Clinical Interventions in Aging

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REVIEW

Age-Related Macular Degeneration: A Disease of Cellular Senescence and Dysregulated Immune Homeostasis

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Abstract: Age-related macular degeneration (AMD) is a degenerative ocular disease primarily affecting central vision in the elderly. Its pathogenesis is complex, involving cellular senescence and immune homeostasis dysregulation. This review investigates the interaction between these two critical biological processes in AMD pathogenesis and their impact on disease progression. Initially, cellular senescence is analyzed, with particular emphasis on retinal damage induced by senescent retinal pigment epithelial cells. Subsequently, the occurrence of immune homeostasis dysregulation within the retina and its mechanistic role in AMD areis explored. Furthermore, the paper also discusses in detail the interplay between cellular senescence and immune responses, forming a vicious cycle that exacerbates retinal damage and may influence treatment outcomes. In summary, a deeper understanding of the interrelation between cellular senescence and immune dysregulation is vital for the developing innovative therapeutic strategies for AMD.

Keywords: age-related macular degeneration, cellular senescence, immune homeostasis dysregulation

Introduction

Age-related macular degeneration (AMD) is a major cause of blindness among the elderly in developed countries, and its prevalence is escalating due to an aging global population. It is estimated that 8.69% of the global population is affected by AMD, impacting 196 million people in 2020. This prevalence is projected to increase to 288 million by 2042, significantly contributing to the global disease burden.[1] The pathogenesis of AMD is complex, involving genetics, environmental influences, metabolic processes, and lifestyle choices.[2] Recent research has highlighted the pivotal roles of cellular senescence and the dysregulation of immune homeostasis in AMD pathophysiology.

Cellular senescence represents a complex biological phenomenon, extensively present within the retina. In particular, senescence of retinal pigment epithelial (RPE) cells significantly impacts the structural and functional integrity of the retina, thereby contributing to AMD progression.[3] The homeostasis of the immune system plays an essential role in maintaining tissue health. In AMD, immune homeostasis disruption is characterized by chronic low-grade inflammation, a critical factor accelerating damage to both the retina and RPE.[4]

The interplay between cellular senescence and the dysregulation of immune homeostasis constitutes a critical characteristic of the pathophysiological process in AMD. In this paper, we will thoroughly examine how these two processes interact via complex molecular and cellular mechanisms, collaboratively contributing to the progression of AMD.

Received: 6 February 2024
Accepted: 11 May 2024
Published: 23 May 2024

AMD and Cellular Senescence

Cellular Senescence

Cellular senescence (also termed "senescence") was first proposed by Hayflick and Moorhead in 1961. It refers to irreversible cell cycle arrest during mitosis, leading to the emergence of senescent cells (SNCs).[5] SNCs play crucial roles in various biological processes, including embryonic development, tissue remodeling, wound repair, tumorigenesis, aging, and age-related diseases.[6] However, alterations in immune system function and the resistance of SNCs to apoptosis result in their accumulation, thereby triggering a range of age-related diseases, including Alzheimer's disease, osteoarthritis, pulmonary fibrosis, and AMD.[7–9] The mechanism of cellular senescence involves two tumor suppressor pathways: $p16^{INK4A}$ -pRB and p53-$p21^{CIP1/WAF1}$. These pathways inhibit the expression of cell cycle-related proteins and proliferation-promoting transcription factors, resulting in cell cycle arrest at G1 or G2 phase.[10] Although SNCs stop replicating and proliferating, they remain in a metabolically active state, accompanied by the upregulation of numerous inflammatory factors, chemokines, growth factors, etc., collectively termed the Senescence-Associated Secretory Phenotype (SASP).[11]

Cellular senescence can be categorized into three types: replicative senescence (RS), stress-induced early senescence (SIPS) and developmentally programmed senescence (DPS). *RS* is caused by telomere shortening during the cell replication process. To prevent genomic instability caused by telomere shortening, the DNA damage response activates a series of cascade reactions, including the activation of ATM/ATR-mediated p53-$p21^{CIP1/WAF1}$ and $p16^{INK4A}$ -pRB pathways, cell cycle arrest and apoptosis. SIPS is induced by factors such as oxidative stress, oncogene activation, genotoxic damage, chemotherapy, and viral infections. DPS primarily occurs during the formation of mammalian embryos and plays a role in development and morphogenesis.[10]

SNCs undergo significant and profound changes in both morphology and function.[10,12] These changes manifest in various ways: (i) morphological changes: the cell's cytosol and nucleus increase in size, the cell becomes flattened and multivacuolated, and intracytoplasmic granules increase; (ii) organelle changes: mitochondria increase in number and dysfunction; lysosomal proteins are up-regulated and increase in content (increased activity of β-galactosidase (SA-β-Gal), accumulation of lipofuscin); endoplasmic reticulum stress, and dysregulation of protein homeostasis; (iii) nuclear changes: chromosomal instability (deletion of the nuclear lamina structural protein LaminB1, release of the high mobility group box 1 protein; accumulation of chromatin modifications (enrichment of senescence-associated heterochromatin foci in the transcriptionally silenced histone H2A variant); decrease in DNA content; (iv) metabolic changes: increased glycolysis and SASP release; (v) increased expression of senescence-associated proteins: p38 mitogen-activated protein kinase, p53, $p21^{CIP1}$, $p16^{INK4A}$, RB and cyclin kinase inhibitors.

