• Review Article •

Molecular mechanisms and intervention strategies for age-related macular degeneration

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Abstract

● Age-related macular degeneration (AMD) is a leading ocular disorder that causes irreversible visual impairment and blindness in the elderly population. Accumulating evidence demonstrates that AMD is the end-stage outcome of various retinal degenerative lesions and vascular anomalies. Its core pathogenic mechanisms mainly involve dysfunction and atrophy of retinal pigment epithelium (RPE) cells, choroidal capillary degeneration, pathological choroidal neovascularization (CNV), chronic inflammation, oxidative stress injury, deposition of extracellular substances such as drusen, and genetic predisposition. Given its multifactorial origin and complicated pathophysiological processes, the full molecular regulatory network of AMD has not been fully clarified, which restricts the development of more efficient intervention regimens. This review systematically summarizes the latest research progress concerning the molecular mechanisms of AMD, and comprehensively discusses mainstream and emerging therapeutic strategies, including anti-vascular endothelial growth factor (VEGF) drugs, antioxidant and mineral supplements, photodynamic therapy, and laser therapy, as well as innovative modalities such as gene therapy, stem cell therapy, and targeted regulation of complement and inflammatory pathways. It is intended to provide theoretical basis and research references for in-depth mechanistic exploration, early prevention and precise clinical management of AMD.

● **KEYWORDS:** age-related macular degeneration; molecular mechanism; intervention therapy; retinal pigment epithelium

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INTRODUCTION

Age-related macular degeneration (AMD) stands as the predominant cause of irreversible vision loss and legal blindness among individuals aged 50 and older in developed countries, posing a significant global health burden[1-2]. The prevalence of AMD escalates dramatically with age, particularly affecting those over 65y, underscoring its profound impact on the quality of life and independence of the elderly population. The progressive deterioration of central vision, crucial for tasks such as reading, driving, and facial recognition, renders AMD a debilitating condition that necessitates comprehensive understanding and effective therapeutic interventions[3]. Clinically, AMD is broadly categorized into two main forms: the "dry" or non-neovascular form, characterized by the presence of drusen and geographic atrophy (GA), and the "wet" or neovascular form (nAMD), distinguished by the growth of abnormal new blood vessels from the choroid into the subretinal space [sub-retinal pigment epithelium (RPE)], known as choroidal neovascularization (CNV)[4-5]. While dry AMD accounts for the vast majority of cases, wet AMD is responsible for the most severe and rapid vision loss, often leading to devastating consequences if left untreated. The distinct clinical presentations and progression patterns of these two forms highlight the need for tailored diagnostic and therapeutic approaches, yet both ultimately converge on the common outcome of photoreceptor damage and irreversible visual impairment.

The intricate pathophysiology of AMD involves a complex interplay of cellular and molecular events primarily affecting the RPE, Bruch's membrane, and the choroid. A hallmark of AMD is the progressive dysfunction and eventual atrophy of RPE cells, which are critical for maintaining the health and function of overlying photoreceptors through metabolic support, waste removal, and visual cycle regeneration[6]. As individuals age, RPE cells accumulate lipofuscin, a heterogeneous mixture of undigested cellular debris, which can become phototoxic upon light exposure, contributing to oxidative stress and cellular damage[7]. Concurrently, the complement system, a crucial component of innate immunity, becomes chronically activated in the AMD-affected eye, leading to sustained inflammation and further RPE degeneration[2,6]. In the wet form of AMD, the pathological process is further exacerbated by abnormal choroidal vascular proliferation, where new, leaky blood vessels invade the sub-RPE space, causing hemorrhage, fluid exudation, and ultimately scar formation[8]. These pathological changes collectively lead to the terminal stage of AMD, characterized by the irreversible apoptosis of photoreceptors, the light-sensing cells of the retina, resulting in profound and permanent central vision loss. The multifactorial nature of AMD, encompassing genetic predispositions, environmental factors, and age-related cellular senescence, underscores the complexity of its pathogenesis and the challenges in developing universally effective treatments.

Understanding AMD's complex molecular drivers (oxidative stress, inflammation, angiogenesis, senescence) is crucial for better therapies. This review systematically analyzes these core pathways and critically evaluates current interventions [*e.g.*, anti-vascular endothelial growth factor (VEGF), antioxidants], highlighting their limitations. It further explores emerging strategies like gene editing, nanotech drug delivery, and multi-omics integration, which hold revolutionary potential. By synthesizing this knowledge, the review aims to deepen AMD pathophysiology understanding, guide early diagnosis/prevention, and advance precision medicine for this debilitating global disease.

MOLECULAR MECHANISMS OF AMD

AMD is a complex multifactorial disease, and its pathogenesis is driven by a confluence of interconnected molecular mechanisms that primarily affect the RPE, Bruch's membrane, and the choroid[9]. AMD is broadly classified into non-neovascular (dry) and neovascular (wet) forms. nAMD is characterized by CNV, which can be further subdivided based on anatomical location. Type 1 CNV is located beneath the RPE (sub-RPE), type 2 CNV extends into the sub-RPE space, and type 3 CNV originates from the retinal circulation. These distinct growth patterns are associated with different structural changes in the retina and have important implications for imaging interpretation and therapeutic targeting. Understanding these core pathological processes is crucial for identifying novel therapeutic targets and developing effective intervention strategies.

