophages expectedly show an association with perivascular spaces prior to migrating

into, and residing in, multiple layers of the retina [26, 46, 50]. After infiltrating the CNS in response to injury, peripheral macrophages adopt morphology and surface markers similar to those of resident microglia [49, 51]. If the microglia population is depleted, macrophages can replace microglia in the central nervous system where they take on similar characteristics, distributions, and gene-expression profiles as resident microglia [52, 53]. In particular, yolk sac-derived macrophages express many signature microglia genes including *Tmem119, Fcrls, Hexb*, and *Olfml3* when injected into the brains of microglia-deficient mice [51]. The similarities between macrophages and microglia complicate efforts to differentiate resident microglia from infiltrating macrophages. Genetic fate mapping approaches have mitigated without entirely resolving this limitation [44, 54–56].

The M1/M2 paradigm is an imperfect, and arguably outdated, way to conceptualize cytotoxic and homeostatic macrophages, respectively, and holds less relevance for microglia [57–59]. M1 macrophages were often described as performing the role of phagocytosing dead or dying tissue and releasing pro-inflammatory cytokines. Thus, they were seen to serve a neurotoxic role in the nervous system [60, 61]. Stimulation by lipopolysaccharides (LPS) and interferon-gamma (IFN-γ) from Th1 helper T cells were shown to induce M1 macrophages to produce pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and nitric oxide synthase (NOS) [60]. M2 macrophages *in vitro*, in contrast, were shown to produce ornithine following stimulation by interleukin 4 (IL-4) from Th2 helper T-cells, and stimulate cell division [58]. So-called M2 macrophages may also inhibit inflammation via cellular signaling, and along with increased expression of neurotrophic factors like brain-derived neurotrophic factor (BDNF), act in a neuroprotective manner in the nervous system [61, 62]. The M1/M2 classification framework represents a simplified approach to macrophage characterization, when in reality these 2 phenotypes may represent 2 functional states among many [58, 60, 61].

Within the retina, as is the case within other parts of the CNS, microglia constantly survey for noxious stimuli. Under sustained toxic stimulation, exaggerated microglial inflammatory responses can lead to the release of pro-inflammatory mediators [40]. A sustained, chronic pro-inflammatory environment is common to many retinal degenerative diseases and neurodegenerative disorders affecting vision, as discussed in detail below [63].

Glaucoma

Glaucoma is the leading global cause of irreversible blindness. The number of people with glaucoma worldwide is expected to increase from 64.3 million in 2013 to 111.8 million in 2040 [64]. Glaucoma encompasses a group of optic neuropathies that share a common phenotype of RGC death and axon degeneration with characteristic optic nerve cupping and visual field loss [65]. The specific etiologies behind glaucoma are being continuously elucidated, but elevated IOP, along with age, sex, and ethnicity, are well-known risk factors in glaucomatous neurodegeneration [66, 67].

More recently, both microglia activation and macrophage recruitment have been implicated in glaucoma pathogenesis. In the eyes of patients with glaucoma, activated microglia have been found clustered at the lamina cribrosa of the ONH and surrounding blood vessels

[68]. Margeta and colleagues identified myeloid cells positive for CD163, a marker of macrophages involved in tissue repair, in the optic nerves of eyes with both early and advanced glaucoma [69]. Macrophage chemoattractant protein-1 (MCP-1), also known as CCL2 (C-C motif ligand 2), is a key chemotactic factor in monocyte recruitment and often implicated in initiating inflammation [70, 71]. A recent prospective, longitudinal study in patients with normal-tension glaucoma demonstrated that elevated systemic levels of MCP-1 are associated with progressive loss on visual field testing [72]. These studies on human patients with glaucoma highlight an emerging role for monocytes in the pathogenesis of glaucoma.

Extravasation of myeloid cells from the ONH has also been implicated in glaucoma pathogenesis and following optic nerve injury. In the DBA/2J mouse model of chronic glaucoma, pharmacological and genetic inhibition of monocyte entry into the eye prevented loss of RGC soma and axons [73]. Crush injury of the optic nerve has also been shown to attract myeloid cells to injured RGCs [74]. Through parabiosis and fate mapping, the responding myeloid cells were demonstrated to be retinal in origin as opposed to derived from circulating macrophages. Interestingly, total optic nerve transection prevented this myeloid cellular response, suggesting that the optic nerve serves as either a reservoir or a conduit for reactive myeloid cells following optic nerve injury [74]. Recently, our group showed that a macrophage-enriched population of retinal cells was responsible for pro-inflammatory cytokine release early on after microbead-induced IOP elevation, whereas a microglia-enriched population did not contribute to the inflammatory response until weeks later, further suggesting monocyte infiltration may be a driver of astrocyte activation [75].

Recent experimental evidence suggests that elevated IOP in one eye was sufficient to elicit early and widespread microglial activation that precedes RGC death. Following laser-induced ocular hypertension in one eye, activation of microglia extended to all retinal layers in both eyes [76]. In a rat model of intermittent ocular hypertension, unilateral IOP elevation also led to bilateral microglial activation and a significant decrease in RGC and axon density [77]. Unilateral microbead-induced IOP elevation has also been found to enhance microglial reactivity in the contralateral, normotensive optic nerve and its central projections in rats [78]. Interestingly, however, RGC death in the contralateral eye did not occur without IOP elevation. Taken together, results suggest that a focal, unilateral insult of IOP elevation is sufficient to induce a global inflammatory response throughout the retina and the central visual system.

IOP elevation also causes transcriptomic changes impacting macrophage/microglial function that vary depending on the timeframe of glaucomatous injury. Early on, after IOP elevation but prior to RGC axon loss, Oikawa and colleagues demonstrated transcriptomic evidence of inflammatory pathway activation and microglial proliferation in the eyes of domestic cats [17]. In the DBA/2J model of chronic IOP elevation and glaucoma, transcriptomic profiling of microglial mRNA from the ONH showed disruptions of homeostatic functions in microglia the authors characterized as neither definitively pro- or anti-inflammatory [79]. Transcriptomic signatures also appeared to differ between infiltrating macrophages and resident microglia in these animals, suggesting a way to distinguish between the two cellular populations.