These features may reflect senescence triggers or consequences, but are not specific to SNCs. Currently, no single biomarker has been identified that can uniquely recognize SNCs. Furthermore, not all SNCs exhibit all biological markers of cellular senescence. Therefore, SNC identification requires simultaneous detection of multiple senescence biomarkers.

Cellular Senescence in AMD

Clinically, AMD is divided into two forms: dry (also known as atrophic or non-exudative) AMD, which may progress to geographic atrophy (GA) and wet (exudative) AMD, characterized by choroidal neovascularization (CNV). In dry AMD, the initial stages are marked by the appearance of large confluent drusen and pigmentary changes due to RPE dysfunction. This can progress to drusen reabsorption and pigmentary attenuation following the loss of RPE cells. Dysfunction and loss of photoreceptors (PRs) and the choriocapillaris (CC) are secondary to RPE cells loss. (Figure 1b) In wet AMD, the initial damage in the PR/RPE/Bruch's membrane (BM)/CC complex is the loss of choroidal vasculature. As AMD progresses, the accumulation of pro-inflammatory factors creates an inflammatory environment. Although the RPE remains intact, hypoxia leads to the production of angiogenic substances such as VEGF, stimulating the formation of CNV. These events result in the death of PRs due to nutrient deprivation. Both dry and wet AMD are characterized by dysfunction and/or death of the PR/RPE/BM/CC complex, which functionally interact as a whole (Figure 1c).[13]