Oxidative Stress and Mitochondrial Dysfunction Oxidative stress is widely recognized as a central pathogenic factor in AMD, playing a pivotal role in initiating and propagating RPE cell damage and subsequent retinal degeneration[2]. The retina, particularly the RPE, is highly susceptible to oxidative damage due to its high metabolic rate, constant exposure to light (especially blue light), and rich oxygen supply[10]. Blue light, a component of visible light, can directly induce RPE oxidative damage by generating reactive oxygen species (ROS), leading to decreased cell proliferation, increased apoptosis, and DNA damage in RPE cells[11-12]. This photooxidative stress is exacerbated by the accumulation of lipofuscin within RPE cells, which, upon light irradiation, can further generate ROS and trigger lysosomal membrane permeabilization, leading to the release of lysosomal enzymes and subsequent cellular damage[7]. Mitochondria, the primary sites of ROS production, are particularly vulnerable to oxidative insults, and their dysfunction is a key contributor to AMD progression[12]. Oxidative stress can induce mitochondrial DNA (mtDNA) mutations and deletions, impairing the electron transport chain and leading to a collapse in cellular energy metabolism[13]. This energy deficit compromises RPE cell function, including its vital phagocytic activity, which is essential for clearing shed photoreceptor outer segments. The accumulation of undigested material contributes to the formation of drusen, extracellular deposits characteristic of early AMD, further exacerbating RPE dysfunction[14]. Key molecular players in this intricate process include the Nrf2 pathway, a master regulator of antioxidant responses, whose dysregulation or decreased activity [*e.g.*, through lncRNA CYLD-AS1 sponging miR-134-5p, which affects Nrf2/nuclear factor (NF)-κB signaling] renders RPE cells more susceptible to oxidative damage and inflammation[15-16]. Similarly, a decline in the activity of antioxidant enzymes like superoxide dismutase 2 (SOD2) further impairs the cell's ability to neutralize ROS[17].

Beyond general oxidative damage, a specific form of iron-dependent programmed cell death, known as ferroptosis, has emerged as a significant mechanism in AMD pathogenesis[18]. Ferroptosis is characterized by excessive iron accumulation, elevated lipid peroxides, and overproduction of ROS, particularly through the Fenton reaction, where divalent iron interacts with hydrogen peroxide to generate highly reactive hydroxyl radicals[19]. These radicals attack cellular components, leading to lipid peroxidation and ultimately RPE cell death. Maintaining iron homeostasis is crucial, involving proteins

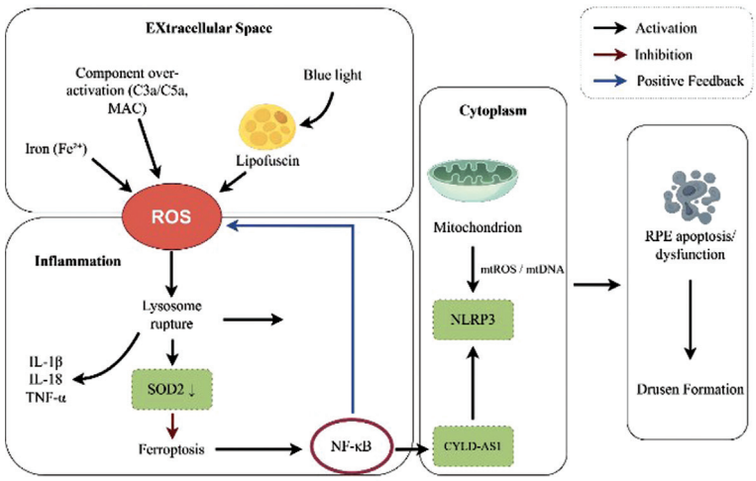

Figure 1 Oxidative stress and mitochondrial dysfunction in AMD pathogenesis C3a: Complement component 3a; C5a: Complement component 5a; MAC: Membrane attack complex; Fe^{2+}: Ferrous ion/iron (II) ion; ROS: Reactive oxygen species; IL-1β: Interleukin-1 beta; IL-18: Interleukin-18; TNF-α: Tumor necrosis factor-alpha; SOD2: Superoxide dismutase 2; NF-κB: Nuclear factor kappa B; mtROS: Mitochondrial reactive oxygen species; mtDNA: Mitochondrial DNA; NLRP3: NOD-like receptor family pyrin domain-containing 3; CYLD-AS1: CYLD antisense RNA 1; RPE: Retinal pigment epithelium.

like transferrin receptor (TfR), ferritin (Ft), and ferroportin (FPn)[18]. Recent studies have identified phosphoethanolamine/phosphocholine phosphatase 1 (PHOSPHO1) as a critical regulator that suppresses ferroptosis in RPE cells by reducing phosphatidylethanolamine (PE) levels and inhibiting autophagy and ferritinophagy, thereby limiting lipid peroxidation and intracellular free iron accumulation[20]. This highlights the intricate balance of iron metabolism and lipid peroxidation in RPE health. Furthermore, the interplay between oxidative stress and autophagy is critical, as autophagy is a cellular process that degrades altered cell components, including dysfunctional mitochondria (mitophagy)[21-22]. Disruptions in redox signaling can impair autophagy, leading to the accumulation of damaged organelles and protein aggregates, further contributing to neurodegeneration[16]. The activation of deacetylase sirtuin (SIRT) 1, for instance, has been shown to protect RPE cells from oxidative stress-induced premature senescence, suggesting its role in maintaining cellular health and potentially mitigating AMD progression[23]. Oxidative stress and mitochondrial impairment trigger RPE apoptosis, leading to photoreceptor degeneration and irreversible macular damage. Figure 1 illustrates the relationship among these processes in AMD pathogenesis. Oxidative stress is an early upstream driver in AMD and contributes to RPE dysfunction and photoreceptor vulnerability.

