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Research Article

The Impact of Oxidative Stress in Age-related Macular Degeneration

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ABSTRACT

The human eye is a highly developed and photosensitive organ that provides a sense of light. It experiences high oxidative stress due to its continuous exposure to light and the presence of structures with high metabolic activity such as retinal pigment epithelium (RPE). Characterized by the accumulation of drusen that leads to progressive degeneration of photoreceptors and RPE, age-related macular degeneration (AMD) is one of the leading causes of vision loss in the elderly. Oxidative stress is believed to play a crucial role in the development of AMD. Oxidative stress arises from the imbalance between reactive oxygen species (ROS) and antioxidant defense systems. When favoring ROS production, it damages DNA, proteins, and lipids in the RPE, leading to RPE dysfunction, inflammation and altered signaling pathways that contribute to AMD development. Current treatments include intravitreal anti-vascular endothelial growth factor (VEGF) drugs, and drugs which targeting the complementary cascade. Still, limitations and challenges remain.

Keywords:
age-related macular degeneration; oxidative stress; retinal pigment epithelium; reactive oxygen species

1. INTRODUCTION

The human eye is a highly developed and photosensitive organ that provides a sense of light. At the same time, the eye experiences high oxidative stress due to its continuous exposure to light and the presence of structures with high metabolic activities. Oxidative stress results from a high amount of reactive oxygen species (ROS) generation and impaired antioxidant defense mechanisms are involved in the pathophysiology of several ocular diseases, including age-related macular degeneration (AMD)[1].

2. STRUCTURE OF THE EYE AND FUNCTION

The eye has three layers surrounding the ocular globe: the external fibrous layer consists of the cornea and the sclera providing protection, the middle vascular layer (uveal tract) includes choroid, ciliary body, and iris, and the internal layer made up of the retina, which communicates with the brain through posterior optic nerve and retinal pigment epithelium (RPE)[2].

Both the cornea and the sclera are soft connective tissues that maintain the structural integrity of the eye and protect the inner components from physical harm. The transparent cornea, together with the lens serves as the primary refractive structure, possessing two key optical properties: refractive power and transparency. The sclera covers the globe posterior to the cornea, mainly to provide an external framework, maintaining the shape of the globe. The iris, ciliary body, and choroid are collectively referred to as uvea. The choroid provides nutrients to the retina. The ciliary body changes the lens shape for far and near vision by adjusting the suspensory ligaments that attach to the lens. Iris controls the amount of light entering the eye.

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The retina has a pigmented layer composed of retinal pigment epithelium, a neural inner multilayer formed by different cell types including photoreceptors (rods and cones), bipolar cells, horizontal cells, and amacrine cells that detect and convert the light into nerve signals and transmitted to the brain through the optic nerve[3,4]. The RPE is a monolayer of pigmented cells located between photoreceptor outer segments and the choriocapillaris, essential for visual function. The melanin granules in RPE protect the macula from intense light energy by absorbing the high density of energy. RPE also transports metabolic waste to the blood and takes up nutrients to photoreceptors. The retinal is constantly transported from the photoreceptors to RPE, where all-trans-retinal is converted into 11-cis-retinal and is then transported back to photoreceptors. Moreover, RPE is responsible for the phagocytosis of shed photoreceptors and the excretion of a variety of growth factors[5].

3. AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration is the leading cause of vision loss in individuals older than 55 years old in developed countries, characterized by the accumulation of drusen that leads to progressive degeneration of photoreceptors and RPE at the internal layer of the eye[6]. Drusen are extracellular materials containing lipids, carbohydrates, proteins, and complement components. Hard drusen are small, round, and well-defined drusen, less than 63 μm, located on the posterior pole and peripheral retina. Soft drusen are yellowish poorly defined elevations of the retinal pigment epithelium found in the central macular region. Soft drusen measure larger than 63 μm and sometimes aggregate[7].

AMD can be categorized into three stages (table 1). A visible drusen size smaller than 63 μm in the eye is considered as normal aging change. An early stage of AMD is recognized by presence of medium size drusen (63 – 125 μm). The appearance of large drusen or pigmentary abnormalities associated with at least medium drusen are considered as intermediate AMD. The late AMD is categorized into wet (neovascular) form and dry (geographic atrophy) form[8]. Around 85 – 90% of AMD cases are dry AMD, and wet AMD accounts for 10 – 15%. These two forms are not mutually exclusive, and wet AMD can develop independently in people with dry AMD[9]

Table 1. Comparison between healthy eye and difference stages of AMD

AMD stages	Characteristics
Healthy eye	No drusen formation, or hard small size drusen (< 63 μm)
Early AMD	Appearance of soft, medium size drusen (63–125 μm)
Intermediate AMD	Large drusen (>125 μm) and /or pigmentary abnormalities associated with at least medium drusen
Late dry AMD	Loss of photoceptors, RPE cells and choriocapillaris
Late wet AMD	Macular neovascularization from the choroid, and/ or fluid accumulation at intraretinal and subretinal region

The wet form can be classified into type 1 macular neovascularization (MNV), type 2, and type 3 depending on the origin of neovascularization. Type 1 MNV, commonly found in Asian populations, refers to ingrowth of vessels initially from the choriocapillaris into and within the sub-RPE space. Type 2 MNV is the neovascularization that starts from the choroid and grows into the Bruch's membrane, the RPE monolayer and subretinal spaces. Type 3 MNV originates from the retinal circulation and grows toward the outer retina[10]. Geographic atrophy typically appears first in the perifoveal macular, and over time involves the central fovea. It is recognized by progressive loss of photoreceptors, retinal pigment epithelium, and choriocapillaris leading to atrophic lesions in the outer retina[11].

