Perspective article

Immune response in retinal degenerative diseases – Time to rethink?

Heping Xu a, b, *, Mei Chen b, **

a Aier Institute of Optometry and Vision Science, Changsha 410000, China
b The Wellcome-Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry & Biomedical Sciences, Queen’s University Belfast, BT9 7BL, UK

ARTICLE INFO

Keywords:
Inflammation
Immune privilege
Retina
Senescence
Microbiota
Neuron-microglia crosstalk

ABSTRACT

Retinal degeneration comprises a group of diseases whereby either the retinal neurons or the neurovascular unit degenerates leading to the loss of visual function. Although the initial cause varies in different conditions, inflammation is known to play an important role in disease pathogenesis. Recent advances in molecular and cell biology and systems biology have yielded unexpected findings, including the heterogeneity of immune cells in the degenerative retina, bidirectional neuron-microglia cross talk, and links to the gut microbiome. Here we discuss the immune response in retinal degenerative conditions, taking into account both regional (retinal) and systemic factors. We propose to classify retinal degeneration into dry and wet forms based on whether the blood-retinal barrier (BRB) is breached and fluid is accumulated in retinal parenchyma. The dry form has a relatively intact BRB and is characterised by progressive retinal thinning. Immune response to degenerative insults is dominated by the retinal defence system, which remains to be regulated by neurons. In contrast, the wet form has retinal oedema due to BRB damaged. Inflammation is executed by infiltrating immune cells as well as the retinal defence system. The gut microbiome will have easy access to the retina in wet retinal degeneration and may affect significantly retinal immune response.

1. Introduction: challenges in understanding the immunopathogenesis of retinal degenerative conditions

The detrimental role of inflammation in retinal degenerative diseases is well acknowledged and targeting inflammatory pathways has been a hot topic of research for decades. Intraocular injection of steroids is proven to be effective in controlling the vascular components of retinal degeneration such as choroidal neovascularisation in neovascular age-related macular degeneration (nAMD) (Becerra et al., 2011) and macular oedema caused by nAMD, diabetic retinopathy (DR), uveitis and retinal vein occlusion (RVO) (Dugel et al., 2015; Jermak et al., 2007). The beneficial effect of immune suppression (including the use of corticosteroids) in controlling retinal neuronal degeneration has been observed in animal studies such as photoreceptor degeneration in rd10 mice (Guadagni et al., 2019) or light damage models (Scholz et al., 2015). However, the knowledge has not been translated into clinical practice. Retinal neurodegeneration is often chronic in nature and therefore requires lifetime management. Corticosteroids may not be suitable to treat the condition due to their adverse effects. More importantly, inflammation is a protective response against infections, tissue insults and damage, therefore, indiscriminately suppressing inflammation will unlikely benefit the damaged tissue. The ideal strategy would be to specifically promote the beneficial effects and suppress the detrimental effects of inflammation. A better understanding of the immune response in retinal degenerative conditions is critical to designing target-specific therapies.

Given the recent advances in understanding molecular and cellular interactions in the neuronal retina in healthy and diseased conditions, it is time to reassess immune response in retinal degeneration. In particular, single-cell RNA sequencing (scRNAseq) studies have revealed the

Abbreviations: ACAID, anterior chamber-associated immune deviation; AGE, advanced glycation end-products; ALE, advanced lipoxidation end-products; AMD, age-related macular degeneration; nAMD, neovascular AMD; AMP, antimicrobial peptides; BBB, blood-brain barrier; BRB, blood-retinal barrier; CR, complement receptor; CSF1, colony stimulating factor 1; CSF1R, colony stimulating factor 1 receptor; CNS, central nervous system; DR, diabetic retinopathy; GA, geographic atrophy; IP, immune privilege; IPL, inner plexiform layer; OPL, outer plexiform layer; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; RVO, retinal vein occlusion; scRNAseq, single cell RNA sequencing; SASP, senescence-associated secretory phenotype; TLR, Toll-like receptor.

* Corresponding author.

E-mail addresses: heping.xu@qub.ac.uk (H. Xu), m.chen@qub.ac.uk (M. Chen).

https://doi.org/10.1016/j.pneurobio.2022.102350
Received 23 May 2022; Received in revised form 24 August 2022; Accepted 2 September 2022
Available online 6 September 2022
0301-0082/© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
cellular heterogeneity of immune cells and the bi-directional neuron-microglia crosstalk the retina, and microbiome studies have uncovered the links between the gut microbiota and retinal diseases. The findings have brought additional players into the battle against degenerative insults.

2. Retinal homeostasis, para-inflammation, and inflammation – the concept

The purpose of inflammation is to maintain tissue homeostasis and functionality. Therefore, to understand if an inflammatory response is beneficial or detrimental to tissue, we must first define the homeostasis functionality. Therefore, to understand if an inflammatory response is beneficial or detrimental to tissue, we must first define the homeostasis function of the tissue. Homeostasis often describes a normal, steady-state condition. However, exactly what is a “normal” condition of a tissue is less clear. Recently, Meizlish and colleagues describe tissue homeostasis as “the active maintenance of certain quantitative characteristics of regulated variables” within the desired range to allow the tissue to perform its function, and close to a target value is the set point” (Meizlish et al., 2021). This definition of homeostasis is based on the concept that any given tissue consists of primary and supportive cells. The primary cells perform the primary function of the tissue, and the supportive cells facilitate the performance of the primary cells (Meizlish et al., 2021). For example, the primary function of the retina is to acquire vision; therefore, retinal neurons are the primary cells. Other cells including macro-/micro-glia, endothelial cells, pericytes, and retinal pigment epithelial (RPE) cells are supportive cells that serve to optimise the performance of retinal neurons (Fig. 1). The regulated variables include the number of different types of retinal cells, the levels of oxygen and nutrients, metabolic wastes, the volume and the pH of retinal interstitial fluid, etc. A normal visual function requires these regulated variables to be maintained in a homeostatic range. The supportive cells (i.e., glial cells, RPE cells, and retinal vasculature) are responsible for maintaining retinal homeostasis.

When these variables deviate slightly from the homeostatic range, a para-inflammatory response (para-inflammation) will be mobilised. For example, in response to age-related oxidative damage, microglia and the complement system are activated at low levels in the retina (Chen et al., 2019; Xu et al., 2009). The accumulation of intermediate metabolic products such as advanced glycation end-product (AGE) and advanced lipoxidation end-products (ALE) in diabetes also leads to microglial and Müller cell activation (Stitt et al., 2016). Retinal hypoxia is detected by Müller glia and microglia, which release VEGFs that act on the blood-retinal barrier (BRB, i.e., vascular endothelial cells or RPE cells) to increase oxygen supply through opening the barrier (Kaur et al., 2008).