Inflammation and Complement System Abnormalities Chronic low-grade inflammation is a fundamental driver in the progression of AMD, intricately linked with oxidative stress and immune system dysregulation[2]. A key component of this inflammatory cascade is the aberrant activation of the complement system, a crucial part of innate immunity (Figure 2).

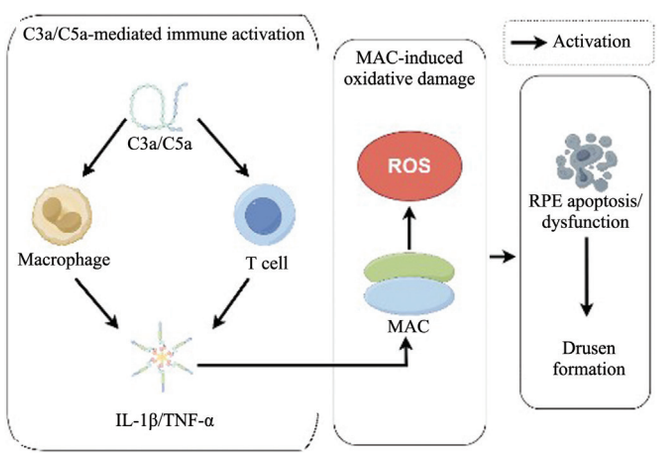

Figure 2 Chronic inflammation and complement system dysregulation in AMD AMD: Age-related macular degeneration; C3a: Complement component 3a; C5a: Complement component 5a; MAC: Membrane attack complex; ROS: Reactive oxygen species; RPE: Retinal pigment epithelium; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor-alpha; T cell: T lymphocyte.

While essential for host defense, its uncontrolled activation in the ocular microenvironment contributes significantly to RPE dysfunction and degeneration[24]. Overactivation of the complement cascade leads to the generation of potent inflammatory mediators such as complement component 3a (C3a) and complement component 5a (C5a), and the formation of the membrane attack complex (MAC), which can directly damage RPE cells[6]. Genetic predispositions, particularly mutations in complement factor H (*CFH*) gene, are strongly associated with increased AMD risk, underscoring the critical role of complement dysregulation in disease susceptibility and progression[25]. These genetic variations can impair the

complement system's ability to regulate itself, leading to persistent activation and chronic inflammation.

Beyond the complement system, the activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome within RPE cells plays a crucial role in perpetuating the inflammatory cycle[26]. Studies have demonstrated that lipofuscin-mediated phototoxicity, induced by blue light irradiation, can trigger lysosomal membrane permeabilization and subsequent activation of the NLRP3 inflammasome in RPE cells[7]. This activation leads to the cleavage and secretion of pro-inflammatory cytokines, notably interleukin-1β (IL-1β) and interleukin-18 (IL-18), which further exacerbate the inflammatory microenvironment in the retina[7,27]. These cytokines, along with tumor necrosis factor-alpha (TNF-α), mediate a broader inflammatory cascade, contributing to RPE cell death and the overall degenerative process. The chronic inflammatory milieu fostered by these mechanisms promotes RPE degeneration and contributes to the formation and growth of drusen, which themselves can serve as a nidus for further inflammatory responses[28].

Furthermore, the interplay between oxidative stress and inflammation is bidirectional and synergistic. Oxidative stress can trigger inflammatory responses, and inflammation, in turn, can generate more reactive oxygen species, creating a vicious cycle that accelerates RPE damage. For instance, oxidative stress-induced long non-coding RNA (lncRNA) CYLD-AS1 has been shown to promote RPE inflammation by modulating the Nrf2/miR-134-5p/NF-κB signaling pathway, highlighting the complex regulatory networks involved[15,29]. The NF-κB pathway is a central mediator of inflammatory responses, and its activation by various stressors, including oxidative stress, leads to the transcription of numerous pro-inflammatory genes. Therefore, the persistent chronic inflammatory microenvironment, driven by complement overactivation and inflammasome signaling, is a critical factor in the pathogenesis of AMD, leading to progressive RPE degeneration and ultimately vision loss. Understanding these inflammatory pathways offers promising targets for therapeutic intervention aimed at dampening the destructive immune responses in the macula.

Angiogenesis Imbalance Abnormal angiogenesis, specifically CNV, is the hallmark and primary cause of severe vision loss in wet (neovascular) AMD[30]. This pathological process involves the uncontrolled proliferation and migration of new blood vessels from the choroid through Bruch's membrane into the sub-RPE space, leading to hemorrhage, fluid leakage, and ultimately scar formation that destroys photoreceptors[8]. The fundamental molecular mechanism driving CNV is a profound imbalance between pro-angiogenic and anti-angiogenic factors, with a significant overexpression of pro-angiogenic signals. VEGF and its receptor (VEGFR) signaling pathway are universally recognized as the central players in pathological angiogenesis in nAMD[31]. Under conditions of chronic oxidative stress, inflammation, and hypoxia in the AMD-affected macula, RPE cells and other retinal cells upregulate the production of VEGF-A. Hypoxia-inducible factor-1 alpha (HIF-1α) plays a critical role in mediating this hypoxic response, acting as a master regulator that promotes the transcription of VEGF and other pro-angiogenic genes in response to low oxygen levels[32-33]. The elevated levels of VEGF-A bind to VEGFRs on endothelial cells, stimulating their proliferation, migration, and tube formation, thereby initiating and sustaining CNV growth. Other key pro-angiogenic molecules implicated include placental growth factor (PlGF) and angiopoietin-2 (Ang-2), which can synergize with VEGF to promote vessel instability and leakage (Figure 3)[34-35].