There were an estimated 19.8 million (12.6%) Americans aged 40 and above living with AMD in 2019[12]. The number of AMD patients worldwide is predicted to increase to 288 million by 2024, including 113 million in Asia and 69 million in Europe[13]. For people with AMD, their quality of life is affected. They may find it challenging with daily tasks such as reading, driving, and facial recognition. AMD is also associated with a higher risk of clinical depression, people with AMD reported feelings of frustration, anxiety, and helplessness[14–16].

AMD is a multifactorial disease, affected by both environmental and genetic risk factors[17]. As a modifiable environmental risk factor, cigarette smoking is significantly associated with an increased risk of AMD[17–19]. Cigarette smoke is comprised of harmful components, including nicotine and toxic chemicals, which penetrate the bloodstream and affect ocular tissues. The oxidative stress and inflammation triggered by smoking play a crucial role in its detrimental effects on ocular health[20]. In cigarette smoke extract treated RPE cells, impaired mitochondrial function and increased reactive oxygen species were observed[21]. Cigarette smoke extract can also trigger complement activation and increase the expression of the pro-inflammatory cytokine IL-1β in RPE cells. The responses were enhanced by Nrf2 deficiency/knockdown, suggesting the protective role of Nrf2 against cigarette smoke extract induced oxidative

stress[22]. Compared with cigarette smoking, excess body weight shows a weak association with an increased risk of AMD[23]. However, late AMD is significantly associated with tobacco consumption in the population with increased waist circumference and body mass index in the obese range[24].

Age is a non-modifiable risk factor for developing AMD. Older age is associated with more advanced stages of AMD[25]. As aging, mitochondrial biogenesis, mitochondrial quality control, and mitophagy are less efficient, resulting in accumulation of dysfunctional mitochondria, exacerbating the aging process, and further contributing to increased ROS generation and oxidative stress[26]. The presence of genetic variants rs10922109 and rs570618 in the *CFH* gene has been consistently reported to be linked with disease progression in AMD. Besides, the variant rs116503776 in the *C2/CFB/SKIV2L* gene, variant rs61985136 in *RAD51B* and variant rs72802342 in *CTRB2/CTRB1* are also reported to be associated with AMD disease progression. The common variant rs3750846, near the *ARMS2/HTRA1* gene, and variant rs2230199 in the *C3* gene are considered risk factors for AMD[27]. The pathogenesis of AMD is not fully elucidated, but it is believed that increased oxidative stress plays an important role[18].

4. OVERVIEW OF ROS

ROS, including oxygen radicals and nonradical oxygen derivatives, are highly reactive chemicals containing one or more unpaired electrons in their outer shells[1]. Oxygen radicals, such as superoxide ($O_2^{\bullet-}$), hydroxyl ($OH^{\bullet-}$), nitric oxide radical ($NO^{\bullet}$), contain at least one unpaired electron and are prone to donate or gain another electron to obtain stability. Nonradical oxygen derivatives, for example, hydrogen peroxide (H_2O_2), are not free radicals but can easily cause free radical reactions in living organisms [28].

ROS originate from both internal sources including mitochondria, peroxisomes, endoplasmic reticulum, and phagocytic cells and external sources, such as air pollution, tobacco smoke, heavy metals, certain drugs, and ultraviolet (UV) light[29]. ROS in general, at a low/moderate level exhibits a beneficial role in defense against infectious agents, cellular signaling pathways, and the overproduction of ROS leads to oxidative stress (Fig 1), causing damage to biomolecules like protein, lipid, and DNA[30].

Cytosolic H_2O_2 can activate the NF-kB pathway through H_2O_2-mediated oxidation and activation of the inhibitor of NF-kB kinases or directly modulate NF-kB because of the oxidizable cysteines in the DNA-binding region of NF-kB[31]. Additionally, ROS also plays a critical role in immune response. Phagocytes increase their oxygen uptake and use nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor to produce large amounts of $O_2^{\bullet-}$ and H_2O_2 when exposed to stimuli. $O_2^{\bullet-}$ and H_2O_2 produced are used as precursors to produce microbicidal oxidants, including oxidized halogens and oxidizing radicals. Oxidizing radicals, such as $OH^{\bullet-}$, can cause damage to proteins, nucleic acids, and lipids, leading to bacterial death[32]. Neutrophils also produce $O_2^{\bullet-}$ when the enzyme NADPH oxidases (NOXs) are activated to eliminate pathogens[33].