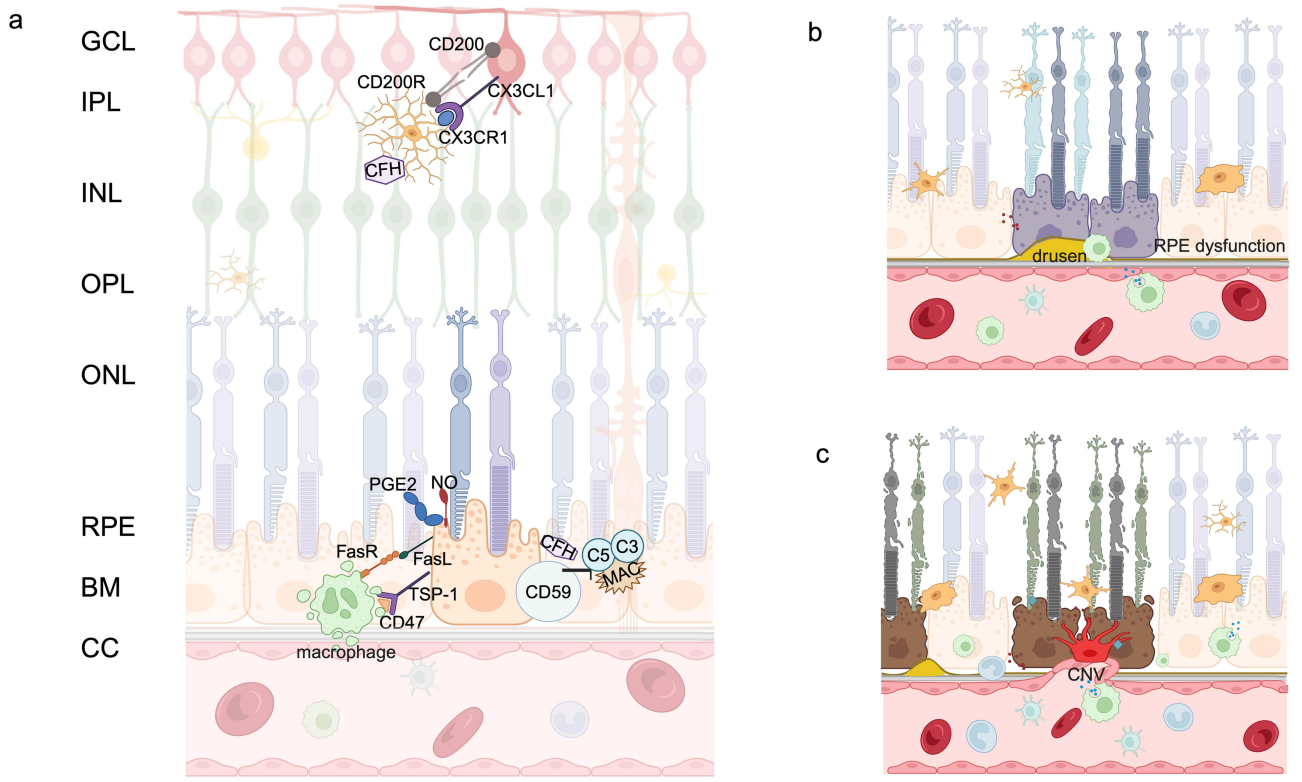

Figure 1 Physiologic and Pathologic Images of the Retina. (**a**) Structure diagram of retinal layers and immunosuppressive mechanism in the retina; (**b**) Pathological changes in dry AMD: drusen formation, RPE dysfunction; (**c**) Pathological changes in wet AMD: CNV formation, photoreceptor/RPE/BM/CC atrophy and dysfunction.
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RPE plays an important role in the pathogenesis of both forms of AMD, whether dry or wet AMD, and the role of RPE cellular senescence in the pathogenesis of AMD has been substantiated by extensive research.[14] RPE cells isolated from donor eyes of AMD patients showed up-regulation of genes characteristic of senescence, such as $p16^{INK4A}$, $p21^{CIP1}$, p53 and bone morphogenetic protein 4 (BMP4).[15,16] A subset of cells within the human RPE, capable of activating RPE stem cells in vitro, has been identified. Lazzarini et al discovered that these RPE stem cells can undergo RS, impacting their proliferative and differentiation capacities. Additionally, they release SASP, creating an inflammatory environment that contributes to the progression of AMD.[17]

Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms in the high-temperature requirement protein A1 (HTRA1) gene as closely associated with AMD. As a serine protease, HTRA1 regulates protein function by cleaving specific peptide bonds, crucial for maintaining extracellular matrix stability and functionality.[18] Elevated HTRA1 protein levels in the RPE of AMD patients correlate with the upregulation of several senescence markers, including $p21^{CIP1/WAF1}$, $p16^{INK4a}$ and SA-β-gal.[19] The role of HTRA1 in AMD cellular senescence is multi-faceted, involving oxidative stress response, mitochondrial function, and regulation of hypoxia-inducible factor-1 and p38 mitogen-activated protein kinase signaling pathways, inducing RPE senescence, extracellular matrix deposition, and AMD-related choroidal vasculopathy.[20,21] The differential expression of bone morphogenetic protein 4 (BMP4) across AMD subtypes is intimately linked to cellular senescence. In dry AMD patients, high BMP4 expression activates p53 via the Smad and p38 signaling pathways, increases $p21^{WAF1/CIP1}$ expression, and decreases pRb levels, thereby mediating RPE senescence.[22] Conversely, in wet AMD, BMP4 expression is reduced, regulated by the SASP such as TNF.[23] Due to the loss of BMP4-mediated inhibition of cellular senescence, neovascularization proliferates extensively. However, when the lesion progresses to scarring, with degeneration and loss of neovascular endothelial cells, BMP4 expression subsequently increases.[22] Transforming growth factor-β-activated kinase 1 (TAK1) is highly expressed in RPE cells, and its expression varies in response to oxidative stress. Inhibition of TAK1 leads to reduced proliferation and cell cycle

arrest in RPE cells, characteristics indicative of cellular senescence. Abnormal TAK1 activity also triggers the secretion of factors by RPE, such as matrix metalloproteinase (MMP) 9, which induce hypertrophy and fibrotic changes in neighboring cells. Thus, TAK1 plays a pivotal role in the pathogenesis of AMD.[24]

In AMD, the formation of Drusen and lipofuscin is a direct result of senescence and metabolic disorders in RPE. These deposits locally trigger inflammatory responses, increase oxidative stress, and damage RPE cells and surrounding tissues, leading to further retinal damage. Drusen is an early marker of AMD with a complex composition containing lipids, proteins, trace metals, pro-inflammatory factors, etc. amyloid-β in drusen promotes RPE cellular senescence, secretes higher concentrations of IL-8 and MMP-9, and contributes to the disruption of the RPE barrier and chronic inflammation, which is an important pathologic alteration in AMD.[25] 7-ketocholesterol (7KC), an oxidative cholesterol, accumulates in AMD-associated Drusen. 7KC mediates RPE senescence and SASP via the mTOR signaling pathway, disrupting the BRB and attracting choroidal endothelial cells (ECs) to the RPE. Furthermore, 7KC induces serine phosphorylation of multi-domain proteins in RPE, which is an important factor in the progression of AMD fibrosis.[26] Lipofuscin accumulation in the RPE increases with age. N-retinylidene-N-retinylethanolamine (A2E), generated from the chemical reaction of retinaldehyde, is the primary fluorescent component of lipofuscin in the RPE. Photosensitized A2E can induce DNA damage, including telomere loss and deprotection, accelerating RPE senescence and SASP, contributing to AMD progression.[27] Additionally, Sun et al discovered that A2E-induced RPE senescence links to the upregulated Caveolin-1. Elevated Caveolin-1 inhibits RPE epithelial-mesenchymal transition, reducing sub-retinal fibrosis. Concurrently, Caveolin-1 blocks the cell cycle, accelerating RPE cell senescence, thus promoting GA progression.[28]