Conversely, a deficiency or reduction in anti-angiogenic factors, such as pigment epithelium-derived factor (PEDF), further contributes to this pro-angiogenic shift. PEDF is a potent anti-angiogenic and neurotrophic factor normally secreted by RPE cells, and its decline in AMD contributes to the permissive environment for CNV development. Beyond the VEGF pathway, other signaling pathways are also implicated in regulating angiogenesis[36-37]. For instance, Notch signaling has been shown to be a key regulator of CNV. Activation of the canonical Notch pathway can reduce the volume of CNV lesions, while its inhibition exacerbates them, suggesting that Notch signaling maintains vascular homeostasis and its disruption can underlie CNV. Notch signaling influences the expression of both pro-angiogenic genes (like *Vegfr2*, *Ccr3*, and *Pdgfb*) and anti-angiogenic genes (like *Vegfr1* and *Unc5b*), highlighting its complex role in vascular regulation[8].

Furthermore, non-coding RNAs, including microRNAs (miRNAs), lncRNAs, and circular RNAs (circRNAs), have emerged as crucial regulators of angiogenesis. Their dysregulation can significantly impact the expression of pro-angiogenic factors and contribute to CNV formation, offering new avenues for therapeutic targeting[38]. The ultimate consequence of this severe angiogenesis imbalance is the formation of fragile, leaky choroidal neovascular membranes that lead to recurrent hemorrhage and exudation, causing rapid and irreversible damage to the overlying photoreceptors and severe central vision loss.

RPE-Bruch's Membrane-Choroid Complex Dysfunction The RPE-Bruch's membrane-choroid complex forms a critical functional unit essential for maintaining retinal homeostasis and vision. Dysfunction within this complex is a central pathological feature of AMD, contributing to both dry and wet forms of the disease. The RPE, a monolayer of pigmented

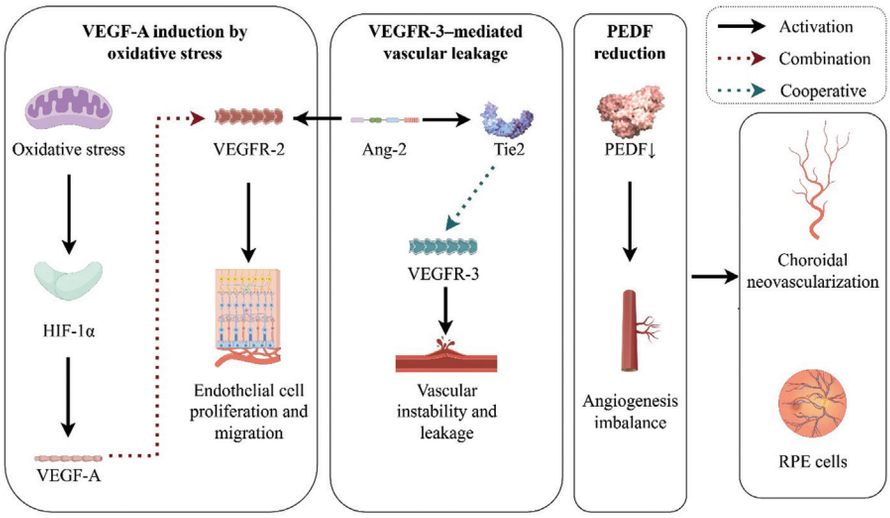

Figure 3 VEGF-mediated pathological angiogenesis in neovascular AMD AMD: Age-related macular degeneration; VEGF-A: Vascular endothelial growth factor A; VEGFR-2: Vascular endothelial growth factor receptor 2; VEGFR-3: Vascular endothelial growth factor receptor 3; HIF-1α: Hypoxia-inducible factor 1-alpha; Ang-2: Angiopoietin-2; Tie2: Tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2; PEDF: Pigment epithelium-derived factor; RPE: Retinal pigment epithelium.

cells, plays a crucial role in the maintenance of photoreceptors by phagocytosing shed photoreceptor outer segments, transporting nutrients from the choroid to the retina, and removing waste products[39]. In AMD, the RPE's phagocytic function declines with age and chronic stress, leading to the accumulation of undigested material, including lipofuscin and lipid-rich debris, within the RPE cells and subsequently in Bruch's membrane[14,40].

Bruch's membrane, a pentalaminar extracellular matrix (ECM) located between the RPE and the choroid, acts as a selective barrier for nutrient and waste exchange. In AMD, this membrane undergoes significant pathological changes, including progressive thickening, lipid deposition, and the accumulation of drusen, which are extracellular deposits composed of proteins, lipids, and cellular debris[41]. This excessive ECM deposition, together with accumulated lipids, can reduce the permeability of Bruch's membrane and hinder the exchange of nutrients (*e.g.*, oxygen and glucose) between the choroidal vasculature and the RPE/outer retina, as well as the clearance of metabolic waste. Importantly, however, not all drusen phenotypes are equally linked to outer retinal dysfunction. Evidence suggests that specific high-risk subtypes, particularly reticular pseudodrusen (RPD, also termed subretinal drusenoid deposits, SDD), are more consistently associated with impaired outer retinal structure and function. Such compromised transport and microenvironmental stress may therefore exacerbate RPE dysfunction and contribute to photoreceptor degeneration, especially in eyes with these high-risk drusen patterns.

