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Protecting the Aging Retina

Shen Nian and Amy C.Y. Lo

Abstract

Aging retina, notably the aging macula, is prone to develop degenerative diseases, such as age-related macular degeneration (AMD), the leading cause of visual loss in individuals aged 65 or above in developed countries. However, current treatments are very limited. Since degeneration, dysfunction, and death of retinal neurons are demonstrated in the pathogenesis of AMD, neuroprotective strategies could serve as a possible way to treat AMD. In this chapter, we will briefly introduce risk factors, pathophysiology, affected neurons, classification, clinical manifestation, and current treatments of AMD. Finally, neuroprotection in both AMD animal models and patients will be discussed.

Keywords: neuroprotection, degeneration, photoreceptor, age-related macular degeneration, vision loss

1. Introduction

Retina, which forms the innermost layer of the eyeball, is considered as the end organ of the central nervous system. Macula, located in the central and posterior part of retina, possesses the highest concentration of photoreceptors and, therefore, is responsible for central vision and high-resolution visual acuity (VA). The fovea is a tiny pit in the center of the macula and in charge of the central, sharpest vision. Unfortunately, the macula is more prone to experience degenerative changes with age, such as age-related macular degeneration (AMD), leading to visual impairment.

Due to the increase of life expectancy worldwide, the size of aging population will become larger in the coming decades [1]. According to “World Population Prospects: The 2017 Revision” released by the United Nations, the number of persons aged 60 or above will more than double, from 962 million in 2017 to 2.1 billion by 2050. The number of people aged 80 or above is predicted to triple by 2050, from 137 million in 2017 to 425 million by 2050 [2]. In mainland of China, people aged above 65 represented 11.4% of the total population in 2017 [3]. As a consequence, the increasing prevalence of AMD will be foreseen globally in the future.

In 2015, it was estimated that AMD was the fourth leading cause of blindness and the third most common cause of moderate to severe visual impairment globally [4]. The meta-analysis performed by Wong and collaborators has estimated that the number of persons with AMD will increase from 196 million in 2020 to 288 million in 2040 worldwide [5]. A similar trend is observed in the projected number of individuals affected by AMD in China, rising from 31.23 million in 2020 to 55.19 million in 2050 [6]. In addition, the prevalence of late AMD did not show significant difference among Asian, European, and North American studies, whereas the number of individuals with early AMD was more in European and North American studies than in Asian studies [7].

2. Anatomy and function of the retina

The eye is composed of three layers, which are the inner retina layer, middle vascular choroid layer, and outer fibrous sclera layer, respectively. Retina, the innermost layer of the eye, consists of two parts: the inner transparent neurosensory retina and outer pigmented epithelial layer—the retinal pigment epithelium (RPE). There is a potential space between neural retina and RPE, called subretinal space. In the neural retina, the neural cell bodies are situated in three layers (**Figure 1**), including the outer nuclear layer (ONL) occupied with nuclei of photoreceptors; the inner nuclear layer (INL) filled with nuclei of horizontal, bipolar, and most of the amacrine cells; as well as ganglion cell layer (GCL) containing nuclei of retinal ganglion cells and the rest of displaced amacrine cells. Additionally, axons and dendrites of these retinal neurons constitute two synaptic layers: the inner plexiform layer (IPL) and outer plexiform layer (OPL) [8]. The RPE cells form a continuous polarized cell monolayer with its apical surface adjacent to the outer segment apices of the photoreceptors and its basal aspect lying on supportive substrate Bruch's membrane.

Retinal neurons are mainly distributed in three layers: ONL with nuclei of photoreceptors; INL with nuclei of horizontal, bipolar, and most of the amacrine cells; and GCL with nuclei of retinal ganglion cells and the rest of displaced amacrine cells. Additionally, axons and dendrites of these retinal neurons constitute two synaptic layers, including IPL and OPL [8].

Photoreceptors are divided into two types: rods, which are dominated in the peripheral retina and responsible for dim light vision and detecting movement and contrast, and cones, which are dominated in the macula, especially the fovea (only cones), and are responsible for bright light vision and sensing color vision

