Inflammation and retinal degenerative diseases

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Introduction

Vision is an ability that depends on the precise structure and functioning of the retina. Any kind of stress or injury can disrupt the retinal architecture and leads to vision impairment, vision loss, and blindness. Immune system and immune response function maintain homeostasis in the microenvironment. Several genetic, metabolic, and environmental factors may alter retinal homeostasis, and these events may initiate various inflammatory cascades. The prolonged inflammatory state may contribute to the initiation and development of retinal disorders such as glaucoma, age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa, which pose a threat to vision. In the current review, we attempted to provide sufficient evidence on the role of inflammation in these retinal disorders. Moreover, this review paves the way to focus on therapeutic targets of the disease, which are found to be promising.

Key Words: age-related macular degeneration; diabetic retinopathy; glaucoma; retina; retinal degeneration; retinitis pigmentosa

Factors Responsible for Inflammation in Retinal Degenerative Diseases

Based on the role of inflammation and the immune response system in retinal degeneration, an array of genetic and non-genetic factors is involved at different phases of the disease. The association of genetic factors with several retinal disorders is well-documented (Singh and Tyagi, 2018). Genetic factors include both pro-inflammatory and anti-inflammatory genes that function in neuroprotection. During the progression of a disease phenotype, several stimuli activate pro-inflammatory genes that are neutralized by anti-inflammatory responses (Lively and Schlicter, 2018). However, the prolonged inflammatory state creates an imbalance in these factors, thereby contributing to the development of retinal disorders. Genetic factors are not only regulated at the transcriptional level but also at the translational level to maintain homeostasis. Classically, these disorders were associated with apoptosis only however, a timely shift on other mechanisms such as necroptosis and pyroptosis has been witnessed (Olivares-González et al., 2021). Recently, the role of NLRP3 inflammasome in retinal degeneration has emerged. Several pattern recognition receptors such as TLR, NLR, and RIG-I-like receptors are present on the surface of microglial cells and macrophages. These pattern recognition receptors recognize various PAMPs and DAMPs, leading to the activation of inflammasome components in microglia via the TLR4-MYD88-NF-kappaB pathway (Haines et al., 2005). NLRP3 inflammasome gets activated by augmenting the expression of inflammasome components such as NLRP3, ASC, and caspase1 followed by maturation and secretion of caspase-1-dependent pro-inflammatory cytokines [interleukin (IL)-1 beta and IL-18]. These pro-inflammatory cytokines are the prime regulators of the innate immune system. The activation of the inflammasome is followed by pyroptosis, a form of caspase-1 mediated cell death (Chen et al., 2017). The inflammatory cells such as microglia and infiltrating macrophages are involved in the innate immune response system of degenerating visual cells. Evidence in the literature reported the elevated expression of inflammatory markers in AMD, diabetic retinopathy, retinitis pigmentosa, and glaucoma (Wooff et al., 2019).

Search Strategy and Selection Criteria

For this review, we conducted a PubMed/MEDLINE search from 2000 to 2022, using the keywords: retinal inflammation, retinal degeneration, inflammation, and retinal degeneration, and retinal regeneration. We also used Google search to look for the current contents and relevant articles related to the role of inflammation on retinal degeneration. We have excluded published papers with text languages other than English. We have read all the 84 articles and have not contacted any authors.

Factors Responsible for Inflammation in Retinal Degenerative Diseases

In the 19th century, biomedical investigators explored and unfolded different spheres of inflammatory processes. Inflammation comprises a cascade of cellular and molecular events, which are involved in simple wound healing to tissue repair. If this cascade fails, inflammation worsens the condition gradually with time and causes disease (Bennett et al., 2018). Degenerative retinal diseases are a group of heterogeneous and multi-etiological disorders that cause vision impairment, for example, glaucoma, age-related macular degeneration (AMD), retinitis pigmentosa (RP), diabetic retinopathy (DR), and many other similar conditions. All the disorders have different etiological aspects with respect to inherited, acquired, or systemic disease. However, progressive death of retinal pigment epithelium or photoreceptor cells is the hallmark of these degenerative retinal diseases (Schwartz et al., 2016). The process initiates with the impairment of retina integrity followed by disintegration of retinal cell lining and death of photoreceptors. These photoreceptors or light-sensitive cells send visual signals and input to the brain. The disintegration of retinal cell lining and photoreceptor death results in visual deterioration, blindness, or complete vision loss (Holán et al., 2021). In the present literature, we reviewed the factors that lead to retinal inflammation and the role of inflammation in retinal degenerative disease particularly, glaucoma, age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa.