Several mediators of RGC death in the setting of ocular hypertension have been elucidated. Multiple studies have demonstrated elevated levels of TNF-α in the aqueous humor, retina, and optic nerves of patients with glaucoma [80–83]. Cueva Vargas and colleagues showed that TNF-α is released by microglia and Müller cells following elevated IOP in a rat model of glaucoma, and that pharmacological inhibition of TNF-α enhanced RGC soma and axon survival [84]. Nakazawa and colleagues demonstrated that inducing ocular hypertension in mice resulted in a sequence of events including upregulation of TNF-α, microglial activation, optic nerve oligodendrocyte death, and RGC death [85]. Genetic deletion of TNF-α or its receptor, and neutralizing antibodies to TNF-α both prevented the damaging effects of ocular hypertension [85]. Inhibition of TNF-α in a mouse model of corneal chemical injury was also shown to prevent monocyte infiltration and microglial activation as well as reduce susceptibility to secondary glaucoma and RGC death [86]. Etanercept is a TNF-α blocking decoy receptor that is approved for the treatment of conditions where pro-inflammatory signaling is central to disease pathophysiology, such as rheumatoid arthritis and psoriatic arthritis [87, 88]. In a rat model of hypertensive glaucoma, etanercept inhibited the activation of microglia around the ONH and promoted RGC survival [89]. In short, existing evidence suggests that TNF-α plays an important role in both IOP-dependent and independent RGC death, while TNF-α antagonism may represent a potential treatment pathway in glaucoma.

Fas is a member of the TNF receptor superfamily that signals apoptotic cell death after binding the Fas ligand. Fas is constitutively expressed in murine microglia and significantly upregulated following TNF-α stimulation [90]. A small peptide antagonist of the Fas receptor inhibited microglia activation and expression of TNF-α, C1q, and C3, and reduced RGC death following microbead-induced IOP elevation [91]. In a separate publication by the same group, inhibition of Fas ligand signaling by its cleavage product was shown to protect against RGC and axon degeneration in both the DBA/2J mouse model of glaucoma and following microbead-induced IOP elevation [92]. These results provide additional evidence that TNF-α-associated pro-inflammatory pathways contribute to glaucomatous neurodegeneration.

The complement cascade actively regulates the inflammatory response and has been implicated in glaucoma [93–98]. C1q, in particular, is a major complement component with upregulated expression in the human glaucomatous retina and animal models of the disease [99]. In a microbead-induced primate model of glaucoma, C1q upregulation was shown in conjunction with decreased RGC axon density after 28 weeks of sustained IOP elevation [100]. Inhibition of the complement cascade prevented RGC dendritic pruning and synaptic loss, which occurs early in the disease process prior to axon and soma degeneration [94]. Genetic and pharmacological inhibition of C1 prevented these early changes in both genetic and induced models of glaucoma [94, 98]. These findings elucidate the role of complement in retinal degenerative processes including glaucoma and highlight the potential for complement-modulating therapeutics in glaucoma treatment.

The IL-1 family containing both pro- and anti-inflammatory cytokines contributes directly to a number of retinal diseases as well as glaucoma [101–105]. In a study of 50 patients with primary open-angle glaucoma, circulating levels of IL-1β mRNA in blood

lymphocytes as well as IL-1β protein in the aqueous fluid were elevated compared to age- and sex-matched controls [106]. The expression of IL-1α, IL-1β, and IL-6 were also shown to be increased in the trabecular meshwork cells of glaucomatous eyes compared to normal eyes [107]. Further, IL-1 was shown to stimulate the activation of the pro-inflammatory transcription factor nuclear factor-kappa B (NF-κB), which upon release from I-κB inhibition, translocates to the nucleus and mediates the expression of a battery of pro-inflammatory cytokines including IL-1α, IL-1β, IL-6, and TNF-α [107, 108].

Recently, our group demonstrated that induced ocular hypertension stimulates macrophage/microglia to upregulate IL-1α, TNF-α, and C1q, a trio of cytokines shown to be necessary and sufficient to induce astrocyte conversion to a neurotoxic (so-called A1) phenotype, causing RGC death [109]. Genetic knockout mice deficient in IL-1α, TNF-α, and C1qa (triple knockout) exhibited reduced astrocyte transformation and RGC death in ocular hypertension [75]. These findings are corroborated by the work of Guttenplan and colleagues, who demonstrated increased survival of electrophysiologically-viable RGCs in triple knockout animals following both optic nerve crush and microbead injections, and showed that focal injury is a prerequisite to astrocyte-induced RGC death [110]. Following optic nerve crush-induced synaptic degeneration in the dorsal lateral geniculate nucleus, microglia, in a process mediated in part by C1q, have been shown to be the responding post-injury phagocytes [111]. It remains to be determined whether this process promotes neuroprotection by removing toxic debris or exacerbates neurodegeneration by further compromising synaptic integrity.

In summary, evidence increasingly suggests that neuroinflammatory pathways play in a role in glaucoma pathogenesis at all stages of the disease process impacting both the outflow pathway in the iridocorneal angle and the retina/optic nerve. In particular, following focal injury or stress, macrophage/microglia activation may directly contribute to RGC death and optic nerve degeneration in glaucoma. Targeting retinal inflammatory pathways and identifying ways to switch microglial activation toward neuroprotection may function in a synergistic fashion with IOP lowering to improve RGC survival.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a progressive, common, and heritable deterioration of the macula impacting central vision [112]. The global prevalence in 2020 is 8.69% (196 million people), with a projected increase to 288 million people by 2040 [113]. Clinical features of AMD include the presence of drusen, consisting of extracellular deposits of lipids, proteins, and inflammation-related cytokines, between the RPE and the underlying Bruch's basement membrane [114, 115]. AMD is categorized by 2 clinical forms: 1) Neovascular or exudative AMD, characterized by the growth of immature, leaky choroidal vessels either beneath or through the RPE into the avascular outer retina, and 2) Nonexudative AMD, in the advanced geographic atrophy form, characterized by slowly expanding areas of degeneration of the RPE and photoreceptors. [112, 116, 117].

An abundance of evidence suggests that subretinal macrophages/microglia are part of a pro-inflammatory milieu contributing to photoreceptor death in retinal degeneration. Under

physiologic conditions, the photoreceptor layer and the subretinal space are inherently immunosuppressive and lack monocytes [118]. In AMD, however, monocytic infiltration and microglial activation have been observed in both regions in all stages of the disease process [118, 119]. Microglia and recruited macrophages produce high levels of pro-inflammatory cytokines including IL-1β, TNF-α, and IL-6, resulting in increased vasodilation and vascular permeability/exudation [120]. A similar pro-inflammatory environment created by subretinal macrophages/microglia has been shown to directly induce the death of nearby photoreceptors in a mouse model of acute retinal degeneration [121]. Conditioned media from reactive human and murine microglial cells have been shown to trigger caspase-mediated photoreceptor cell death *in vitro* [122, 123]. In addition to MCP-1, other chemokines implicated in retinal macrophage recruitment include the Cx3cr1 receptor ligand fractalkine and the complement receptor C5aR [124, 125]. In summary, accumulation of retinal macrophages/microglia and their pro-inflammatory cytokine production may play a mechanistic role in worsening photoreceptor degeneration and disease progression in AMD.

