Recent developments of neuroprotective agents for degenerative retinal disorders

From the Contents

Introduction 1919
Search Strategy and Selection Criteria 1919
Main Etiologies of Degenerative Retinal Diseases 1919
Conclusion 1925

Introduction
Retinal degeneration (RD) is a consequence of progressive, chronic neuroretinal disorders as a result of genetic mutations and/or environmental or inflammation/vascular or acquired degenerative pathology. All conditions may lead to partial or complete visual loss throughout life, and are more prevalent in the elderly (Cremers et al., 2020). Complex multifactorial acquired RD disorders include age-related macular degeneration (AMD) (Ammar et al., 2020), diabetic retinopathy (DR) (Wang and Lo, 2018) and glaucoma (Weinreb et al., 2014). Although these retinal diseases are associated with assorted pathophysiological mechanisms, they share some common causative or contributing factors, such as genetic polymorphisms associated with increased risk or severity of disease, oxidative stress, inflammation, metabolic perturbation, and cellular senescence (Weinreb et al., 2014; Copland et al., 2018; Sahajpal et al., 2019; Lee et al., 2021).

Neuroprotective agents are pharmacological or natural substances that are intended to prevent or slow down neuronal loss and neurodegeneration by combating inflammation, oxidative stress, and apoptosis (Boia et al., 2020). Treatments using neuroprotectants via oral, intravenous, intra-arterial or intra-muscular routes are normally required for the treatment of chronic neurological diseases (Mikitish and Chacko, 2014). The approved neuroprotectants have documented pharmacokinetics, bioactivities and demonstrate minimal adverse effects, facilitating long-term administration and compliance that are normally required for the treatment of chronic neurological diseases (Mikitish and Chacko, 2014). In this review, we overview therapeutic targets for the major acquired degenerative retinal diseases: AMD, DR and glaucoma. We highlight the development of novel neuroprotective agents being assessed either experimentally or in clinical trials.

Search Strategy and Selection Criteria
Studies cited in this review published from 2000 to 2021 were searched by medical and science databases, PubMed and Web of Science, using the following keywords “neuropeptides in retina”, “exosomes in retina”, “mitochondrial-derived peptides in retina”, “complement in retina”, “senescence in retina”, “oxidative stress in retina”, “autoaghy in retina”, “resveratrol in retina”, “cannabis in retina” for search strategy.

Main Etiologies of Degenerative Retinal Diseases
AMD is currently the leading cause of blindness in people aged 65 and over (Wong et al., 2014). With increasing life expectancy, AMD has become a major public health challenge as the global burden is projected to reach 288 million people by 2040 (Datta et al., 2017). AMD is a progressive, polygenic and multifactorial disease
of complex etiology. Characterized by drusen deposits, atrophy of the retinal pigment epithelium (RPE) and photoreceptor loss, AMD can progress to visual loss via acute wet or neovascular AMD (nAMD) or, in the majority of patients, an insidious geographic atrophy (aAMD). With age as the primary risk factor for AMD, the incidence of both wet and dry retinal diseases is associated with chronic inflammation (Heesterbeek et al., 2020), lipid metabolism, endocytosis and extracellular matrix organization, and environmental risk factors, particularly smoking and high-fat diet (García-Layana et al., 2017), conspire to initiate and accelerate the development of AMD. Mechanisms operating in AMD progression encompass changes in mitochondrial function (Kaarniranta et al., 2020), enhanced ROS and oxidative stress (Ruan et al., 2020), dysregulated microglia/macrophage responses (Alves et al., 2020), and decline in retinal pigment epithelial cells, choroidal endothelial cells and photoreceptors (Ma et al., 2021). For example, altered mitochondria in the RPE serve as the main source of excessive reactive oxygen species (ROS), which induces oxidative-stress-related damage to the RPE: a key early event in AMD progression. Consequently, cellular damage induced by ROS causes a decline in housekeeping autophagy, which activates immune responses and immune-mediated inflammation. The over-activation of inflammation further provokes damage in photoreceptors, ultimately leading to vision loss (Copland et al., 2018; Wang et al., 2019). Although it has been previously thought that the photoreceptors and RPE are two mostly affected cell types in AMD, recent advances in single-cell (sc) transcriptomic atlases of the human donor eyes have defined leading AMD risk genes associated with additional cell types, such as glia, vascular cells and microglia (Menon et al., 2019; Voigt et al., 2019). For example, the motif chemokine ligand 14, WAP four-disulfide core domain 1 and calcitonin related polypeptide beta are top differential expressed DEGs of macular RPE; tissue inhibitor of metalloproteinase 3 and complement factor I (CFI) are top DEGs of Müller glia; and transforming growth factor beta receptor 1 and complement 3 (C3) are both top DEGs of retinal glial cells (Menon et al., 2019; Voigt et al., 2019). The immune, metabolic and tissue responses occurring in retinal degeneration involve the integrated function of different cell types and a combination of cell-type specific risk genes.