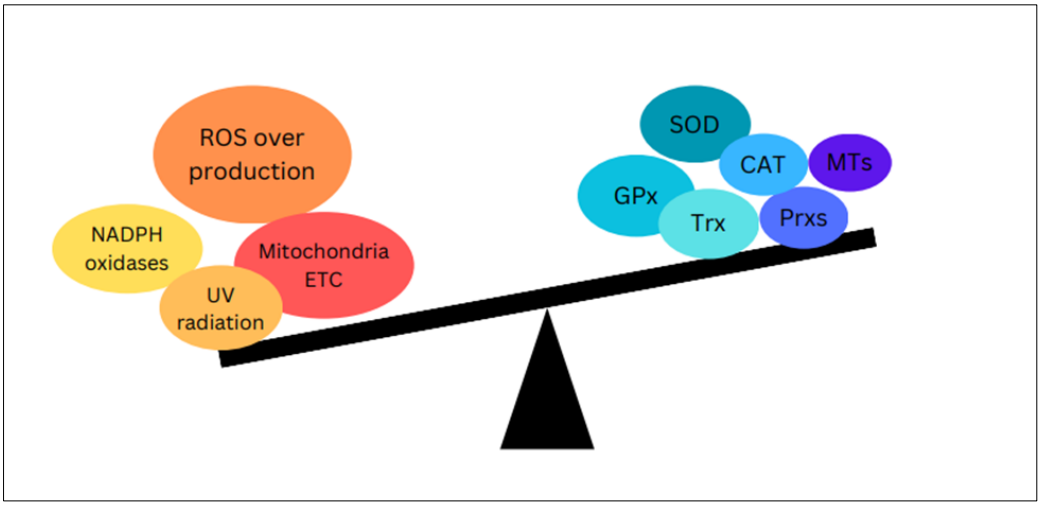

Figure 1. Major ROS sources and antioxidants in the eye. Oxidative stress occurs when the ROS production overwhelms the antioxidant system. ROS: reactive oxygen species; ETC: electron transport chain; UV: ultraviolet; SOD: superoxide dismutase; GPx: glutathione peroxidase; CAT: catalase; Trx: thioredoxin; Prxs: peroxiredoxin; MTs: metallothioneins

5. ROS SOURCES IN THE EYE

One of the major sources of ROS in the cell is mitochondria. The electron transport chain (ETC) located at mitochondria transfers electrons from NADH to oxygen molecules (O_2). O_2 is reduced to H_2O upon receiving four electrons[34]. However, when a small number of electrons leak to oxygen during the energy transduction in the mitochondrial electron transport chain, O_2 is reduced to $O_2^{\bullet-}$[29]. Around 2 – 5% of the oxygen remains incompletely reduced under normal conditions, resulting in increased ROS/$O_2^{\bullet-}$ production. Mitochondrial ROS increases with aging and age-related disease[35]

NOXs, membrane-spanning enzymes which produce ROS in a NADPH-dependent way, are another primary source of ROS. NOXs have a catalytic core composed of a dehydrogenase domain and a transmembrane domain. Electrons travel from cytosolic NADPH to flavin adenine dinucleotide (FAD) in the dehydrogenase domain, next to the inner and outer heme in the transmembrane domain and then to O_2 on the opposite side of the cell membrane producing $O_2^{\bullet-}$ or H_2O_2[36]. There are seven NADPH oxidase isoforms, among them NOX1, NOX2, and NOX4 are the most studied in eye pathology. NOX1 and NOX2 generate $O_2^{\bullet-}$ and NOX4 produce mainly hydrogen superoxide[37].

Externally, constant exposure of the human eye to solar UV radiation makes UV radiation and blue light two major contributors to ROS generation in the eye. ROS formation can be achieved through photosensitized UV radiation reactions type I and II. In the type I reaction, a chromophore is excited by light and undergoes direct electron or hydrogen exchange with a substrate, producing free radicals, resulting in the production of $O_2^{\bullet-}$. For type II process, direct energy transfer from the excited chromophore to oxygen occurs, creating reactive single oxygen, which in turn reacts with lipids to generate peroxides or react with other substrates to produce reactive free radicals[38,39].

The UV radiation includes UV-A (320 – 400 nm), UV-B (280 – 320 nm), and UV-C (200 – 280 nm) region, the ozone layer protects human from the bulk of UV-C and UV-B radiation[40]. When exposed to UV radiation, the light is mainly absorbed by the cornea and lens, blocking it from reaching the retina[41]. However, visible light ranging from 400 to 800 nm can reach retinal tissue in physiological conditions.[42] Prolonged exposure to blue light (400 – 500 nm), commonly used in light-emitting diode, electronic devices induced ROS production may put retina under the accumulation of photo-oxidative stress[43,44].

Adult human lens has an abundance of yellow chromophore 3-hydroxykynurenine. It protects the eye by filtering UV light as well as absorbing blue light, however, it is converted to xanthurenic acid as aging, and the absorption of light by xanthurenic acid results in production of single oxygen and other ROS which cause oxidative damage[40]. In RPE cells, melanin containing organelles melanosomes protects the RPE cells from blur light exposure and ROS. However, the melanosome concentration drops as aging[45].