Macrophages are the primary infiltrating immune cells in choroidal neovascularization (CNV), a hallmark of exudative AMD [126]. Higher levels of MCP-1 have been identified in the serum of patients with exudative AMD compared to unaffected age- and gender-matched controls [127]. Blocking Müller MCP-1 expression reduced monocyte/microglial infiltration and activation in a rat model of light-induced retinal degeneration [128]. The monocyte marker CD163, along with other cytokines implicated in inflammation, may be an indicator of disease status in AMD. The levels of multiple cytokines including CD163 in the peripheral blood of human patients differed between exudative AMD, nonexudative AMD, and age-matched controls, depending on the presence of active leakage in exudative cases [126]. Higher peripheral blood levels of C-reactive protein and IL-6, for example, have been associated with AMD progression [129, 130]. Recurrent CNV leads to subretinal scarring and fibrosis, an important contributor to vision loss [131]. Infiltrating macrophages may also contribute directly to macular fibrosis by transdifferentiating into myofibroblasts in experimental CNV and in human eyes with exudative AMD [132]. Targeting specific populations of proangiogenic and pro-fibrotic macrophages represents a potential therapeutic strategy for AMD.

Recently, the AMD-associated minor haplotype of the chromosome 10q26 was shown to account for a large proportion of the genetic risk of AMD [133]. Disease risk increased up to tenfold in homozygous carriers [134, 135]. The disease-associated haplotype and the common non-risk haplotype only differ by several single nucleotide polymorphisms, located in a non-coding DNA sequence within the promoter of the high-temperature requirement A serine peptidase 1 (HRTA1) [136, 137]. In both *in vitro* and *in vivo* experiments, HTRA1 reduced the ability of thrombospondin-1 to form CD47 complexes in mice, a step that mediates monocyte elimination from the subretinal space [137, 138]. Injection of HTRA1 into the subretinal space increased the survival of monocytes in a CD47-dependent manner, and monocytes from homozygous carriers of the minor haplotype were shown to express high levels of HTRA1 [137]. Conversely, HTRA1-induced monocyte survival is dependent on the induction of osteopontin, and genetic ablation of osteopontin reduced subretinal inflammation and monocyte survival [137]. These studies suggest that the mechanism

behind 10q26 haplotype-associated AMD risk is the promotion of monocyte survival and inflammation within the retina.

In summary, retinal inflammation and macrophage/microglial activation clearly contribute to retinal degeneration in AMD. Developing effective therapies for AMD necessitates a clear understanding of the inflammatory responses at all stages of the disease process.

Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a heterogeneous group of inherited retinal degenerative disorders characterized by the progressive loss of photoreceptors resulting in severe vision loss [139]. In human retinas with RP, activated, amoeboid myeloid cells are found in the ONL containing debris from phagocytosed rod cells in regions of photoreceptor degeneration [119]. A retrospective, observational study identified increased density of inflammatory cells and higher levels of pro-inflammatory cytokines including IL-1α, TNF-α, and MCP-1 in the aqueous humor and anterior vitreous cavity of RP patients compared to controls [140]. Using the rd10 mouse model of RP, the same group also found microglial activation and elevated expression of pro-inflammatory cytokines IL-1β, MCP-1, and TNF-α preceding photoreceptor apoptosis [141]. They further demonstrated anti-inflammatory effects as well as photoreceptor rescue following treatment with the antioxidant N-acetylcysteine (NAC). Topical and oral NAC were also shown to reduce superoxide radicals, as well as rescue and maintain cone function in the rd1 and rd10 mouse models of RP [142]. More recently, a phase I clinical trial evaluated the effect of oral NAC administration in RP patients, and demonstrated improvements in best-corrected visual acuity after 24 weeks of treatment [143].

Inhibition of a specific pro-inflammatory pathway demonstrated the treatment potential of strategies that mitigate exaggerated immune activation in an animal model of RP. Myeloid differentiation factor 88 (MyD88) is an adaptor protein for the IL-1 receptor and Toll-like receptor (TLR) families of innate immunity receptors, and mediates inflammatory responses to cellular injury by activating NF-κB [144]. Using a MyD88-blocking peptide in a mouse model of RP, Garces and Hackam demonstrated increased rod photoreceptor function and reduced apoptosis compared to controls [145]. MyD88 inhibition also resulted in fewer microglia/macrophage cells in the photoreceptor layer, while the total number of microglia/macrophages within the retina was unchanged, suggesting that MyD88 promotes the migration of microglia/macrophages within the retina to site of injury.

Activated microglia, rather than recruited monocytes, have been shown to phagocytose stressed, but viable photoreceptors in models of retinal degeneration [40]. In the rd10 mouse model of RP, activated microglia in the ONL contributed to retinal degeneration by phagocytosing non-apoptotic rods in early rod degeneration [40]. Further, both genetic microglia ablation induced by tamoxifen pulse and inhibition of the phagocytosis receptor vitronectin ameliorated photoreceptor death in these animals. Compared to microglia, recruited macrophages appeared to play a lesser role in photoreceptor clearance. Recruited monocytes were found to localize to the subretinal space more than the ONL and morphologically showed little evidence of phagocytosis [40]. In a follow up publication

by the same group, longitudinal tamoxifen treatment was unexpectedly found to reduce microglial activation *in vivo* independent of depletion, and this modulation was linked to improved photoreceptor survival *in vitro* [146]. Taken together, these results raise the possibility that tamoxifen administration to ablate CX3CR1-expressing microglia may have also rescued photoreceptors by blunting microglia activation [40].

Consistent with the finding that microglia play a larger role than recruited monocytes in models of retinal degeneration, rd10 mice with genetic deletion of CCR2, the receptor to the major macrophage chemokine MCP-1, demonstrated only moderate, if significant, decrease in the numbers of F4/80 positive myeloid cells in the retina. CCR2 deletion also delayed, but did not ultimately reduce, photoreceptor degeneration relative to rd10 mice with functional CCR2 [147]. These results suggest that while macrophage recruitment may contribute to pathogenesis early on in RP retinal degeneration, microglia instead of recruited macrophages are primarily responsible for photoreceptor death [147]. Findings highlight myeloid activation as both a cause and a response to photoreceptor loss, and support targeting myeloid cell infiltration and activation in therapeutic strategies in RP treatment.