DR is responsible for most cases of visual loss in adults aged 20–74 years (Wang and Lo, 2018). By definition, the incidence of DR is directly linked to the prevalence of diabetes, which is on a sharp rise due to population ageing, obesity and an increase in metabolic syndrome in ever younger populations. Mild obesity-related diabetes is the largest group consisting of the most elderly patients. Mild obesity-related diabetes and mild age-related diabetes are both associated with metabolic syndrome and lifestyle factors such as obesity, stress, and lack of physical activities (Thomas and Philipson, 2015; Ahlqvist et al., 2018). Group I, severe autoimmune diabetes, which largely overlap with type 1 diabetes and latent autoimmune diabetes in adults, is characterized by onset at a young age, poor metabolic control, required insulin treatment and the development of glutamic acid decarboxylase antibodies. Severe autoimmune diabetes is associated with more than 40 gene markers including AIRE gene, FoxP3, HLA-DQB1 and many others (Erlich et al., 2008; Yi et al., 2018). Group II, severe insulin-deficient diabetes, includes individuals with high hemoglobin A1C, impaired insulin secretion and insulin resistance. This group has the highest incidence of retinopathy. Group III, severe insulin-resistant diabetes, is characterized by obesity and severe insulin resistance and has the highest incidence of kidney damage. Group IV, mild obesity-related diabetes, includes obese patients who fall ill at a relatively young age. Group V, mild age-related diabetes, are the largest group consisting of the most elderly patients. Mild obesity-related diabetes and mild age-related diabetes are both associated with metabolic syndrome and lifestyle factors such as obesity, stress, and lack of physical activities (Thomas and Philipson, 2015; Ahlqvist et al., 2018). Regardless the types of diabetes, long-term cellular exposure to the high levels of pro-inflammaotory factors in the retina (Khan et al., 2021) acting via the polyol pathway, advanced glycation end products (AGEs) accumulation, the protein kinase C pathway and the hexosamine pathway (Brownlee, 2005). In particular, mitochondrial dysfunction in endothelial cells is present in hyperglycemic conditions, which is an important source of superoxide production in the retina (Du et al., 2000). The massive production of free radicals in mitochondria increases oxidative stress, which induces excessive local expression of pro-inflammatory mediators. As a consequence, such chronic, low-grade inflammation can influence the immune cell activation, extracellular glutamate accumulation, imbalance of local production of inflammatory and anti-inflammatory cytokines, and p53 and p21 upregulation and p53 and p21 down-regulation, which can lead to apoptosis of the patients or treating late in disease course. For example, VEGF-blocking medicines are effective for nAMD, but no licensed treatment is available for treating late in disease course. Notably,}

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Neuropeptides

To date, nearly 20 neuropeptides have been identified in the human retina. Neuropeptides are produced by neural elements (amacrine cells and RGCs) and non-neural elements (Müller cells and the RPE), some of which are found to promote the development of RD, whereas others slow down or eliminate the progression of RD (Gabriel, 2013).

Somatostatin (SST) is a polypeptide that acts as an inhibitor of endocrine and exocrine hormone secretion in mammals. SST synthetic analogs are widely used in the clinic due to their longer half-life compared to native SST, as well as its significant antisecretory, endocrine and exocrine hormone secretion in mammals. SST contains abundant SST, while proliferative DR and DME patients have antiproliferative and immunomodulatory activities. Human RPE, some of which are found to promote the development of RD, whereas others slow down or eliminate the progression of RD (Gabriel, 2013).