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The role of epigenetic factors in transcriptional factors (nuclear factor-kB and forkhead box O transcription factor) regulation in retinal diseases is poorly understood. In the case of tissue injury, genes encoding for histone deacetylases and histone acetyltransferases contribute to chronic inflammation via activated microglia influx (Shukla and Tekwani, 2020). Lastly, microRNA has also been shown to target the expression of the N-methyl-D-aspartate receptor in hippocampal neurons by upregulating mir-155 (Pasco et al., 2020). Future studies are needed to identify the promising genes that are involved in the pathogenesis of retinal disorders. In addition to genetic factors, non-genetic factors such as environmental risk factors may trigger the initiation of multifactorial retinal diseases. Various environmental risk factors such as sunlight exposure, smoking, age, body mass index, alcohol consumption, diabetes, and physical activity contribute to retinal disorders and they are modifiable except for age (Thornton et al., 2005). Lifestyle and behavioral habits reduce the progression of the disease or provide protection. The Beaver Dam Eye Study has reported diabetes as an associative factor of refractive errors (Bomotti et al., 2018) that can be maintained by lifestyle modifications. Several studies have suggested that regular physical activity can prevent AMD progression. A prevalence rate of 52.37% has been reported in subjects aged 60 years and above in epidemiological studies on retinal disorders. Furthermore, smoking is associated with a reduction in the concentration of macular pigment by 50% due to arachidonic acid formation. In a study, Espinosa et al. (2006) observed that hydroquinone in cigarette tar causes retinal lesion formation in mice models. The non-genetic factors are only considered risk factors that may or may not be involved in the pathophysiology of the disease.

Glaucoma
Glaucoma is a leading cause of blindness in people of age 60 years and above. The progressive loss of retinal ganglion cells (RGC) as well as their axons in the optic nerve has been reported in glaucoma results in gradual loss of the visual field. Glaucoma is of three types: open-angle glaucoma, angle-closure glaucoma, and normal-tension glaucoma. The open-angle glaucoma is further categorized as high-pressure and low-pressure glaucoma (Nakazawa et al., 2006). The primary open-angle glaucoma is associated with high intraocular pressure (IOP) without any structural abnormality. In past, IOP was considered a diagnostic feature of glaucoma, but now it is regarded as an important risk factor of glaucoma. Substantial evidence in the literature has shown that a person with a normal level of IOP can also develop glaucoma. Elevated intracranial IOP also plays a pivotal role in the progression of glaucoma. RGC loss may or may not be associated with IOP levels contributing to the glaucoma pathology. Conversely, low-pressure glaucoma is known as normal-tension glaucoma (Leung and Tham, 2022). Various animal models of RGC death have been developed, but the investigation on pathophysiological changes of glaucomatous damage are limited due to the long delay in RGC death. However, the models of RGC death in primary open-angle glaucoma have shown that inflammation is directly linked with increased RGC death (Figure 1B, Table 1; Wang et al., 2008).

Inflammation occurs as a result of ischemic injury and is characterized by the secretion of a series of inflammatory cytokines, chemokines, and mediators (hypoxia-inducible factor-1α, C-reactive protein, endothelin-1, vascular endothelial growth factor, tumor necrosis factor-alpha and serum amyloid A). Clinical and experimental studies have shown that these inflammatory cytokines are upregulated in glaucoma (Table 1). The infiltration of inflammatory cells into the ischemic tissue via vascular endothelial cells promotes glaucoma development (Wareham and Calkins, 2010). These cells also promote the invaginates and mediates the crossing of molecular components into and out of the retina. BRB impairment is correlated with aging, and causes vascular dysfunction, molecular alteration, and might reduce the ability to supply blood to the optic nerve head. Notably, the inflammatory mediators decrease the efficacy of BRB. These events suggest that BRB participates in the inflammatory response in glaucoma pathophysioloogy with respect to RGC loss (Zeng and Shi, 2018).