In the *RhoP23H/wt* mouse model of autosomal dominant RP, O'Koren and Saban found age-related accumulation of IBA1-positive myeloid cells in the subretinal space [26]. Cx3cr1-positive cells in the subretinal space adherent to the RPE were shown to be microglia using lineage tracing. Further, microglia depletion resulted in decreased number of IBA1-positive cells in the subretinal space [26]. Following photoreceptor damage, macrophages did not occupy the subretinal space even after microglia depletion, suggesting that recruited monocytes and resident microglia occupy different niches in response to disease. Interestingly, the authors also showed that different sub-populations of microglia contributed to different steps of visual transduction, with ablation of all retinal microglia resulting in reduction of both photoreceptor and bipolar signaling on ERG testing [148]. In addition, subretinal microglia was shown to improve photoreceptor-RPE interdigitation, thereby functioning in a protective capacity in this model of RP [26]. These findings provide evidence that activated microglia can also function in neuroprotective in addition to the traditionally-recognized cyto-destructive roles. Selective immunomodulation will be an important consideration in the development of therapies to prevent and treat RP-like retinal degeneration.

Posterior Uveitis

Inflammation of the posterior uveal tract can also involve the retina and the optic nerve, and are otherwise referred to as choroiditis or chorioretinitis depending on the level of affected tissues [149]. Posterior uveitis has both infectious and non-infectious/autoimmune causes. Autoimmune uveitis is a vision-threatening ocular inflammatory condition in which the retina and uveal tissues are targeted by autoreactive immune activation, and is often associated with systemic manifestations [150]. Autoimmune uveitis include some of the most common causes of posterior inflammation, including Behçet's disease, sarcoidosis, and Vogt-Koyanagi-Harada disease [151, 152]. Animal models of posterior uveitis have recently highlighted the dynamic function of myeloid cells in this disease.

Microglia have been shown to be essential for inducing the retinal inflammatory response in experimental autoimmune uveitis (EAU) [150]. EAU is a T cell-mediated mouse model of chorioretinitis whereby inflammation is induced by immunization with retinal antigens [153]. Microglia ablation prior to the development of EAU was sufficient to block the inflammatory response [150]. When microglia were depleted after inflammation had already begun, however, disease timeline and severity remained unchanged. EAU mice with locally inducible microglia ablation had significantly fewer adherent leukocytes at retinal vessels compared to control mice, suggesting that microglia recruited leukocytes by promoting vascular cell adherence and extravasation at the BRB, and mediate the entry of circulating leukocytes into the retina [150]. Following microglia depletion, circulating immune cells were therefore unable to penetrate the BRB.

In vivo fundus imaging in an animal model of posterior uveitis has revealed the relative contribution and migration pattern of macrophages in this disease, further elucidating their function in inflammatory retinal conditions. Cx3cr1+ and CD11c+ myeloid cells have been shown to accumulate around the ONH and retinal vessels 2 weeks after immunization in EAU [154]. Bremer and colleagues used *in vivo* two-photon microscopy to track the motility pattern of immune cells, and found that CD4+ T cells and LysM+ peripheral phagocytes radially migrated within the retina away from the ONH following immunization [155]. CD4+ T cells were shown to arrive in the retina prior to phagocytes, with migration away from the ONH. Taken together, these results suggest that peripheral macrophages may be attracted by T cells and subsequently use the optic nerve as a conduit for entering the retina.

Breakdown of the BRB is strongly implicated in the pathogenesis of posterior uveitis [150, 155, 156]. In addition to leukocyte extravasation, BRB breakdown also allows fluid and protein leakage into the retina to cause uveitic macular edema, an often refractory condition impacting visual acuity in more than 40% of patients [157–159]. In EAU, CD4+ T cells and macrophage/microglia have been shown in the retina both perivascularly and in tertiary lymphoid clusters [154, 160]. When EAU mice were given an inhibitor to integrin VLA-4, an adhesion molecule implicated in CD4+ T cell recruitment, fewer Th17+ subset of T cells and Ly6C+ monocyte/macrophages crossed the BRB, resulting in reduced clinical disease severity [153]. Repeated exposure to systemic LPS also led to BRB breakdown, retinal microglia proliferation and activation, and macrophage infiltration [161]. Treatment with the colony-stimulating factor 1 receptor inhibitor PLX5622 resulted in microglia depletion and normalization of cytokine levels following LPS challenge, preserving BRB integrity [161]. Results suggest that microglia activation may lead to increased vascular permeability to facilitate infiltration of immune cells into the retina and exacerbate retinal inflammation in posterior uveitis.

Ocular Manifestations of Neurodegenerative Processes

The retina and brain share the same embryological origin as extensions from the neural tube [162]. The retina responds similarly to the brain following many forms of cellular injury, and certain central neurodegenerative processes can be detected, and more importantly, directly visualized in the retina. We will review recent findings describing the ocular manifestations

of Alzheimer's and Parkinson's diseases and highlight the role myeloid cells play in disease pathogenesis.

Alzheimer's Disease

Alzheimer's disease (AD) is the leading cause of dementia worldwide [163]. It is associated with a cumulative economic burden of $305 billion in 2020, and predicted to surpass $1 trillion by 2050, making it the most costly disease in the United States [164]. AD is a group of heterogeneous neurodegenerative processes characterized by early hippocampal involvement impacting memory and executive function [165–167]. Definitive diagnosis of AD occurs postmortem following demonstration of extracellular amyloid-β (Aβ) plaques cleaved from amyloid precursor protein and intracellular accumulation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau [168]. Few diagnostic biomarkers of AD currently exist, and there is a critical need to identify reliable biomarkers earlier in the disease process [169].

Visual perception and abnormalities of the retina have been investigated to provide diagnostic clues in AD. AD pathology may manifest in visual field defects, changes in contrast sensitivity and visual acuity, and impaired color recognition [170–177]. RGC degeneration, Aβ deposition with local myeloid and astrocyte infiltration, hyperphosphorylated tau, and optic nerve axon loss have all been described in AD eyes [178–183]. Retinal structural alterations reported in patients with AD include thinning of the inner retina on optical coherence tomography (OCT), specifically the RNFL and the ganglion cell-inner plexiform layer [184–187]. Thinning of the RNFL in AD is associated with decreased retinal function, as evidenced by reduced amplitude on pattern ERG [188]. Circadian dysfunction is a hallmark of AD, and loss of melanopsin RGCs, a retinal cell type associated with circadian rhythm regulation, has been associated with Aβ deposition in postmortem AD retinas [181]. While these findings suggest RNFL and GCL degeneration are potential ocular biomarkers for AD, still other studies failed to demonstrate a strong association between AD and RNFL thinning, challenging the utility of inner retinal degeneration as a reliable biomarker for AD [189–191]. In contrast, another related neurodegenerative disease, frontotemporal dementia, has been associated with thinning of the photoreceptor layer, which may prove helpful as a diagnostic discriminator between AD and frontotemporal dementia [192].