Neuropeptide Y (NPY), one of the most abundant peptides in the mammalian central nervous system (CNS), is present in wide-field amacrine cells and large human RGCs. In some species NPY is detected in non-neural elements too (Müller glia, endothelial cells and microglia (Alvaro et al., 2007). NPY is activated by glutamate through a purinergic paracrine mechanism, which in turn inhibits osmotic glial cell swelling, thus crucially influencing the volume homeostasis of the retina (Učelj et al., 2018). The most important known physiological action of NPY on retinal neurons is that it inhibits the increase of intracellular Ca concentration in response to depolarizing stimuli through Y1, Y4 and Y5 receptors (Alvaro et al., 2009) and it inhibits adenyl cyclase activity through Y2 receptors (Gabriel, 2013). Our recent in vivo studies have highlighted the inhibitory effects of NPY on pathological neovascularization and inflammation in the retina (Ou et al., 2020). In a Streptozotocin-induced rat DR model, hyperglycemic condition decreases the mRNA levels of NPY in the retina, as well as the protein levels of NPY and Y5 receptor (Santos-Carvalho et al., 2013). Intravitreal treatment with NPY increased retinal endothelial expression of ZO-1, accompanied by reduction of phosphorylated mitogen-activated protein kinase (MAPK) isofoms which contribute to the maintenance of vascular integrity under DR conditions (Takano et al., 2014). NPY treatment also regulates inflammatory responses in retinal microglia through inhibiting nuclear translocation of NF-κB, and production of inflammatory cytokines (Gabriel, 2013). Moreover, NPY pretreatment can prevent N-methyl-D-aspartic acid receptor-induced retinal ganglion cell (RGC) apoptosis in the mouse glaucoma model (Alvaro et al., 2008). Through the inhibition of inflammation and neovascularization, NPY may impact AMD outcomes (Ou et al., 2020).

Substance P (SP) is a neuropeptide secreted by neurons and is involved in many biological processes, including vasodilatation, cell proliferation, anti-apoptosis and inflammatory regulation (D’Alessandro et al., 2014). There are detailed data demonstrating the circuitry of SP-positive amacrine cells in the primate retina. The SP-immunoreactive amacrine cell dentrites mostly target bipolar cell axon terminals and ganglion cell dendrites (Williams et al., 2016). SP is found to be decreased in the serum of type 1 diabetes patients, especially in those with diabetic neuropathy. Restoration of expression of SP caused marked inhibition of TNF-α and IL-1β, and the activity of caspase-3 in the diabetic rats’ neurons (Troger et al., 2001; Yang et al., 2013). One of the therapeutic mechanisms of SP in treating RD has been delineated as the involvement of p38 MAPK signaling. p38 MAPK is activated by tumor necrosis factor α and interferon y, leading to down-regulation of occludin, ZO-1 and claudin-2, which contributes to the increase in paracellular permeability in endothelial cells (Patrick et al., 2006). In our previous experiments, we found that both phosphorylated forms of MAPK (p38 and p44/42) were reduced upon SP treatment, alongside ZO-1 upregulation, supporting that SP inactivated MAPK to maintain vascular integrity (Ou et al., 2019).

Pigment epithelium-derived factor (PEDF) belongs to a serpin superfamily and naturally exists in assorted tissues, including the interphotoreceptor matrix (Imen, 2012). However, the expression of PEDF was significantly reduced with degenerative retinal diseases, evidenced by decreased level in not only Bruch’s membrane and RPE of donor eyes with AMD and DR (Ogata et al., 2002; He et al., 2014), but also in the vitreous from eye of patients with AMD (Holenkamp et al., 2002). Data have shown that PEDF has antiangiogenic, antioxidant, neurotrophic properties against neurodegeneration in the CNS as well as in the retina. For example, PEDF can preserve mitochondrial and barrier functions of RPE from oxidative stress, and promote retinal neuron survival against nutrient deprivation or stresses by suppressing apoptotic and inflammatory pathways through modulating PI3K/Akt signaling (Ho et al., 2015; He et al., 2014; Michels et al., 2021). Given the therapeutic potential of PEDF in retinal neuroprotection, a Phase 1 trial using a replication-deficient adeno virus vector, Ad(GV)PEDF.11D, containing the human PEDF gene has been currently investigated for nAMD treatment (Table 1).

Exosomes

Exosomes are extracellular shuttling nanovesicles secreted from cells and packaged with diverse biomolecules cargo, such as miRNAs, mRNAs, lipids and various proteins to facilitate intercellular communication (Biasutti et al., 2013; Klingeborn et al., 2018). The role of exosomes in regulating angiogenesis, apoptosis and inflammation has been well established (Gurunathan et al., 2019). For example, hepatocyte-derived exosomes could transfer sphingosine kinase 2 to form sphingosine-1-phosphate in target...
### Table 1  Current clinical trials of neuroprotectants for major degenerative retinal diseases