6. ANTIOXIDANT DEFENSE SYSTEM

The antioxidant defense systems in the human body can be divided into enzymatic and non-enzymatic systems. The important players in the enzymatic system include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). The non-enzymatic antioxidants include vitamins, such as vitamin A, vitamin C (ascorbic acid), vitamin E (tocopherols), carotenoids, α-lipoic acid (ALA), and minerals such as copper[46,47]. In terms of function, antioxidants can be categorized into three groups. The first group consists of enzymes like SOD, CAT, and GPx, which remove the free radicals and reactive species. The second group works as electron donors to scavenge free radicals, such as glutathione (GSH), tocopherols, ascorbic acid, and thioredoxin (Trx). The last mechanism involves binding of pro-oxidant metal ions, such as iron and copper by specific metal-binding proteins (e.g., metallothionein)[48]

$O_2^{\bullet-}$ is one of the major ROS that interacts with other molecules to generate other "secondary" ROS (e.g., H_2O_2)[29]. H_2O_2, generated from $O_2^{\bullet-}$ by SOD, can easily penetrate a cell membranes and generate the most reactive form of oxygen, $OH^{\bullet-}$, via Fenton's reaction ($H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^- + OH\cdot$) (Fig 2)[49]. SOD has three isoforms: extracellular superoxide dismutase (ECSOD), manganese superoxide dismutase (MnSOD) in mitochondria, and copper-zinc superoxide dismutase (Cu/ZnSOD) in the cytosol. Under oxidative stress, Cu/ZnSOD enters the cell nucleus to regulate antioxidant activity via gene regulation[46]. Complex I and complex III are the major sites of mitochondrial $O_2^{\bullet-}$. $O_2^{\bullet-}$, because of its short half-life, once produced from NOXs in the cytosol and from mitochondrial ETC (mtETC), is rapidly converted to H_2O_2 by CuZnSOD and mitochondrial MnSOD respectively[50]

GPx reduces H_2O_2 into water and O_2 with the help of electron donor GSH, Subsequently, GSH is oxidized into glutathione disulfide (GSSG) (Fig 2). Among all GPx isoforms, GPX3 is the most expressed in the retina followed by GPx4[51]. Glutathione reductase (GR) catalyzes the recycling of GSH from GSSG, needing NADPH as an electron donor, the GSH is then recycled and can be used again to reduce H_2O_2 by GPx[50]. Located mainly in peroxisomes[52], catalase neutralizes H_2O_2 by breaking down two H_2O_2 into one molecule of oxygen and two molecules of water (Fig 2) like glutathione peroxidase[53]. The peroxiredoxin (Prxs)

family also plays a role in detoxifying H_2O_2 in the retina, but mainly complementing the SOD/GPx H_2O_2 detoxification system[51].

The Trx system is composed of NADPH, thioredoxin reductase (TrxR), and it is another key thiol-dependent antioxidant system apart from the GSH system. It is a major disulfide reductase system which provides electrons to a large number of enzymes, for instance, Prxs, methionine sulfoxide reductases (MSRs) that defend against oxidative stress (Fig 2). The Trx system can transfer electrons to Prx to remove H_2O_2, ROOH, and $ONOO^-$. Under oxidative stress, free methionine and protein methionine can be oxidized to methionine sulfoxide, affecting protein function. MSRs repair the free and protein bound S- and R-methionine sulfoxides back to methionine, indirectly involved in the removal of ROS[54]. Trx is found ubiquitously across all living organisms, including all the eye tissues. Trx levels tend to be higher in the anterior segment of the eye, particularly the cornea and the ciliary body compared to the posterior segment[55]. Trx1 has three additional extra cysteines in its primary Trx isoform, widely distributed in the cytosol, nucleus, and plasma membrane, while mitochondrial Trx2 has only two cysteines in its active site[56].

Metallothioneins (MTs) are a group of cysteine rich, metal-binding proteins present in all eukaryotes. One MT molecule can bind up to seven zinc ions under normal conditions. MT1 and MIT2 isoforms are most expressed in all the ocular tissues and MT3 is mainly expressed in the retina. MTs function as the main intracellular zinc reservoir. MTs protect the cells from the toxic effects of ROS in three ways: 1) When zinc is released from MTs, the free sulfhydryl groups may act as scavengers of free radicals under oxidative stress. 2) MTs sequester copper or iron, preventing their involvement in redox reactions, such as the Fenton reaction. Therefore, the release of free radicals is avoided. 3) MTs provide metal cofactors for antioxidant enzymes such as SOD (Fig 2), serving as indirect antioxidants[51,57].

