REVIEW

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Exploring the role of inflammation in age-related macular degeneration: new insights and implications for future therapies

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Abstract

The retina consists of one of the body's most delicate organs, being sensitive to various metabolic disturbances, vascular abnormalities and inflammatory processes. Age-related macular degeneration (AMD) impacts millions of people worldwide and represents a notable cause of blindness. Chronic inflammation, implicated in several degenerative diseases including Parkinson's and Alzheimer's diseases, as well as atherosclerosis, has been linked to AMD. Both histopathological and genetic investigations have underscored the immune system's role in AMD progression. The objective of this literature review was to summarize the actual knowledge, identify research gaps and to serve as a basis for future studies regarding the correlations between inflammation and AMD. We conducted a thorough search of the primary databases (*Web of Science*, *Cochrane Library*, *PubMed*/*MEDLINE*), using keywords such as 'age-related macular degeneration', 'inflammation', 'neurodegeneration', and 'C-reactive protein'. We included systematic reviews and meta-analyses that offer the most relevant results in this research area. We also included the results from recent studies that have not yet been widely approached. Our strategy also consisted of looking for relevant articles in the reference list.

Keywords: age-related macular degeneration, chronic inflammation, neurodegeneration.

Introduction

The retina consists of one of the body's most delicate organs, representing a neural tissue that forms the posterior inner surface of the eyeball. Its structure comprises vascular cells, pigment epithelium, neurons, Müller cells and microglia. It is sensitive to various metabolic disturbances, vascular abnormalities and inflammatory processes which manifest in distinct ways [1, 2].

Age-related macular degeneration (AMD) impacts millions of people worldwide and represents a notable cause of blindness. It is divided into neovascular and non-neovascular AMD, each with further subtypes based on particular disease characteristics. Non-neovascular AMD, widely known as "dry" AMD, represents approximately 80% to 85% of all cases and typically has a more favorable visual outlook. Alternatively, neovascular AMD, also referred to as "wet" AMD, affects around 15% to 20% of cases and is responsible for approximately 80% of severe vision impairment resulting from AMD. The following retinal photographs, optical coherence tomography (OCT) and OCT angiography pictures illustrate examples of neovascular and non-neovascular AMD (Figure 1, A and B; Figure 2, A–C) [3, 4].

AMD has various pathological processes likely to contribute to its development, aging being the primary risk factor. Other environmental elements like smoking, diet, and exposure to light can significantly elevate the risk. Additionally, genetic variations play a role. Chronic inflammation, implicated in several degenerative diseases including Parkinson's disease (PD) and Alzheimer's disease (AD), as well as atherosclerosis, has been linked to AMD. Both histopathological and genetic investigations have underscored the immune system's role in AMD progression. Significant associations have been observed between various immunological and inflammatory gene variations and AMD, highlighting the involvement of inflammation and immune-mediated mechanisms, particularly complement activation, in the disease's onset and progression [5–7].

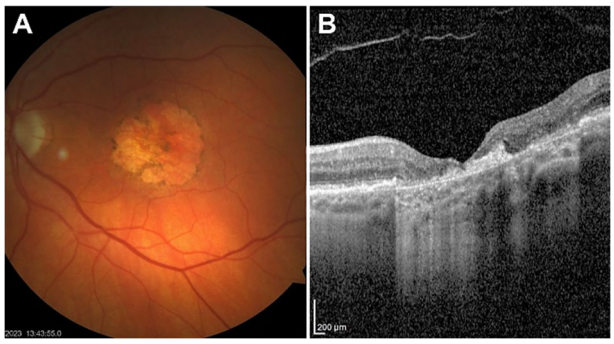

Figure 1 – ***Non-neovascular (dry) age-related macular degeneration: (A) Fundus image showing macular geographic atrophy; (B) OCT image showing hyper-transmission due to the atrophy of the photoreceptor layer. The image is shared with the courtesy of Dr. Monica Gavriș. OCT: Optical coherence tomography.***