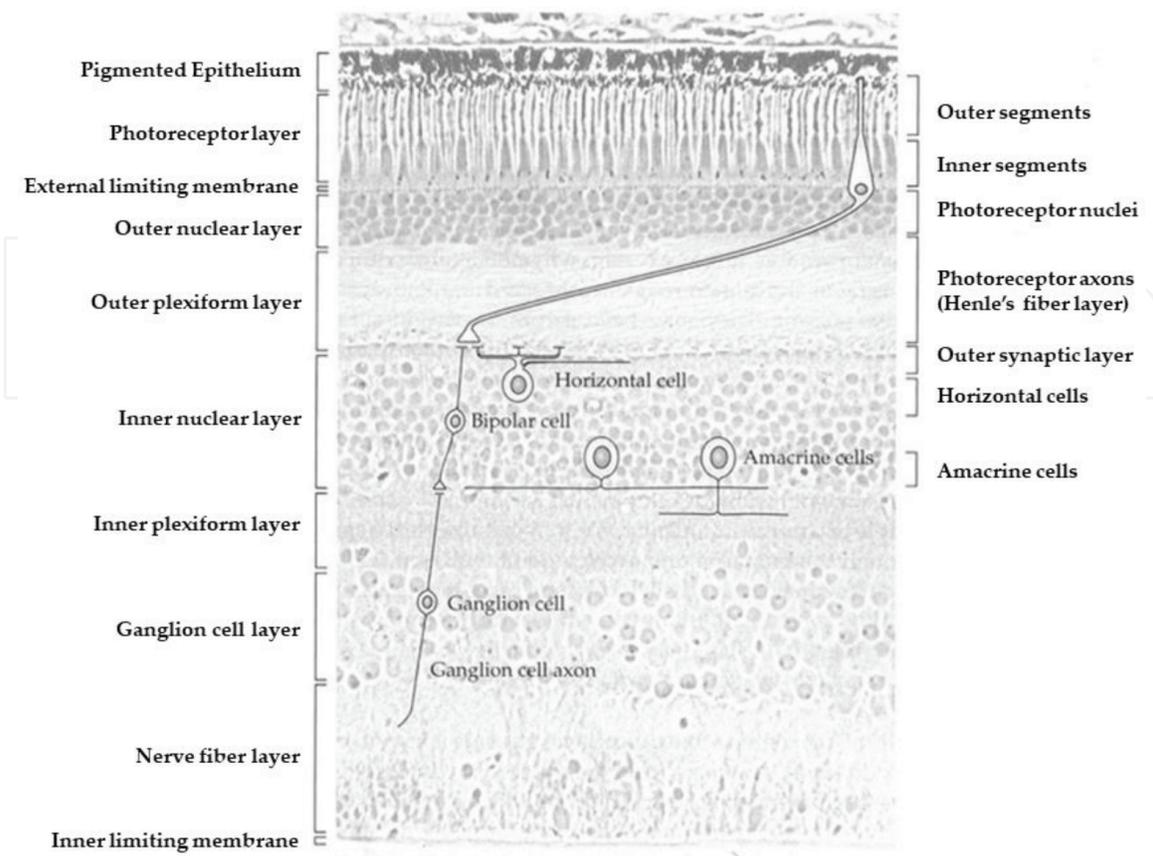


Figure 1.
Retinal layers of the human eye.

and resolution. Outer segments of the photoreceptor are generated by the cell body, and the distal parts of outer segments are phagocytosed by RPE every day. There are abundant mitochondria in inner segments to supply energy for these cells with high metabolic rate. Bruch's membrane, where the RPE cells are tightly attached, consists of five layers including, from inner to outer, the RPE basal lamina, inner collagenous zone, elastic layer, outer collagenous zone, and basement membrane of the choriocapillaris [9].

In brief, the function of the retina is to convert the external light signals into electrical impulses by photoreceptors. The impulses, which are partly integrated locally by horizontal cells and amacrine cells, are then processed by bipolar cells and sent to ganglion cells which further transmit them to the brain. Moreover, RPE is crucial for maintaining the microenvironment of neural retina by exchanging nutrients and wastes between neural retina and choroid, secreting numerous growth factors, phagocytosing shed photoreceptor outer segments (POS), absorbing light and converting all-trans-retinal into 11-cis-retinal [10]. Any defects in any of these functions may result in retinal degeneration, deficits of visual function, and eventually loss of sight.

3. Current knowledge of AMD

3.1 Classification and clinical manifestations

A variety of classification systems are employed for both clinical and basic research of AMD. However, the most commonly used classification is the one defined by the Age-Related Eye Disease Study (AREDS) in terms of the characteristics of drusen (yellow deposits in the macula), abnormal hypo- or hyperpigmentation in the first eye, and how it affected the fellow eye. Based on the above criteria, AMD is classified into 4 categories: (1) no clinical manifestation of AMD if there was no drusen or only non-extensive, small drusen (<63 μm in diameter) in both eyes; (2) mild AMD classified by extensive small drusen, non-extensive intermediate drusen (63–124 μm in diameter), or abnormalities of pigments in at least one eye; (3) intermediate AMD characterized with large drusen (>124 μm in diameter), extensive intermediate drusen, or noncentral geographic atrophy (GA) in at least one eye; (4) advanced AMD defined as central GA or choroidal neovascularization (CNV) resulting in VA less than 20/32 [11–13].

There are two clinical types of advanced AMD: a non-exudative or atrophic (dry) form, accounting for 90% of AMD, and an exudative (wet) form, accounting for only 10% of AMD. The atrophic form is characterized by progressive degeneration of RPE cells and photoreceptors in the macula, affecting central vision to varying degrees over months or years [14, 15]. The exudative form is associated with CNV in the submacular area and subsequent retinal hemorrhage due to leakage of these newly formed fragile blood vessels, leading to severe central vision loss within a very short period of time [15].