Molecular mechanisms underlying these changes include the dysregulation of matrix metalloproteinases (MMPs), enzymes responsible for ECM remodeling. An imbalance in MMP activity can lead to abnormal ECM accumulation and altered tissue architecture. Furthermore, integrin signaling abnormalities, which mediate cell-ECM interactions, can contribute to RPE cell detachment and migration. A critical process implicated in the dysfunction of this complex is the epithelial-mesenchymal transition (EMT) of RPE cells[5,42-43]. EMT is a cellular process where epithelial cells lose their polarity and cell-cell adhesion, gaining migratory and invasive properties characteristic of mesenchymal cells. This excessive ECM deposition, including collagen and various lipids, impairs the permeability of Bruch's membrane, creating a significant barrier to the efficient transport of nutrients (*e.g.*, oxygen, glucose) from the choroidal vasculature to the RPE and photoreceptors, and the removal of waste products from the retina. Importantly, these consequences are not uniform across all drusen phenotypes, and outer retinal dysfunction is more consistently associated with specific high-risk subtypes (*e.g.*, reticular pseudodrusen/subretinal drusenoid deposits). This compromised transport may further exacerbates RPE dysfunction and contributes to photoreceptor degeneration[43]. This transformation is orchestrated by a sophisticated network of molecular interactions and signaling cascades, including oxidative stress, mitochondrial dysfunction, hypoxia-inducible factor signaling, autophagic flux dysregulation, chronic inflammatory responses, complement system overactivation, epigenetic regulation through microRNA networks, and key developmental signaling pathway reactivation[6]. Transforming growth factor-beta (TGF-β) is a key cytokine orchestrating both EMT and endothelial-mesenchymal transition (EndMT) of choroidal endothelial cells, further contributing to fibrosis and

the pathological remodeling of the choroid[5]. Such choroidal structural and vascular alterations can impair choroidal perfusion and metabolic support to the RPE-photoreceptor complex, thereby creating a permissive microenvironment for AMD progression, particularly in neovascular and fibrotic stages. The dysfunction of the RPE-Bruch's membrane-choroid complex, characterized by impaired RPE function, thickened and compromised Bruch's membrane, and altered choroidal vasculature, collectively creates an environment conducive to retinal degeneration and the progression of AMD.

Epigenetic and Aging-Related Mechanisms Building on the oxidative stress-mitochondrial dysfunction framework, this subsection focuses on how impaired autophagy/mitophagy affects RPE homeostasis and debris clearance in AMD. Age is the most significant non-modifiable risk factor for AMD, underscoring the profound influence of aging-related cellular and molecular processes on disease pathogenesis. Beyond the direct damage from oxidative stress and inflammation, the fundamental mechanisms of cellular aging contribute significantly to RPE and retinal degeneration. These mechanisms include telomere shortening, which limits cellular replicative capacity and leads to cellular senescence[44-45]. As RPE cells age, they accumulate DNA damage, and their ability to repair this damage declines, further contributing to cellular dysfunction and senescence[13].

Epigenetic modifications, such as changes in DNA methylation patterns and microRNA (miRNA) regulation, play crucial roles in modulating gene expression without altering the underlying DNA sequence, profoundly influencing cellular aging and AMD susceptibility[46-47]. For instance, specific miRNAs, like miR-146a, have been implicated in regulating inflammatory responses, and their dysregulation can contribute to the chronic inflammatory environment observed in AMD. The intricate network of miRNA regulation can impact various pathological axes, including oxidative stress, inflammation, and cellular senescence, by modulating gene expression post-transcriptionally[48-49].

Another critical aging-related mechanism involves the activity of sirtuins (SIRTs), a family of nicotinamide adenine dinucleotide (NAD+) dependent deacetylases that regulate cellular metabolism, stress resistance, and longevity. A decrease in the activity of SIRT1, for example, has been linked to cellular senescence and impaired cellular resilience. Activating SIRT1 has been shown to protect RPE cells from oxidative stress-induced premature senescence, suggesting its potential as a therapeutic target in AMD[50]. Furthermore, the concept of the senescence-associated secretory phenotype (SASP) is highly relevant to AMD. Senescent cells, including RPE cells, acquire SASP, characterized by the secretion of a diverse array of pro-inflammatory cytokines, chemokines, growth factors, and matrix-remodeling enzymes[51]. This secreted cocktail contributes to the chronic inflammatory microenvironment, promotes ECM remodeling, and can induce senescence in neighboring healthy cells, thereby propagating tissue damage and contributing to drusen formation and RPE degeneration.

Other aging-related factors, such as mitochondrial dysfunction, which is closely intertwined with oxidative stress and mitophagy, also contribute to the aging phenotype in RPE cells[21]. The loss of NAD+ levels, impaired macro-autophagy, and stem cell exhaustion are additional facets of the aging process that contribute to the overall decline in cellular function and tissue integrity in the retina[52]. The circadian clock gene *Bmal1*, for instance, has been implicated in aging-related disorders, and its deficiency can promote oxidative stress and inflammation, suggesting a broader systemic link between aging and disease pathogenesis[53]. Understanding these fundamental aging mechanisms and their epigenetic regulation provides a comprehensive framework for appreciating the chronic, progressive nature of AMD and offers novel targets for interventions aimed at slowing or reversing the aging process in the retina.