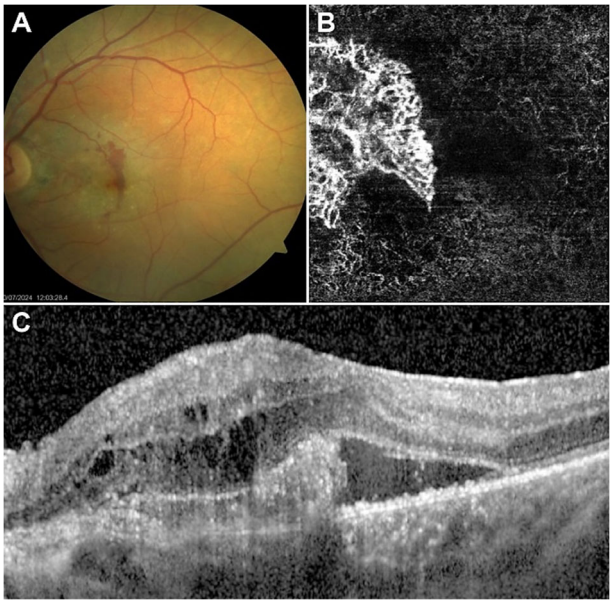

Figure 2 – ***Neovascular (wet) age-related macular degeneration: (A) Fundus image showing greyish subretinal macular lesion associated with overlying subretinal fluid, lipid exudation and hemorrhage; (B) OCT angiography image showing the choroidal membrane in the avascular zone; (C) OCT image showing retinal thickening with intraretinal and subretinal fluid. The image is shared with the courtesy of Dr. Monica Gavriş.***

The actual understanding of systemic inflammation and retinal pathology represents a promising area of research with profound implications for both ophthalmology and systemic health. Recent studies have started to admit the potential role of inflammation biomarkers for retinal pathology, including both exudative and non-exudative AMD, retinal vascular occlusion or diabetic retinopathy (DR). Researchers are exploring how elevated biomarkers levels are linked with a higher risk of developing these conditions or exacerbating their progression. Given the absence of a cure for AMD, it is crucial to pinpoint biomarkers for disease screening, early diagnosis, treatment monitoring, progression mitigation, and the exploration of new therapeutic approaches. Therefore, the objective of this literature review was to synthesize and critically assess the existing knowledge, identify research gaps and provide a foundation for future studies regarding inflammation in AMD. We conducted a thorough search of the primary databases (*Web of Science*, *Cochrane Library*, *PubMed*/*MEDLINE*), using keywords such as 'age-related macular degeneration', 'inflammation', 'neurodegeneration', and 'C-reactive protein'. We included systematic reviews and meta-analyses that offer the most relevant results in this research area. We also included the results from recent studies that have not yet been widely approached. Our strategy also consisted of looking for relevant articles in the reference list.

Age-related macular degeneration and inflammation

Pathophysiology

AMD is a chronic and progressive condition that affects primarily the macular region, which is the central part of the retina and is a major contributor to vision impairment globally. The most significant vision loss in AMD typically occurs during its advanced stages, which can be categorized into two main processes: neovascular or "wet" AMD and geographic atrophy, known as "dry" AMD.

In neovascular AMD, abnormal vessels grow from the choroid layer, penetrate into the neural retina and results in leakage of fluids, lipids and blood that ultimately forms a fibrous scar. On the other hand, geographic atrophy leads to gradual deterioration of the retinal pigment epithelium (RPE), choriocapillaris and photoreceptor cells. Vision loss in AMD is typically associated with these advanced forms of the disease [8].

The blood–retinal barrier (BRB) has a fundamental role in the microenvironment of the retina. It consists of the inner BRB (iBRB) and outer BRB (oBRB) that are responsible for the control of the flow of fluids and molecules between the blood vessels and the tissues of the retina [9].

The iBRB is formed by tight junctions (TJs), also known as *zonula occludens* (ZO), located between adjacent endothelial cells in the retinal blood vessels. TJs limit the molecules to diffuse through the retinal endothelial layer, with a permeability rate of approximately 0.14×10^{-5} cm s^{-1} for substances like fluorescein [10, 11].

The oBRB is constituted by the formation of TJs between cells in the RPE. These junctions have an important role in controlling the movement of solutes and fluids, regulating the transfer of nutrients and waste materials between the choriocapillaris and the retina. Changes of the oBRB integrity like alterations in the levels of TJ proteins like ZO-1 and occludin can harm the neurovascular unit. TJs involve transmembrane proteins like claudins, occludin and junctional adhesion molecules, while ZO-1, ZO-2 and ZO-3 interact with these transmembrane proteins on the intracellular side of the cell membrane, anchoring them to the actin cytoskeleton [12–14].