At the early stage of AMD, patients are normally asymptomatic and may be diagnosed by the presence of round, yellowish drusen through the routine ophthalmological examinations. Patients with CNV usually suffer from sudden loss of vision, describing unexpected deterioration of central visual field, distorted straight line (metamorphopsia), and/or a dark area in the central visual field (scotoma). On fundus examination, macular edema and hemorrhage are observed and fluorescein angiography shows leakage. In non-exudative AMD, it takes years for patients to develop visual loss gradually, and fundus examination shows a well-defined RPE atrophic area with depigmentation (**Figure 2**) [15].

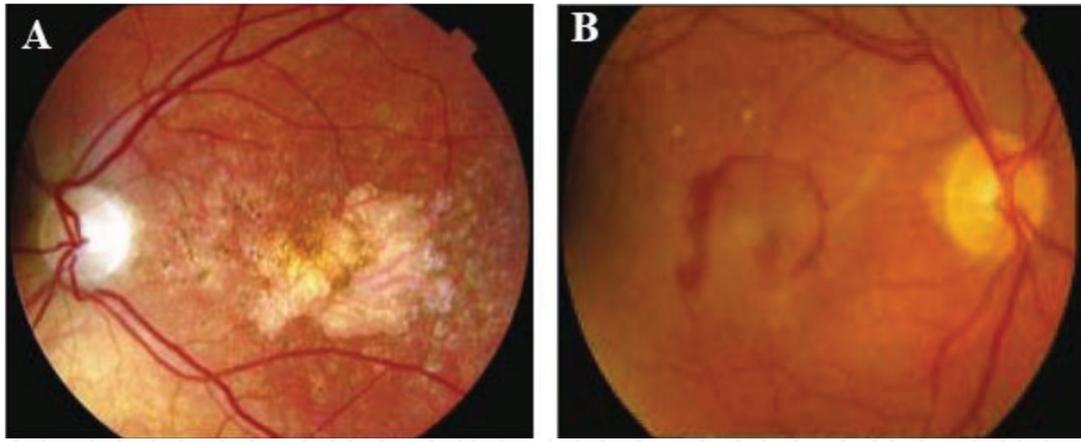


Figure 2. Representative fundus of AMD patients. (A) Non-exudative form of AMD with a well-defined atrophic region and (B) exudative form of AMD with retinal hemorrhage and macula edema [16].

3.2 Risk factors

A number of risk factors are thought to be related to the pathogenesis of AMD, such as increasing age, smoking, family history of AMD, overweight or obesity, cataract and cataract surgery, eye exposure to the sunlight, etc. Of these factors, age is the strongest risk factor, with around 30% of cases older than 85 years diagnosed with AMD in US [17, 18]. The risk of developing AMD was reported to be more than triple in patients above 75 years than patients aged between 65 and 74 years [18, 19]. In populations of European ancestry, the projected prevalence of late AMD was 0.08% at age 50, 0.33% at age 60, 1.38% at age 70, 5.60% at age 80, and 20.10% at age 90, respectively [20]. Similarly, the estimated prevalence of any AMD increased from 2.44% in persons at the age of 45–49 years to 18.98% in persons at the age of 85–89 years [6].

Ethnicity and family history are also strongly related with AMD prevalence. The highest rate was reported in Caucasians, followed by Hispanics and Asians, while African Americans showed the lowest morbidity rate [21]. Increased risk of AMD was observed in individuals with positive family history, approximately three to six times higher than it was for those from the general population [22]. Furthermore, genetic studies have revealed 34 loci linked to AMD until now, of which complement factor H (CFH) on 1q31.3, age-related maculopathy susceptibility 2 (ARMS2) on 10q26, and CFB/C2 on 6q21.3 were the most discussed genes [15, 23, 24].

The strong relationship between cigarette smoking and development of AMD has been widely accepted [17, 25, 26]. Several studies revealed that current smoking was strongly associated with the progression of AMD [27]. Moreover, past smoking was reported to be a risk factor to develop AMD as well, especially in the rural areas [28]. There was an increased risk for individuals with high intake of several types of fat, such as omega-6 polyunsaturated fatty acids and saturated fats, whereas diets rich in monounsaturated fatty acids might reduce the prevalence of AMD [29]. Inadequate uptake of antioxidants also resulted in AMD, and numerous studies have suggested that antioxidant supplementation, including vitamins, lutein, zeaxanthin, beta-carotene, zinc, etc., helped to halt the progression of AMD to some extent [12, 30, 31].

The effects of sunlight exposure on the occurrence of AMD are controversial. A study performed by Khan and colleagues demonstrated that no significant association between light exposure and AMD was observed when comparing patients at the end stage of AMD with spouse controls [32]. However, other studies suggested that damages induced by either ultraviolet (UV) or visible sunlight might lead to

AMD [33–35]. There was conflicting evidence regarding the role of cataract surgery in the progression of AMD [36]. Earlier, a large population-based research indicated a stronger relationship between cataract surgery with the development of end-stage AMD, especially neovascular AMD, in older patients [36, 37]. On the contrary, several recent clinical studies failed to demonstrate similar results [36, 38].