CURRENT INTERVENTION APPROACHES

Current intervention strategies for AMD primarily focus on managing the symptoms and slowing disease progression, with significant advancements made particularly in treating the wet form of the disease. However, effective therapies for dry AMD remain a major unmet medical need. Table 1 summarizes the main approaches, representative therapies, and their mechanisms of action, drawing upon the molecular mechanisms discussed previously[2,6,8,17,20,23,54-55].

Antioxidant and Mineral Supplementation Antioxidant and mineral supplementation represents a cornerstone intervention for dry AMD, primarily aimed at mitigating oxidative stress, a central driver of disease pathogenesis[56]. The Age-Related Eye Disease Study (AREDS) and its successor, AREDS2, have provided robust evidence for the efficacy of high-dose formulations containing vitamins C and E, zinc, copper, lutein, and zeaxanthin in slowing the progression of intermediate to advanced dry AMD[17]. These compounds work synergistically to enhance the antioxidant capacity of RPE cells, neutralize ROS, and reduce lipid peroxidation, thereby protecting the retina from oxidative damage. Lutein and zeaxanthin, in particular, are macular pigments that absorb blue light, further shielding the retina from phototoxic damage[57]. However, while AREDS formulations have demonstrated a significant reduction in the risk of progression to advanced AMD, their benefits are primarily limited to patients with intermediate-stage disease, and they do not halt or reverse early-stage pathology. Moreover, compliance with high-dose supplementation regimens can be

Table 1 Current intervention approaches

AMD type	Approaches	Representative therapies/targets	Mechanism of action
Dry AMD	Antioxidant and mineral supplementation	AREDS/AREDS2 Formulations (vitamins C, E, zinc, copper, lutein, zeaxanthin)	Reduces oxidative stress by neutralizing ROS, enhancing antioxidant defenses in RPE cells, and slowing drusen accumulation[17,54]
Dry AMD	Neuroprotection and anti-inflammatory agents	Flavonoids (*e.g.*, EGCG), resveratrol	Mitigates chronic neuroinflammation, scavenges free radicals, and activates SIRT1 to protect RPE cells from senescence[23,54]
Wet AMD	Anti-VEGF therapy	Ranibizumab, aflibercept, bevacizumab	Inhibits VEGF-A binding to VEGFR, reducing CNV growth, vascular leakage, and hemorrhage[8]
Wet AMD	PDT	Verteporfin	Selectively occludes CNV vessels by generating ROS upon light activation, minimizing damage to surrounding tissues[2]
Dry AMD	Complement pathway modulation	Pegcetacoplan (C3 inhibitor), lampalizumab (anti-CFD)	Inhibits complement overactivation, reducing inflammation and MAC formation in RPE and choroid[6]
Both	Emerging therapies (gene/stem cell-based)	AAV-mediated gene therapy, iRPE cell transplantation	Corrects genetic defects (*e.g.*, CFH mutations) or replaces dysfunctional RPE cells to restore retinal function[20,55]

AMD: Age-related macular degeneration; ROS: Reactive oxygen species; EGCG: Epigallocatechin-3-gallate; CFD: Complement factor D; RPE: Retinal pigment epithelium; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; CNV: Choroidal neovascularization; MAC: Membrane attack complex; CFH: Complement factor H; AREDS: Age-Related Eye Disease Study; AAV: Adeno-associated virus; SIRT: Sirtuin; PDT: Photodynamic therapy.

challenging due to gastrointestinal side effects and variable patient response, potentially linked to genetic polymorphisms affecting antioxidant metabolism[25]. The limited scope of this intervention highlights the need for more targeted approaches that address additional pathological mechanisms beyond oxidative stress.

Neuroprotection and Anti-inflammatory Agents Neuroprotective and anti-inflammatory strategies have gained traction as potential therapies for both dry and wet AMD, given the critical role of chronic inflammation in disease progression[58]. Flavonoids, such as (-)-epigallocatechin-3-gallate (EGCG), have shown promise due to their potent antioxidant and anti-inflammatory properties. EGCG, a polyphenol abundant in green tea, scavenges free radicals, reduces neuroinflammatory processes, and protects RPE cells from oxidative stress-induced damage[54]. Similarly, resveratrol, a SIRT1 activator, has been demonstrated to mitigate oxidative stress-induced premature senescence in RPE cells by enhancing deacetylase activity, thereby reducing levels of acetyl-p53 and p21 (Waf1/Cip1)[23]. These agents offer a dual benefit by addressing both oxidative stress and inflammation, which are intricately linked in AMD pathogenesis. However, their clinical translation is hindered by challenges such as poor bioavailability, limited retinal penetration, and the need for frequent dosing to achieve therapeutic effects. Furthermore, while these compounds show promise in preclinical models, large-scale clinical trials are lacking, and their efficacy in diverse patient populations remains uncertain. The potential of these agents to modulate the NLRP3 inflammasome and other inflammatory pathways warrants further investigation, particularly in combination with other therapeutic modalities[7].