C-reactive protein

C-reactive protein (CRP) is a key element in the acute-phase reactant that exists in at least two different structural forms: monomeric CRP (mCRP) and pentameric CRP (pCRP). The pentameric form can exhibit both anti-inflammatory and proinflammatory properties depending on the specific context. In contrast, mCRP shows strong proinflammatory effects on various cellular components like leukocytes, platelets, endothelial and endothelial progenitor cells that can increase the inflammatory reaction. The conversion from pentameric to monomeric form directly connects CRP to the inflammation process. CRP stands as a valuable serum biomarker for individuals with acute inflammatory responses. Furthermore, an increase in baseline CRP levels is considered an indicator for the assessment of tissue injury caused by excessive inflammation or the insufficiency of the initial inflammatory response [15–17].

CRP triggers the production of inflammation and the release of reactive oxygen species (ROS) by binding to Fcγ receptors, which include Fcγ receptor I and II [cluster of differentiation (CD)64 and CD32]. When CRP binds to these receptors, it can trigger the nuclear factor-kappa B (NF-κB) signaling cascade that leads to the production of ROS and the upregulation of proinflammatory mediators

like cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor-alpha (TNF-α) (Figure 3). Moreover, a recent investigation demonstrated that CRP promotes angiogenesis in microvascular endothelial cells [18–21].

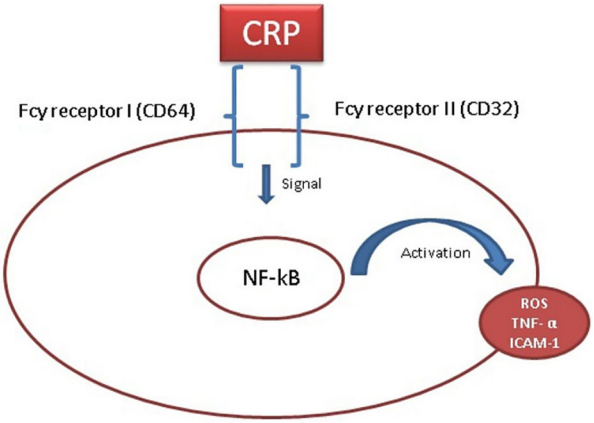

Figure 3 – ***CRP induced ROS production and inflammation through Fcγ receptor-mediated NF-κB signaling. CD: Cluster of differentiation; CRP: C-reactive protein; ICAM-1: Intercellular adhesion molecule-1; NF-κB: Nuclear factor-kappa B; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor-alpha.***

In the initial 10 to 72 hours of an inflammatory response, it has been shown that serum levels of pCRP rise remarkably, going from no more than 3 µg/mL to over 90–100 µg/mL. pCRP, which circulates in the blood as a 115 kDa homopentamer, undergoes an irreversible transformation into 23 kDa monomers when it binds to abnormal, apoptotic or damaged cell membranes and it activates platelets or microparticles derived from blood. This transformation results in the formation of mCRP, which is primarily found in tissues since it undergoes a structural change that makes it mostly insoluble [22–25]. In an *in vitro* investigation led by Romero-Vázquez *et al.*, a transwell model was employed to observe that both pCRP and mCRP have the capability to traverse choroidal endothelial cells and reach the RPE. Moreover, the study revealed that specifically mCRP, not pCRP, could permeate the RPE monolayer when tested on ARPE-19 cells. It is worth noting that mCRP exists in drusen, the characteristic deposits associated with AMD and was also identified as a factor causing disruption in the oBRB [26].

AMD has garnered the highest volume of research attention in relation to CRP levels compared to other retinal diseases. In a meta-analysis performed by Hong *et al.*, in 2011, evaluated the association between CRP and AMD on 13 articles published in the first decade of this century. They documented a significant association between high blood CRP levels and late AMD, suggesting that a CRP level that exceeds 3 mg/L is linked to a twofold increase in the risk. However, the supporting evidence for a relationship between CRP and early stage AMD is less robust, emphasizing the necessity of additional research in this area [27].