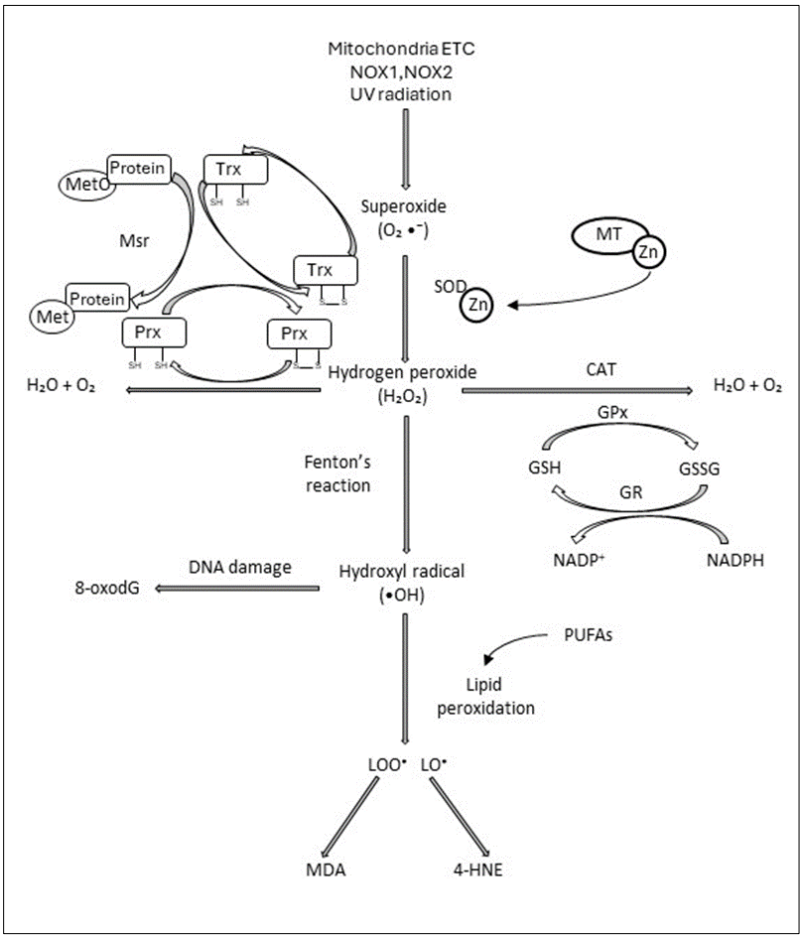

Figure 2. ROS scavenge process by major antioxidants and cellular damage caused by ROS. Superoxide generated from mitochondria electron transport chain, NADPH oxidases, and UV radiation are reduced by SOD using the metal cofactor from MT to hydrogen peroxide. Hydrogen peroxide can be neutralized by CAT, GPx, Prx. Msr is also indirectly involved in the removal of ROS by repairing oxidized proteins using electrons from Trx. Hydrogen peroxide can further undergo Fenton's reaction to produce hydroxyl radical, which react with DNA and lipids to cause cellular damage. ROS: reactive oxygen species; ETC: electron transport chain; UV: ultraviolet; NOXs: nicotinamide adenine dinucleotide phosphate oxidases; SOD: superoxide dismutase; GPx: glutathione peroxidase; CAT: catalase; Trx: thioredoxin; Prx: peroxiredoxin; MTs: metallothioneins; Zn: zinc; GSH: glutathione; GSSG: glutathione disulfide; GR: glutathione reductase; NADPH: nicotinamide adenine dinucleotide phosphate; Met: methionine; MetO: methionine sulfoxide; Msr: methionine sulfoxide reductase; PUFAs: Polyunsaturated fatty acids; 8-oxodG: 8-hydroxydeoxyguanosine; MDA: malondialdehyde; 4-HNE: 4-hydroxy-nonenal

7. CELLULAR DAMAGE OF ROS TO PROTEIN, DNA, AND LIPIDS

ROS, in particular $OH^{\bullet -}$, generated from the Fenton reaction, play a crucial role in causing oxidative damage to various biomolecules. ROS is capable of oxidizing both the protein backbone and the side chains, leading to the formation of carbonyl functional groups. All amino acids are sensitive to oxidation, especially cysteine and methionine[58]. In addition, H_2O_2, primarily produced from O_2 by NOXs and SOD by mtETC, reacts with a target protein cysteine thiolate to form the sulfenate, leading to a change in protein function[31].

The $OH^{\bullet -}$, reacting with DNA bases and sugar-phosphate backbone, lead to incorrect base pairing, reacting with the deoxyribose moiety resulting in the loss of DNA bases, generating base-free sites, which may cause the break of single or double DNA strand(s). Among all the DNA oxidations, 8-oxodG formed via hydroxylation of the C8 residue of guanine is the most abundant (Fig 2) and commonly considered as a biomarker of DNA oxidation[59]

Polyunsaturated fatty acids (PUFA), particularly those with a high number of double bonds such as arachidonic acid, docosahexaenoic acid, and linoleate, are highly susceptible to ROS. The initiation of lipid peroxidation occurs when $OH^{\bullet -}$ extract a reactive hydrogen atom from the methylene group of polyunsaturated fatty acids forming carbon-centered radicals ($L^{\bullet}$). The carbon-centered radicals interact with oxygen molecules forming a lipid peroxyl radical ($LOO^{\bullet}$). Peroxyl radicals are further reduced within the membrane by the reduced form of Vitamin E (T-OH) producing lipid hydroperoxide (LOOH) and a radical of Vitamin E (T- $O^{\bullet}$). The T-$O^{\bullet}$ is reduced back to T-OH by ascorbic acid and by GSH, leaving behind the ascorbyl radical, and GSSG respectively, which are reduced back to GSH and ascorbic acid by dihydrolipoic acid (DHLA), using NADPH, converted itself to ALA. LOOH can react quickly with Fe^{2+} and react much slower with Fe^{3+} to give rise to lipid alkoxyl ($LO^{\bullet}$) and $LOO^{\bullet}$ respectively to propagate and amplify the process. The $LO^{\bullet}$ from arachidonic acid undergoes a cyclisation reaction to form a six-membered ring hydroperoxide, which further gives rise to 4-hydroxy-nonenal (4-HNE). Malondialdehyde (MDA) is formed from $LOO^{\bullet}$ undergoing two cyclisation reactions. Peroxidation of polyunsaturated fatty acids leads to isoprostanes[30,58,59].