The inflammatory mediators such as IL-1β, IL-6, and tumor necrosis factor-alpha, induce the expression of matrix metalloproteinases (MMPs) and stimulate fibroblasts for tissue remodeling. MMPs such as MMP-3, MMP-9, and collagenase are involved in ECM degradation by the increase of aqueous humor outflow. In a study, Chintala et al. (2002) demonstrated the role of MMP-9 on RGC in MMP-9 knock-out mice and observed that MMP-9 promotes RGC loss and death. This study further explains the role of the two MMPs in RGC-mediated RGC death. Among these, oxidative stress and hypoxia-inducible factor-1α alpha activation overstimulated the N-methyl-D-aspartate receptor, thus resulting in elevated MMP-9 expression causing RGC death. On the other hand, the inflammatory cytokines such as TNF-α and IL-1β are associated with increased expression of MMPs. The elevated expression of MMPs increases the production of collagen type IV by lamina cribrosa cells (Akhter et al., 2013). Overall, inflammation or inflammatory mediators result in RGC death, thereby promoting glaucoma.

Age-Related Macular Degeneration
AMD is a common eye disease, which is responsible for causing irreversible and severe vision loss. AMD, as the name suggests, is related to aging and mostly happens in older age. The appearance of extracellular deposits called drusen in the macular region is the clinical hallmark of AMD. The incidence of AMD gradually increases with age, with an average onset at 60 years (Colijn et al., 2017). A systematic review and meta-analysis carried out by Wong et al. (2014) estimated 288 million cases of AMD by 2040. AMD is of two types: dry and wet (neovascular) AMD. Dry AMD is characterized by an increase in subretinal drusen appearance, thickened Bruch's membrane, and photoreceptor degeneration (Kanda et al., 2008; Ambati et al., 2013; Mitchell et al., 2013). The dry AMD is also associated with non-neovascular, non-exudative, or atrophic AMD. Notably, there is no effective treatment for the dry form (Boyer et al., 2017). On the other hand, choroidal neovascularization is the characteristic feature of wet AMD resulting in severe vision impairment. Anti-vascular endothelial growth factor therapies, particularly ranibizumab and aflibercept are considered an effective clinical treatment for wet AMD. Other names of wet AMD are neovascular or exudative AMD. The data suggest that 90% of the AMD cases are of dry AMD, whereas 10% of cases are of the wet form (Ferrara and Adams, 2016; Handa et al., 2019).

The innate and adaptive immune responses play a central role in the pathophysiology of AMD. Primarily, oxidative stress is the prime trigger of degenerative diseases (Singh et al., 2019). Oxidized lipids and lipoproteins, mitochondrial dysfunction, and DNA damage contribute to “oxidation-specific epitopes” such as malondialdehyde and advanced glycation end products (AGE), which induce inflammatory response (Datta et al., 2017). Numerous studies have shown crosstalk between oxidative stress and inflammation in the etiology of AMD. Oxidative stress due to free radical accumulation in the retinal and choroidal tissues triggers an innate immune response. However, it is difficult for innate immunity to restore tissue homeostasis, thus a low-grade inflammation may trigger an adaptive immune response, described as “para-inflammation” (Dü et al., 2016).

In addition, the retinal pigment epithelium expresses a wide range of cytokine receptors including IL-1R, IL-4R, IL-6R, IL-10R, and interferon-α. Retinal pigment epithelium regulates these pro- and anti-inflammatory cytokines and thus, induces low-grade chronic inflammation. This low-grade chronic inflammation further promotes the pathogenesis of AMD. However, there are no stable trends in the secretion of these cytokines in the biological samples such as serum, plasma, vitreous, and aqueous membranes (Spindler et al., 2018; Cheng et al., 2019). Several in vitro and in vivo studies have supported the pivotal role of cytokines and chemokines in AMD (Table 2). Furthermore, the NLRP3 inflammasome gets activated in senescent and advanced DAMPs. These proteins are involved in the secretion and maturation of pro-cytokines, such as IL-1 beta and IL-18. These inflammatory cytokines then initiate an innate immune response to inflammation and play a decisive role in AMD pathogenesis (Wolf et al., 2019).