A more recent meta-analysis carried out by Feng *et al.*, in 2020, on 53 studies, has provided clarity on the previously uncertain association between early-stage AMD and raised CRP levels. This analysis concluded that there is no significant association between early-stage AMD and CRP. However, it also revealed that small to moderate increase in systemic CRP is associated with neovascular and late AMD [28].

Since the last meta-analysis, several new studies have been conducted to investigate the relationship between AMD and the CRP levels. Newer studies focus on multiple inflammatory factors. The heightened risk might arise due to various combinations of analyte levels, suggesting a complex relationship rather than a straightforward elevation in just a few markers. These studies are presented in a dedicated table for references (Table 1).

Table 1 – ***Characteristics of four studies on the relationship between CRP and AMD***

Author	Methods	Results
Wagner *et al.* (2021) [29]	Examined a set of 27 inflammatory markers present in the bloodstream. These markers encompassed complement factors, cytokines, chemokines and hsCRP. In the study, there were 99 individuals diagnosed with intermediate AMD. Among these participants, 21 individuals progressed to advanced stages over a median follow-up of two to 50 months.	Strongest correlation observed among the complement factors. Additionally, correlations were identified among a limited group of complement and cytokine signaling factors including CRP.
Chen *et al.* (2021) [30]	Evaluate the CRP levels and reduction in CT, both factors associated with increased risk of late stage AMD. They measured hsCRP in serum samples and encompassed 213 eyes belonging to 107 patients with average age of 76.8 years.	Elevated CRP levels were found to be linked to a reduction in CT in the initial analysis (p=0.01). This association between higher CRP and decreased CT remained statistically significant even after accounting for factors such as age and reticular pseudodrusen.
Weaver *et al.* (2020) [31]	Protein levels of ASC, IL-18 and CRP were assessed in serum of both healthy controls and patients with AMD.	ASC, IL-18 and CRP were high in the serum of AMD patients compared to normal controls.
Shijo *et al.* (2020) [32]	A case-control study was conducted to compare CRP levels between patients with exudative AMD and CRP levels in a group of healthy control subjects. Plasma CRP levels were assessed in all participants using latex nephelometry.	In a group of 125 patients with exudative AMD, as well as 150 control subjects, it was observed that CRP levels were elevated in exudative AMD compared to the control group.

AMD: Age-related macular degeneration; ASC: Apoptosis-associated speck-like protein containing a caspase-1 recruitment domain; CRP: C-reactive protein; CT: Choroidal thickness; hsCRP: High-sensitivity CRP; IL-18: Interleukin-18.

Cytokines and chemokines

Mediators released from macrophages or T-cells can influence the immune status of the RPE by interacting with T-cells. For instance, both interferon (IFN)c and TNF-α have been demonstrated to induce the increased expression of chemokines, complement proteins, and vascular endothelial growth factor (VEGF) in RPE cells *in vitro*. TNF-α binds to various receptors, including TNF receptor II, which is primarily exhibited on endothelial and immune cells. Upon secretion of TNF-α, this receptor is transformed into a soluble form (sTNFRII). Due to its elevated concentration

and a longer half-life, the levels of the soluble form of TNF receptor II may correlate with higher TNF-α secretion. Although there are no known markers comparable to sTNFRII for IFNc, utilizing a high-sensitivity assay presents a different approach for measuring this cytokine [33–35]. In the study performed by Faber *et al.* on 136 subjects with early and late AMD forms, the plasma levels of sTNFRII were found to be higher than controls supporting the systemic inflammatory status of the disease [36].

Interleukin (IL)-13 plays crucial roles in allergic inflammation and the formation of fibrosis. The production of several matrix metalloproteinases (MMPs) is controlled at the transcriptional level by various inflammatory cytokines, hormones, growth factors, and cellular changes. Human IL-1 serves as a pivotal mediator in the body's response to inflammatory, immunological and infectious threats. This cytokine family comprises 11 members that play central roles in modulating inflammatory reactions to sterile infections. Additionally, IL-1 is a strong neurotropic cytokine involved in various neurodegenerative conditions like stroke, PD, amyotrophic lateral sclerosis, AD and AMD (Figure 4) [37, 38].