If the variables deviate to extreme levels or the deviations persist for a prolonged period that exceeds the homeostatic capacity of supportive cells, the tissue eventually loses homeostasis resulting in structural and functional alterations, thus inflammation occurs. The death of photoreceptors in retinitis pigmentosa or ganglion cells in glaucoma results in the reduction of the number of retinal neurons over the extreme limit; inflammation, therefore, follows (Karlstetter et al., 2015). Sustained oxidative stress in AMD or diabetes causes extensive retinal neuronal and vascular damage beyond the repair capacity of supportive cells leading to chronic inflammation (Chen and Xu, 2015; Stitt et al., 2016). Severe ischemia in RVO causes retinal (macular) oedema and inflammation (Noma et al., 2012). The way that the immune system responds to extreme deviation of regulated variables differs in different tissues. The retina, as part of the central nervous system (CNS), operates a unique immune regulatory system.

3. Regulation of retinal inflammation

Compared to peripheral tissues, the retina has greater control over immune response and is considered an immune privileged tissue. First, the neuroretina is physically separated from the systemic immune system due to 1) the lack of a lymphatic system, and 2) the existence of BRB, including inner BRB (BRB, tight junctions between retinal vascular endothelial cells) and outer BRB (tight junctions between RPE cells). The physical barrier controls the blood-to-retina and retina-to-blood movement of various substances. It prevents retinal antigens from accessing the systemic immune system and avoids the invasion of circulating immune cells/molecules and blood-borne pathogens to the retina.

Second, retinal cells, including neurons and RPE cells express or release various molecules that form chemical and immunological barriers. This secondary layer of protection has been studied extensively in recent years under the topic of neuron-immune system crosstalk in the CNS and is known to be critical to CNS homeostasis (Veiga-Fernandes and Artis, 2018). When the physical barrier is intact, the neuron-immune system interaction ensures retinal microglia and the complement system are under control. Neurons express various immune checkpoint proteins such as CX3CL1, CD200 and CD47 (Chen et al., 2019; Forrester and Xu, 2012; Liu et al., 2020), which bind cognate receptors in microglia to avoid uncontrolled activation (Fig. 2). Retinal neurons also express various complement inhibitors including Cl-inhibitor (Serping1), factor H (CFH) and CDS9 that critically control complement activation (Liu et al., 2020). When the BRB is breached, the infiltrating immune cells and inflammatory mediators form a hostile microenvironment. Retinal neurons along with RPE cells are programmed to mitigate the threats by inducing the death of infiltrating immune cells (e.g., through Fas/Fasl, TRAIL/TRAIL-Rs (Ferguson and Apte, 2008; Ferguson and Griffith, 2007), CTLA-2α/PDL-1 (Sugita et al., 2008)) or converting them into immune suppressive phenotypes (Keino et al., 2018; Taylor and Ng, 2018).

In addition to monitoring and regulating microglial activation, neurons also provide critical support to microglia. The development, maintenance and proliferation of microglia require TGFβ, colony stimulating factor (CSF1) and IL-34 (Butovsky and Weiner, 2018), which are secreted by neighbouring neurons (Kana et al., 2019; Liu et al., 2020; O’Koren et al., 2019). Both CSF1 and IL-34 bind CSF1R, and this signalling pathway is essential for microglial survival (Green et al., 2020).
Using scRNAseq analysis, we have shown that microglia interact primarily with rod cells (Fig. 2). Blocking CSF1R by either neutralising antibody or pharmacologically (e.g., PXL5622) or genetic ablation of the Csf1r gene results in microglial depletion (Green et al., 2020). A key role of microglia is to maintain a healthy dynamic synaptic structure in the CNS, a process known as synaptic pruning mediated by the C1q, complement receptor (CR) and CX3CL1-CX3CR1 pathways (Cho, 2019; Paolicelli et al., 2011) (Fig. 2). Microglia are strategically located in the inner plexiform layer (IPL) and outer plexiform layer (OPL) to ensure healthy synaptic connectivity in these two locations. A previous study has shown that the maintenance of IPL microglia is mostly dependent on IL-34 produced by retinal ganglion cells (O’Koren et al., 2019), whereas OPL microglia are IL-34 independent (presumably maintained by neuron-/glial-derived CSF1) (Fig. 2). Using scRNAs eq analysis, we have shown that IL34 is expressed predominantly by retinal pericytes and ganglion cells in mice (Liu et al., 2020). In the human retina, ligand-receptor communication network analysis showed that microglia interact primarily with rod, bipolar and Müller cells (Hu et al., 2022). The neuron-microglia cross-talk is an important element to be considered when assessing the immune response in retinal degeneration.

Third, once foreign antigens get into the eye, they induce antigen-specific systemic immune suppression by generating immune suppressive or regulatory T and B cells (Egan et al., 1996; Reyes et al., 2017; Streilein, 1995). The phenomena are known as anterior chamber-associated immune deviation (ACAID) (Streilein, 1995), vitreous cavity-induced immune deviation (VCAID) and subretinal space-induced immune deviation (Jiang et al., 1993; Wenkel et al., 1999). Retinal immune privilege (IP) functions as a homeostatic mechanism preserving visual function (Forrester and Xu, 2012). Conversely, the IP may allow the eye (and the CNS) to act as a reservoir of pathogens, which can remain undetected for the lifetime of the host but may be activated to cause sight- (and life-) threatening inflammation in states of immune deficiency (Forrester et al., 2018, 2022). Thus, IP may furnish a niche for latent infection which may underlie the pathogenesis of non-infectious uveitis (Forrester et al., 2022). With the discovery of disease-specific intraocular (Deng et al., 2021) and intracranial microbiota (Link, 2021), it is reasonable to speculate that the IP may also furnish a niche for disease-specific microbiota, which may alter the intraocular microenvironment in favour of neurodegeneration.

4. Systemic factors in retinal immune regulation

The retinal immune response can be affected by various systemic factors including genetic predisposition and environmental factors (lifestyle, smoking, water and food intake/diet, air pollution etc.). The impact of genetic and environmental factors on different types of retinal degeneration has been studied extensively in recent years and the majority of the studies have focused on their contribution to retinal pathologies. Very few studies examined their roles in retinal inflammation. Here, we highlight the influence of three systemic factors, namely genetic factors, ageing and gut microbiome, in retinal immune regulation.