Leukocytes and immune cells play an active part in the inflammatory stage of AMD. During AMD development, innate immune cells such as macrophages, dendritic cells, and T-lymphocytes are recruited to the subretinal area. The resident microglial cells maintain normal function of the retina however, senescent microglia act slowly, resulting in the migration of cells in the subretinal area (Teliga et al., 2018). This cascade of events initiates complement and immune cell activity leading to the development of retinal neovascularization. In normal conditions, the basal levels of complement factors, such as complement factor H protein (Y402H),

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**Table 1** | Exemplary cytokines and mediators in glaucoma

| Cytokines or mediators | Experimental model | Inference | References |
|------------------------|-------------------|----------|------------|
| TGF-β2                 | Aqueous humor     | Associated with POAG | Aggarwal et al., 2015 |
| TNF-α and IL-2         | Human samples     | Associated with POAG | Alapati et al., 2021 |
| Renin, and Angiotensin II | Human plasma     | Elevated renin levels in normal tension glaucoma | Jeon et al., 2020 |
| ET-1, MMP-9, MCP-1, and hsCRP | Human samples   | Inflammatory role in normal tension glaucoma as global hypoxia stimulus | Lee et al., 2012 |
| VEGF and HIF-1α        | Brown Norway retired breeder rats | ET-1 in primary open-angle glaucoma and neovascular glaucoma, and VEGF in neovascular glaucoma patients | Ergorlue et al., 2010 |
| ET-1 and VEGF          | Human patients    | ET-1 in primary open-angle glaucoma and neovascular glaucoma, | Iwase et al., 2010 |
|                        |                   | and VEGF in neovascular glaucoma patients |          |

**Table 2** | Exemplary cytokines and mediators in AMD

| Cytokines or mediators | Experimental model | Inference | References |
|------------------------|-------------------|----------|------------|
| CRP                    | Human plasma      | Associated with normal tension glaucoma | Leibovitch et al., 2005 |
Diabetic Retinopathy

Diabetes mellitus is a metabolic disorder associated with several microvascular complications such as nephropathy, neuropathy, and DR. Among these complications, DR is the most common cause of visual impairment in adults aged 40 years or more. Based on visible vascular lesions, DR has been categorized into nonproliferative and proliferative forms. Nonproliferative is an early-stage DR, characterized by retinal hemorrhage, tortuosity, microaneurysms, and lipid exudates. On the other hand, proliferative is an advanced stage DR, characterized by the development of fragile aberrant vessels (Wang and Lo, 2018). Diabetic macular edema and breakdown of the blood-retinal barrier (BRB) are the underlying causes of vision loss in both levels of DR. Diabetic macular edema is the accumulation of fluid into the neural retina resulting in thickening and cystoid edema whereas BRB is associated with vascular leakage (Zhang et al., 2014).

Inflammation is a non-specific response to any stress or injury and includes a wide array of cellular and molecular mediators. The retinal immune cells not only provide structural support, but also maintain the retinal homeostasis by regulating the metabolism, cycling of photoreceptors or trophic factors, and phagocytosis of retinal tissue debris (Figure 2; Rubsam et al., 2018). Several DAMPs and PAMPs are perceived by pattern recognition receptors, such as TLRs, NLRs, and RIG-I-like receptors. On entry of a pathogen or stress, these receptors recognize patterns and activate the nuclear factor-kappa B signaling pathways. Nuclear factor-kappa B is a transcription factor that stimulates pro-inflammatory cytokines via inflammasome activation or other responses. The expression or activation of these cytokines are responsible for inflammation and result in dire pathological consequences if persist for long (Daruihich et al., 2018; Noma et al., 2021).

Chronic hyperglycemia leads to protein kinase C activation, polyols accumulation, advanced glycation end product formation, and free radical generation. These biochemical changes lead to the secretion of inflammatory cytokines, chemokines, and other mediators. Several cytokines including IL-1, IL-6, vascular endothelial growth factor, interferon gamma, intercellular adhesion molecule 1, and monocyte chemotactant protein-1 have been reported to be associated with DR (Table 3; Hang et al., 2014; Wu et al., 2017; Vujosevic and Toma, 2018).

The resident microglial cells expressing CD45 are involved in neuronal and vascular networks to prune and maintain the neurotrophic environment. However, the genetic variabilities and susceptibility regulate the microglial cells and promote DR. These cells sense advanced glycation end product accumulation, reactive oxygen species generation, and dyslipidemia. On chronic inflammation, these mediators can damage the retinal ganglion cells, thus causing retinal neuron dysfunction and cell death (Sun et al., 2014; Rashid et al., 2019).