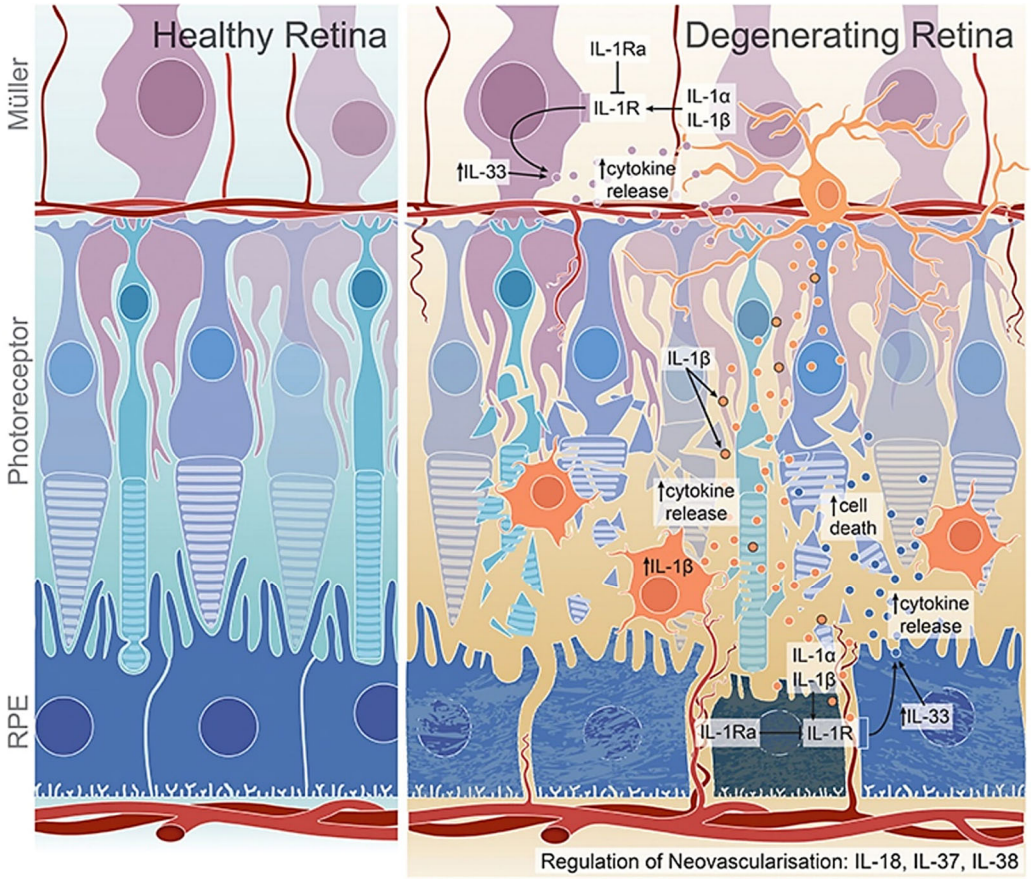

Figure 4 – ***The involvement of IL-1 family cytokines in retinal degeneration. Adapted from Wooff et al. [39]. IL: Interleukin; RPE: Retinal pigment epithelium.***

The IL-6 cytokine family, which includes IL-6, consists of proteins structurally and functionally related to each other. These cytokines regulate diverse biological processes such as hematopoiesis, immune responses, inflammation, cell growth, differentiation, cardiovascular functions, reproduction and neuronal survival. IL-6, particularly generated as a reaction to infections and tissue injury, plays a significant role in host defense mechanisms by promoting acute phase responses, blood cell production and immune reactions. It triggers the assembly of acute-phase proteins like serum amyloid A, CRP and fibrinogen in hepatic cells. Moreover, IL-6 might indirectly enhance vascular permeability by promoting the production of VEGF or directly enhance endothelial permeability. VEGFs have been linked to the formation of choroidal neovascularization (CNV) associated with AMD (Figure 5). Elevated levels of IL-6 in the serum of AMD patients suggest its potential as a risk factor for CNV [40, 41].