As a consequence of cellular senescence, the SASP also plays a role in the pathophysiological changes of AMD. The SASP drives the senescence of neighboring cells through autocrine or paracrine mechanisms and exerts deleterious effects in the tissue microenvironment.[11] In the oxygen-induced retinopathy (OIR) mice model, cellular senescence observed in neurons can spread to other cell populations in the retina (such as microglia(MG) cells and ECs), further exacerbating retinal pathology.[29] The SASP produced by SNCs is a major and persistent source of age-related chronic inflammation, with its components varying depending on the disease, triggering factors, and cell type. RPE cells primarily undergo *RS* or SIPS, involving a series of changes of SASP, including interleukin-6 (IL-6), IL-8, IL-10, IL-12, IL-17, monocyte chemotactic protein 1 (MCP-1), tumor necrosis factor-α (TNF-α), VEGF, MMP-9, IFN-γ, complement factor B (CFB), and TGF-β.[17,25] In addition to damaging RPE cells and surrounding tissues, the inflammatory response resulting from RPE cell senescence will trigger abnormal activation of the immune system. Senescent mononuclear-phagocytes within the retina also express higher levels of inflammatory factors, including IL-1α, IL-1β, IL-6, IL-8, IL-12, TNF-α, C3, CFB, CXCL1, TGF-β, nitric oxide (NO), and superoxide anion.[8,30]

In the pathophysiological alterations of AMD, cellular senescence is not limited to RPE cells. Neuronal cells, immune cells, and vascular endothelial cells also undergo senescence. The specific processes and mechanisms of senescence in these cell types in AMD will be elaborated in the subsequent sections of this paper.[22,29,31–33]

AMD and Immune Homeostasis Dysregulation

GWAS identified 52 independent variants associated with AMD across 34 genetic loci in a comprehensive genomic variant analysis conducted on a large cohort of AMD patients and control subjects. These variants contribute to the majority of the genetic risk for AMD. Several of these genes are expressed in retinal immune cells and play roles in various inflammatory pathways. The association between AMD risk and these inflammatory genes suggests that alterations in the immune system might be a primary factor leading to the onset of AMD.[18]

Historically, adaptive immunity was not considered a major trigger for AMD, primarily due to the lack of lymphatic systems in the retina and choroid, and the scarcity of AMD-related target antigens in the retina. However, recent studies have found an increase in the $CD56^+$ and $CD28^-$ subgroups of $CD8^+$ T cells in the peripheral blood of AMD patients,[34] and the presence of $CD8^+$ T cells in the macula.[35] Additionally, levels of anti-retinal autoantibodies in the peripheral blood of AMD patients are elevated,[36] but there is no conclusive evidence linking B cells with the induction or progression of AMD. Therefore, while current research is limited, these studies suggest a correlation between the adaptive immune system and the pathogenesis of AMD. Given the current ambiguity in the research on the adaptive

immune system's mechanisms in AMD, this paper focuses on elucidating the role of innate immune system dysregulation in AMD pathogenesis.

Immune Privilege of the Retina

When discussing the immune homeostasis of the retina, it is essential to mention its unique feature: immune privilege. This refers to specific mechanisms reducing immune responses to protect vision. This privilege is mainly achieved through two mechanisms. First, the blood-retinal barrier (BRB), composed of ECs and RPE cells, effectively limits immune cell and macromolecule entry into the retina.[37] Second, the expression of immunosuppressive molecules like Fas ligand and CD200 reduce immune responses and maintain retinal stability. While retinal immune responses are suppressed (Figure 1a),[38,39] in disease states, this privilege can be compromised, leading to retinal lesions and vision decline.

Innate Immune Cell

The Mononuclear Phagocyte System (MPs) in the retina is derived from two main sources: resident microglia and circulating macrophages. Microglia and macrophages are often difficult to distinguish, and are thus frequently conflated in many studies. In the following sections, they are not differentiated unless specifically indicated in the research. The accumulation of MPs in the subretinal space (SRS) is a key step in early AMD,[40] involving mainly two chemokine pathways: CCL2-CCR2 and CX3CL1-CX3CR1. These pathways mediate the recruitment and activation of systemic and local myeloid cell populations in response to exogenous and endogenous inflammatory stimuli.[41]

MG cells, the primary tissue-resident macrophages in the retina, express high levels of CX3CR1 and are regularly distributed in the inner layers of the retina, with fewer numbers in the outer layers.[42] MG cells are involved in processes such as removal of apoptotic neurons and maintenance of synaptic structure and function.[43] Upon tissue injury, MG cells are activated, increasing in number, changing morphology, releasing inflammatory mediators, phagocytosing, and clearing cellular debris to repair lesions.[44] However, the activation of MG cells can also lead to detrimental effects. In dry AMD, reactive microglia accumulate on the apical surface of RPE, covering and residing within drusen, promoting the formation of drusen and secreting inflammatory factors that contribute to PRs and RPE cells death.[42,45] In nAMD, MG cells migrating to the SRS is associated with CNV. MGs secrete VEGF and other angiogenic factors, such as platelet-derived growth factor-β, fibroblast growth factor-1, fibroblast growth factor-2, and TGF-β1, promoting pathological choroidal vascular growth.[46] Under normal conditions, macrophages are absent from the retina but are distributed in the choroid. The choroid contains proliferative resident macrophages and inflammatory macrophages recruited from the blood monocytes.[39] In AMD, macrophages are recruited from the choroid or systemic circulation into the retina, where they perform phagocytic functions, clearing lipid-rich membranous debris and drusen.[47] Macrophages can exhibit different polarization states, including pro-inflammatory M1 phenotypes and anti-inflammatory reparative M2 phenotypes. In GA patients, the proportion of M1 macrophages is higher, while in nAMD patients, the proportion of M2 macrophages is higher.[48] In the early stages of AMD, increased and overactivated M1 macrophages lead to an increase in proinflammatory cytokines, which damage RPE cells and PRs and promote disease progression. M2-type macrophages play a protective role by limiting inflammation through the removal of cellular debris and inhibiting the production of inflammatory factors. In the later stages, an increase in IL-10 expression leads to a shift from M1 to M2 phenotype, with M2 macrophages participating in neovascularization. Therefore, the transition of macrophages from M1 to M2 phenotype is a driving factor in AMD progression.[49]