8. THE EFFECTS OF ROS/OXIDATIVE STRESS IN AMD

8.1. Higher levels of oxidative stress markers in AMD

ROS has an extremely short life. Therefore, products produced from oxidative damage, such as protein carbonyls from protein oxidation, MDA, or isoprostanes from lipid peroxidation, 8-hydroxydeoxyguanosine (8-OHdG) from nucleic acid oxidation are often used to measure the level of oxidative damage[60]. Protein carbonyl groups from protein oxidation and 8-OHdG form nucleic acid oxidation were found higher in patients with wet AMD than in control group, while SOD, GPx, and GR, the primary defense against oxidative damage were significantly decreased in wet AMD patients compared with the control group[61,62]. Malondialdehyde, the end product of lipid peroxidation, also showed significantly higher levels in AMD patients regardless of dry or wet form compared to people without AMD[63–65]. The serum malondialdehyde level is higher in wet AMD than in early dry AMD, found in Chinese AMD patients[66]

8.2. Oxidative stress and the inner layer of the eye

Retina is highly sensitive to oxidative damage, because it contains high levels of PUFA, which can easily become oxidized[39]. The oxidation of PUFA leads to the development of peroxides and organic radicals which form adducts with proteins and are accumulated in the outer retina and in drusen[49]. Photoreceptor outer segments are largely composed of docosahexaenoic acid (DHA). Higher levels of carboxyethylpyrrole (CEP), a lipid peroxidation product from DHA under oxidative stress were reported from donor eyes with AMD in the Bruch's membrane suggesting increased vulnerability to oxidative damage in the retina[67].

The blood-retina barrier (BRB) is composed of choriocapillaris, Bruch's membrane, and retinal pigment epithelium. Oxidative stress can lead to the thinning of choriocapillaris and reduced blood flow which hinders the delivery of nutrients and removal of waste to and from the retina. Increased thickness, calcification, and decreased elasticity of Bruch's membrane due to oxidative stress reduces its permeability. Oxidative stress can also lead to accumulation of lipofuscin in RPE cells which impair cellular function and contribute the formation of drusen[68]. Lipofuscin can generate ROS upon exposure with visible light, most effectively under blue light, and is an important contributor to increased oxidative stress in the RPE cells as lipofuscin accumulated as aging[45]. One key component of lipofuscin arises due to the RPE's inability to convert all all-trans-retinol into 11-cis-retinal. The visual cycle starts when the pigment rhodopsin in the rod cells absorbs light, leading the transformation of 11-cis-retinal to all-trans-retinal and back to 11-cis-retinal under the facilitation of a series of RPE enzymes. The retina contains high levels of rhodopsin, high amount of free all-trans retinal accumulate in both photoreceptors and RPE cells under intense or prolonged light

exposure. Two all-trans-retinal molecules and one phosphatidylethanolamine forms N-Retinylidene-N-retinylethanolamine (A2E), the most prominent photosensitive fluorophore in lipofuscin and the major component of drusen in the retinas of AMD patients. When A2E is exposed to blue light, it transfers energy to ground-state oxygen molecules accelerates the pro-oxidation reaction, resulting in more ROS production. A2E may also inhibit lysosomal degradative functions, leading to retinal degeneration[43]. A2E can interrupt the electron flow in the respiratory chain, reduce energy metabolism efficiency and produce more reactive oxygen species[5].

8.3. Oxidative stress and RPE dysfunction

The high metabolic activities of the retinal pigment epithelium to maintain retina health makes it highly susceptible to oxidative damage. RPE has many mitochondria which contribute to the production of ROS. Lipid oxidation from phagocytosed outer segments also contributes to excess ROS in RPE. Lipid oxidation can affect normal cellular membrane lipid and lipoprotein function, triggering inflammation[69]. Inefficient RPE metabolism of substrate degradation and/or damaged RPE cells give rise to debris, and local chronic inflammation due to activation of complement system as activated microglia are recruited to areas where debris is present contributing to the formation of subretinal lipid/protein deposits[67]. Impaired antioxidant defense leads to an accumulation of excess ROS and hence oxidative damage to DNA, proteins, and lipids**.** All these damages cause the breakdown of intracellular organelles like mitochondria, lysosomes, and further result in RPE dysfunction or death[69]. RPE dysfunction and loss of RPE can cause photoreceptor degeneration[5].

Mitochondrial DNA (mtDNA) is particularly susceptible to oxidative damage because it is located close to the mtETC, the primary endogenous source of ROS. Damage to genes that encode mtETC components leads to their dysfunction and in return causes increased ROS production, which may further induce more damage to these genes. 8-oxoG, the major oxidative modification of mtDNA, if base excision repair in mitochondria fails to remove it, it can be further oxidized to produce more stable and mutagenic forms to interfere with DNA replication[70]. H_2O_2 treatment in RPE cells can cause a significant increase in mtDNA damage and decreased mitochondrial redox function [71]. The DNA repair mechanism, base excision repair appears to be less efficient in RPE cells, which leads to persistent mtDNA damage. The mtDNA damage may cause a decrease in mt mRNA and protein synthesis, impair electron transport and lead to a vicious cycle of oxidative damage[72].