Studies in human retina and mouse models of AD demonstrate microglia/macrophage activation. Retinal microglia/macrophages in a mouse model of AD showed a ramified, resting phenotype before symptom onset [193]. Following symptom onset, however, myeloid cells transitioned to an activated, amoeboid morphology in the retina. The same group also demonstrated histological evidence of neurotoxic astrocytes and microglia activation in the retinas of AD patients [194]. Co-localization of microglia/macrophages with tau oligomers has been demonstrated in the retinas of a mouse model of AD and in the brains of human AD patients, suggesting that tau oligomers are pro-inflammatory in AD [195]. Aβ deposits were also shown to accumulate with age in the retinas of a mouse model of AD, and correlated with increased expression of the macrophage chemokine MCP-1 and microglia proliferation in the GCL [196]. Microglial recognition and phagocytosis of Aβ

plaques, and subsequent formation of dense-core Aβ plaques possibly as a way to confine toxic Aβ oligomers, has been shown to be mediated by the TAM receptor tyrosine kinases Axl and Mer [35]. Aβ deposition disrupted retinal function in a mouse model of AD and was associated with increased retinal microglia activity [197].

Evidence of microglia-mediated neuroprotection is plentiful in the AD brain if comparatively lacking in the AD retina. Mutations affecting the microglia gene triggering receptor expressed on myeloid cells 2 (TREM2) have been associated with decreased sensing, compaction, and phagocytosis of Aβ plaques by microglia in the brains of mice and humans with AD [198]. The protective barrier effect of microglia is further demonstrated by the finding that Aβ plaque regions not enveloped by microglia are associated with more severe axonal damage [199]. A subtype of microglia associated with neurodegenerative diseases (DAM) may be activated for plaque clearance to possibly restrict AD progression through both TREM2-dependent and independent mechanisms [200]. These findings link plaque depositions characteristic of AD with an increase in focal, specific microglia/macrophage reactivity, potentially as an inducible mechanism to mitigate the accumulation of toxic protein aggregates.

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder following AD [201]. PD is characterized by the progressive loss of dopaminergic neurons in the substantia nigra and nerve terminals of the striatum [202]. Ocular disturbances associated with PD include blepharospasm, blepharitis/dry eye, visual hallucinations, as well as impaired acuity and decreased contrast sensitivity, motion perception and color vision [203–205]. The depletion of retinal dopamine may play a causative role in many of the visual processing impairments observed in PD [206, 207]. Structural changes in PD eyes include decreased small vessel and perfusion density in both the retina and the choroid [208]. Retinal and specifically, RGC, dysfunction have been demonstrated using ERG early in the disease process, and was found to correlate with disease severity [209, 210].

Lewy bodies are intracytoplasmic aggregates found in the neurons of patients with PD, and are comprised mainly of α-synuclein [211, 212]. In the normal retina, α-synuclein is found in photoreceptor outer segments and axons, bipolar, and amacrine cells [213]. In patients with PD, aggregates of α-synuclein localized to the inner retina, including the GCL, IPL, and INL [214]. α-synuclein has been shown to induce the activation of microglia [215], initiating a pro-inflammatory cascade that leads to accumulation of activated glial cells in the substantia nigra [215, 216]. Accordingly, increased reactivity of microglia/macrophages, astrocytes, and Müller cells were shown to first occur in the inner retina of a mouse model of MPTP-induced PD [217]. A transgenic mouse model overexpressing human α-synuclein also demonstrated an association between α-synuclein deposition, Müller and microglia/macrophage activation, and photoreceptor death within the retina [218]. Human postmortem tissue from AD and PD patients demonstrated the presence of reactive, neurotoxic astrocytes, which were shown to be induced by activated microglia [109].

Several mechanisms for myeloid cell activation in PD have been described. In one, α-synuclein deposits are identified by cell surface TLRs, resulting in microglia activation and secretion of pro-inflammatory cytokines IL-1β, IL-6 and IL-18 by astrocytes [219–222]. Specifically, α-synuclein has been shown to stimulate the NF-κB pathway downstream of microglia activation [223]. In another, an *in vitro* model of PD showed that α-synuclein phagocytosis is mediated by Fcγ receptors on microglia, and when these receptors are genetically ablated, NF-κB mediated pro-inflammatory signaling was reduced [215].

The increasing characterization of myeloid cell-mediated pro-inflammatory pathways in the pathogenesis of neurodegenerative conditions like AD and PD has led to the development novel therapeutics, a class of which will be discussed in the following section.

GLP-1R Agonists as Disease Modifying Agents in Neurodegenerative Diseases

In light of the prominent role neuroinflammation plays in AD and PD pathogenesis, treatments that target inflammatory pathways are increasingly sought after to curtail neurodegenerative processes. The incretin hormone glucagon-like peptide 1 (GLP-1) is best known for its role in regulating glucose homeostasis, weight, and satiety by acting through the GLP-1R. Agents that activate the GLP-1R, such as GLP-1R agonists and dipeptidyl peptidase 4 (DPP-IV) inhibitors, constitute popular classes of therapy for type 2 diabetes, which can cause retinopathy and is a risk factor for glaucoma [224–226]. In mice with diet-induced obesity and insulin resistance, treatment with the GLP-1R agonist liraglutide improved cognitive function and hippocampal synaptic plasticity [227]. In human patients, long-term treatment with the GLP-1R agonist dulaglutide was associated with moderate improvements on cognitive testing in patients with type 2 diabetes [228]. The most common side effect of GLP-1R agonists is gastrointestinal symptoms, which are often self-limiting and rarely results in discontinuation of therapy [229]. Additional benefits include weight-loss and long-term cardiovascular protection associated with decreased mortality in patients with diabetes [230–233].

GLP-1R activation enhances protein synthesis, cellular proliferation, and mitochondrial biogenesis, while inhibiting apoptosis, inflammation, and protein aggregation, jointly leading to improved cellular survival [234]. GLP-1R agonists readily cross the blood-brain barrier, and GLP-1R is expressed in neurons, microglia, and astrocytes of the CNS [235–240]. In the eye, GLP-1R expression has been localized to the GCL, INL, and ONL of the mouse retina [241, 242]. The specific retinal cell types mediating the effects of GLP-1R agonists in the eye, however, are not known.

Over a decade of preclinical studies have demonstrated the potential of GLP-1R agonists for improving neuronal survival and function in neurodegenerative diseases. GLP-1 reduced the level of Aβ in the brain of diabetic mice and decreased the level of amyloid precursor protein in cultured neuronal cells, while GLP-1 and the GLP-1R agonist exendin-4 protected cultured hippocampal neurons from Aβ or iron-induced death [243]. Exendin-4 has also been shown to reduced brain levels of Aβ and amyloid precursor proteins in mouse models of AD [244]. GLP-1R agonists Val(8)GLP-1 and liraglutide effectively prevented

Aβ-induced deficits in spatial learning and memory in rats [245, 246]. Val(8)GLP-1 was also shown to improve both pathological and age-related synaptic degeneration in a mouse model of AD, and to enhance dentate gyrus neurogenesis in wild type mice [247, 248]. Liraglutide similarly improved memory, synaptogenesis, and neurogenesis in a mouse model of AD [249].