In addition to the risk factors mentioned above, other relevant factors included hypertension, cardiovascular diseases, iris color, hyperlipidemia, diabetes, alcohol consumption, and so on [22]. According to a systematic review of 18 prospective and cross-sectional studies and 6 case-control studies engaging 113,780 individuals, advancing age, cigarette smoking, previous cataract surgery, and family history of AMD were considered as the strong risk factors of AMD, while hypertension, cardiovascular disease, overweight or obesity, and elevated plasma fibrinogen were regarded as the moderate risk factors [17].

3.3 Pathophysiology

AMD is regarded as a complicated multifactorial disease, although the exact pathogenesis still remains poorly understood. It is generally recognized that impairment of aged RPE cell functions served an important role in the progression of non-exudative AMD. The aged RPE cells were less efficient in phagocytosing and degrading POS, resulting in the progressive accumulation of lipofuscin consisting of phagosomal and lysosomal constituents in the cytoplasm. The cytotoxic elements in lipofuscin, such as bisretinoid fluorophore, were able to generate reactive oxygen species leading to the damage of DNA, lipids, and proteins [39].

Another age-dependent change was the formation of focal extracellular yellow deposits known as drusen, the hallmark of AMD, between the RPE and Bruch's membrane. Accumulation of drusen relied on the changes in the permeability of Bruch's membrane due to the decline of RPE cell functions with aging [40]. In addition, it has been estimated that breakdown of choriocapillaris, which was next to RPE and Bruch's membrane, resulted in insufficient elimination of extracellular wastes causing drusen [41]. According to their shape and size, drusen are separated into small (<125 μm), round hard drusen with well-defined borders, and relatively large, (125–250 μm) soft drusen with poorly defined borders. Soft drusen, especially with depigmentation or pigment abnormalities, was considered to be an indication to give rise to severe vision loss at the late stage.

The mechanism of drusen causing adjacent RPE and photoreceptors' damage was not only dependent on the structural disturbance of RPE and photoreceptor by them, but also on the indirect effects through stimulation of local inflammation and immune system [42, 43]. Components in complement pathway and inflammatory processes were observed in drusen and aged RPE cells that are closely related to drusen [42]. It was demonstrated that in AMD, genetic variation of factor H gene (HF1/CFH) induced the abnormal activities of factor H (the inhibitor of complement cascade) in drusen, leading to the activation of complement pathway and subsequent inflammation in subretinal tissues [44]. Furthermore, in AMD patients, decreased CFH level was reported in smokers than nonsmokers, suggesting the activation of complement cascade might contribute to the significantly higher risk of AMD progression in cases with smoking [45].

DICER1, the ribonucleic acid (RNA)-cleaving enzyme, was decreased in RPE cells in cases with non-exudative AMD. A group of researchers in the University of Kentucky suggested that the lower level of DICER1 led to the lower rate of Alu RNA degradation in RPE cells. Therefore, accumulation of Alu RNA in cytoplasm resulted in RPE cytotoxicity and consequent degeneration via activating NLRP3 inflammasome [46, 47].

In exudative AMD, local nonspecific inflammation stimulated the upregulation of angiogenic factors, such as vascular endothelial growth factor (VEGF), and/or downregulation of anti-angiogenic factors, such as pigment epithelium-derived factor (PEDF), causing CNV development in the avascular outer 1/3 retina. The new vessels are fragile, thus macular edema and hemorrhage occur due to the leakage of these new blood vessels, which finally resulted in the fibrovascular scars in the macula [41, 48].

3.4 Affected neurons

Due to the dysfunction of aged RPE cells, especially the failure of POS phagocytosis, photoreceptor loss occurs subsequently. Although the most remarkable clinical and pathological injuries are present in RPE and its underlying Bruch's membrane, it is the structural and functional disruptions, even the death of photoreceptors, via either atrophic or neovascular process, that take responsibilities for the visual impairment in AMD. Furthermore, the condition of photoreceptors directly reflects the significance of lesions in RPE/Bruch's membrane complex.