Thioredoxin interacting protein (TXNIP), also known as thioredoxin binding protein-2 (TBP-2), regulates oxidative stress via interaction with Trx. TXNIP is primarily located in the nucleus and cannot translocate to the cytoplasm. Under oxidative stress, TXNIP expression is upregulated by inhibition of the phosphorylation of adenosine 5'-monophosphate-activated protein kinase (AMPK) and translocates to cytosol and/or mitochondria to bind and oxidize Trx[56]. There is a clear inverse relationship between TXNIP and Trx[55], suggesting greater expression of TXNIP in the posterior eye segment.

TXNIP expression is significantly reduced under H_2O_2-induced oxidative stress. TXNIP knockdown activates p53, which in turn activates AMPK, leading to autophagy. Downregulation of TXNIP also increases tight junction disruption and cell mobility through Src kinase activation. Moreover, TXNIP knockdown promotes angiogenesis through increasing Hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF) expression, suggesting oxidative stress-mediated TXNIP loss causes RPE dysfunction[73].

8.4. Oxidative stress and Inflammation

Oxidative stress and inflammation are closely related. While inflammation produces oxidative stress, there is evidence suggesting oxidative stress induces inflammation in AMD[74]. During inflammation, the activated phagocytic cells, such as neutrophils and macrophages produce large amounts of ROS to kill pathogens. H_2O_2, on the other hand, can induce inflammation through activation of transcription factor NF-kB[48]. Moreover, the accumulations of H_2O_2 and lipid peroxidation products promote the upregulation of inflammatory cytokines. Continuous accumulation of oxidized lipids, complement activation products, and membrane attack complex accumulation in drusen further promotes inflammation[75].

The addition of 4-HNE, a product of lipid peroxidation, activates Nod-like receptor protein 3 (NLRP3) inflammasomes, leading to a significant increase in pro-inflammatory cytokines IL-1β and IL-18 in APRE-19 cells. It is also suggested that the involvement of caspase-1 in the inflammatory response to oxidative stress as the presence of caspase-1 inhibitor reduced the production of IL-1β and IL-18[76]. Moreover, H_2O_2 treatment in APRE-19 cells promotes the translocation of TXNIP from the nucleus to cytoplasm, where it activates the NLRP3 inflammasomes, increasing the production of pro-inflammatory cytokines IL-1β and IL-18. Results also indicated that Nrf2 acts as a negatively regulated TXNIP, as the activation of Nrf2 increases TXNIP expression in the nucleus and decreases its expression in the cytoplasm[77]. In glucose oxidase induced oxidative stress in APRE-19 and hTRT-RPE1

cells, it was found that IL17RA, which is the principal receptor of IL 17 signaling was the most upregulated inflammatory gene in human RPE cells upon oxidative stress exposure. Knockdown of IL17RA reduced the inflammatory response in RPE cells. In addition, the transcription factor KLF4 directly activates IL7RA expression, which in return increases the production of IL1β and IL8 in an IL17RA-dependent manner[78]. ARPE-19 cells, under long-term oxidative stress induced by H_2O_2, activate NF-kB, the key regulator of inflammation, and lead to increased pro-inflammatory cytokines IL-6 and IL-1β expression, and the expression of full length caspase-1[79].

The complement system is a protein cascade that recognizes and eliminates cellular debris and infectious microbes to maintain homeostasis[80]. A higher number of complement system activation products was found in AMD patients. Patients with intermediate AMD and late dry AMD show higher levels of complement activation compared to both controls and early AMD group[81]. H_2O_2-treated ARPE-19 cells showed an increase in gene expression and accumulation of complement proteins such as complement component 3 (C3), complement component 5 (C5), and complement receptor 3. Under oxidative stress, the increased NLRP3 and FOXP3 expression subsequently enhanced secretion of proinflammatory and proangiogenic factors[82].

8.5. Oxidative stress and VEGF/angiogenesis

The molecular mechanisms behind the upregulation of VEGF in senescent RPE cells were investigated and it was found that in H_2O_2-induced senescent RPE cells, oxidative stress-damaged DNA activates STING/NF-κB/HIF-1α signaling and impaired autophagy flux which reduced the STING degradation while further up-regulating VEGF expression. Inhibition of STING significantly reduced HIF-1α expression, alleviating the up-regulation of VEGF as HIF-1α is a master regulator of VEFG under hypoxic conditions [83].

MDA, a byproduct of polyunsaturated fatty acid peroxidation, when modified with photoreceptor outer segment (POS), induced VEGF expression, cell junction disruption and autophagy dysfunction in APRE-19 cells. Interestingly, possibly because of the cytotoxicity of MDA, MDA-modified POS showed a biphasic effect on VEGF expression. The VEGF expression was increased by lower concentrations of MDA-modified POS while a higher concentration resulted in decreased VEGF expression[84].