4.1. Potential effect of genetic factors in retinal immune response

Among various retinal degenerative conditions, retinitis pigmentosa (RP) is a group of inherited disorders associated with dysfunction or death of photoreceptors and/or RPE cells. So far, over 260 genes with about 4500 causative mutations have been implicated in inherited retinal diseases (Parrar et al., 2017). Other diseases such as glaucoma, DR and AMD, have genetic predispositions (Sharma et al., 2019; Tuo et al., 2012; Zukerman et al., 2020). Some of the risk genes (e.g., CFH, APOE, TLR4, CX3CR1, TNF, IL1, etc.) are directly involved in the immune response. For example, the AMD risk gene variants in the 1q31 locus, CFH/H402 (Calippe et al., 2017) and the 10q26 locus, ARMS2/HTRA1 (Beguier et al., 2020), and even the APOE2 isoform (Levy et al., 2015) are known to increase the risk of AMD by promoting subretinal inflammation through interrupting the thrombospondin-1/CD47 signalling pathway. Other genes, in particular RP-related gene mutations, may not be related to immune function. It is believed that the RP-related genes encode proteins critically for photoreceptor and/or RPE function and survival (Ferrari et al., 2011). Their mutations lead to the malfunction of relevant proteins and the death of photoreceptors or RPE cells. Anti-retinal autoantibodies have been detected in 21–51 % of RP patients and inflammation is known to play a role in RP progression (McMurtrey and Tso, 2018). The autoantibodies may be induced by retinal antigens released from damaged photoreceptors or RPE cells (McMurtrey and Tso, 2018).

With the recent advancement in scRNAs eq, we can now identify each retinal cells that express disease-casing (or risk) genes. Using the Spectacle platform (Voigt et al., 2020) with the dataset of Voigt et al. (Voigt et al., 2019), we can check the expression of any gene of interest in each type of retinal cell in the human fovea and peripheral retina. Surprisingly, some genes thought to be expressed by photoreceptor/RPE cells are also expressed by many other cells. For example, the Arl3 gene that can cause autosomal recessive (Fu et al., 2021) and autosomal dominant (Ratnapriya et al., 2021) RP is expressed not only by rods and cones but also by bipolar, horizontal and Müller cells (Fig. 3). The Prp/R gene that causes autosomal dominant RP (Maubaret et al., 2011) is also highly expressed in other retinal cells including bipolar, amacrine and glial cells (Fig. 3). There was a clear difference in the expression levels of Arl3 and Prp/R genes between fovea and peripheral glial cells (Fig. 3). The DR risk gene St2/A1 is widely expressed by many retinal cells including glial cells (Fig. 3). On the other hand, FoxC1, one of the glaucoma risk genes, was detected only in retinal pericytes and endothelial cells (Fig. 3). It will be interesting to know how mutation (or polymorphism) of these genes affects the function of the retinal glia and vascular system, and such knowledge is important to understanding retinal immune response in disease conditions.

It should be noted that gene expression could change under disease conditions. The mutated genes that are not expressed in retinal microglia in the healthy eyes might be induced in disease conditions. Further
Ageing. Senescent cells can affect surrounding cells by producing SASP (inflammatory cytokines) and this is believed to contribute to the pathogenesis of many age-related pathologies such as dementia, Alzheimer disease and AMD. Neutrophilic and macrophage activation exists in the ageing retina (Chen et al., 2019). The expression of retinal degeneration-related genes in human fovea and peripheral retinal cells. Image was plotted using the Spectacle platform (Voigt et al., 2020) with the dataset of Voigt et al. (Voigt et al., 2019). Arl3 and Prpf8 are RP related genes. Sc220a1 is a DR risk gene (Sharma et al., 2019). Foxc1 is a glaucoma risk gene (Ziukerman et al., 2020).

scRNAseq analysis of retinal tissues from patients may offer additional insights into the impact of a gene mutation in retinal degeneration and immune response.

4.2. Ageing and retinal immune regulation

The majority of retinal degenerative diseases are age related. AMD occurs in people older than 55 years of age. The incidence of DR and glaucomatous retinopathy increases with age (Coleman and Miglior, 2008; Stitt et al., 2016). Previously we have shown that a low-level of chronic inflammation (para-inflammation) characterised by mild microglial and complement activation exists in the ageing retina (Chen and Xu, 2015; Xu et al., 2009). We also showed that retinal immune regulation in the ageing retina is altered (Chen et al., 2019). In this section, we discuss recently discovered process in ageing that may affect retinal immune response under degenerative conditions.

Ageing is associated with the development of systemic chronic low-grade inflammation (in the absence of infection, also known as inflammation) and this is believed to contribute to the pathogenesis of many age-related pathologies such as dementia, Alzheimer disease and AMD. With advanced age, innate immunity (e.g., macrophages and neutrophils) is increasingly activated, accompanied by higher levels of proinflammatory cytokines such as IL-1β, IL-6 and TNFα (Goto, 2008). The proinflammatory macrophages are responsible, at least partially, for the decline of NAD+ levels during age as they express CD38, an ectoenzyme that hydrolyses NAD+ (Abdelatif et al., 2021). NAD+ metabolism critically controls inflammation during senescence (Nacarelli and Zhang, 2019). It will be interesting to know how age-related decline in NAD+ levels and low-levels of systemic immune activation may affect retinal immune response in degenerative conditions.

Cellular senescence and senescence-associated secretory phenotype (SASP) are one of the major sources of inflammatory cytokines during ageing. Senescent cells can affect surrounding cell by producing SASP and this is known to contribute to the pathogenesis of many degenerative diseases. In the retina, cellular senescence contributes to pathological angiogenesis (Crespo-Garcia et al., 2021). Senescence can be triggered by oxidative stress, DNA damage, and replicative exhaustion. Oxidative stress exists in almost all retinal degenerative conditions. The microenvironment of the degenerative retina may foster cellular senescence, which may further alter retinal immune regulation.

4.3. Microbiome and retinal immune regulation

Microbiota and their metabolites can be translocated into the bloodstream (D’Aquila et al., 2021; Manfredo Vieira et al., 2018). Neumorous microbes including many previous unidentified members have been detected in circulating cell-free DAN samples from patients with organ transplantation (Kowarsky et al., 2017), breast cancer and even healthy individuals (Huang et al., 2018). A recent study has reported a positive association between blood bacterial DNA levels and circulating leukocytes (D’Aquila et al., 2021). The gut microbiome is known to be able to modulate the blood-brain barrier (BBB) and brain function (Parker et al., 2020). During ageing, gut dysbiosis increases intestinal permeability that facilitates the translocation and accumulation of microbiota and metabolites such as N(6)-carboxymethyllysine (CML) to the CNS (Mossad et al., 2022). CML accumulation in the brain led to mitochondrial damage, the production of reactive oxygen species (ROS) and oxidative stress in microglia of aged mice (Mossad et al., 2022). Whether gut dysbiosis plays a role in inflamming remains to be elucidated.

