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Review

Significance of Macrophage-Mediated Inflammatory Response in Ocular Inflammatory Complications

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Abstract

Immune cells such as macrophages play a significant role in ocular inflammation by activating or inhibiting several cellular pathways. Systemic infections and autoimmune diseases could activate macrophages by releasing various pro-inflammatory cytokines, chemokines, and growth factors, which reach the eyes through the blood-retina barrier and cause immune and inflammatory responses. In addition, environmental pollutants, allergens, and eye injuries could also activate macrophages and cause an inflammatory response. Further, the inflammatory response generated by the macrophages could recruit additional immune cells and enhance the inflammatory response. The inflammatory response leads to ocular tissue damage and dysfunction and affects vision. Macrophages are generally implicated in the clearance of pathogens and debris, generate reactive oxygen species, and initiate immune response. However, uncontrolled immune and inflammatory responses could damage the ocular tissues, leading to various ocular inflammatory complications such as uveitis, scleritis, diabetic retinopathy, and retinitis. Recent studies describe the role of individual cytokines in the mediation of specific ocular inflammatory diseases. In this article, we discussed the potential impact of macrophages and their mediated inflammatory response on the development of various ocular inflammatory diseases and possible treatment strategies.

Keywords: macrophages; eye; oxidative stress; inflammation; infections; uveitis

1. Introduction

Uveitis, retinitis, scleritis, and others, such as age-related macular degeneration (AMD) and diabetic retinopathy (DR), are the most common inflammatory complications of the eye. Ocular inflammatory diseases are the major cause of vision problems in patients worldwide. These are different ranges of disorders, each characterized by inflammation in various parts of the eye. The eyes are constantly exposed to inflammatory processes from external stimuli, such as pollutants, pathogens, allergens, and internal stimuli due to systemic infections and autoimmune diseases. The external stimuli directly affect the eyes locally by inducing oxidative stress, increased production of inflammatory cytokines and chemokines, and disruption and damage to various parts of the eye. Some of these events cause infiltration of inflammatory cells and release of cytokines in the aqueous and vitreous humor, leading to difficulty in vision [1,2]. These inflammatory cytokines damage the ocular tissues, leading to the infiltration of inflammatory cells and other factors in the aqueous and vitreous humor and causing blindness. Some of these complications have still unknown etiology. Therefore, understanding the pathological mechanisms of ocular inflammatory responses is crucial for developing effective treatments that can restore vision and improve the quality of life of affected individuals.

During infections and autoimmune diseases, immune cells such as T-cells, neutrophils, and macrophages are activated and reach the eyes. In most of the cases, immune cells collaborate with each other and contribute to the immune and inflammatory responses in various tissues, including the eyes. Among these, macrophages play a significant role in ocular inflammatory complications because of their ability to initiate, regulate, and resolve inflammation.

Generally, during pathogen attack or injury, monocytes are differentiated into active macrophages. The active macrophages then migrate to various tissues as a defense mechanism, including the eyes [3]. Further, it is well known that macrophages are significantly adaptable and perform different functions based on the stimuli they receive from external and internal stress conditions [4]. They also perform various functions, such as pathogen clearance, tissue repair, and regulation of inflammation. Macrophages play both protective and pathological roles in the eyes [5]. In general, systemically, macrophages are very critical in responding to infections. They help phagocytize and clear infectious pathogens and debris while coordinating the broader immune response with other immune cells, such as T-cells [6]. Some studies indicate their involvement in inflammation is necessary for defense and repair [6–8]. Macrophages could also lead to chronic inflammation by releasing various pro-inflammatory cytokines and chemokines. These inflammatory factors in autocrine and paracrine manner cause ocular tissue damage and dysfunction, exacerbating ocular diseases. Li *et al.* [3] have sug-

gested that, unlike other immune cells, macrophages are found in the various tissues of the eye (uvea, cornea, retina) and play a significant role in sustaining ocular cell homeostasis and protecting against infection. Usually, the resident macrophages located in the ocular tissues play an important role in immune surveillance in the eye. These resident macrophages identify and respond to potential threats without causing excessive inflammation and damage to the ocular tissues. However, when eyes are initially exposed to various oxidant stimuli, activated macrophages release various innate immune inflammatory markers such as interleukin (IL)-1β and IL-18. These cytokines are critical in causing an innate immune response and recruiting other immune cells like neutrophils and T-lymphocytes.

Further, macrophage-mediated oxidative and inflammatory signaling plays a significant role in the pathophysiology of ocular inflammatory complications, and understanding their role is very important in developing novel therapeutic strategies. Recently, various studies have shown a substantial correlation between macrophage-mediated immune response and the pathophysiology of ocular inflammatory complications. Although a few recent articles discussed the critical role of macrophages in the pathophysiology of ocular diseases, not specifically in all ocular inflammatory diseases [3,6–8]. Further, these researches emphasized on how macrophages or individual cytokines or chemokines contribute to inflammation in individual eye diseases such as uveitis, diabetic retinopathy, and age-related macular degeneration. Further, few studies have only discussed the significance of macrophage polarization in different eye diseases [3,6–8]. This review article discusses recent findings on how macrophages are comprehensively involved across various ocular inflammatory diseases. We conducted PubMed and Google scholar search to find articles published in the last ten years or so, using keywords such as macrophages, immune cells, lymphocytes, inflammation, immune response, oxidative stress, autoimmune diseases, infectious diseases, uveitis, scleritis, retinitis, age-related macular degeneration (AMD) and diabetic retinopathy (DR). In this narrative review article, we have included research articles, narrative reviews, systematic reviews, and clinical and pre-clinical researches to discuss the significance of macrophages in ocular inflammatory complications. Understanding the significance of macrophages is very important for the potential development of novel therapies to regulate immune and inflammatory responses leading to ocular inflammatory complications.