Anti-VEGF Therapy Anti-VEGF therapy has revolutionized the management of wet AMD, offering a targeted approach to inhibit pathological CNV. Agents such as ranibizumab, aflibercept, and bevacizumab bind to VEGF-A, preventing its interaction with VEGFRs on endothelial cells, thereby suppressing CNV growth, reducing vascular leakage, and stabilizing vision[59]. These therapies have significantly improved visual outcomes for patients with wet AMD, with many achieving stabilizations or even improvement in visual acuity. However, anti-VEGF treatments require frequent intravitreal injections, which pose a significant burden on patients and healthcare systems due to cost, risk of complications (*e.g.*, endophthalmitis), and the need for long-term treatment. Moreover, a subset of patients exhibits suboptimal responses or develops resistance to anti-VEGF therapy, potentially due to compensatory upregulation of other pro-angiogenic factors like PlGF or Ang-2, or due to genetic variations affecting VEGF signaling pathways[38]. The transient nature of VEGF inhibition also means that CNV can recur upon cessation of treatment, highlighting the need for sustained delivery systems or complementary therapies targeting additional angiogenic pathways, such as Notch signaling, which has been shown to modulate CNV development[8]. Recent anti-VEGF agents have further expanded therapeutic options. Brolucizumab, a single-chain antibody fragment, enables high molar dosing and may allow longer treatment intervals, although post-marketing safety concerns (*e.g.*, intraocular inflammation and retinal vasculitis) warrant careful patient selection and monitoring. Faricimab, a bispecific antibody targeting both VEGF-A and Angiopoietin-2 (Ang-2), has demonstrated durability benefits and provides an additional option for treat-and-extend regimens.

Photodynamic Therapy Photodynamic therapy (PDT) using verteporfin is an established treatment for wet AMD, particularly for patients with specific CNV subtypes.

Verteporfin, a photosensitizing agent, is administered intravenously and activated by a low-energy laser in the retina, generating ROS that selectively occlude CNV vessels while minimizing damage to surrounding healthy tissues[60]. PDT is particularly effective for classic CNV lesions and has been used in combination with anti-VEGF therapy to enhance outcomes. However, its application is limited by its inability to address non-classic CNV and the risk of photosensitivity reactions in patients[61]. Additionally, PDT does not address the underlying inflammatory or oxidative processes driving AMD, and its efficacy is generally lower than that of anti-VEGF therapies, making it a less preferred option in current clinical practice. The selective nature of PDT, however, makes it a valuable tool for specific patient subsets, and ongoing research aims to refine its application through improved photosensitizers and combination strategies[2].

Complement Pathway Modulation Given the pathogenic role of complement dysregulation in AMD, therapeutic strategies targeting the complement cascade have been actively explored. Pegcetacoplan, a C3 inhibitor, and lampalizumab, an anti-complement factor D (CFD) antibody, aim to reduce complement-mediated inflammation and MAC formation, thereby protecting RPE cells and slowing GA progression[6,62]. Preclinical and early clinical studies have shown that these agents can reduce inflammatory damage and preserve retinal integrity, particularly in patients with CFH mutations, which are strongly associated with AMD risk[25]. However, clinical trials have revealed significant inter-individual variability in response, likely due to genetic heterogeneity and the complex interplay of multiple inflammatory pathways. Moreover, systemic complement inhibition carries risks of immune suppression and increased susceptibility to infections, necessitating localized delivery approaches to minimize off-target effects. The limited success of complement inhibitors in large-scale trials underscores the need for biomarkers to identify responders and combination therapies targeting additional pathways, such as NLRP3 inflammasome activation[7].

Emerging Gene and Stem Cell Therapies Gene therapy and stem cell-based approaches represent cutting-edge interventions with the potential to address the root causes of AMD. Adeno-associated virus (AAV)-mediated gene therapy targets genetic defects, such as CFH mutations, to restore complement regulation and reduce inflammation-driven damage[55]. Similarly, induced retinal pigment epithelial (iRPE) cell transplantation offers a regenerative approach by replacing dysfunctional RPE cells with healthy, reprogrammed cells that exhibit resistance to ferroptosis and improved therapeutic efficacy[20]. These therapies hold immense promise for both dry and wet AMD, as they can restore retinal function and halt disease progression at a cellular level[63]. However, significant challenges remain, including the risk of immune responses to viral vectors, the complexity of achieving precise gene editing, and the need for long-term safety data[64]. Additionally, the high cost and technical demands of these therapies may limit their accessibility, particularly in resource-constrained settings. Despite these hurdles, the precision and regenerative potential of gene and stem cell therapies position them as transformative approaches for future AMD management.

CHALLENGES AND FUTURE PERSPECTIVES

Current Limitations Despite significant advancements in AMD research and treatment, several limitations persist that hinder the development of universally effective therapies. For dry AMD, the lack of robust therapeutic options remains a critical challenge. While antioxidant supplementation (AREDS/AREDS2) can slow progression in intermediate stages, it does not prevent or reverse early disease, and no approved therapies exist for GA, the advanced form of dry AMD[17]. Anti-VEGF therapies, while transformative for wet AMD, require repeated intravitreal injections, which impose a significant burden on patients and healthcare systems, with risks of complications and variable response rates[65]. Complement inhibitors, though promising, have shown inconsistent efficacy in clinical trials, likely due to the heterogeneity of AMD' s molecular drivers and the complexity of complement regulation[66]. Moreover, current interventions often target single pathways (*e.g.*, VEGF or complement), failing to address the multifactorial nature of AMD, which involves oxidative stress, inflammation, angiogenesis, and aging-related mechanisms. The lack of reliable biomarkers to predict disease progression or treatment response further complicates personalized treatment strategies, underscoring the need for integrative approaches that combine multiple therapeutic modalities.