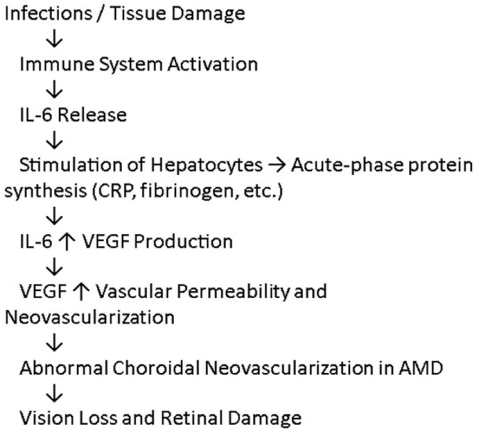

Figure 5 – ***IL-6 and its pathophysiological impact on vascular permeability and choroidal neovascularization. AMD: Age-related macular degeneration; CRP: C-reactive protein; IL-6: Interleukin-6; VEGF: Vascular endothelial growth factor.***

Budiene *et al.* evaluated the impact of MMPs and systemic cytokines on the onset of wet AMD on 282 patients with random controls. The MMP1 *rs1799750 1G/2G* genotype was observed to have a notable impact on the onset of early AMD in individuals younger than 65 years old. In incipient AMD patients, there was an important elevation in IL-1β concentration for those with the MMP1 *rs1799750 1G/1G* genotype and the MMP7 *rs11568818 A/G* genotype in comparison to subjects in the control group [42]. Nassar *et al.*, also assessed 30 patients with AMD and controls serum proinflammatory cytokines. The increase in serum levels of IL-1α, IL-1β, IL-4, IL-5, IL-10, IL-13, and IL-17 among individuals with AMD suggests the inflammatory nature of the disease. Patients exhibiting elevated levels of TNF-α and IL-17 in their serum are more predisposed to experience a positive response to VEGF therapy. These cytokines could serve as accessible biomarkers for diagnosis and monitoring of AMD [43]. Also, Fu *et al.*, in an *in vitro* study, evaluated the effects of IL-13 on RPE and its level in aqueous humor in patients with AMD. Results shown that *in vitro*, IL-13 inhibits the proliferation of ARPE-19 cells and its expression in the aqueous humor, potentially linking it to AMD [44].

Leukocytes

Leukocytes are innate and adaptive immune cells that have important roles in AMD pathogenesis. Microglia resides in the retina and has the role of maintaining homeostasis by phagocytosing deteriorated cell components. They have a role, especially in wet AMD, where senescent microglia migrate into the subretinal space, where they promote inflammation and neovascularization. They release neurotoxic factors that contribute to photoreceptor degeneration. Macrophages are modulators of tissue repair and angiogenesis that polarize into the following two phenotypes: proinflammatory M1 or anti-inflammatory M2. M1 macrophages play a role in early CNV by suppressing its formation, while M2 macrophages, in later stages promote angiogenesis and tissue remodeling. Both macrophage recruitment and polarization are influenced by extracellular deposits, such as drusen [45–47].

Neutrophils initiate a second wave of immune reactions by the activation of T-cells and recruitment of macrophages. In AMD, the severity of the disease can be evaluated through a neutrophil/lymphocyte ratio. Neutrophils produce VEGF, IL-8, and MMP-9, which affect the extracellular matrix and compromise the RPE barrier resulting in CNV [48, 49].

Dendritic cells (DCs) act as antigen-presenting cells and in AMD. They become activated when retinal injury occurs, helping T-cell activation and promoting inflammation. Immature DCs contribute to CNV expansion in experimental models, while injured RPE cells attract DCs, leading to antigen presentation, thus perpetuating the disease [50, 51].

B-lymphocytes act as anti-retinal autoantibodies and appear to contribute to the onset of AMD. Higher levels were detected in early AMD patients compared to controls. Studies such as the Blue Mountains Eye Study showed increased autoantibodies against retinal polypeptides in early AMD indicating that their role is primarily in initial stages of the disease [52, 53].

T-cells are involved in AMD through the production of proinflammatory cytokine and immune modulation. T-helper (Th)1 and Th17 cells promote M1 macrophage polarization, neovascularization, and neurodegeneration, while Th2 and Th17 contribute to subretinal fibrosis. Lower C-X-C motif chemokine receptor 3 (CXCR3)+CD4+ T-cells promote CNV and T-cell immunosenescence is linked to wet AMD progression [54, 55].