Randomized clinical trials assessing GLP-1R agonists in patients with AD demonstrated mixed results. In a double-blind pilot, 38 patients with AD were randomized to either liraglutide treatment or placebo [250]. While Aβ load was no different between groups after 6 months, liraglutide was shown to halt the decline of glucose metabolism on PET imaging [250]. The follow-up randomized, double-blinded phase IIb clinical trial of liraglutide versus placebo (the ELAD study), failed to show a treatment effect in its primary endpoint of cerebral glucose metabolism after 12 months [251, 252]. The study did find a positive difference in the secondary endpoint of a measure of cognitive function. A longer-duration clinical trial with a greater number of subjects per treatment group may be necessary to definitively assess for protective effects of GLP-1R agonists in AD.

In preclinical models of PD, exendin-4 increased the number of neural stem/progenitor cells isolated from the subventricular zone *in vitro*, normalized dopamine balance and increased the number of cells expressing markers of dopaminergic neurons following 6-hydroxydopamine injury *in vivo* [253]. Exendin-4 also arrested the progression of nigral lesions following 6-hydroxydopamine and LPS injections in rats [254]. Liraglutide and lixisenatide, both GLP-1R agonists with longer half-lives than exendin-4, improved measures of motor impairment following MPTP-induced neuro-injury [255]. In human PD, a small 45-patient single-blind trial evaluated the effect of exenatide, a synthetic version of exendin-4, versus controls and found improvements in off-medication motor and cognitive measures after 12 months of treatment [256]. Subsequently, a double-blind trial with 62 patients evaluated the effect of exenatide versus placebo in PD [257]. Following 12 months of treatment and a wash-out period of 3 months, patients given exenatide at a dose approved for diabetes treatment scored higher on the motor subscale of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) compared to placebo. This study also showed that exenatide readily crossed the blood-brain barrier and was detectable in human cerebral spinal fluid at a concentration comparable to those reported in preclinical animal models.

Mechanistically speaking, evidence suggests that GLP-1R agonists slow the progression of neurodegeneration in AD and PD by inhibiting the release of pro-inflammatory cytokines, macrophage/microglia activation, and the formation of neurotoxic astrocytes [234]. Exenatide was shown to inhibit the streptozocin-induced increase in pro-inflammatory cytokine TNF-α in a rat model of AD [258]. In the MPTP-mouse model of PD, exendin-4 prevented microglia activation and expression of pro-inflammatory cytokines MMP-3, IL-1β and TNF-α in the substantia nigra and striatum, rescued dopaminergic neurons while maintaining dopamine levels, and improved motor function [259, 260]. In cultured dopaminergic neurons, GLP-1 and exendin-4 conferred neuroprotection following 6-hydroxydopamine administration in a GLP-1R-dependent manner [260]. Exendin-4 has also been shown to inhibit monocyte/macrophage adhesion to arterial walls prior to

extravasation, mediated by a reduction in TNF-α expression [261]. Following exendin-4 treatment, expression of NF-κB, a key mediator of activated myeloid cells, was shown to be decreased in rats with high-fat diet-induced obesity [262]. Finally, liraglutide has been shown to reduce TNF-α production by monocytes, and halved microglia activation in a mouse model of AD [249, 263]

NLY01 is a pegylated form of exendin-4 with a long half-life in both non-human primates (88 hours) and mice (38 hours), where it penetrates the blood-brain barrier resulting in elevated concentrations in the CNS [264]. NLY01 has been shown to act on microglial GLP-1R to dampen neuroinflammatory signaling, thereby reducing dopaminergic cell death in a mouse model of PD [264]. Recently, NLY01 was also shown to block microglial-induced neurotoxic astrocyte transformation, resulting in preservation of spatial learning and memory in mouse models of AD [265]. Ongoing phase IIb trials are evaluating whether NLY01 treatment can manifest meaningful clinical benefits in patients with early, untreated PD and AD [266].

Following microbead-induced IOP elevation, our group showed that treatment with NLY01 reduced expression of IL-1α, TNF-α, and C1q by microglia/macrophages in the retina, decreased neurotoxic astrocyte activation, and rescued RGCs [75] (Figure 3). Experimentation by our group is underway to examine the mechanisms driving GLP-1R agonist-induced RGC rescue. In a separate retrospective database study, we showed that treatment with GLP-1R agonists halved the risk for a new diagnosis of glaucoma among diabetic patients [267]. A larger scale study is necessary to examine whether GLP-1R agonists alter the risk of glaucoma progression.

Conclusions

Underlying the dissection of ocular and neurological diseases in this review is the role of inflammation in chronic diseases affecting vision. Glaucoma, AMD, RP, posterior uveitis, AD, and PD exhibit similar inflammatory changes, marked by microglia and macrophage activation and migration. The leading cause of irreversible blindness worldwide, glaucoma, is associated with activated microglia and recruited macrophages [68, 69]. In AMD, pro-inflammatory cytokines produced by macrophages and subretinal microglia may worsen subretinal fibrosis [118, 132]. Inflammation in RP is mediated by microglia as opposed to macrophages; these microglia phagocytose both stressed and dying photoreceptors [119]. Experimental models of posterior uveitis have implicated microglia in the induction of an autoimmune response and the breakdown of the BRB [150, 161]. In AD, the presence of hypertrophic retinal microglia and perivascular macrophages implicate increased myeloid reactivity in pathogenesis [193, 194]. Activated microglia have also been shown to induce neurotoxic reactive astrocytes in AD and PD [109, 265]. Further work is needed to identify the mechanisms that can be pharmacologically modulated to tip the macrophage and microglia balance from a neurotoxic to a neuroprotective milieu in the retina. Recent findings suggest that one such novel strategy may involve GLP-1R agonists.

Interestingly, several common themes arise from the comparison of these diseases. Macrophage infiltration, either from a compromised BRB or from the ONH, which serves

as a reservoir for myeloid cells, plays an important inciting role in ocular diseases such as glaucoma, AMD, and posterior uveitis [73, 74, 119, 120, 128, 132, 153–155, 160, 268]. Corroboratively, elevated levels of MCP-1, a major chemokine in macrophage recruitment, is associated with pathogenesis and disease progression in animal models of glaucoma, AMD, RP, and AD [72, 118, 127, 128, 140, 141, 147, 161, 196]. Further, upregulation of pro-inflammatory cytokines including TNF-α, the IL-1 family, and complement constitute a common pathway through which activated myeloid cells exert their downstream effects, possibly by promoting transformation of astrocytes into neurotoxic states.