It is crucial to identify which type of photoreceptors are most severely damaged in AMD, not only for the potential therapeutic strategies targeting the most affected cells, but also for investigation of mechanism of these pathological changes. The rate of rod and cone degeneration is representative in different situations affecting photoreceptors. In aging retina without age-related maculopathy, the number of cells in the cone-dominated fovea remained stable, while the number of rods in the parafovea was reduced by 30% [49]. In both non-exudative and exudative forms of AMD, photoreceptors were lost. In addition, more rod loss was observed than that of cones; gradually, only degenerated cones were left; finally, all photoreceptors might die [50]. The pathological changes mentioned above were consistent with the functional research exhibiting that scotopic sensitivity decreased more than photopic sensitivity in cases with AMD [51]. Maeda and colleagues revealed the apoptosis of photoreceptors after RPE damage caused by intravitreal injection of ornithine in rats, indicating the important role of RPE cells in maintaining photoreceptor integrity [52]. In AMD patients, apoptotic photoreceptors and RPE cells (TUNEL positive) were observed as well. Most of TUNEL-positive photoreceptors were rods and located at the edge of RPE atrophy. Moreover, Fas was upregulated in apoptotic photoreceptors, indicating Fas/FasL might be involved in the apoptosis process [53]. Studies performed by Kim and collaborators demonstrated that significant reduction of photoreceptors was shown in the areas where RPE cells were totally lost in GA, and where disciform scar formed in wet AMD [54, 55]. In terms of disciform scar, thickness of the scar was closely associated with photoreceptor loss, which means that the thicker the disciform scar, the less photoreceptors survived [56].

In addition to photoreceptors, other retinal neurons are also affected. Joshua et al. first reported that TUNEL-positive cells were detected in the inner side of INL, indicating that these cells might be amacrine cells [53]. In cases with GA, retinal ganglion cells were significantly decreased by 30.7% compared to age-matched control. However, cell nuclei in INL were not significantly different [54]. In wet form of AMD, a decrease of ganglion cells and increase of cells in INL were observed, but there was no significant difference [55].

3.5 Current treatments

Several treatments have been adopted for AMD management. However, current therapeutics can only slow the progression of the disease, trying to delay the onset of vision loss as much as possible.

To date, there are no approved drugs for the dry form of AMD. Therefore, much effort has been made to reduce risk factors. Among various risk factors, oxidative stress induced by inflammation, light exposure, and so on is considered as one of the most important risk factors for the occurrence and progression of AMD. Numerous studies have been conducted to evaluate the relationship between antioxidant nutrition supplementation and AMD. In the Age-Related Eye Disease Study (AREDS), it was demonstrated that oral dietary supplementation containing vitamin C (500 mg/day) and E (400 IU/day), zinc oxide (80 mg/day), cupric oxide (2 mg/day), and beta-carotene (15 mg/day) can decrease the risk of development of AMD from intermediate stage to advanced stage [11]. Since beta-carotene was observed to increase the risk of lung cancer in cigarette smokers, and 80 mg/day zinc is out of tolerance for individuals, there were elimination of beta-carotene, decreased dose of zinc (25 mg/day), and adding of lutein and zeaxanthin in the AREDS2 formula [12, 57, 58]. A 10% reduction in developing to advanced AMD was present in patients treated with AREDS2 formula containing lutein and zeaxanthin [59]. In addition, healthy diet rich in fish, green leafy vegetables, and nuts together with healthy lifestyle are strongly recommended to reduce AMD risk factors [15].

For the wet form of AMD, therapies mainly focus on halting the progression of CNV. Thermal laser photocoagulation is the first treatment to stop the progression of CNV successfully, but with no significant vision improvement and high recurrence of CNV. Photodynamic therapy with verteporfin can selectively damage the CNV tissue without additional injuries of neighboring tissue, but this therapy has no effects on visual improvement either. In terms of upregulation of VEGF in the development of CNV, intravitreal injection of anti-VEGF drugs has been widely used by ophthalmologists as a standard treatment. Anti-VEGF drugs (Pegaptanib sodium, Ranibizumab, and Bevacizumab) for exudative AMD have demonstrated exciting results: the vision in the majority of patients remained stable for 1 year, of which 40% of patients had visual improvement. Surgical intervention to remove CNV and submacular hemorrhage did not improve VA, which is the result of recurrence of CNV [15, 60].

4. Neuroprotection in AMD experimental studies and clinical approaches

Neuroprotection comprises a large number of therapeutic interventions to improve survival of neurons by modifying the structure and function of neurons, and/or their microenvironment. Initially, neuroprotective therapies are focused on central nervous system diseases including stroke, Alzheimer's disease, Parkinson's disease, etc. Since retina is regarded as the end part of central nervous system, a series of neuroprotective strategies has been applied to prevent vision loss by protecting retinal neurons. Furthermore, tremendous neuroprotective strategies are under investigation in both experimental and clinical research.