| Disease | NCT number | Drug name | Phase | Target classification | Mechanism | Current status |
|---------|------------|-----------|-------|-----------------------|-----------|----------------|
| DR      | NCT03452657 | Ranibizumab | Phase 3 | Angiogenesis | Ranibizumab combines with all VEGF-A subtypes to block cascade reactions. | Unknown |
|         | NCT04418427 | Afibercept | Phase 2 | Angiogenesis | Afibercept acts as a bait receptor to combine with VEGF-A, VEGF-B and PIGF dimer, inhibiting VEGF and PIGF at the same time. | Active, not recruiting |
|         | NCT01189461 | Pegaptanib | Phase3 | Angiogenesis | Pegaptanib mainly combines with VEGF-165 (isomer of VEGF-A), inhibits the binding of the isomer to VEGFR-2 and blocks the downstream pathway of VEGF-165, thus inhibits angiogenesis. | Completed (well tolerated with evidence of efficacy) |
|         | NCT00131144 | Octreotide | Phase 3 | Neuropeptides | Octreotide, a specific SST analogue, can effectively reduce cell death and VEGF overproduction induced by high glucose. | Completed (confirmed the safety profile of long-acting Octreotide) |
|         | NCT01702441 | Nesvacumab | Phase 1 | Neuropeptides | Nesvacumab activates Tie-2 signaling and decreases vascular permeability by inhibiting Ang-2, an antagonist of Tie-2. | Completed (results pending) |
|         | NCT01702441 | SubcutaneousAKB-9778 | Phase 1 | Neuropeptides | AKB-9778 activates Tie-2 signaling by inhibiting VE-PTP, a negative regulator of Tie-2. | Completed (results pending) |
|         | NCT02348918 | Luminate | Phase 2 | Oxidative stress | Luminate is an integrin inhibitor, which inhibits macular edema and improves visual acuity by blocking a variety of integrin receptors. | Completed (results pending) |
|         | NCT02511067 | Tcilizumab/Ranibizumab | Phase 2 | Oxidative stress | Tcilizumab blocks IL-6-mediated signaling by binding to both soluble and transmembrane IL-6 receptors. | Withdrawn |
|         | NCT02314299 | MTP-131 | Phase 2 | Oxidative stress | MTP-131 shows a protective effect on visual function in a diabetic mouse model by attenuating mitochondrial oxidative stress. | Completed (results pending) |
|         | NCT02062034 | Ubiquinone (Q10) | Phase 2 | Oxidative stress | Coenzyme Q10 promotes RGC survival by modulating Bax and Bad protein expression and by preserving mitochondrial DNA content and mitochondrial transcription factor A/oxidative phosphorylation complex IV protein expression. | Completed (ubiquinone improves clinical outcomes and reduces oxidative stress without significant adverse events) |
|         | NCT01726075 | COLIOBASN070660 | Phase 2 | Oxidative stress | Somatostatin eye drops cause general excitation; it also increases the signal-to-noise ratio and leads to a shift in centre-surround balance towards a more dominant centre | Completed (results pending) |
|         | NCT04537884 | UBX1325 | Phase 1 | Oxidative stress | Inhibiting the anti-apoptotic proteins BCL-2 and BCL-XL and selectively kill Senescent cells. | Recruiting |
| AMD     | NCT01175395 | IBI-20089/Lucentis | Phase 1 | Angiogenesis | IBI-20089/Lucentis combines with all VEGF-A subtypes to block cascade reactions. | Completed (Combination therapy IBI-20089 and ranibizumab was well-tolerated and resulted in fewer ranibizumab retreatments. Transient intraocular pressure elevation and cataract progression occurred) |
|         | NCT03668054 | Bevacizumab | Phase 3 | Angiogenesis | Bevacizumab combines with VEGF-A to reduce the binding of VEGF and VEGFR on endothelial cells, thus reducing the permeability of neovascularization. | Completed (well tolerated and resulted in a sustained response regarding VA improvement and CRT reduction) |
|         | NCT02770722 | Squalamine | Phase3 | Complement | Squalamine inhibits multiple angiogenic factors (VEGF, PDGF, and b-FGF). | Unknown |
|         | NCT02684578 | Metformin | Phase 2 | Autophagy | Metformin may protect the visual function of retinal degenerative mice through neuroprotective, anti-inflammatory and anti-apoptotic effects. | Recruiting |
|         | NCT02247531 | Lampalizumab | Phase 3 | Complement | Antibody targeting complement factor D. | Terminated (lampalizumab did not reduce GA enlargement) |
|         | NCT02686658 | Zimura | Phase 2 | Complement | Aptamer targeting complement component 5. | Completed (results pending) |
|         | NCT02503332 | Pegcetacoplan (APL-2) | Phase 3 | Complement | Cyclic peptide inhibitor of complement component 3. | Completed (results pending) |
|         | NCT00935883 | Eculizumab | Phase 2 | Complement | Complement inhibition with Eculizumab to evaluate the effects of CS inhibition on drusen and geographic atrophy. | Completed (Systemic complement inhibition with eculizumab did not significantly reduce drusen volume) |
|         | NCT04756310 | Retilut | Not applicable | Complement | Resveratrol inhibits NADPH oxidase-mediated production of ROS by down-regulating the expression and activity of the oxidase | Completed (results pending) |
hepatoctyes, thus leading to cell proliferation and liver regeneration (Nojima et al., 2016). The fact that exosomes are released by various cell types in both normal and pathological conditions to transport nucleic acids, lipids and proteins between cells, makes exosomes an ideal drug and gene delivery carriers. In particular, exosomes possess edges over other carrier options because of their nano-scale size, low immunogenicity, long circulation time and biodegradability (Ortega et al., 2020).