The process of unpacking risk factors in these diseases has identified several pathways that can be targeted by selective therapeutics. In AMD, the 10q26 minor haplotype induced the overexpression of the serine peptidase HTRA1, which prevented the clearance of retinal monocytes in an osteopontin-dependent fashion. Inhibition of osteopontin reversed this effect and reduced retinal inflammation, suggesting that inhibition of monocyte activation and cytokine release may also provide a therapeutic benefit in AMD [137]. In AD, microglia exert a neuroprotective effect through Aβ plaque clearance, mediated by both TREM2-dependent and independent pathways [198–200]. In glaucoma, PD, and possibly AD, the pro-inflammatory milieu appears to be incited, in part, through the Fas receptor, TNF-α, the IL-1 family of cytokines, and complement activation [84–86, 89, 91, 92, 94, 98–100, 107, 215, 216, 219–223]. Inhibition of some of these pathways with GLP-1R agonists decreased the activation of neurotoxic astrocytes by microglia/macrophages, and rescues neurons in animal models of glaucoma, PD, and AD [75, 249, 258–265]. The efficacy of GLP-1R agonists as a disease modifying agent in these neurodegenerative diseases require validation in human studies, which are largely ongoing [75, 243–251, 253–259, 264, 266]. These clinical trials may help to identify effective treatments for multiple progressive neurodegenerative diseases and lessen the significant burden placed on patients, caregivers and health system resources.

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Abbreviations:

AD	Alzheimer’s disease
AMD	age-related macular degeneration
BRB	blood-retina barrier
C1q	complement component 1q
CNS	central nervous system
ERG	electroretinography

GLP-1R	glucagon-like peptide-1 receptor
IL	interleukin
IOP	intraocular pressure
MCP-1	macrophage chemoattractant protein-1
NF-κB	nuclear factor-kappa B
ONH	optic nerve head
PD	Parkinson's disease
RGC	retinal ganglion cell
RP	retinitis pigmentosa
RPE	retinal pigment epithelium
TLR	Toll-like receptor
TNF-α	tumor necrosis factor α

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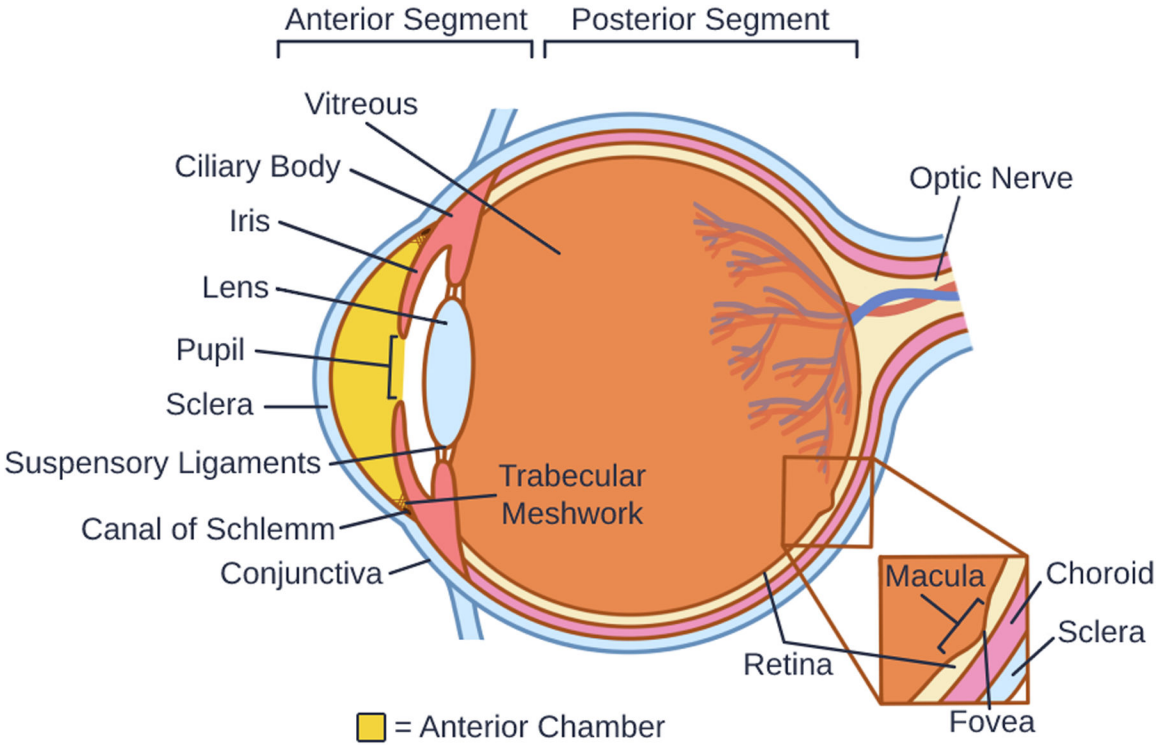