Neutrophils are one of the most abundant leukocyte types in the immune system and play multiple roles in immune defense, inflammation regulation, and tissue repair.[50] In AMD, the amyloid β component in drusen can activate neutrophils via TLR4 and NADPH oxidase-dependent pathways. Activated neutrophils produce a large amount of Neutrophil Extracellular Traps (NETs), and inhibiting NETs formation can effectively reduce retinal inflammatory responses.[51] François et al found that in OIR mice, neutrophils promote retinal vascular remodeling by clearing senescent vascular cells through the release of NETs.[52] Increased levels of interferon-λ (IFN-λ) in early AMD also trigger neutrophil activation and upregulation of lipocalin-2 (LCN-2). LCN-2, by modulating levels of integrin β1, stimulates the adherence and migration of activated neutrophils to the retina and choroid, thereby promoting inflammation.[53,54]

Therefore, neutrophils play a significant role in the pathological changes of AMD, and targeting NETs could be a potential strategy for treating AMD.

Natural Killer cells (NKs) are an important component of the innate immune system and play a key role in the recognition and elimination of infected and tumor cells.[55] Goverdhan et al found that the combination of the HLA-Cw*0701 allele and the inhibitory receptor AA haplotype of NK cells was significantly associated with AMD, suggesting that NK cells may contribute to AMD pathogenesis through interactions with specific HLA-I class molecules.[56] Zeng et al identified complement C1s, adrenomedullin, and immediate early response 5-like as AMD diagnostic biomarkers, and these genes are associated with infiltration of NK cells.[57] Lee et al found that NKs facilitate the expression of VEGF in macrophages through the secretion of IFN-γ, thereby playing a promotive role in the CNV process.[58]

Mast cells (MCs) are key inflammation effector cells, and the choroid contains numerous MCs.[59] In AMD patients, there is an increased and activated MCs population in the macular region and the sub-macular choroid. These activated MCs undergo degranulation, releasing substantial cytokines and enzymes. In GA, proteases released by MCs cause choroidal thinning and BM degradation, consequently killing RPE and causing CC degeneration. In nAMD, MC degranulation releases factors such as heparin and VEGF, interacting with ECs to promote their proliferation and CNV formation.[59] Moreover, MC activation can facilitate macrophage recruitment and inflammation onset.[60]

Voigt et al identified a Dendritic cells (DCs) population via choroidal transcriptomics. Their analysis of choroidal AMD genetic risk factors found DCs highly express VEGF and MMP9 genes, associated with nAMD.[61] However, in laser-induced nAMD models, DCs show no significant role.[62] Therefore, the specific role of DCs in AMD pathogenesis requires further investigation.

Complement System

The complement system, comprising over 50 plasma proteins, membrane-bound receptors, and regulatory proteins, is the principal humoral component of the innate immunity, performing diverse functions including pathogen clearance and immune cell recruitment. Most complement components are inactive proenzymes, which can be activated via the classical pathway, alternative pathway, or lectin pathway. These three pathways converge at C3, initiating a cascade reaction through C3 convertase, leading to the formation of immunostimulatory byproducts like C3a, C5a, and the membrane attack complex (MAC, C5b-9).[63] In retina, MG cells and RPE cells can locally synthesize certain complement components, such as complement C1q, C3, and complement regulatory factors like CFH, CFB, and CD59.[64]

The notion that complement plays a major role in AMD has been supported by genetic studies.[18] The complement system is a double-edged sword for the retina. Low levels of complement activation facilitate maintenance of immune privilege, whereas overactivation damages retinal tissue and elicits chemotactic aggregation of immune cells. As AMD progresses, complement activation levels gradually increase, especially in individuals with a heavier genetic burden of complement genes.[65] In AMD patient plasma, there is an increased concentration of activated products such as C3a, C3b, Ba, Bb, C5a, and CFH.[66] Elevated complement C5a levels significantly stimulate T cells to produce IL-22 and IL-17, promoting the onset of AMD-related inflammation.[67] The presence and activation of C3 and C5 in drusen lead to chronic inflammation and exacerbate subretinal damage.[68] MAC-mediated lysis of ECs is a key factor in the formation of CNV in nAMD.[31,69]