Neurodegeneration

The human macula displays distinct types of neurodegeneration and gliosis. Notably, photoreceptors with lengthy axons are intertwined with the outer branches of Müller glia in the Henle fiber layer, a characteristic unique to this region. Recent histologically validated longitudinal imaging, utilizing OCT, has affirmed earlier findings that the boundary of atrophy within the retinal photoreceptors manifests as a downward movement of the external limiting membrane (ELM) towards Bruch's membrane. The ELM serves as a junctional complex photoreceptors and Müller cells, acting as a natural barrier to fluid movement and controlling the photoreceptor environment. In cases of complete RPE and outer retinal atrophy, when the ELM curves downward, the normally vertical Müller glia shifts horizontally and shows a significant increase in glial fibrillary acidic protein expression, indicating reactive gliosis. Formerly studied as an indicator of visual function in macular atrophy, the ELM holds the potential as a measure of photoreceptor survival following injury. Li *et al.* examined, in a case study, the spatiotemporal and cellular aspects of gliosis and neurodegeneration in a patient experiencing submacular hemorrhage caused by type 1 macular neovascularization associated with neovascular AMD. Findings indicate significant macular gliosis and neurodegeneration, characterized by a compacted ELM, shortly after the onset of hemorrhage. Increased OCT reflectivity of the ELM, which serves as a crucial retinal barrier, shows promise as a biomarker for pronounced photoreceptor damage and gliosis [56–59].

Farinha *et al.* showed in a large population, cross-sectional, OCT based study demonstrated that in early AMD, the majority of both inner and outer neuroretinal layers exhibit reduced thickness, particularly in higher stages, suggesting the presence of early and advancing neurodegeneration. The thickness of neuronal retinal layers could serve as quantitative indicators of disease advancement in early AMD, especially as segmentation algorithms enhance accuracy over time. Additionally, biomarkers like subretinal drusenoid deposits may correlate with more pronounced and accelerated neurodegeneration, as their presence tends to associate with thinner retinal layers and choroid [60].

Receptor for advanced glycation end-products

Receptor for advanced glycation end-products (RAGE) has been likened to Toll-like receptors due to its localization on the cell membrane and its proinflammatory actions mediated by NF-κB signaling. Belonging to the immunoglobulin superfamily, RAGE also promotes leukocyte recruitment to inflamed tissues by functioning as an endothelial adhesion receptor. Originally recognized as a receptor for advanced glycation end-products (AGEs), which are biomolecules that undergo non-enzymatic glycation or oxidation, RAGE has been found to recognize other ligands as well, like those emitted from damaged cells

or injured tissue. These ligands include the high mobility group box 1 protein (HMGB1), which is typically found in the nucleus, and calcium-binding S100 proteins. Notably, RAGE can also be triggered by β-amyloid, a component strongly associated with the onset of neurodegenerative diseases such as AD and AMD [61–63].

Discussions and future perspectives

Our review findings strongly indicate a significant role of inflammation in AMD, particularly emphasizing the role of various inflammatory markers such as CRP, cytokines, complement proteins, and AGEs. These inflammatory mediators are involved in processes such as angiogenesis, BRB disruption and neurodegeneration, all of which are critical factors in the pathogenesis of AMD. The interplay between inflammation and AMD shows the complexity of the disease and suggests that targeting inflammatory pathways may hold promise for therapeutic interventions aimed at mitigating disease progression.

Anti-inflammatory therapies

Various anti-inflammatory therapies have been employed in AMD management, yielding diverse outcomes. Markomichelakis *et al.* investigated the impact of intravenous Infliximab, typically used for rheumatoid arthritis treatment, on three patients diagnosed with both wet AMD and inflammatory arthritic diseases. Among these patients, one who had not previously received treatment and two who were resistant to photodynamic therapy displayed improved visual acuity and reduction in CNV membrane size after three months. Notably, the treatment-naïve patient showed sustained improvement even at 12 and 18 months with continuous Infliximab treatment. Numerous preclinical and clinical studies have been conducted to evaluate the safety and effectiveness of complement regulators in AMD treatment. ARC1905 (a C5 inhibitor) and TNX-234 (a humanized antibody targeting factor D) have been developed in preclinical trials to address neovascular AMD. Other ongoing clinical trials seek to gather preliminary data on the safety and tolerability of intravitreal complement inhibitors for treating AMD patients, although the results remain inconclusive [64–66].