Regarding the role of gut dysbiosis and retinal degeneration, microbial dysbiosis may modulate the systemic metabolic pathway and immune functions that lead to dysregulated retinal inflammation (Fig. 4). This may contribute to the development of autoimmune uveoretinitis (Horai and Caspi, 2019; Li et al., 2020; Molzera et al., 2020), diabetic retinopathy (Bel et al., 2018), choroidal neovascularization (CNV)(Andriessen et al., 2016), AMD (Rowan et al., 2017), glaucoma (Chen et al., 2018) and RP (Kutsyr et al., 2021). A low-grade systemic inflammation characterized by increased plasma levels of C-reactive protein, inflammatory cytokines (e.g., IL-1β, IL-6, TNFα), and neutrophil counts exists in various retinal degenerative conditions such as AMD and DR (Chen and Xu, 2015; Obasammi et al., 2020; Xu and Chen, 2017). However, whether this is related to gut dysbiosis remains to be elucidated.

A recent study reported the existence of intraocular microbiota and disease-specific microbial signatures in eyes with senile cataract, AMD and glaucoma (Deng et al., 2021). This is interesting as microbiome has been detected in human brain and it is believed that the microbes can colonise but not necessarily actively replicate in the brain (Link, 2021). Although the intraocular microbiota in healthy eyes is yet to be confirmed by others, the result by Deng et al. suggests that the commensal microbiota is a part of the retinal ecosystem and they may alter the intraocular microenvironment and modulate retinal immune response directly in retinal degeneration. The question is now the microbiota gain access to the intraocular compartments and what they do to the retina. The virulent pathogens are normally eliminated by...
When the BRB is damaged, the leakage causes oedema and the retina becomes "dry." The immune response to the degenerative retina with an intact BRB will be very different from that with a damaged BRB. The common causes of retinal degeneration include genetic mutation (e.g., RP), ageing (e.g., AMD), systemic diseases (e.g., diabetes and autoimmune diseases) and other eye diseases (e.g., glaucomatous retinopathy, myopic retinopathy). To understand how the immune system responds to retinal degeneration, we propose to classify the disease into "dry" and "wet" forms based on whether the BRB is damaged that causes fluid extravasation and accumulation. If the BRB is functional, the retina remains "dry" and degeneration leads to progressive retinal thinning. When the BRB is damaged, the leakage causes oedema and the retina becomes "wet". The immune response to the degenerative retina with an intact BRB will be very different from that with a damaged BRB. The treatment strategies will also be different in the two groups of degenerative conditions. It is important to note that immune cells can migrate across the intact BRB in normal (Xu et al., 2003b) and inflamed retina (Xu et al., 2003a) and the process is regulated by chemokines and adhesion molecules (Xu et al., 2003a, 2003b). This is also true in the CNS whereby the immune cells can traffic into brain parenchyma under normal conditions (Marchetti and Engelhardt, 2020). Only when the barrier integrity is damaged immune cell infiltration is accompanied by fluid extravasation.

Typical examples of dry retinal degeneration include RP, glaucomatous retinopathy, geographic atrophy (GA) type of AMD, certain types of myopic retinopathy such as lacquer cracks, Fuch’s spots, chorioretinal atrophy, staphyloma, etc. The original cause of dry retinal degeneration is the dysfunction or death of retinal neurons although damages in supportive cells such as RPE or microglia may also trigger dry retinal degeneration (see below). This would reduce oxygen and nutrient demands and ease the workload of the vascular system. Therefore, the BRB would normally remain intact. In DR patients, pan-retinal photocoagulation (PRP) can effectively preserve macular function. One of the mechanisms is that the PRP-mediated extensive neuronal degeneration reduces retinal oxygen and nutrient demands (Landers et al., 1982). Clinically, dry retinal degeneration presents as a slow deterioration of visual function and retinal thinning.

Wet retinal degeneration includes (but is not limited to) DR, wet AMD, uveoretinitis, and RVO. The key feature of wet retinal degeneration is the damage of BRB (ibBRB or oBRB or both) that leads to the leakage of fluids into retinal parenchyma. The BRB may be damaged from inside the blood vessels by systemic factors or from outside the blood vessels by an altered retinal microenvironment. Müller cells are an important component of the neurovascular unit (Bringmann et al., 2006), and Müller cell dysfunction can lead to BRB damage and the development of wet retinal degeneration. In mice, selective depletion of Müller cells resulted in photoreceptor death, vascular telangiectasis, BRB breakdown and neovascularisation – typical signs of wet retinal degeneration (Shen et al., 2012). In wet retinal degeneration, neuronal degeneration is the consequence of BRB dysfunction (e.g., due to insufficient oxygen and nutrient supply and uncontrolled inflammation) and patients often experience a rapid visual loss and retinal/macular oedema.

6. Inflammation in dry retinal degenerative diseases

Although dry retinal degeneration is predominately caused by the dysfunction or death of retinal neurons, i.e., retinal primary cells, in some cases, malfunction of supportive cells may also lead to dry retinal degeneration. For example, RPE dysfunction can result in dry AMD. Primary microglia malfunction can induce retinal neurodegeneration.
during ageing, known as retinal microgliopathy (Du et al., 2021). Interestingly, a recent study showed that subclinical disturbance of iBBR (through claudin-5 depletion) in high-cholesterol fed mice induced dry AMD-like pathology (Hudson et al., 2019) although the underlying mechanism remains to be elucidated. The authors hypothesized that cessation of claudin-5 cyclical expression at the iBBR may lead to the accumulation of Drusen and the subsequent RPE degeneration and atrophy (Hudson et al., 2020). It will be important to know if retinal permeability changes in patients with early stages of AMD.

As the BRB is normally intact and functional in dry retinal degeneration (e.g., IP, glaucoma and GA), the systemic immune system may have limited effects on the retinal immune response. The inflammatory response is often executed by the retinal innate defence system e.g., microglia, Müller cells and the complement system (Table 1). The damaged neurons release alarmins such as glutamine, ATP, HMGB1, histones, succinate etc., which are detected by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on microglial cells (Baudouin et al., 2021). Stress response-related proteins such as heat shock proteins (HSPs) can also serve as an immunogenic molecule that participates in the pathogenesis of chronic inflammatory diseases (van Eden et al., 2005) including glaucomatous retinopathy (Chen et al., 2018).

In the case of retinal outer layer (i.e., RPE or photoreceptor) damage, it has been shown that microglia in both inner and outer plexiform layers can migrate to subretinal space, indicating that they are primary responders. Interestingly, a recent study using the Cx3cr1CreERT2; Rosa26-tdTomato mice (8 weeks after Tamoxifen treatment) showed that the majority (> 80 %) of subretinal phagocytes in laser-induced CNV were microglia (Wieghofer et al., 2021), further highlighting the role of retinal resident innate immune cells in subretinal wound healing and repair, even when the physical barrier is breached. Microglia in the subretinal space undergo transcriptional reprogramming that is associated with the protection of RPE cells (O‘Koren et al., 2019).