The Interplay of Cellular Senescence and Immune Homeostasis Dysregulation in AMD

In the retina, PRs, ECs, ganglion cells, MG cells, and RPE cells all actively participate in suppressing immune cell activation.[70] For instance, neurons exert immunosuppressive functions through the CX3CL1-CX3CR1 axis or various cell surface molecule interactions (such as CD200-CD200R, CD47-signal regulatory proteins).[71] RPE cells may regulate the antigen-presenting properties of MG cells by secreting immunomodulators like Prostaglandin E2 and NO, thereby protecting the retina.[70] RPE cell senescence often triggers abnormal activation of immune cells and complement. Senescent RPE cells release SASP, causing a substantial increase in proinflammatory and immunologic factors in the extracellular environment. Moreover, senescence-induced autophagy defects result in reduced phagocytic function of RPE cells towards PR outer segments, accumulated lipofuscin within cells, and increased SRS waste.[3] All these factors

trigger the activation and migration of MG cells. Additionally, neuronal cell senescence leads to decreased expression of CX3CL1 and CD200, weakening their inhibitory effect on MGs and further amplifying their activation (Figure 1a).[72]

MG cells transition from a branched to an amoeboid morphology, migrating from the neural retina to the SRS. On the apical side of the RPE, MG cells digest and phagocytose deposits, exerting a protective role on the aging retina.[42] The presence of MG cells in the SRS induce RPE cells to express more chemokines and adhesion molecules (such as CCL2, CCL5, vascular cell adhesion molecular-1, intercellular cell adhesion molecular-1, etc.), creating a chemotactically attractive environment in the outer retina and recruiting more immune cells from the choroidal and systemic circulation.[73] Recruited monocytes partly enter the retina to replenish the MG cells population, while others differentiate into macrophages, MCs, DCs, etc, infiltrating the basal side of RPE cells.[74] Activated MPs express inducible NO synthase, which is deposited near drusen and waste products[75] that exert scavenging and phagocytic functions through P2X7 receptors.[76] Immune cell-mediated clearance of senescent retinal cells is crucial for maintaining retinal homeostasis. Studies in skin tissue have shown that senescent fibroblasts evade immune clearance by upregulating HLA-E expression, thereby inhibiting NK and $CD8^+$ T cell responses.[77] The relevance of HLA and NK cells to the pathogenesis of AMD is significant, and whether retinal senescent cells also use HLA for immune evasion is an intriguing topic that warrants further research.

The overactivation and accumulation of MPs have neurotoxic effects. To prevent damage, RPE cells can induce apoptosis in immune cells. RPE cells possess Fas Ligand (FasL) which interacts with the Fas receptor on MPs, leading to the clearance of MPs from the SRS.[78] The CD47/Thrombospondin-1 (TSP-1) signaling pathway is crucial for MPs elimination beneath the retina.[79] RPE cells produce TSP-1, which interacts with CD47 on macrophages, reducing their phagocytic ability and increasing FasL sensitivity (Figure 1a).[80] However, in AMD, RPE cell senescence decrease FasL and TSP-1 expression,[81] diminishing the clearance of MPs. Different CFH variants also affect MPs clearance efficiency, CFH binding to CD11b hinders the CD47/TSP-1 pathway, prolonging MPs lifespan.[79] The continuous accumulation of MPs promotes degenerative changes in the retina.

It is important to note that immune cells also undergo cellular senescence. Following senescence in MG cells, there is an accumulation of lipofuscin within cells, and a decrease in their capacity to respond to injury and phagocytic ability.[82] In senescent MG cells, key genes controlling inflammatory responses (eg nuclear transcription factor-κB (NF-κB), C3, CFB) exhibit significant changes, promoting complement activation and immune dysregulation, driving chronic inflammation in the retina.[30,44] In senescent macrophages, the cholesterol efflux regulators ATP-binding cassette transporter A1 (ABCA1) and ABCG1 are downregulated, leading to impaired lipid efflux and cholesterol-rich drusen deposition in early AMD.[33] Furthermore, elevated lipid levels promote macrophage polarization to M2, and senescence itself also induces polarization to M2. These factors collectively contribute to the development of CNV in AMD.[33] Additionally, studies have found that senescent macrophages express high miRNA-33 and 150, causing abnormal lipid metabolism and mediate inflammation and pathologic angiogenesis by down-regulating ABCA1 and stearoyl coa desaturase 2 expression.[83]

Under pathological AMD conditions, retinal cells contact and interact with immune cells, amplifying the inflammatory response and exacerbating retinal damage. MPs secrete IL-1β, which is toxic to neuronal cells and can induce PRs death, especially cone cells.[84] TNF-α secreted by MPs inhibits the key transcription factor Orthodenticle homeobox 2 in RPE cells, disrupting RPE homeostasis and damaging the visual cycle.[85] IL-6 secreted by MPs further reduces FasL expression in senescent RPE, interfering with the immunosuppressive ability of RPE to clear macrophages.[78] IL-1β and TNF-α synergistically stimulate RPE cells to produce recruitment factors (MCP-1 and IL-8), continuously recruiting monocytes to the CNV site, amplifying pathological angiogenesis.[86] Additionally, MPs are associated with late-stage fibrotic lesions in nAMD. MPs can trigger the expression of integrins α1 and α5 on the RPE surface through TNF-α, promoting RPE cells migration on fibronectin and type I collagen, leading to fibrotic scarring.[87] Furthermore, Little et al found that C3a and TGF-β can induce MPs transformation to myofibroblasts, directly promoting fibrosis progression, with 20–30% of infiltrating macrophages at nAMD lesion sites expressing the myofibroblast marker α-smooth muscle actin (Figure 2).[88] The AKT2/NF-κB/LCN-2 signaling axis in AMD reveals the dynamic interactions among RPE cells, MG cells and neutrophils. Senescent RPE cells release cytokines and chemokines that activate MG cells pro-inflammatory transformation via Akt2. Activated MG cells release pro-inflammatory mediators NF-κB, upregulating