Recently, the protective role of RPE-derived exosomes (RPE-Exos) in the retina has been recognized (Wang et al., 2021). Due to their minuscule dimensions and lipid membrane, RPE-Exos can readily pass across the retinal-blood barrier, making them ideal therapeutic substances to be delivered into retinal lesions (Wang et al., 2021). Subretinal delivery of RPE-Exos can benefit photoreceptor survival and enhance the retinal function in N-methyl-D-aspartic acid-induced RD models by suppressing inflammatory responses, prompting cell differentiation and inhibiting apoptotic cascades. Besides the protective role of RPE-Exos, studies also show that exosomes derived from mouse neural progenitor cells (NPC-exos) could be specifically internalized by retinal microglia, which protects photoreceptors from cell death. A recent study demonstrated that HN interacted with the polarized RPE, HN is predominantly expressed in the cytosol and largely localized in the mitochondria. It has been reported that HN, encoded from the 16S rRNA region of the mtDNA, is the first MDP discovered within the mammalian mitochondrial genome. In the induced human primary RPE senescence model, HN co-treatment with STAT3 and MAPK signaling pathways.

**Mitochondria-derived peptides**

MDPs have been well-characterized in preclinical assessment in models of macular degeneration, including Humainin (HN), Small Humanin-Like Peptides (SHLP) nicotinamide adenine dinucleotide phosphate; NMDA: N-methyl-D-aspartic acid receptor; PDGF: platelet derived growth factor; PIGF: placental growth factor; RGC: retinal ganglion cell; ROS: reactive oxygen species; SST: somatostatin; VE-PTP: vascular endothelial protein tyrosine phosphatase; VEGF: vascular endothelial growth factor.

| Disease | NCT number | Drug name | Phase | Target classification | Mechanism | Current status |
|---------|------------|-----------|-------|-----------------------|-----------|---------------|
| Theawit |            |           |       |                       |           |               |
| NCT03891875 | Elamipretide | Phase 2 | Mitochondria | Binding to cardiopin and protecting it from oxidation | Completed (results pending) |
| NCT00109499 | AdGVPEF1.11D | Phase 1 | Angiogenesis | AdGVPEF:1.11D is a replication deficient [E1, E3 and E4 deleted] adenovirus vector containing the gene for the PEDF protein, which has anti-angiogenic and neuroprotective efficacy. | Completed (results pending) |
| Glaucous | NCT00476138 | Epigallocatechin-gallate | Phase 1 | Oxidative stress | By counteracting directly oxidative stress to RGC, increasing blood flow in the inner retina, counteracting glutamate toxicity, or by exerting an anti-inflammatory action on retinal tissue. | Unknown |
| NCT00626782 | Ranibizumab | Phase 2 | Angiogenesis | Ranibizumab combines with all VEGF-A subtypes to block cascade reactions. | Completed (more patients in the ranibizumab group required additional glaucoma surgery during the study period) |
| NCT00317577 | Brimonidine | Phase 2 | Autophagy | Brimonidine decreases RGC apoptosis upregulating EAAT1 and downregulating NMDA receptors. | Completed (low-pressure glaucoma patients treated with brimonidine 0.2% who do not develop ocular allergy) |
| NCT01254006 | Forskolin | Not applicable | | Forskolin prevents RGC apoptosis induced by retinal ischemia/reperfusion by acting on the PI3K/Akt signaling pathway. | Completed (results pending) |
| NCT00404729 | Citicoline | Phase 4 | Metabolism | Citicoline acts as an intermediary in the synthesis of phosphatidylcholine through the activation of the biosynthesis of structural phospholipids in neuronal membranes, increases the metabolism of cerebral structures, inhibits phospholipid degradation and induces an increase in the levels of different neurotransmitters and neuromodulators, including noradrenaline in the Central Nervous System. | Completed (significantly improves retinal and cortical bioelectrical responses) |
| NCT01408472 | CNTF | Phase 1 | Neurotrophic factor | Binding of CNTF to its receptor complex activates the JAK/STAT, MAPK/ERK, and PI3K/Akt signaling pathways. | Completed (results pending) |
| Dry eye | NCT04213248 | Umbilical Mesenchymal Stem Cells derived Exosomes | Phase 1 | Exosomes | Umbilical mesenchymal stem cells derived exosomes regulate the activity of intraocular immune cells. | Recruiting |