Is the retina still in control of the immune response in dry retinal degeneration? Although the BRB is intact and functional in dry retinal degeneration, the immunological barrier, i.e., the immune suppressive property of neurons and RPE cells, may be compromised. This may lead to uncontrolled microglial and complement activation that further damages retinal neurons. Microglial phagocytosis of “stressed-but-viable” neurons has been observed in various neurodegenerative conditions (Butler et al., 2021). Certain genetic predispositions may also lead to uncontrolled microglial or complement activation. For example, when the microglial checkpoint protein, Cx3cr1, is absent in Cx3cr1 knockout (Semlaub et al., 2013) or LysM-Socs3/Cx3cr1 double knockout mice (Du et al., 2021), or in people carrying the AMD-associated ApoE2 risk allele (Levy et al., 2015), microglia become over-activated, which then induces CCR2+ monocytes infiltration into the retina or subretinal space leading to neuronal death (Yu et al., 2020). Complement factor H (CFH) gene polymorphism, in particular the Y402H variant, increases the risk of AMD and is associated with uncontrolled systemic inflammation including cytokine production and complement activation (Cao et al., 2013). The CFH Y402H variant is also related to retinal lipoprotein dysregulation and oxidative stress (Lindowski et al., 2019; Shaw et al., 2012), as well as the inhibition of the resolution of subretinal inflammation (Calippe et al., 2017). Uncontrolled microglial and complement activation may result in over-production of inflammatory mediators such as CCL2, IL-6 and IL-1β, leading to monocyte recruitment (Yu et al., 2020). Therefore, the immune response in dry retinal degeneration may be assisted by infiltrating circulating immune cells, particularly in the late stages of the disease (Fig. 5A).

The microbiome may also play a role in dry retinal degeneration-related inflammation. Recent studies have reported an altered gut microbiome in the serum of glaucoma patients (Gong et al., 2022, 2020) and irritable bowel syndrome is a risk factor for glaucoma (McPherson et al., 2021). Commensal microflora-induced T cell response is known to play an important role in glaucomatous neurodegeneration (Tang et al., 2020). Gut dysbiosis also exists in the RD10 mice, a mouse model of retinitis pigmentosa (Kutsyr et al., 2021). Nevertheless, the results suggest a role for dysbiosis in dry retinal degeneration. Whether gut dysbiosis modulates retinal inflammation directly by altering the intracellular microenvironment or indirectly through activating circulating immune cells remains to be elucidated (Fig. 5A). Improved knowledge of disease-specific gut dysbiosis and the intraocular ecosystem of dry retinal degeneration will be crucial for a better understanding of the immune response.

7. Inflammation in wet retinal degenerative diseases

BBR dysfunction is the primary cause of wet retinal degeneration. Malfunction of the vascular system reduces oxygen and nutrient supply, which is detected by microglia, Müller cells and retinal neurons. The breakdown of BBR leads to infiltration and accumulation of circulating immune cells and plasma proteins in retinal parenchyma. As a result, multiple regulated variables (e.g., oxygen and nutrients, metabolic wastes, retinal interstitial fluid, the constitution and number of retinal cells) deviate to extreme levels, which triggers retinal inflammation (Table 1). In diabetic retinopathy, the process may take years and decades, but it can happen within hours in RVO.

The BBR may be damaged from inside (endothelial failure) or outside the blood vessels (i.e., dysfunction of the neurovascular unit including pericytes, Müller cells, microglia etc.). The inflammatory response is executed initially by retinal glial cells and the complement system and is accelerated by infiltrating immune cells after the physical barrier is breached (Fig. 5B). Müller cell and microglial activation has been observed in animal models of DR in the absence of immune cell infiltration (Kezic et al., 2013). As resident innate immune cells, the principal function of microglia is to maintain retinal homeostasis and their activation is supposed to be beneficial (e.g., by removing debris and cleaning alarms). However, uncontrolled or prolonged microglial activation may be harmful. It has been shown that under hypoxic conditions, active microglia can release IL-1β, which stimulates Müller cell VEGF production leading to BBR dysfunction (Inada et al., 2021). The cytokines and chemokines released by active glial cells can summon

| Primary cause          | Immune responses                                                                 | Systemic immune system                                                                 | Clinical features                                                                 |
|------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Dry RD                 | Damage to retinal neurons or RPE cells                                            | Activation of retinal microglia, Müller cells and the complement system                 | Early stage: not involved                                                        |
|                        |                                                                                  | IP maintained initially, may be compromised in the late stage                           | Late stage: innate followed by adaptive immune cell infiltration, which is tightly |
|                        |                                                                                  |                                                                                        | regulated                                                                        |
|                        |                                                                                  |                                                                                        | May be influenced by microbiome                                                   |
| Wet RD                 | Damage to the neurovascular unit or RPE-Bruch’s membrane                          | Activation of retinal microglia, Müller cells and the complement system                 | Infiltration of innate and adaptive immune cells, plasma proteins, etc.           |
|                        |                                                                                  | Loss of IP when disease starts                                                          | Influenced by microbiome                                                         |
|                        |                                                                                  |                                                                                        |                                                                                  |

Table 1
Characteristics of dry and wet retinal degeneration (RD).

*H. Xu and M. Chen* Progress in Neurobiology 219 (2022) 102350

6
circulating immune cell infiltration, which can further damage the BRB by producing inflammatory cytokines and chemokines.

Endothelial failure of the BRB is likely caused by systemic factors such as diabetes or systemic inflammation. Once the BRB is damaged, circulating immune cells will have free access to retinal parenchyma. Therefore, any alterations in the systemic immune system will influence the neuroretina (Fig. 5B). For example, retinal antigen-specific CD4 T cells in patients with autoimmune uveitis can damage the BRB, infiltrate the retina and attack photoreceptors. Monocyte-derived macrophages exposed to sustained high glucose are sensitized to cytokine stimulation and have impaired phagocytic function (Pavlou et al., 2018). They can be entrapped in retinal microvasculature (Serra et al., 2012) and infiltrate the retina. Inside the retina, they may produce excessive amounts of inflammatory cytokines such as IL-1β and TNFα, but may not be able to uptake and remove debris (Pavlou et al., 2018). In diabetic patients, it has been reported that impaired B-cell immunity may play a role in the initiation of DR; whereas altered T-cell and neutrophil response may contribute to DR progression (Obasannu et al., 2020).

In addition to the immune components (i.e., cells and circulating proteins including cytokines, complements etc.), the blood microbiome will also have free access to the intraocular compartments in wet retinal degeneration. Indeed, an AMD-specific intraocular microbiota has been observed (Deng et al., 2021). Gut dysbiosis has been reported in nAMD (Zinkernagel et al., 2017) and DR (Das et al., 2021) patients, and in animal models of retinal angiogenesis (Andriessen et al., 2016; Li et al., 2021) and DR (Padakandla et al., 2021; Prasad et al., 2022). The altered microbiome will affect both systemic and local retinal immune responses (Fig. 5).