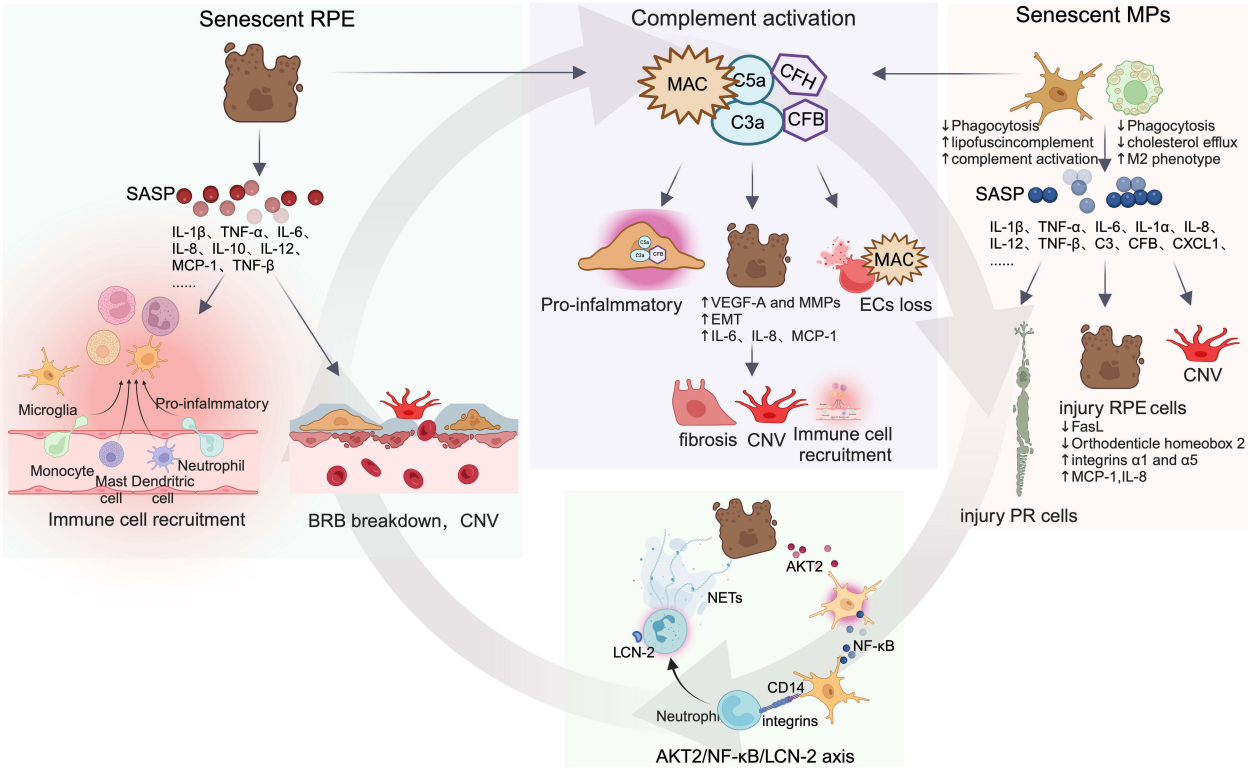

Figure 2 Vicious Cycle. Mechanisms of interaction between cellular senescence and dysregulation of immune homeostasis in retina.
Note: Created with BioRender.com.

CD14. CD14, an important ligand for integrins, binds with adhesion proteins on neutrophils (eg integrins β1 and α4), causing neutrophil activation. Activated neutrophils exhibit increased LCN-2 and NETs, triggering inflammatory responses in AMD (Figure 2).[89]

The interaction between immune cells and the complement system also drives the progression of AMD. On the one hand, inflammatory cytokines from activated MG cells or infiltrating macrophages increase complement genes expression. For instance, the accumulation of senescent MG cells decrease CFH and CFB expression, leading to complement activation.[90] On the other hand, complement activation releases complement fragments C3a and C5a, further affecting MPs activation and migration (Figure 2). In addition to immune cells, RPE cells also interact with the complement system. RPE cells can promote the expression of complement regulators C1INH and CD59a in macrophages, exerting an inhibitory effect on the complement system. However, this ability is reduced when RPE cells undergo senescence, promoting complement activation and deposition at the retina-choroid interface.[91] Complement fragments C3a and C5a signal through their respective G-protein coupled receptors to upregulate VEGF-A and MMPs expression in RPE cells, promoting CNV formation.[92,93] C5a also mediates the epithelial-mesenchymal transition of RPE cells, playing a significant role in subretinal fibrosis secondary to nAMD.[94] Generally, the MAC does not deposit on RPE cells. Apart from being directly inhibited by complement regulatory factors expressed by RPE cells (such as CD59), RPE cells also process surface-bound MAC through endocytic pathways and lysosomal degradation. However, in senescence, RPE cells are more susceptible to MAC attack due to autophagy dysfunction.[95] MAC promotes RPE cells to produce IL-6, IL-8, and MCP-1, creating a pro-inflammatory environment in early AMD and recruiting immune cells; it also increases MMPs and VEGF expression, associated with neovascularization.[96] As previously discussed, MAC disrupts choriocapillaris ECs. With the senescence of ECs, local production of CFH may decrease, leading to excessive complement activation and MAC deposition. Additionally, senescent ECs exhibit increased stiffness, associated with elevated Rho activity, which in turn increases their sensitivity to MAC damage, contributing to choroidal degeneration in AMD (Figure 2).[31,97]