4.1 Studies in animal models

Neurotrophic factors, belonging to the family of growth factors, have the ability to promote survival of retinal neurons. Ciliary neurotrophic factor (CNTF) is one of the most extensively studied neurotrophic factors for neural retina protection. La Vail and collaborators first reported that intraocular injection of CNTF obviously prevented photoreceptor death from light-induced damage in Sprague Dawley rats [61]. Subsequently, intravitreal injection of adenoviral vector containing CNTF cDNA in rd1 mice, a naturally occurring mouse model for

retinal degenerative diseases, demonstrated the reduction of photoreceptor loss, conservation of ONL thickness, and increase of photoreceptor segments' length. Moreover, the amplitudes of a-wave and b-wave in electroretinogram (ERG) were significantly increased compared with those of the control group, suggesting the preservation of retinal functions [62, 63]. Later, long-term protective effects of photoreceptors were shown using adeno-associated virus to deliver CNTF to the retina [64]. In order to sustainably deliver neurotrophic factors, encapsulated human RPE cells secreting CNTF were transplanted into the vitreous of rcd1 dog (a dog model of retinal degeneration). A significant increase of ONL thickness was observed in the treated eye as a result of continuous release of CNTF at the nanogram level [65]. No adverse effects were exhibited in the retina of transplanted eyes during the whole experiment period (7 weeks). In addition, CNTF was proved to protect loss of cone outer segments, an early sign of cone degeneration, indicating that CNTF could not only slow or halt progression of degeneration but also might reverse degeneration [66].

Placental growth factor (PIGF), one of the members of vascular endothelial growth factor family, was believed to prevent neuronal injury in the brain. In the retina, the role of PIGF was exhibited quite differently in *in vitro* and *in vivo* studies. Blue light-induced murine photoreceptor cell death was significantly attenuated after the treatment of PIGF by suppressing caspase-3/7 activity through the mitogen-activated protein kinase (MEK) and phosphoinositide 3-kinase (PI3K) pathway. Anti-PIGF antibody eliminated these protective effects [67]. However, in the light-induced retina-damaged mouse model, PIGF induced decreased ONL thickness and dysfunction of retina. Anti-PIGF antibody diminished neuroretinal injury and disruption of RPE cell-cell junctions after exposure to the white light for 3 h [68]. The opposite effects of PIGF and its antibody in mice were later found to be due to the hyperpermeability of RPE induced by PIGF, leading to the breakdown of retina-blood barrier and subsequent damages [68].

Ursodeoxycholic acid (UDCA) and its taurine-conjugated derivative tauroursodeoxycholic acid (TUDCA) were first found in the bile acid of hibernating bears. They have been used for liver detoxification, dissolution of gallstone and kidney stone, suppression of convulsions, and visual improvement in traditional Chinese medicine for a very long time. According to the theory of modern medicine, UDCA and TUDCA exhibit neuroprotective effects through prevention of cell apoptosis [69]. TUDCA treatment significantly preserved the number and structure of photoreceptors and retinal functions in different murine models of photoreceptor degeneration, including rd10 mice, rd1 mice, BALB/c mice, Bardet-Biedl syndrome type 1 mice, and transgenic P23H rats [69]. Furthermore, TUDCA manifested greater protective effects in cones [70]. *In vitro* studies using photoreceptor 661 W cells revealed that reduced endoplasmic reticulum (ER) stress and improved trafficking of cyclic nucleotide-gated channels in cones contributed to neuroprotective effects of TUDCA [71]. In addition, TUDCA improved phagocytosis of POS in H₂O₂-treated RPE cells via activating Mer tyrosine kinase receptor (MerTK), which indirectly protected photoreceptors [72].

Endogenous and exogenous progesterone have been certified to have neuroprotective effects in brain and retina for several decades. A broad range of studies have been conducted in either light-damaged or genetic murine models of retinal degeneration, demonstrating improvement in photoreceptor survival, decreased gliosis, and reduced retinal dysfunction after administration of progesterone or synthetic progestins [69]. A group of researchers in Spain revealed that rd1 mice orally administered with progesterone (100 mg/kg body weight) at postnatal day 7 (P7) exhibited significantly decreased number of apoptotic cells in ONL in the far peripheral retina and increased amplitude of ERG b-wave at P15, but no

significant change was observed at P17. There was also a transient reduced gliosis in the treated rd1 mice [73]. Similar results were observed with oral administration of synthetic progestin, known as the FDA-approved Norgestrel, showing reduction of photoreceptor death by 70 and 75% in light-damaged mouse model and rd10 mice, respectively [74]. The rescue effects were achieved by increasing production of basic fibroblast growth factor and its downstream pro-survival reactive oxygen species [74, 75].

Crystallins, critical family members of small heat shock proteins, have been identified to have novel functions in both retina and RPE as in the lens, such as anti-apoptosis and anti-inflammation. α B-Crystallin is secreted in exosomes released from apical surface of polarized RPE cells and accumulates in the matrix among photoreceptors, and therefore may protect neighboring RPE and photoreceptors [76]. RPE cells in α B-crystallin knockout mice exhibited high susceptibility to oxidative stress and endoplasmic reticulum stress compared to the RPE cells from wild-type mice. Furthermore, RPE cells overexpressing α B-crystallin were more resistant to apoptosis, indicating the protective effects of α B-crystallin [77]. In the mouse model of AMD induced by sodium iodate (NaIO₃), absence of α B-crystallin accelerated RPE apoptosis with subsequent death of photoreceptors through upregulation of AKT phosphorylation and expression of peroxisome proliferator-activator receptor- γ , suggesting α B-crystallin, especially the small peptide called mini cry, may play an important role in the protection of retinal degeneration [77]. In order to prolong the life of mini cry in the vitreous, free mini cry was fused to form an elastin-like polypeptide (ELP), which could be detected in the vitreous for up to 2 weeks. One intravitreal injection of ELP-linked peptide prevented RPE cells from apoptosis, inhibited activation of caspase-3 activation, and protected neural retina for up to 1 month after NaIO₃ challenge [78].