The immune response in iBRB dysfunction (e.g., DR and RVO) and oBRB dysfunction (e.g., CNV in wet AMD, myopic retinopathy or choriotoretinitis) mediated retinal degeneration may have different characteristics. The inflammation-induced pathology in iBRB-mediated retinal degeneration involves predominately the neuroretina, whereas pathology in oBRB-mediated retinal degeneration is located in the subretinal space and photoreceptors.

In wet retinal degeneration, the IP state is severely compromised due to BRB damage and overt inflammation. It is worth noting that retinal resident immune cells still play a major role in retinal defence and repair evidenced by the fact that microglia constitute the majority (~80%) of subretinal phagocytes in laser-induced CNV (Wieghofer et al., 2021). Their activation, however, is likely dysregulated due to the disruption of neuron-microglial crosstalk and the loss of IP (Table 1).

8. Complexity

The classification of retinal degeneration into dry and wet forms based on the state of BRB can be complicated in some cases. Dry retinal degeneration may develop oedema or angiogenesis at advanced stages. For example, AMD patients with GA may develop CNV. Interestingly, many GA patients never develop CNV, indicating that RPE defect alone is insufficient to cause CNV. The Bruch’s membrane (BrM) must be breached to allow new vessels to grow into the sub-RPE or sub-retinal space. In addition, a higher level of VEGF is essential to induce neovascularisation. In GA, RPE damage is often associated with overlying photoreceptor degeneration. If photoreceptor degeneration falls behind RPE loss, the demand on oxygen and nutrients supply from remaining photoreceptors may create a hypoxic microenvironment and induce angiogenesis, although evidence is needed to support this hypothesis. In addition, the inflammatory response resulting from dead RPE cells may induce metalloproteinase production, which may degrade the BM and induce CNV. Understanding the underlying mechanisms of CNV secondary to GA will be crucial to developing strategies for disease prevention and therapy.

The development of cystoid macular oedema (CMO) in RP patients is another example of wet retinal degeneration that originates from dry retinal degeneration. Clinically, approximately 25% of RP patients develop CMO (Huckfeldt and Comander, 2017). Interestingly, the oxygen saturation in retinal vessels of RP patients with CMO was found to be higher than that in RP patients without CMO (Bojinova et al., 2018) and the aqueous VEGF levels were lower in RP patients than that in control (Salom et al., 2008). Furthermore, intravitreal injection of steroids or VEGF inhibitors had limited effects on RP related CMO (Huckfeldt and Comander, 2017; Strong et al., 2017). The evidence suggests that CMO in RP patients is unlikely caused by hypoxia.

One possibility would be the failure of the retinal drainage system. The water is constantly transported out of the neuronal retinal by RPE and Müller cells. RPE cells dehydrate the subretinal space (Pederson, 2006) and Müller cells dehydrate the inner retinal tissue (Bringmann et al., 2006). The CMOs are mostly located in the inner nuclear layer in RP patients (Strong et al., 2017), indicating that RPE dysfunction may not be involved. Müller cells co-express the water channel aquaporin-4 and the K+ channel, Kir4.1, through which, they take up water from the...
retinal interstitial and release it into the blood, thus controlling retinal osmotic pressure (Bringmann et al., 2006). The genes associated with RP are believed to affect the function of photoreceptors and/or RPE cells (Ferrari et al., 2011). However, scRNAseq studies have shown that many of the RP-related genes are also expressed in other retinal cells including Müller cells (Fig. 3). The knowledge of how Müller cell function is affected by RP-related gene mutation and the death of photoreceptors will help to understand the mechanism of CMO.

9. Concluding remarks

The retina has a high level of control over its immune response due to its unique anatomical and immunological properties i.e., the IP state. When degeneration occurs, the immune response can be quite different from other peripheral tissues. We propose to classify retinal degenerative disorders into dry and wet forms based on whether the disease involves BRB damage and fluid extravasation. We believe that this classification will help to understand retinal immune response as well as develop strategies for disease prevention and therapy. The dry form is caused predominately by the loss of neurons and the BRB is largely unaffected. The immune response is dominated by the retinal defence system. Diseases caused by BRB dysfunction constitute the wet form of retinal degeneration. The inflammatory response involves both the retinal defence mechanism and the systemic immune system. It is now clear that in both cases, the disease-related genetic factors, cellular senescence and gut dysbiosis can affect the immune response. Understanding the mechanisms of immune dysregulation in dry and wet retinal degeneration will help to develop safe and effective immunotherapies.

Declaration of Competing Interest

The authors declare no competing interests in relation to this work.

Acknowledgements

The authors acknowledge the funding supports from Medical Research Council (UK) (MR/W004681/1, HX), European Union’s Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement (No 722717, HX), Fight for Sight (UK) (5057/5058, 5105/5106 HX), Fight for Sight/National Eye Research Centre joint fund (24NER173, MC), Science Research Foundation of Aier Cancer Hospital Group (China) (AM1913D1, AR2003D1, HX). Figures were created with Biorender.com. The authors thank Daniel C. Xu for helping in proofreading of the manuscript. The authors acknowledge the funding supports from Medical Research Council (UK) (MR/W004681/1, HX), European Union’s Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement (No 722717, HX), Fight for Sight (UK) (5057/5058, 5105/5106 HX), Fight for Sight/National Eye Research Centre joint fund (24NER173, MC), Science Research Foundation of Aier Cancer Hospital Group (China) (AM1913D1, AR2003D1, HX). Figures were created with Biorender.com. The authors thank Daniel C. Xu for helping in proofreading of the manuscript.
Progress in Neurobiology 219 (2022) 102350

Li, Y., Cai, Y., Huang, Q., Tan, W., Li, B., Zhou, H., Wang, Z., Zou, J., Ding, C., Jiang, B., Li, J.J., Yi, S., Wei, L., 2020. Ocular microbiota and intraocular inflammation. Front Immunol. 11, 609765.

Kana, V., Desland, F.A., Casanova-Acebes, M., Ayata, P., Badimon, A., Nabel, E., Inada, M., Xu, H., Takeuchi, M., Ito, M., Chen, M., 2021. Microglia increase tight-junction permeability in idiopathic choroidal neovascularization. Proc. Natl. Acad. Sci. U. S. A. 118, 2281.

Huang, Y.F., Chen, Y.J., Fan, T.C., Chang, N.C., Chen, Y.J., Midha, M.K., Chen, T.H., Landowski, M., Kelly, U., Klingeborn, M., Groelle, M., Ding, J.D., Grigsby, D., Bowes, H.M., 2012. Complement factor H genotypes impact risk of age-related macular degeneration (AMD) pathology. Neuronal Regen. Res 15, 10192.

McMurrty, J.J., Too, M.O.M., 2018. A review of the immunologic findings observed in retinitis pigmentosa. Surv. Ophthalmol. 63, 769-781.