Conclusion

The interplay of cellular senescence and immune homeostasis dysregulation creates a chronically worsening inflammatory environment in the retina, driving AMD progression. Therapies targeting these two mechanisms could ameliorate retinal pathological changes. Current strategies for reversing cellular senescence primarily include two aspects. First, senolytics, inducing apoptosis of SNCs to eliminate them, such as dasatinib+quercetin, Bcl-2/BET protein inhibitors. In the OIR mice model, the BCL-xL inhibitor UBX1967 effectively eliminates senescent ECs and inhibits neovascularization.[98] Second, senostatics, reducing SASP levels by modulating the NF-κB, mTOR, and AMPK pathways. In the OIR mice model, metformin (an AMPK activator) can reduce destructive retinal neovascularization by inhibiting SASP.[29] The clearance of SNCs mediated by immune cells demonstrates the potential of immunotherapy in anti-senescence strategies. For instance, NETs can clear senescent ECs;[52] LXR agonists or miR-33 inhibitors can restore cholesterol homeostasis in macrophages, reversing retinal senescence in mice.[33] However, several important issues need consideration when applying these therapies clinically. How can drugs be delivered effectively to the SRS? Which cells in the retina are targeted by the drugs? Does the removal of SNCs impact function due to tissue loss?

With immunology research deepening in AMD, targeted complement therapy has become a new focus.[99] However, several clinical trials of complement inhibitors yielded unsatisfactory results, with poor visual acuity improvement and disease progression control. The failure of lampalizumab, a CFD inhibitor, to prevent GA progression in a Phase 3 study exemplifies this.[100] AMD pathogenesis is complex and involves persistent local inflammation and reduced retinal injury repair. AMD treatment should not be solely anti-inflammatory, but rather create a permissive environment for repair, possibly including promoting the complement system alongside systemic immunotherapy.[101] The goal should be developing effective treatments optimizing aging immune system performance to enhance tissue repair. Panmacular subthreshold diode micropulse (SDM) laser shows promise, regular SDM significantly reducing risk of dry AMD converting to wet form and improving vision.[102] SDM preserves RPE cells, normalizes VEGF and chemokine levels, and promotes retinal repair, showing great therapeutic potential.[103]

In summary, the interaction between cellular senescence and immune homeostasis dysregulation reveals a complex yet crucial pathological mechanism in AMD. This interplay not only deepens our understanding of AMD pathology but also offers potential directions for developing new therapeutic strategies.

Abbreviations

AMD, age-related macular degeneration; RPE, retinal pigment epithelial; SNCs, senescent cells; SASP, Senescence-Associated Secretory Phenotype; RS, replicative senescence; SIPS, stress-induced early senescence; DPS, developmentally programmed senescence; SA-β-Gal, senescence-associated β-galactosidase; GA, geographic atrophy; CNV, choroidal neovascularization; PRs, photoreceptors; CC, choriocapillaris; BM, Bruch's membrane; BMP4, bone morphogenetic protein 4; GWAS, Genome-wide association studies; HTRA1, high-temperature requirement protein A1; TAK1, Transforming growth factor-β-activated kinase 1; MMP, matrix metalloproteinase; 7KC, 7-ketocholesterol; ECs, endothelial cells; A2E, N-retinylidene-N-retinylethanolamine; OIR, oxygen-induced retinopathy; MG, microglia; IL-6, interleukin-6; MCP-1, monocyte chemotactic protein; TNF-α, tumor necrosis factor-α; CFB, complement factor B; NO, nitric oxide; BRB, blood-retinal barrier; MPs, Mononuclear Phagocyte System; SRS, subretinal space; IFN-λ, interferon-λ; NF-κB, nuclear transcription factor-κB; ABCA1, ATP-binding cassette transporter A1; NETs, Neutrophil Extracellular Traps; LCN-2, lipocalin-2; NKs, Natural Killer cells; MCs, Mast cells; DCs, Dendritic cells; MAC, membrane attack complex; FASL, Fas Ligand; TSP-1, Thrombospondin-1; SDM, subthreshold diode micropulse.

Acknowledgments

The authors appreciate the help of Dr. Ming Ming Yang in providing editorial assistance and support in the preparation of the manuscript. At the same time, we thank Shenzhen Science and Technology Program and Shenzhen Natural Science Foundation for their support.

Funding

This study was supported in part by Shenzhen Science and Technology Project (No. JCYJ20220818102603007), and the General Project of the Shenzhen Natural Science Foundation (No. JCYJ20210324113808023).

Disclosure

The authors report no conflicts of interest in this work.

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