Limitations

The most significant limitation encountered in this body of research is the substantial diversity observed across studies. A noteworthy aspect lies in the evaluation of different forms of CRP in relation to retinal diseases. Various forms, including high-sensitivity CRP (hsCRP), serum CRP and pCRP/mCRP, were considered in different studies when examining their associations with these retinal conditions. This multiplicity of CRP forms used in research introduces complexity and makes it challenging to draw uniform conclusions or comparisons across studies, emphasizing the need for more standardized approaches in future investigations. One interesting finding that should draw attention to future studies is that from the study led by Romero-Vázquez *et al.* that revealed that specifically mCRP, not pCRP, could permeate the RPE monolayer and was also identified as a factor causing disruption in the oBRB [26].

The observed associations should be also interpreted with caution in AMD, as they do not imply causation in all cases. It is important to note the presence of significant confounding factors. For instance, factors like smoking, a known risk factor for AMD, and physical inactivity, which tend to be more prevalent among individuals with visual impairment and can contribute to the observed associations. While statistical adjustments for these factors can provide a more refined estimate of the association, they do not definitely establish a causal relationship.

Future research endeavors should prioritize the investigation of the clinical utility of inflammation biomarkers when combined with other predictors of AMD. This exploration aims to identify high risk individuals more accurately and to assess the potential efficacy of therapeutic interventions in preventing the onset or progression of AMD.

Inflammation and other retinal diseases

While much research has concentrated on understanding the relationship between AMD and inflammation, it's imperative to recognize that these changes also play a significant role in other ocular diseases. For example, DR stands as the main cause behind vision loss not related to injury in individuals aged 20 to 70. Increasingly, research points to a connection between inflammation, obesity and diabetes mellitus (DM). DM is linked to low-level inflammation and inflammatory indicators significantly contribute to the onset of diabetes and its small blood vessel-related complications, including retinopathy. The prevailing assumption is that elevated blood sugar levels trigger the activation of cytokines like TNF-α and VEFG, cumulating in the emergence of DR. TNF-α, a cytokine with proinflammatory properties, is generated by macrophages, endothelial cells and fibroblasts. It is believed that TNF-α has a role in insulin resistance, influencing the expression of adhesion molecules and advancing various inflammatory processes [67–71]. A systematic review and meta-analysis conducted by Song *et al.*, in 2015, that included two cross-sectional studies, and twenty case-control studies (involving 3679 participants) concluded that CRP levels were higher in the case group compared to the control group [standardized mean difference (SMD): 0.22, 95% confidence interval (CI): 0.11–0.34]. Additionally, blood CRP levels in the proliferative DR group were found to be higher than those in the non-proliferative DR group (SMD: 0.50, 95% CI: 0.30–0.70) [72].

Murakami *et al.* (2018) studied the relationship between the progression of visual loss and *retinitis pigmentosa* (RP). Their research encompassed 58 RP patients under the age of 40 with 29 age and gender matched controls. Through the examination of serum hsCRP they found a significant difference, with the RP patients showing higher levels that the control group. Furthermore, baseline hsCRP was correlated with the MD progression on visual field examination. This indicates that alterations in the systemic inflammatory profile may have a role in the progression of RP, offering insights into potential pathways for understanding and managing this condition [73].

Kesler *et al.* (2009) aimed to investigate whether 33 individuals affected by non-arteritic anterior ischemic optic neuropathy (NA-AION) show an elevated micro-inflammatory response when compared to 151 matched

control group. The inflammatory indicators included white blood cells, erythrocyte sedimentation rate (ESR), quantitative fibrinogen levels and hsCRP. They noted significantly elevated concentrations for hsCRP in NA-AION group compared with controls (p=0.021) [74].

Based on these studies, future investigations should focus more on the exploration of the inflammation in other retinal diseases, exploring its potential role and therapeutic implications in diverse ocular conditions.

Conclusions

Inflammation plays a major role in AMD, affecting various parts of the retina in complex ways. Research into inflammation's role not only helps us understand the disease better but also offers perspective to innovative therapies. By admitting inflammation's importance in AMD and its connections with neurodegeneration, angiogenesis and BRB disruptions, we're opening the path to better ways to address this major cause of vision loss.

Conflict of interests

The authors declare that they have no conflict of interests.

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