McPherson, Z.E., Sorensen, H.T., Horvath-Pabbi, E., Agar, A., Coronato, M.T., White, A., Francis, I.C., Poupaute, I.R., Kang, J.H., Petersson, S., et al., 2021. Irritable bowel syndrome and risk of glaucoma: an analysis of two independent population-based cohort studies. European. Gastroenterol. J. 9, 1057-1065.

Marchetti, L., Engelhardt, B., 2020. Immune cell trafficking across the blood-brain barrier in the absence and presence of neuroinflammation. Vasc. Biol. 2, HI-H118. Manfredoni, C.G., Vlachakis, V.K., Lappas, M.G., Rosem, N.H., Churchill, A., Holder, G.E., Moore, A.T., Bhattacharya, S.S., Webster, A.R., 2011. Autosomal dominant retinitis pigmentosa with intralaminar variability and incomplete penetrance in two families carrying mutations in PRPF8. Invest Ophthalmol. Vis. Sci. 52, 3534-3539.

Marchesi, J.R., Ravel, J., 2015. The vocabulary of microbiome research: a proposal. Microbiome 3, 31.

Marx, L., Kornfeld, H., Stein, E., 2008. Inflammaging (inflammation + aging): a driving force for human aging based on an evolutionarily antagonistic pleiotropy theory? Bioess. Trends 2, 548-551.

Green, K.N., Crapper, J.D., Hofsleld, L.A., 2020. To kill a Microglia: a case for CSFIR inhibitors. Trends Immunol. 41, 771-784.

Guadagni, V., Biagini, M., Novelli, E., Aretili, P., Mazzanti, C.M., Stretti, E., 2019. Reversing clues and daylight vision in retin pigmento disease. Fase B 33, 10177-10192.

Horai, R., Caspi, R.R., 2019. Microbiome and autoimmune uveitis. Front Immunol. 10, 2281.

Hu, F., Ma, Y., Xu, Z., Zhang, S., Li, J., Sun, X., Wu, J., 2022. Single-cell RNA-seq reveals the cellular diversity and developmental characteristics of the retinas of an infant and a young child. Front Cell Dev. Biol. 10, 803466.

Huang, Y.F., Chen, Y.J., Fan, T.C., Chang, N.C., Chen, Y.J., Midha, M.K., Chen, T.H., Yang, H.H., Wang, Y.T., Yu, A.L., et al., 2018. Analysis of microbial sequences in plasma cell-free DNA for early-onset breast cancer patients and healthy females. BMC Med Genom. 11, 16.

Heckel, D.M., Comeron, J., 2017. Management of cytokid macula edemas in retinitis pigmentos. Semin Ophthalmol. 42, 36-43.

Hudson, N., Celkova, L., Hopkins, A., Greene, C., Storti, F., Ozaki, E., Fahey, E., Theodoropoulou, S., Kenna, P.F., Humphries, M.M., et al., 2019. Dysregulated claudin-5 cycling in the inner retina causes retinal pigment epithelial cell atrophy. J Clin Investig. 145 (11), e130273.

Hudson, N., Cahill, M., Campbell, M., 2020. Inner blood-retina barrier involvement in dry age-related macular degeneration (AMD) pathology. Neuronal Regen. Res 15, 10196-10207.

Inada, M., Xu, H., Takeuchi, M., Ito, M., Chen, M., 2021. Microglia increase tight-junction permeability in coordination with Müller cells under hypoxic condition in an in vitro model of inner blood-retinal barrier. Exp. Eye Res. 205, 108490.

Jermak, C.M., Dellacasa, C., Kollami, K., Peyman, G.A., 2007. Tricamcinolone acetic in ocular therapeutics. Surv. Ophthalmol. 52, 503-522.

Jiang, L.Q., Jordrera, M., Streilein, J.W., 1993. Subretinal space and vitreous cavity as immunologically privileged sites for retinal allografts. Invest Ophthalmol. Vis. Sci. 34, 3574-3579.

Kana, V., Denfeld, F.A., Casanova-Acebes, M., Ayata, P., Badimon, A., Nabel, E., Yamamura, K., Sneeboer, M., Tan, L.L., Flanagan, M.E., et al., 2019. CSF-1 controls cerebellar microglia and is required for motor function and social interaction. J. Exp. Med. 216, 2205-2218.

Karlstetter, M., Scholz, R., Rutar, M., Wong, W.T., Provis, J.M., Langman, T., 2015. Retinal microglia: just bystander or target for therapy? Prog. Retin. Eye Res. 45, 30-57.

Kaur, C., Foulds, W.S., Ling, E.A., 2008. Blood-retinal barrier in hypertensive conditions: basic concepts, clinical features and management. Prog. Retin. Eye Res. 27, 622-647.

Keino, H., Horte, S., Sogita, S., 2018. Immune privilege and eye-derived T-regulatory cells. J. Immunol. Res. 2018, 1679197.

Kiez, J.M., Chen, X., Rakoczy, E.P., McElmann, P.G., 2013. The effects of age and Ca(2+)-deficiency on retinal microglia in the In2/AtiaX diabetic mouse. Invest Ophthalmol. Vis. Sci. 54, 854-863.

Kowarsky, M., Camanet-Soler, J., Kertesz, M., De Vlamincck, I., Koh, W., Pan, W., Martin, L., Nef, N.F., Okamoto, J., Wong, R.J., et al., 2017. Numerous uncharacterized and highly diversified microbes which colonize humans are revealed by metagenomic sequencing. Proc. Natl. Acad. Sci. U. S. A. 114, 9623-9628.

Kutty, O., Maestre-Carballa, L., Llue-moena, G., Martinez-Garcia, M., Cuonca, N., Lax, P., 2021. Retinitis pigmentos is associated with shifts in the gut microbiome. Exp. Eye. Res. 119, 66.

Landers 3rd, M.B., Stefansson, E., Wallbars, M.L., 1988. Panretinal photocoagulation and retinal oxygenation. Retina 2, 167-175.

Landowski, M., Kelly, U., Klienberg, M., Groelle, M., Ding, J.D., Grigsby, D., Bowes, H.M., 2012. Complement factor H genotypes impact risk of age-related macular degeneration phenotype and lipoprotein dysregulation in mice. Proc. Natl. Acad. Sci. U. S. A. 110, 3703-3711.

Levy, O., Lavallette, S., Hu, S.J., Houset, M., Raod, E., Candii, S.,Jahann, J.A., Sullivan, P., Giontono, A., Senblau, F., 2015. APOE isoforms control pathogenic subretinal inflammation in age-related macular degeneration. J. Neurosci.: Off. J. Soc. Neurosci. 35, 13568-13576.

Li, J.J., Yi, S., Wei, L., 2020. Ocular microbiota and intraocular inflammation. Front Immunol. 11, 609765.