Ang-2: Angiopoietin 2; b-FGF: basic fibroblast growth factor; BCL-2: B-cell lymphoma-2; CNTF: ciliary neurotrophic factor; IL-6: interleukin-6; NADPH: nicotinamide adenine dinucleotide phosphate; NMDA: N-methyl-D-aspartic acid receptor; PDGF: platelet derived growth factor; PIGF: placental growth factor; RGC: retinal ganglion cell; ROS: reactive oxygen species; SST: somatostatin; VE-PTP: vascular endothelial protein tyrosine phosphatase; VEGF: vascular endothelial growth factor.
Complement inhibitors

Modulation of the complement system by targeting the regulating components has now the new focus on treatment modalities for AMD, DR and glaucoma (Kassa et al., 2019a). Genetic evidence of complement association in the pathogenesis of AMD was discovered in 2005, when a common variant in complement factor H (CFH) gene was noted to be associated with a 7.4 fold increased risk of developing AMD in individuals homozygous for the risk allele (Toomey et al., 2018). Several other genetic variants in complement genes, such as CFB/C2, C3, C5 and CFI, have since been associated with AMD (Heesterbeek et al., 2020). Genome-wide association studies have revealed that of the many complement components, C3 and C5 play prominent parts within the complement cascade and have risen as the leading therapeutic targets in many inflammatory diseases, including AMD (Park et al., 2019; Heesterbeek et al., 2020). Activation of C3 ultimately leads to cleavage of C5 to form key terminal fragments (C5a and C5b). The C5a fragment, found in drusen of AMD patients, is an important inflammatory activator that induces VEGF expression from RPE cells (Liu et al., 2019). C5b leads to the formation of membrane attack complex (MAC) in humoral activation that leads to the amounts of MAC are sub- lytic and protective during inflammation but when the amount of MAC reaches a certain level, MAC becomes lytic, which leads to membrane and cell apoptosis (Kumar-Singh, 2019). Deposition of MAC in Bruch’s membrane and chorio capillaris increases significantly with aging as well as in the AMD (Jaffe et al., 2021). In light of the traditional role of MAC in the pathogenesis of AMD, the importance of cell types, in particular the microglia, that express relevant complement receptors have been acknowledged (Madeira et al., 2015). Microglia constitute the retinal resident immune cell population essential for both tissue homeostasis and pathology (Alves et al., 2020). C5a receptor (C5Ar) and C3ar in microglia/macrophages are required for the cell recruitment and tissue repair following insults, but dysregulated cell response and disturbed C5ar/C3ar activation have been demonstrated to induce inflammation-associated retinal diseases, including uveitis, choroidal neovascularization and macular damage (Nozaki et al., 2006; Zhang et al., 2016). Conversely, depletion of C5aRs suppresses light exposure-induced microglia-mediated inflammatory inflammation and preserves retinal integrity in murine models (Nozaki et al., 2006; Song et al., 2017). Understanding of complement genetic risk has driven approaches to develop therapeutics in both dry and wet AMD, including inhibitors and gene therapies targeting complement pathway (Holz et al., 2018; Lee et al., 2021). A phase II study on APL-2 treatment, a C3 inhibitor, achieved a significantly retarded progression of geographic atrophy (GA, an advanced form of dry AMD) at 12 months by 29% compared with sham treatment when administered monthly, awaiting the validation in extensive phase III clinical trials (Kassa et al., 2019b) (Table 1). Eculizumab is a monoclonal antibody that binds to C5 and blocks its proteolytic activation (Rother et al., 2007). Approved for the treatment of paroxysmal nocturnal hemoglobinuria in 2007, eculizumab has become the first complement inhibitor available to patients. Although some complement inhibitors did not show tractable effects in clinical trials for GA, there are still ongoing trials that evaluate C3 inhibition (pegcetacoplan, Apellis Pharmaceuticals; NCT03525600, NCT01826319) or C5 inhibition (activa pegylated C5 antibody; NCT04435366) as treatments for atrophic or neovascular AMD (Kim et al., 2020) (Table 1). The use of ocular gene therapy through targeting complement components has also been under phase I trials for aAMD, including GT005 that induces CFI expression and HMR59 that expresses C59 to prevent the formation of MAC (Lee et al., 2021). In progressive DR subjects, the vitreous proteome studies have demonstrated several complement components, such as C3, CFI, CFB, C4A, C4C and C5 (CFH) (Lu et al., 2020). A recent study identified a localized elevation of C3, especially the 110 kDa activated fragment C3b2a, and a concurrent upregulation of CFH along with activated microglial infiltration in the progressive DR vitreous (Shahulhameed et al., 2020). Notably, a disease course-dependent increase in microglial-mediated activation of the alternative complement pathway from the early to late DR suggests a clinical relevance of the alternative complement pathway as a possible biomarker for the disease progression (Xu and Chen, 2016). Although the traditional glaucoma medication focuses on IOP reduction, recent focus has been targeted to immune-mediated processes and complement regulation of the ganglion cell dendritic tree (Williams et al., 2016). For example, increased expression of several complement factors (C5, C3 CHF) in retinal protein samples of glaucoma patients was noted (Gassel et al., 2020a; Hubens et al., 2021). In increased levels of protein C3 was a downstream feedback mechanism of the bystander cells, C3 and C5b are involved in the neuroprotection of glaucoma. Notably, the injection of C5 antibody preserves optic nerve in experimental glaucoma (Gassel et al., 2020b). C1q subunit, comprised of C1qa, C1qb and C1qc, is the initiator of the classical complement cascade. Studies indicated that C1qa deficiency prevented RGC loss in glaucoma and was protective in other neurodegenerative diseases, whereas C3 deficiency showed opposite effects (Kumari et al., 2015; Harder et al., 2017).