Retinitis Pigmentosa

RP is a type of inherited retinal dystrophy that leads to loss of night vision or night blindness in adolescents, peripheral vision in adults, and concentric vision in the older population (Wooff et al., 2019). The prevalence of the disease is approximately 1:4000. RP is usually non-syndromic that is characterized by pigmented retinopathy, optic nerve pallor, progressive degeneration and ultimately death of photoreceptors, and nystagopia, thus resulting in severe vision loss. In addition, inflammatory vitreous cells, subcapsular cataracts, and macular edema were also associated with RP (McMenemy et al., 2019). Reports suggest that RP is a hereditary disease caused due to genetic mutation in 80 different genes. The primary cause of RP is a genetic mutation, and the secondary is chronic inflammation resulting in alterations in retinal homeostasis. Early evidence in the literature suggested apoptosis as the primary cause of rod cell death, however, other mechanisms like necrosis, necroptosis, pyroptosis, and parthanatos are also shown to be involved in rod cell death (Newton and Megaw, 2020). In Figure 3, we have shown that the retinal anatomy and physiology of mouse rd mutants are like that of RP patients, and rd mutants are used as a model to study the role of inflammation in RP (Veleri et al., 2015).

Table 1 | Exemplary cytokines and mediators in age-related macular degeneration

| Cytokines or mediators | Disease form | Experimental model | Inference | References |
|------------------------|-------------|--------------------|-----------|------------|
| VEGF, PDGF, IL-6, IL-8, IL-10, TNF-α, | Dry and wet | Serum samples of human patients | Elevated in AMD | Li et al., 2022 |
| TGF-β | Wet | Retinal microglia isolated from Cx3cr1−/−, Tgfb2−/− mice | regulates AMD and neovascularization | Ma et al., 2019 |
| Oxidative stress | Dry | VMD2-Cre;Sod2−/−/BaliCl/cI mice | RPE and photoreceptor damage | Brown et al., 2019 |
| IL-1 | Dry | Primary human RPE cells and ARPE-19 cells | Inflammasome activation & pyroptosis | Brandstetter et al., 2016 |
| IL-6 | Wet | Murine brain-derived capillary endothelial cell line (b-End3) and RAW264.7 cells | IL-6 receptor-mediated activation of STAT3 | Izumi-Nagai et al., 2007 |
| IL-4, IL-10 and IL-13 | Wet | RAW264.7 cell line, HDMECs and human PBMCs | IL-10 activates STAT3 signalling but not IL-4 or IL-13, leading to activation of macrophages and vascular proliferation | Nakamura et al., 2015 |
| IFN-β | Wet | Ifnar1–/–, litter-treated Cx3cr1(Cre) (ER)Ifnar1m8 mice | Ifnar signalling protect retinal immune homeostasis | Luckoff et al., 2016 |
| TGF-β | Dry and wet | Human fetal RPE cells, ARPE-19, and RPE cells | Increases BMP4 expression in CNV | Xu et al., 2011 |
| CRP and CHF | Wet | Donated human eyes | complement activation and tissue damage | Bhutlo et al., 2011 |

Table 2 | Exemplary cytokines and mediators in diabetic retinopathy

| Cytokines or mediators | Experimental model | Inference | References |
|------------------------|--------------------|-----------|------------|
| 26 cytokines (IL-6, IL-15, IL-16, VEGF, CRP, Saa, and ICAM1) | | Novel cytokines such as IL-15 and IL-16 found associated with proliferative DR | Loporchio et al., 2021 |
| NO, TNF-z, and hsCRP | | Suggestive factors of DR | Khaleo et al., 2020 |
| VEGF, TNF-z, and CRP | | Risk factors and biomarkers have possible relationship responsible for DR | Mathala et al., 2020 |
| Angiopoietin-like 3 and 4, CRP, VEGF, ICAM-1 | | Association of Angiopoietin-like 3 with the progression of DR | Yu et al., 2018 |
| IFN-γ, IL-1α/β3/10, RANTES & MCP-2 | | Considered as retinal neuroinflammatory biomarkers | Vujosevic and Toma, 2018 |
| IL-1β, IL-1α/β3/5/6/10, TNF-α, and VEGF | | Increased aequorin concentrations of cytokines with DR severity | Wu et al., 2017 |
| 19 cytokines (sCD40L, GM-CSF, IFN-α, IL-12/40, MCP-3, and VEGF) | | 16 cytokines are predictors of disease risk | Bromberg-White et al., 2010 |
| IL-1α/β/RA, IL-2 to IL-10, IL-13/15/17, IL-10, MCP-1/3, TGF-β, TNF-α, β/VEGF | | TNF-α is involved in the progression of DR stages. | Hang et al., 2014 |
| Fetal-A levels, VEGF, and CRP | | Serum samples of patients with T2DM | Zhou et al., 2016 |
| Chemerin, VEGF, and CRP | | Serum levels are directly associated with the severity of DR | Du et al., 2016 |