Li, Y., Cai, Y., Huang, Y., Tan, W., Li, B., Zhou, H., Wang, Z., Zou, J., Ding, C., Jiang, B., et al., 2016. Altered fetal microbe communities and metabolite in a mouse model of choroidal neovascularization. Front Microbiol 12, 738796.

Link, C.D., 2021. Is there a brain microbiome? Neurosci. Insights 16, 2603150552118709.

Liu, J., Tang, M., Harkin, K., Du, X., Luo, C., Chen, M., Xu, H., 2020. Single-cell RNA-seq sequencing study of retinal immune regulators identified CD47 and CD59a expression in photoreceptors—implications in subretinal immune regulation. J Neurosci. Res. 98, 1498-1513.

Liu, J., Yi, C., Ming, W., Tang, M., Tang, X., Luo, C., Lei, B., Chen, M., Xu, H., 2021. Retinal pigment epithelial cells express antimicrobial peptide lysozyme—a novel mechanism of innate immune defense of the blood-retina barrier. Invest Ophthalmol. Vis. Sci. 62 (7), 21.

Manfredo Vieira, S., Hiltensperger, M., Kumar, V., Zegarra-Ruiz, D., Dehner, C., Khan, N., Costa, F.R.C., Tinikaiu, E., Grelting, T., Ruff, W., et al., 2018. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science 359, 1156-1161.

Marchesi, J.R., Ravel, J., 2015. The vocabulary of microbiome research: a proposal. Microbiome 3, 31.
macular degeneration by interaction with oxidized phospholipids. Proc. Natl. Acad. Sci. U. S. A. 109, 13757–13762.
Shen, W., Fruttiger, M., Zhu, L., Chung, S.H., Barnett, N.L., Kirk, J.K., Lee, S., Coorey, N. J., Killingsworth, M., Sherman, I.S., et al., 2012. Conditional Müller cell ablation causes independent neuronal and vascular pathologies in a novel transgenic model. J. Neurosci. 32, 15715–15727.
Stitt, A.W., Curtis, T.M., Chen, M., Medina, R.J., McKay, G.J., Jenkins, A., Gardiner, T.A., Lyons, T.J., Hamnes, H.P., Simo, R., et al., 2016. The progress in understanding and treatment of diabetic retinopathy. Prog. Retin. Eye Res. 51, 156–186.
Streilein, J.W., 1995. Immunological non-responsiveness and acquisition of tolerance in relation to immune privilege in the eye. Eye (Lond. Engl.) 9 (Pt 2), 236–240.
Strong, S., Liew, G., Michaelides, M., 2017. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. Br. J. Ophthalmol. 101, 31–37.
Sugita, S., Horie, S., Nakamura, O., Putagami, Y., Takase, H., Keino, H., Aburatani, H., Katunuma, N., Ishidoh, K., Yamamoto, Y., et al., 2008. Retinal pigment epithelium-derived CTLA-2alpha induces TGFbeta-producing T regulatory cells. J. Immunol. (Baltim. Md.: 1950) 181, 7525–7536.
Tang, J., Tang, Y., Yi, I., Chen, D.F., 2020. The role of commensal microflora-induced T cell responses in glaucoma neurodegeneration. Prog. Brain Res. 256, 79–97.
Taylor, A.W., Ng, T.F., 2018. Negative regulators that mediate ocular immune privilege. J. Leukoc. Biol. 103, 1179–1187.
Tuo, J., Grob, S., Zhang, K., Chan, C.C., 2012. Genetics of immunological and inflammatory components in age-related macular degeneration. Ocul. Immunol. Inflamm. 20, 27–36.
v van Eden, W., van der Zee, R., Prakken, B., 1995. Heat-shock proteins induce T-cell regulation of chronic inflammation. Nat. Rev. Immunol. 5, 318–330.
Veiga-Fernandes, H., Artis, D., 2018. Neuronal-immune system cross-talk in homeostasis. Science 359, 1465–1466.
Voigt, A.P., Whitmore, S.S., Flammé-Wiese, M.I., Riker, M.J., Wiley, L.A., Tucker, R.A., Stone, E.M., Mullins, R.F., Scheetz, T.E., 2019. Molecular characterization of foveal versus peripheral human retina by single-cell RNA sequencing. Exp. Eye Res. 184, 234–242.
Voigt, A.P., Whitmore, S.S., Lessing, N.D., DeLuca, A.P., Tucker, B.A., Stone, E.M., Mullins, R.F., Scheetz, T.E., 2020. Spectacle: an interactive resource for ocular single-cell RNA sequencing data analysis. Exp. Eye Res. 209, 108204.
Wenkel, H., Chen, P.W., Ksander, B.R., Streilein, J.W., 1999. Immune privilege is extended, then withdrawn, from allogeneic tumor cell grafts placed in the subretinal space. Invest. Ophthalmol. Vis. Sci. 40, 3202–3206.
Wieghofer, P., Hagemeier, N., Sankowski, R., Schlecht, A., Staszewski, O., Amann, L., Gruber, M., Koch, J., Hausmann, A., Zhang, P., et al., 2021. Mapping the origin and fate of myeloid cells in distinct compartments of the eye by single-cell profiling. Embo J. 40, e105123.
Wildkow, M., Weeks, T.L., Hazen, S.L., 2020. Gut microbiota and cardiovascular disease. Circ. Res. 127, 553–570.
Xu, H., Chen, M., 2017. Diabetic retinopathy and dysregulated innate immunity. Vis. Res. 139, 39–46.
Xu, H., Forrester, J.V., Liversidge, J., Crane, I.J., 2003a. Leukocyte trafficking in experimental autoimmune uveitis: breakdown of blood-retinal barrier and upregulation of cellular adhesion molecules. Invest. Ophthalmol. Vis. Sci. 44, 226–234.
Xu, H., Manivannan, A., Liversidge, J., Sharp, P.F., Forrester, J.V., Crane, I.J., 2003b. Requirements for passage of T lymphocytes across non-inflamed retinal microvessels. J. Neuroimmunol. 142, 47–57.
Xu, H., Chen, M., Forrester, J.V., 2009. Para-inflammation in the aging retina. Prog. Retin. Eye Res. 28, 348–368.
Yu, C., Roubbie, C., Semmlau, F., Saban, D.R., 2020. Microglia versus monocytes: distinct roles in degenerative diseases of the retina. Trends Neurosci. 43, 433–449.
Zinkernagel, M.S., Zysset-Burri, D.C., Keller, I., Berger, L.E., Leichtle, A.B., Largiadèr, C. R., Fiedler, G.M., Wolf, S., 2017. Association of the intestinal microbiome with the development of neovascular age-related macular degeneration. Sci. Rep. 7, 40826.
Zukerman, R., Harris, A., Vercellin, A.V., Siesky, B., Pasquale, L.R., Ciulla, T.A., 2020. Molecular genetics of glaucoma: subtype and ethnicity considerations. Genes (Basel) 12 (1), 55.