Figure 1.
Anatomy of the Eye

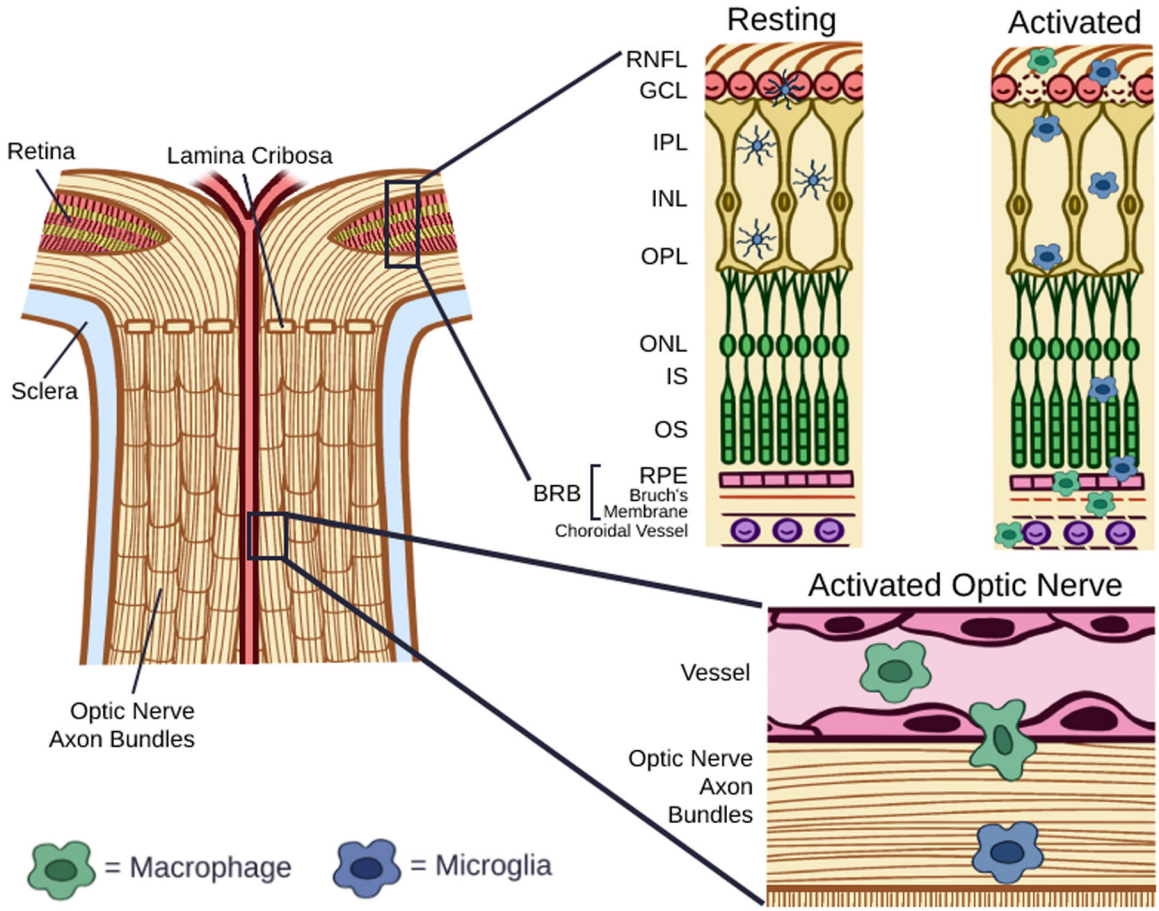

Figure 2. Resting and Activated Myeloid Cells in the Retina and Optic Nerve

In the resting state, microglia have a dendritic morphology and localize to the ganglion cell layer (GCL), inner plexiform layer (IPL), and outer plexiform layer (OPL), and macrophages are largely absent in the retina. Following activation, microglia take on an enlarged, amoeboid shape and migrate to the subretinal space above the RPE. Within the retina, activated microglia release pro-inflammatory cytokines, including interleukin-1α (IL-1α), tumor necrosis factor α (TNF-α), complement component 1q (C1q), reactive oxygen species (ROS), and nitric oxide (NO), and are associated with the death of both retinal ganglion cells and photoreceptors. Recruited macrophages have been shown to infiltrate the retina via the optic nerve.

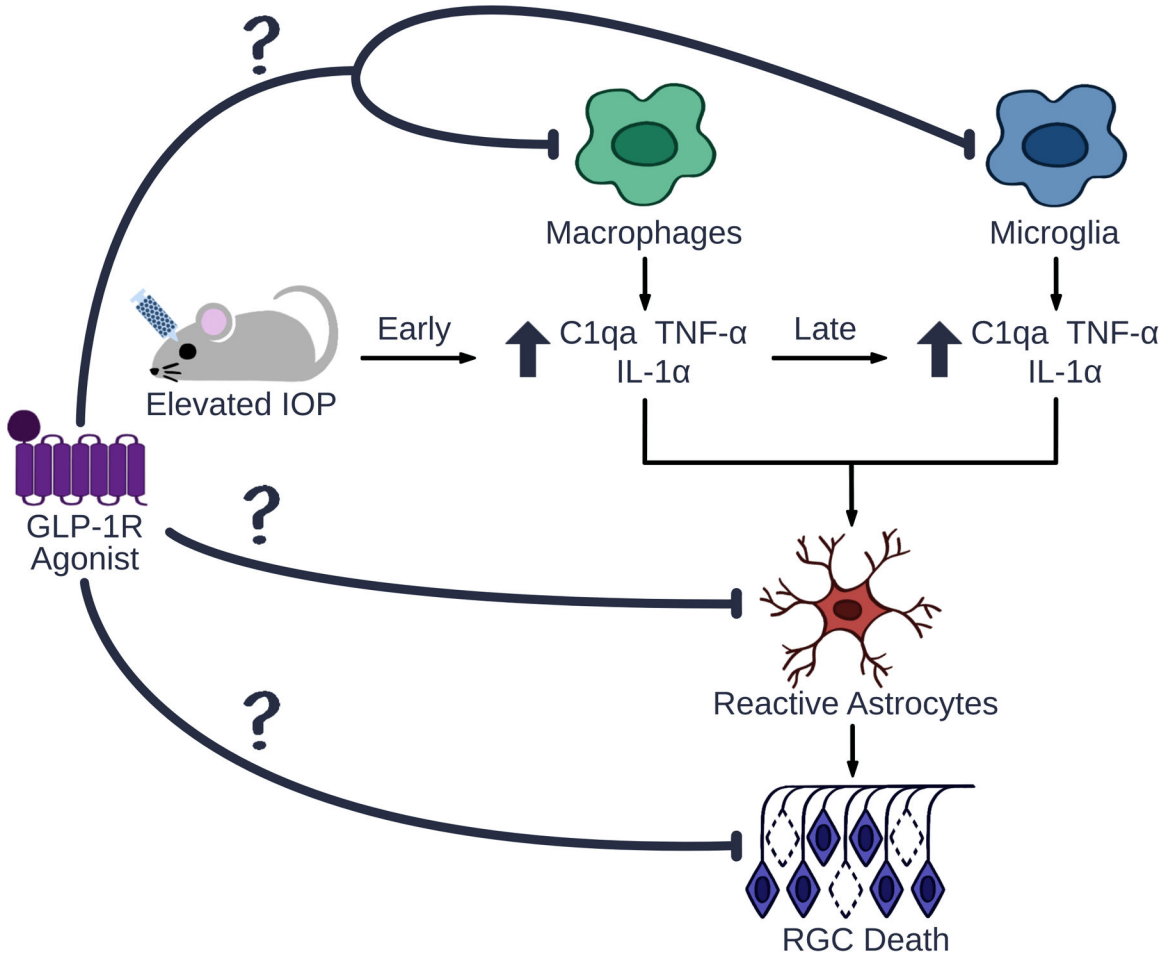

Figure 3. Glucagon-Like Peptide-1 Receptor (GLP-1R) Agonists Decrease Retinal Inflammation

Elevated intraocular pressure (IOP) increases production of the pro-inflammatory cytokines interleukin-1α (IL-1α), tumor necrosis factor α (TNF-α), and complement component 1q (C1q) by activated microglia and recruited macrophages. These cytokines activate neurotoxic astrocytes, and results in retinal ganglion cell (RGC) death. Our lab has shown that the GLP-1R agonist NLY01 inhibits activation of microglia, macrophages, and astrocytes, and prevents RGC death in eyes with microbead-induced IOP elevation. However, the mechanism behind NLY01-induced RGC rescue, including the cell types mediating its protective effects as well as the relative contribution of macrophages versus microglia, has not been examined.