NF-E2-related factor 2 (Nrf2) is a transcription factor that regulates antioxidant responses in many tissues and cell types, providing protection against oxidative stress. Under the oxidative stress, Nrf2 is translocated from cytoplasm to nucleus, and subsequently binds to the corresponding sites to activate transcription of a wide range of antioxidant genes. In the central nervous system, Nrf2 was proved to slow the neurodegeneration by means of antioxidative stress and neuroinflammation [79]. In the mice undergoing optic nerve crush (an animal model of glaucoma), retinal ganglion cells were significantly decreased than in the wild-type mice. With the treatment of Nrf2 activator, retinal ganglion cell loss was decreased by upregulating gene expression of antioxidant and phase II detoxifying enzymes [80]. After retinal ischemia-reperfusion injury, Nrf2 knockout mice showed greater loss of retinal ganglion cells when compared with the wild-type mice. Moreover, after ischemia-reperfusion injury, Nrf2 activator increased survival of retinal ganglion cells in wild-type mice, but not Nrf2 knockout mice, indicating the neuroprotective effects of Nrf2 [81]. An *in vitro* study has demonstrated that siRNA knockdown of Nrf2 led to significant increase of reactive oxygen species and cell death after blue light exposure in murine photoreceptor cells, suggesting that Nrf2 could be used to protect photoreceptors in AMD and other retinal degeneration [82].

There is no direct evidence that dopamine protects retinal neurons through anti-inflammation, apoptosis, and oxidative stress. However, decreased expression of dopamine may play a negative role in neuron survival in the brain [83]. Thus, dopamine receptor agonists may achieve the goal to promote retinal neuron survival and function by restoring the lost dopamine resulting from certain diseases. Dopamine receptor agonist pramipexole was shown to ameliorate structural and functional injuries in the light-damaged mice, exhibiting decreased photoreceptor death, damage of photoreceptor outer and inner segments, TUNEL-positive cells in ONL, and preservation of a-wave and b-wave in ERG [84]. Additionally, pramipexole

inhibited ARPE-19 cell (an immortalized RPE cell line) death after H₂O₂ treatment, suggesting its antioxidative effects [84].

Regular general physical exercise is not only a part of healthy life style, but also a rehabilitation strategy showing neuroprotective effects in numerous diseases. Recently, exercise has been proven to be neuroprotective in animal models of retinal degeneration [85–87]. Wild-type BALB/c mice were forced to exercise for 5 days/week for 2 weeks before being exposed to bright light. Exercised mice showed greater improved amplitude of ERG b-wave and photoreceptor nuclei than the mice without exercise after light exposure [85]. In order to exclude the impact of stress caused by forced exercise, voluntary wheel running was adopted in rd10 mice, which also demonstrated protection of VA, and the number of cones and total photoreceptors [86]. No matter if it was involuntary or voluntary exercise, either one benefited damaged photoreceptors in animal models of retinal degeneration through increased expression of brain-derived neurotrophic factor (BDNF) and activation of tropomyosin-related kinase B (TrkB) signaling pathway [85, 86].

Electrical neurostimulation has developed rapidly in recent years, covering a range of neurological diseases, such as neurostimulation for epilepsy, spinal cord stimulation for chronic pain, brain stimulation for Parkinson's disease, and so on [88]. Electrical neurostimulation in vision research has also made a great improvement, from transcorneal, subretinal, to whole-eye electrical stimulation. Transcorneal electrical stimulation (TES) was performed in SD rats before or after exposure to the intense light for 14 days. Both the stimulation before and after light exposure slowed the progression of photoreceptor degeneration. Furthermore, TES after light exposure exhibited a longer and better protective effect. The neuroprotection effects may result from anti-apoptosis (upregulation of Bcl-2 and downregulation of Bax) and increased expression of neurotrophic factors (CNTF and BDNF) [89]. Subretinal electrical stimulation (SES) in the eye of Royal College of Surgeons (RCS) rats, a commonly used model of retinal degeneration, significantly preserved amplitudes of b-wave and oscillatory potential, and implicit times of a-wave and b-wave, suggesting the preservation of not only photoreceptors, but also signal transmission in the retina [90]. Although the whole-eye electrical stimulation did not provide protection for rod structure in P23H rats, b-wave amplitudes and rod sensitivity were significantly increased [91].