CRP: C-reactive protein; GM-CSF: granulocytoc-macrophage colony-stimulating factor; hsCRP: high-sensitivity C-reactive protein; ICAM1: intra-cellular adhesion molecule 1; IFN-γ: interferon gamma; IL-10: inducible protein-10; MCP-1: monocyte chemotactant protein-1; NO: nitric oxide; RANTES: regulated upon activation, normal T cell expressed and presumably secreted; SAA: serum amyloid A; sCD40L: soluble CD40-ligand; T2DM: type 2 diabetes mellitus; TGF-β: transforming growth factor beta; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor.
Figure 1 | Glaucoma and BRB disruption. BRB disruption results in imbalance in ET-1 concentrations in retina and choroid with leads to increased caspase-3 levels, and retinal ganglion cell death. Increased ET-1 enhances vessel contraction and reduces ocular perfusion, resulting in ischemia. Ischemia induces oxidative stress, which further promotes Müller and retinal ganglion cell death. Ischemia also upregulate TNF-α levels, which via binding to its receptor TNFR1 or COX-2 induction promote retinal ganglion cell death. TNF-α reduces Müller cell ability to uptake glutamate, resulting in glutamate excitotoxicity. BRB: Blood-retinal-barrier; COX-2: cyclooxygenase 2; ET-1: endothelin-1; NMDA receptor: N-methyl-D-aspartate receptor; RGC: retinal ganglion cells; TNFR1: tumor necrosis factor receptor 1; TNF-α: tumor necrosis factor-alpha. Reprinted from Vohra et al. (2013) with permission.

Figure 2 | Graphical presentation of retina showing interactions between endothelial cells, neurons, and glia with respect to inflammatory chemokines. The blood vessels and endothelial cells are shown in pink (9), leukocytes are shown in purple (5), muller glial cells are shown in green (7,8), microglia are shown in brown (2,3) and neurons are shown in blue (6a–c) color. The graphic also shows potassium homeostasis, glutamate metabolism and secretion of chemokines, interleukins, and trophic factors. AGES: Advanced glycation end products; bFGF: basic fibroblast growth factor; GDNF: glial cell line-derived neurotrophic factor; ICAM-1: intercellular adhesion molecule 1; IL-1 beta: interleukin-1 beta; IL-6: interleukin-6; MCP-1: monocyte chemoattractant protein 1; NGF: nerve growth factor; NO: nitric oxide; PEDF: pigment epithelium-derived factor; TNF-alpha: tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor. Reprinted from Rübsam et al. (2018).

Figure 3 | Elucidation of retinal photoreceptor degeneration in human retinitis pigmentosa patients and mouse rd1 mutants. (A, B) Human and mouse ocular fundus photographs, OCT and electroretinograms are shown. (i) The ocular fundus photographs and OCT images of an adult human and C57BL/6 mouse retina is shown. (ii) The ocular fundus photographs and OCT images of an adult patient with RP and 3-month-old rd1 mouse retina is shown. The black arrow in the human fundus images and the green line in the mouse fundus images depict the location of the OCT scan across the macula. The fundus images of patient with retinitis pigmentosa, shows pigmentary changes with atrophic areas indicating degeneration of photoreceptors. The OCT images of rd1 mouse retina shows marked thinning, reflecting loss of photoreceptors and degeneration. The fundus images of rd1 mouse retina shows atrophy, discoloration, and loss of blood vessels showing degenerating retina. The area in the red rectangle is magnified in the right image. (iii) Retinal functions in response to light stimulation were measured by ERG. In dark conditions (scotopic), a normal eye when exposed to dim or bright white light flash, either initiates a well-formed rod response (black wave, left panel) or a type of mixed rod/ cone response (black wave, left panel). In light conditions (photopic), single light stimulation of the eye leads to a cone response (black wave, lower left panel), and rapid light stimulation results in flicker waveform (black wave, lower right panel). In RP patients and in rd1 mutant mouse, the electrophysiological responses are reduced or non-detectable (red traces). ERG: Electroretinography; OCT: optical coherence tomography; RP: retinitis pigmentosa. Reprinted from Veteli et al. (2015).
The degeneration of rod photoreceptors leads to the release of inflammatory molecules and free radicals, which affects the survival of cones. The resident microglia is a potential regulator of inflammation and performs immune surveillance. Monocyte chemoattractant protein-1 and tissue damageactivate microglia and recruit inflammatory cells including monocytes, T cells, and dendritic cells, at the site of injury (Murakami et al., 2020). Microglia acquire amoeboid morphology in a reactive state. Activated microglia secrete pro-inflammatory mediators (cytokines and chemokines) through several signaling pathways such as nuclear factor-κB, mitogen-activated protein kinase, or Janus kinase/signal transducer and activator transcription. The pro-inflammatory mediators including tumor necrosis factor-alpha, IL-6, IL1α, IL1β, and platelet derived growth factor, are responsible for the progression of RP (Okita et al., 2020). Conclusively, inflammation and the immune system play a significant role in the pathogenesis and progression of RP.