Senolytics

Recent experimental and clinical evidence reveals multiple roles of senescence in health and disease (Lee et al., 2021). Cellular senescence is an adaptive cell process in response to stress, initiated by the activation of tumor suppressor proteins such as p53/p21CIP1 and p16INK4A/retinoblastoma protein (RB). Recent data demonstrate that senescence can occur in both mitotic and postmitotic cells, heightened with an inflammatory secretome and altered cell metabolism. The senescent state is complex with an array of molecular and cellular characteristics (Kim et al., 2021). The loss of cell senescence in GA, photoreceptor cells and neural retina cells have been demonstrated to be effective in reducing senescent cell burden pharmacologically using senolytic, such as a cocktail of dasatinib, a pan-tyrosine kinase inhibitor, and quercetin, a naturally occurring flavonoid (Zhu et al., 2015), or genetically inducing cell suicide via caspase 8 gene transfection. So far, several senolytics, including dasatinib plus quercetin, navicloaxil and 17-DMAG and a peptide that targets the Bcl-2- and p53-related anti-apoptotic pathways, have been demonstrated to be effective in reducing senescent cell burden in mice. UBX1325, an inhibitor of Bcl-2 protein (BCL-xL), is currently under phase I trial for diabetic macular edema, also with ongoing evaluation for AMD (Lee et al., 2021) (Table 1). Interestingly, a recent study demonstrates promising senolytic effects of another BCL- xl inhibitor, UBX1967, which can eliminate senescent endothelial cells and promotes vascular repair in a mouse model of retinopathy (Crespo-Garcia et al., 2021).

Antioxidants

The retina represents one of the highest oxygen-consuming tissues in...
the human body. During ageing, the retina suffers from a low-grade oxidative stress caused by environmental factors such as continuous exposure to light, intensive oxygen metabolism, and the presence of photosensitizers. The oxidative insult sustains for decades and increases in level with advancing age. Increased levels of ROS generated by chronic oxidative stress may exceed the anti-oxidation capability of the retina and lead to modification of biological macromolecules and damage of the cells (Khanda and Lotery, 2010).

In AMD, oxidative stress works in concert with other risk factors, such as ageing, smoking, phototoxicity, and genetic factors, leading to sub-RPE drusen deposition, RPE/photoreceptor cell death, and the resultant inflammatory and immune responses (Hanus et al., 2015). These processes may aggravate oxidative stress and inflammation, forming a vicious cycle propelling AMD pathogenesis. Antioxidant supplements and ROS scavengers have been proposed as potential therapies for assorted AMD. Nutritional supplementation (lutein, zeaxanthin, and polyunsaturated fatty acids) with antioxidants and micronutrients can effectively reduce the progression toward advanced forms of AMD (Bonds et al., 2014).