Although the neuroprotective strategies mentioned above have acquired promising results in animal models, damaged human retina can be only partially rescued. Miller and colleagues have investigated the underlying reasons using many animal models. There are three types of cell death including caspase-mediated apoptosis, autophagy-mediated cell death, and necrosis which is regulated by receptor-interacting protein kinases (RIPK). In the animal model of retinal detachment, elevated expression and phosphorylation of RIPK together with activation of caspases were observed. When either RIPK or caspases were inhibited, no obvious rescue effects were demonstrated. However, inhibition of both RIPK and caspases resulted in significant protective effects. Similar results were found in the animal model of retinal degeneration which experienced both photoreceptor and RPE cell death. In this animal model, the dominant type of cell death in photoreceptors was apoptosis, while necrotic RPE cells were mainly exhibited. Therefore, therapies that block both RIPK and caspase pathways may provide more satisfactory neuroprotection [92].

4.2 Current medicine/neuroprotective agents in clinical trials

Neurotech Pharmaceuticals developed an intraocular drug delivery system using encapsulated cell technology, called NT-501, to consistently release CNTF in the vitreous for more than 2 years [93]. A double-masked, randomized,

sham-controlled, phase II study enrolling 51 GA patients who were randomly divided into 3 groups, high-dose NT-501 implant, low-dose NT-501 implant, and sham control group, demonstrated promising outcomes after a 2-year evaluation [94]. Another phase II study using intraocular implant secreting CNTF in GA patients has also been completed. In this multicenter, double-masked, randomized, sham-controlled, 1-year, dose-ranging phase II study, VA stabilization, defined as loss of less than 15 letters, was observed in the high-dose group (96.3%) versus low-dose group (83.3%) and sham surgery (75%). All the patients with best corrected VA $\geq 20/63$ in the high-dose group lost less than 15 letters, while it was only 55.6% in the combined group of patients treated with low-dose implant and sham surgery. Additionally, increase of retinal thickness was consistent with the stabilization of VA [95].

Brimonidine, an α -2 agonist, is usually used to treat glaucoma patients in ophthalmology. Since brimonidine has been reported to protect neuroretinal cells in murine models, the effects of this drug on dry AMD patients were under evaluation [96]. A randomized, double-masked, sham-controlled, phase II study involved 119 patients with bilateral GA who were randomly divided into 3 groups including 200 μg treatment, 400 μg treatment, and sham control group. The efficacy and safety of brimonidine on biodegradable implant were evaluated after intravitreal transplantation [97]. But the results were not reliable, so another multicenter study is currently performed with larger samples (311 eyes receiving either treatment of 400 μg brimonidine on biodegradable implant or sham treatment) and longer evaluation period (up to 24 months) [98].

A retrospective analysis was performed to analyze the association between intake of L-DOPA and incidence of AMD. The results showed that the onset of AMD in individuals prescribed with L-DOPA was 8 years later when compared with those without the uptake of L-DOPA. The protective effects of L-DOPA might be through GPR143 (the only known L-DOPA receptor) pathway [99, 100].

There are few studies about exercise as a clinical intervention in AMD, and the published papers are observational research showing the correlation between exercise and prevalence of AMD. A study lasting for 15 years demonstrated that active lifestyle with physical exercise 3 times per week or more was associated with reduced risk to develop wet AMD [101]. In another cohort study, an inverse relation was observed between vigorous exercise (≥ 3 times/week) and occurrence of intermediate AMD in women, not in men [102]. In addition, low physical exercise was related to the formation of drusen larger than 63 μm [103].

Electrical neurostimulation has already been applied to patients using less invasive approaches, such as transcorneal or whole-eye electrical stimulation, to protect the structure and function of retinal neurons. In a clinical trial conducted by Anastassiou and colleagues, 22 patients with dry AMD received transpalpebral electrical stimulation twice a day for 5 days. Most of the patients demonstrated the improvement in VA and contrast sensitivity at 4 weeks after the treatment; however, only contrast sensitivity was significantly different when compared with sham control group [104]. Similarly, microcurrent stimulation (150 μA for 35 min) once a week for 3 months was applied to both dry and wet AMD. Significantly increased VA was demonstrated in dry AMD, but not in wet AMD. Moreover, the number of patients showing increased VA was twice as those exhibiting deterioration [105].

5. Conclusions

AMD is believed to have stronger relationship with age. With increase of aging population worldwide, more individuals are suffering from visual damage,

resulting in poor quality of life for the aged people and elevated cost of medical care. In AMD, it is not only the degeneration of RPE cells, but also the neural retina degeneration, especially photoreceptors, that leads to the visual impairment. Therefore, neuroprotection can be one of the therapeutic strategies to slow, halt, or even reverse the progression of retina degeneration. Although the neuroprotective interventions that are currently investigated in both animal models and patients demonstrate promising results, it is of importance to identify the long-term efficacy and safety of these interventions. Only after that, the therapeutics will be provided to patients to help them maintain vision and further improve the quality of life.

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Conflict of interest

The authors declare no conflict of interest.

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