Conclusion
Currently, there is no definite cure that has been approved for retinal degenerative diseases, which are the cause of persistent vision deterioration and vision loss. Initially, these retinal degenerative diseases were not considered inflammatory, but recent clinical and experimental studies have provided sufficient evidence on the inflammatory nature of these retinal diseases. Several cell death mechanisms have been proposed for photoreceptor degeneration, such as apoptosis, pyroptosis, necroptosis, and parthanatos. Inflammation and photoreceptor cell death are interdependent, and they influence each other. Based on the inflammatory processes and underlying mechanisms, the development of targeted therapies could be promising in slowing the progression and development of retinal degenerative diseases.

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References
Agarwal P, Daher MA, Agarwal R (2015) Aqueous humor TGF-β2 levels in patients with open-angle glaucoma: a meta-analysis. Mol Vis 21:612-620.
Akhter N, Nix M, Abdul Y, Singh S, Husain S (2013) Delta-opiod receptors attenuate TNF-a-induced MMP-2 secretion from human ONH astrocytes. Invest Ophthalmol Vis Sci 54:6605-6611.
Alapati T, Sagai KM, Gudiseva HV, Pizzillli M, Pyfer M, Chavali VR, O’Brien JM (2021) Evaluating TNF-a and interleukin-2 (IL-2) levels in African American Primary Open-Angle Glaucoma Patients. Genes 13:54.
Ambati J, Atkinson JP, Gelfand BD (2013) Immunology of age-related macular degeneration. Br J Ophthalmol 95:1323-1330.
Baudouin C, Kolko M, Melik-Parsadaniantz S, Messmer EM (2021) Inflammation in retinal pigment epithelial cell susceptibility to lipofuscin phototoxicity by retinoic acid: a potential mechanism. PLoS One 16: e0252415.
Brown EE, DeWeerd AJ, Ildefonse CJ, Lewin AS, Ash JD (2019) Mitochondrial oxidative stress in the retinal pigment epithelium (RPE) led to metabolic dysfunction in both the RPE and retinal photoreceptors. Redox Biol 24:101201.
Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L (2017) Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 9:7204-7218.
Cheng SC, Huang WC, S Pang JH, Wu YH, Cheng CY (2019) Quercetin inhibits the production of IL-1β-induced inflammatory cytokines and chemokines in ARPE-19 cells via the MAPK and NF-κB signaling pathways. Int J Mol Sci 20:2957.
Chintala SK, Zhang H, Austin JS, Fimi ME (2022) Deficiency in matrix metalloproteinase gelatinase B (MMP-9) protects against retinal ganglion cell death after optic nerve ligation. J Biol Chem 277:47461-47468.
Colijn JM, Buitendijk GHS, Prokopceva E, Alves D, Cachalo S, Marwaha AP, Couogan-Gregoire A, Meri BMI, Korb C, Erke MG, Bron A, Anastasopoulos E, Meester-Smoo MA, Segato T, Pierramarco S, de Jong PTVM, Vingerling JR, Topouzis F, Creuzot-Garcher C, Bertelsen G, et al. (2017) Prevalence of age-related macular degeneration in Europe: the past and the future. Ophthalmology 124:1753-1763.
Daruiuch A, Matet A, Moulin A, Kowalczuk L, Nicolas M, Sellam A, Rothschild PR, Omri S, Gélièze J, Jonet L, Delaunay K, De Kozak Y, Berdugo M, Zhao M, Crisanti P, Behar-Cohen F (2018) Mechanisms of macular edema: beyond the surface. Prog Retin Eye Res 63:20-68.
Datta S, Cano M, Ebrahimli K, Wang L, Handa JT (2017) The impact of oxidative stress and inflammation on RPE degeneration in non-neovascular AMD. Prog Retin Eye Res 60:201-218.