The hyperglycemic microenvironment in diabetes mellitus can promote a nonenzymic binding of glucose to macromolecules (amino acids in proteins, lipids, and nucleic acids), forming AGEs (Sahajpal et al., 2019), a group of highly reactive compounds prevalent in diabetic vasculature. AGEs bind to their receptors, known as RAGE (Receptor for AGE), and induce the transcription of NF-κB with disorders in endothelial cell function (Stitt, 2010). NADPH oxidase is a main enzymatic source of ROS and is directly related with promoting pathological neovascularization in the retina by hyperglycaemia. The development of specific NADPH oxidase inhibitors, such as diphenyleneiodonium and apocynin, may improve DR treatment (Akimoto et al., 2019). Another option for DR treatment is α-LA inversely regulates p-AMPK and OGT or TXNIP levels, as well as ROS modified proteins, and increased GPx levels in the retinas of diabetic patients (Cicero et al., 2015). Moreover, α-LA inhibits p38α MAPK (El-Remessy et al., 2006). However, the potential benefit of acetylcholine-stimulated retinal barrier breakdown in diabetic animals by inhibiting p38-MAPK and A2A adenosine receptor and suppresses late-stage neuroinflammation (Zantut et al., 2020). Their endogenous counterparts, including endocannabinoid, the binding receptors and their metabolic enzymes, together constitute the endocannabinoid system in the retina. The balanced composition of this system plays important neuroprotective and neuro-regenerative roles upon intrinsic or extrinsic insults. In addition to the expression of both CB1 and CB2 receptors in human RPE cells, CB1 receptors are also expressed in the outer segments of photoreceptors, the inner plexiform layer, outerplexiform layer, inner nuclear layer and ganglion cell layer. The two primary endocannabinoid ligands, 2-arachidonoylglycerol (2-AG) and anandamide, are also detected in the human retina (Matias et al., 2006).

Studies across different species including human have demonstrated the therapeutic effect of CBDs in lowering the intraocular pressure in glaucoma, as well as in the cell protection of both glaucoma and DR (Rapino et al., 2018). CBD has also been used in clinic, it has been shown to prevent acute cerebral ischemia, phototoxicity in the mouse model, and scotopic sensitivity in glaucoma patients (Chen et al., 2005). Studies across different species including human have demonstrated the therapeutic effect of CBDs in lowering the intraocular pressure in glaucoma, as well as in the cell protection of both glaucoma and DR (Rapino et al., 2018). CBD has also been used in clinic, it has been shown to prevent acute cerebral ischemia, phototoxicity in the mouse model, and scotopic sensitivity in glaucoma patients (Chen et al., 2005). In the ischemia-reperfusion injury of glaucoma model (Reardon et al., 2003), CBD blocks retinal inflammation by equilibrating the nucleoside transporter and A2A adenosine receptor and suppresses the release of TNF-α (Li et al., 2006). Their endogenous counterparts, including endocannabinoid, the binding receptors and their metabolic enzymes, together constitute the endocannabinoid system in the retina. The balanced composition of this system plays important neuroprotective and neuro-regenerative roles upon intrinsic or extrinsic insults. In addition to the expression of both CB1 and CB2 receptors in human RPE cells, CB1 receptors are also expressed in the outer segments of photoreceptors, the inner plexiform layer, outerplexiform layer, inner nuclear layer and ganglion cell layer. The two primary endocannabinoid ligands, 2-arachidonoylglycerol (2-AG) and anandamide, are also detected in the human retina (Matias et al., 2006).

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**Conclusion**

RD progresses through perturbation in multiple pathways including cellular metabolism, oxidative stress, cellular senescence, autophagy housekeeping and associated inflammatory responses both locally and systemically. As such, different strategies are needed to be optimally targeted in order to reverse RD and prevent its progression. Among the molecular compounds that regulate autophagic activities, Autophagy is regulated by mTOR or AMPK-dependent pathways (Danesh-Meyer, 2021). Strategies counteracting oxidative stress and enhancing autophagic flux and slows down DR progression (Palmieri et al., 2017; Lotti et al., 2018).
complexity and convergence of affected pathways, it may be that an identification of a cross-regulatory drug or a portfolio consisting of poly-drugs in low doses of each, together with gene or cell therapies, could create improved outcomes for RD and other age-associated diseases. Secondly, under certain stresses, the different types of neuropathology underlying diseases and resident macropathies in the retina may not necessarily change in a synchronized way. The heterogeneity can be reflected by the diverse contribution of cell subgroups to the course of degeneration. In light of that, regimes accurately matching the tempo-spatial aspects of the degenerative program in the eye should be carefully designed. Thirdly, similar to other neurological diseases, RD and other typical chronic conditions, drug treatment usually requires long term and frequent administration. Drug accessibility crossing the blood-retinal barrier is an issue requiring special addressing. Therefore, coupling therapy with an efficient drug delivery is essential to ensure bioavailability and selective targeting, as well as controlled drug release with minimized dosing frequency. For instance, a single or cargo of small molecules targeting particular cell types, such as photoreceptors and vascular cells, could be encapsulated into or conjugated with nanoparticle or nanoscale PEGylated lysosomes to enable intracocular and even intracellular targeting (Gahluaut et al., 2015; Himawan et al., 2019).

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