9. CURRENT TREATMENT

Currently, the intravitreal anti-VEGF drugs are the first-line treatment option for wet AMD[85]. They function by blocking the activation of the VEGF pathway, reducing vascular permeability, inhibiting neovascularization, and improving visual acuity. However, anti-VEGF drugs are typically administered intravitreally and require repeated injections which may increase the risk of complications and the patient's economic burden. Some patients with AMD do not respond to anti-VEGF drugs, suggesting that there are other factors involved in the pathogenesis of AMD that are not addressed by inhibiting VEGF alone. Some of the anti-VEGF drugs are Pegaptanib, Bevacizumab, Ranibizumab, Aflibercept, Conbercept, and Faricimab[86].

Regarding dry AMD, Avacincaptad pegol and Pegcetacoplan are the only two Food and Drug Administration (FDA)-approved drugs for the treatment of geographic atrophy secondary to AMD so far. Targeting the complementary cascade (Fig 3), Avacincaptad pegol, approved by the FDA in 2023, is a C5 inhibitor that inhibits the cleavage of C5 into C5a and C5b, reducing cell lysis and death, slowing the retinal degeneration[87]. Pegcetacoplan is a highly selective bicyclic peptide that inhibits the cleavage of C3[88]. Clinical trials have shown the effect of these two drugs in reducing geographic atrophy growth by up to 20%, but challenges remain. These treatments appear to only slow the degenerative process and do not improve visual function. Unexpected adverse events such as conversion to wet AMD and occlusive retinal vasculitis occur[89].

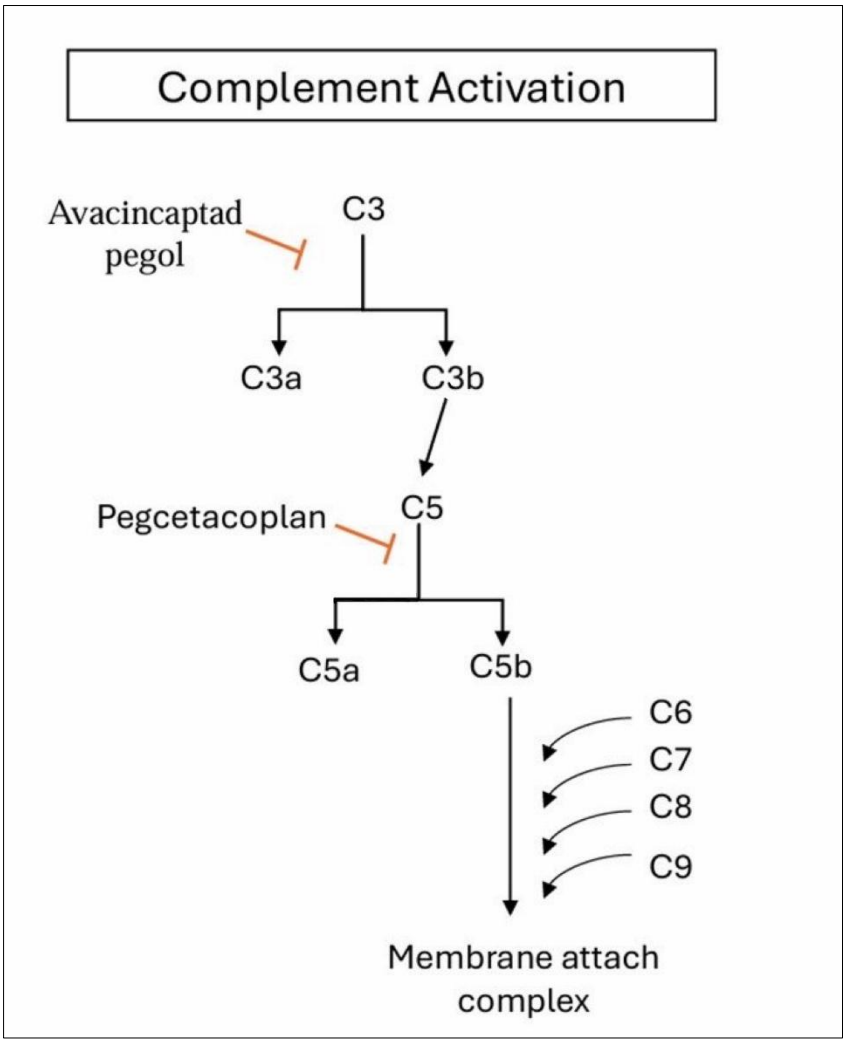

Figure 3. Approved drugs for the treatment of geographic atrophy secondary to AMD target at the complementary cascade.

10. CONCLUSION

In conclusion, the high metabolic activities in photoreceptors and RPE cells, especially those involved visual cycle and continuous exposure to UV radiation like blue light generate large amounts of ROS. This causes damage to DNA, mtDNA, proteins and lipids, leading to RPE dysfunction. The declining antioxidant system, along with accumulation of lipofuscin as aging, intertwined with inflammation and altered signaling pathways, further accelerate ROS generation and oxidative damage, contributing to AMD development. Current treatments primarily target the late stages of AMD and options for dry AMD are limited. Therefore, understanding the impact of oxidative stress on pathogenesis may provide preventative and new therapeutic strategies to combat AMD.

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Y. L.: investigation, data curation, writing - original draft; W. S.: conceptualization, supervision, writing - review & editing.

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