de Jong S, Gagliardi G, Garanto A, de Breuk A, Lechanteur YTE, Katti S, van den Heuvel LP, Volokhina EB, de Hollander AI (2021) Implications of genetic variation in the complement system in age-related macular degeneration. Prog Retin Eye Res 84:100952.
Du J, Li R, Xu L, Ma R, Liu J, Cheng J, Zhang Z, Sun H (2016) Increased serum chemerin levels in diabetic retinopathy of type 2 diabetic patients. Curr Eye Res 41:114-120.
Du Z, Wu X, Song M, Li P, Wang L (2016) Oxidative damage induces MCP-1 secretion and macrophage aggregation in age-related macular degeneration (AMD). Graefes Arch Clin Exp Ophthalmol 254:2469-2476.
Ergorul C, Ray A, Huang W, Wang DY, Ben Y, Cantutti-Castelvetri I, Grosskreutz CL (2010) Hypoxia inducible factor-1alpha (HIF-1alpha) and some HIF-1 target genes are elevated in experimental glaucoma. J Mol Neurosci 42:183-191.
Espinoza-Heidmann DG, Suner IJ, Catapano R, Hernandez EP, Marin-Castano ME, Cousins SW (2006) Cigarette smoke-related oxidants and the development of sub-RPE deposits in an experimental animal model of dry age-related macular degeneration. Invest Ophthalmol Vis Sci 48:3737-3745.
Ferrara N, Adamsis AP (2016) Ten years of anti-vascular endothelial growth factor therapy. Nat Rev Drug Discov 15:385-403.
Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM, Gallins P, Spencer KL, Kwan SY, Nourdine D, Gilbert JR, Schnetz-Boutaud N, Agarwal A, Postel EA, Pericak-Vance MA (2005) Complement factor H variant increases the risk of age-related macular degeneration. Science 308:419-421.
Handa JT, Bowes Rickman C, Dick AD, Gorin MB, Miller JW, Toth CA, Ueffing M, Zarbin M, Farrer LA (2019) A systems biology approach towards understanding and treating non-neovascular age-related macular degeneration. Nat Commun 10:3347.
Hang H, Yuan S, Yang Q, Yuan D, Liu Q (2014) Multiplex bead array assay of plasma cytokines in type 2 diabetes mellitus with diabetic retinopathy. Mol Vis 20:1137.
He S, Prasanna G, Yorio T (2007) Endothelin-1-mediated signaling in the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in astrocytes. Invest Ophthalmol Vis Sci 48:3777-3787.
Holam V, Palacka L, Hermankova B (2021) Mesenchymal stem cell-based therapy for retinal degenerative diseases: experimental models and clinical trials. Cells 10:58.
Hu ML, Quinn J, Xue K (2021) Interactions between apolipoprotein E metabolism and retinal inflammation in age-related macular degeneration. Life Sci 124:35-46.
Izumi-Nagai K, Nagai N, Ozawa Y, Mihara M, Ohsugi Y, Kurihara T, Koto T, Satofuka N, Iwabe S, Lamas M, Vásquez Pélaez CG, Carrasco FG (2010) Aqueous humor TGF-β2 levels in patients with open-angle glaucoma. Retina 37:819-835.
Iwabe S, Lamas M, Vásquez Pélaez CG, Carrasco FG (2010) The pathophysiology of geographic atrophy secondary to age-related macular degeneration. Life 11:635.
Jean P, Burke AL, Litwin ME, Jampel HD, Scott IU, Ou JZ, Guymer RH, Wong TY (2013) Hypertensive retinopathy in type 2 diabetes mellitus. JAMA 310:3347.
Kowalczuk L, Nicolas M, Sellam A, Rothschild PR, Omri S, Gélièze J, Jonet L, Delaunay K, De Kozak Y, Berdugo M, Zhao M, Crisanti P, Behar-Cohen F (2018) Mechanisms of macular edema: beyond the surface. Prog Retin Eye Res 63:20-68.
Kurisu H, Ishida S, Inoue M, Tsubota K, Okano H, Oike Y, Ishida S (2007) Interleukin-6 receptor-35:287-294.
Lee KE, Klein BEK, Klein R, Duggal P, Klein AP (2018) Refraction.