Emerging Directions Emerging therapeutic strategies hold immense potential to overcome the limitations of current AMD treatments by targeting the disease's multifactorial etiology with innovative approaches. Notably, gene-based therapies aimed at sustained intraocular anti-VEGF expression have progressed into early-stage (and in some cases late-stage) clinical evaluation for neovascular AMD, offering a practical strategy to reduce injection burden. ABBV-RGX-314 (REGENXBIO/AbbVie) is being evaluated in clinical studies for neovascular AMD, while ixoberogene soroparvovec (Ixo-vec; formerly ADVM-022, Adverum) is designed for durable aflibercept expression following intravitreal administration and has advanced into late-stage development. In addition, SAR402663 (Sanofi), which delivers genetic material encoding a soluble VEGF inhibitor (sFLT01), is under evaluation in a Phase 1/2 study for neovascular AMD. Earlier clinical

experience with rAAV.sFLT-1 (AAV2-sFLT01; Avalanche/Genzyme) further supports the feasibility of ocular anti-VEGF gene delivery approaches. By contrast, genome-editing strategies (*e.g.*, CRISPR-Cas9) remain at an earlier translational stage in AMD and are currently better viewed as longer-term directions rather than near-term clinical options[67]. Retinal rejuvenation therapy (2RT; subthreshold nanosecond laser) has also been explored as an early-intervention strategy for dry AMD. This approach delivers ultrashort, non-thermal laser pulses to selectively stimulate an RPE repair response, with the goal of improving Bruch's membrane turnover and retinal metabolic exchange. Clinical studies (*e.g.*, the LEAD study) suggest that its potential benefit may be phenotype-dependent, highlighting the need for careful patient selection and further validation. Nanotechnology represents another transformative approach, enabling targeted drug delivery to the RPE and choroid using lipid-based nanoparticles or liposomes[55]. These nanocarriers can improve the bioavailability and specificity of therapeutic agents, such as anti-VEGF drugs or complement inhibitors, while reducing systemic side effects. For instance, nanoparticle-mediated delivery of fullerenol has shown potential in protecting RPE cells from oxidative stress-induced senescence, offering a novel strategy for early intervention[23]. Multi-omics integration, combining genomics, proteomics, and imaging data, provides a comprehensive framework for predicting disease progression and identifying novel therapeutic targets[68-70]. By leveraging bioinformatics and artificial intelligence, multi-omics approaches can uncover personalized biomarkers and tailor treatments to individual patients' molecular profiles[71]. Integrative medicine, including traditional Chinese medicine (TCM), is also gaining attention. Compounds like Astragaloside IV and Triptolide have shown potential in modulating autophagy and inflammation, respectively, offering complementary approaches to Western therapies[72]. These emerging directions highlight the potential for precision medicine in AMD, combining advanced technologies with holistic strategies to address the disease's complexity.

Clinical Translation Bottlenecks Translating these emerging therapies into clinical practice faces several bottlenecks. Animal model limitations pose a significant challenge, as most preclinical models fail to fully recapitulate the multifactorial and chronic nature of human AMD, limiting their predictive value for therapeutic efficacy[55]. For instance, rodent models often lack the anatomical and physiological complexity of the human macula, complicating the evaluation of therapies targeting the RPE-choroid complex. Long-term safety assessments are another critical hurdle, particularly for gene therapies and nanotechnologies, where risks such as immune reactions, off-target effects, or nanomaterial toxicity require rigorous evaluation. The high cost of developing and administering these advanced therapies, such as CRISPR-based gene editing or iRPE cell transplantation, may also limit accessibility, particularly in low-resource settings[73]. Furthermore, the complexity of AMD's pathogenesis necessitates large-scale, longitudinal clinical trials to validate the efficacy and safety of combination therapies targeting multiple pathways (*e.g.*, oxidative stress, inflammation, and angiogenesis). Overcoming these bottlenecks will require interdisciplinary collaboration, innovative trial designs, and robust regulatory frameworks to ensure the safe and equitable translation of these promising therapies into clinical practice.

CONCLUSION

AMD is a complex, multifactorial disease driven by a convergence of oxidative stress, chronic inflammation, aberrant angiogenesis, and aging-related mechanisms, all of which converge to cause RPE dysfunction, choroidal abnormalities, and irreversible photoreceptor loss. This review has systematically elucidated the molecular mechanisms underpinning AMD, highlighting the critical roles of oxidative stress and mitochondrial dysfunction, complement system overactivation, VEGF-driven angiogenesis, RPE-Bruch's membrane-choroid complex dysregulation, and epigenetic aging processes. Current interventions, including antioxidant supplementation, anti-VEGF therapies, photodynamic therapy, and complement inhibitors, have significantly improved outcomes, particularly for wet AMD, but are limited by their inability to address the full spectrum of AMD's pathogenesis, especially in dry AMD. Emerging strategies, such as CRISPR-based gene editing, nanotechnology-driven drug delivery, multi-omics integration, and integrative medicine, offer transformative potential by targeting the disease's molecular roots with unprecedented precision. However, challenges such as animal model limitations, long-term safety concerns, and high costs underscore the need for continued research and innovation.

Significant research gaps remain, including the need for reliable biomarkers to predict disease progression and treatment response, and the development of therapies that address the multifactorial nature of AMD through combination approaches. Future directions should focus on personalized medicine, leveraging genetic and multi-omics data to tailor treatments to individual patients' molecular profiles. Combination therapies, integrating anti-VEGF agents, anti-inflammatory drugs, and neuroprotective strategies, hold promise for addressing the synergistic interplay of AMD's pathological mechanisms. Moreover, the integration of advanced technologies like artificial intelligence and nanotechnology could enhance diagnostic accuracy and therapeutic delivery, paving the way for early intervention and prevention. Ultimately, a deeper

understanding of AMD's molecular network, coupled with innovative therapeutic strategies, will be critical for reducing the global burden of this debilitating disease and restoring vision for millions of affected individuals.

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