2. Macrophage Polarization in Ocular Inflammatory Complications

During infections and autoimmune conditions, macrophages change their polarization phenotype (pro-inflammatory M1 and anti-inflammatory M2) in response to inflammatory stimulus. M1 macrophages are classic macrophages that are mainly stimulated by pathogen stimuli and cytokines such as interferon-gamma (IFN-γ). M2 macrophages are alternative and stimulated with cytokines such as interleukin (IL)-4. M1 macrophages are pro-inflammatory and induce an inflammatory response, while M2 macrophages are anti-inflammatory and help in tissue repair and resolve inflammation [8]. Further, polarized M1 macrophages and other immune cells release additional cytokines such as tumor necrosis factor-alpha (TNF-α), IL-6, 1L-17, and IFN-γ, which cause inflammatory responses at the site of infection or injury [9]. However, unstopped production of inflammatory mediators leads to tissue damage and disruption of normal function of the ocular system. Thus, excessive inflammatory response leads to the development of ocular inflammatory complications such as uveitis, retinitis, scleritis, and others such as age-related macular degeneration (AMD), diabetic retinopathy (DR), and glaucoma (Fig. 1) [10]. Generally, M1 macrophages are associated with chronic ocular inflammation. For example, in uveitis, increased inflammation leads to uveal tissue damage. In DR, they cause microvascular damage and neovascularization, and in AMD, they are responsible for damage to retinal pigment epithelium and photoreceptors. Thus, these changes lead to a sustained inflammatory environment in the ocular tissues, resulting in visual impairment. On the other hand, M2 macrophages help repair damaged ocular tissues such as retina, photoreceptors, and uvea and promote tissue integrity. Thus, macrophage polarization change between M1 and M2 plays a significant role in inflammation and immunomodulation in various tissues, including eyes [11]. In the following sections on respective ocular inflammatory complications, we have discussed the significance of macrophage polarization in detail. Although this review mainly focused on the general role of macrophages in the mediation of ocular inflammatory complications, please refer to specific review articles [8,11] for understanding the significance of macrophage polarization in ocular diseases.

3. Role of Macrophages in Uveitis

Uveitis, one of the most common and severe inflammatory diseases of the eye, is characterized by uveal tract inflammation, including the iris, ciliary body, and choroid. This inflammation can extend to adjacent tissues such as the sclera, retina, and vitreous humor [12]. Autoimmune uveitis (AIU) involves an inflammatory response in these uveal tissues due to an autoimmune reaction against self-antigens or an innate inflammatory response triggered by external stimuli [13,14]. The blood-retinal barrier must be disrupted for AIU to develop, activating ocular antigen-specific cluster of differentiation (CD) 4^+ T cells. These T cells infiltrate the eye and recruit macrophages, which become classically activated, generate reactive oxygen and nitrogen species, and cause damage to uveal tissues [15,16]. Ocular antigens such as arrestin (S-antigen), interphotore-

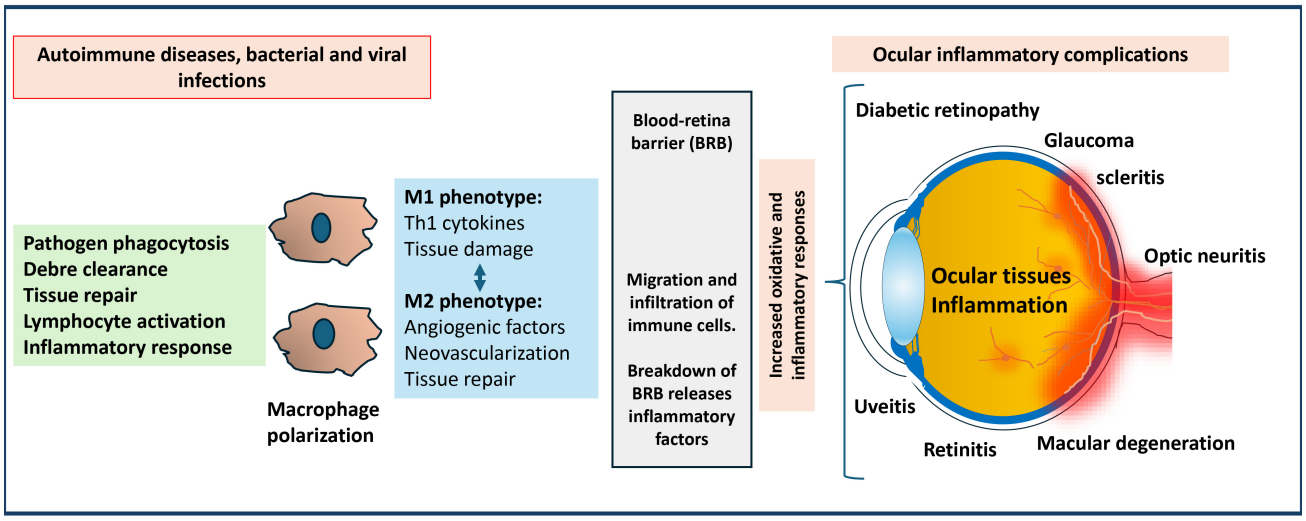

Fig. 1. Significance of macrophage-mediated inflammatory response in developing ocular inflammatory complications. Macrophages polarize into M1 and M2 phenotypes in response to stimuli during autoimmune diseases and infections. M1 macrophages generate pro-inflammatory type-1 T helper (Th1) cytokines. M2 macrophages generate angiogenic factors and anti-inflammatory markers. These factors can damage ocular tissues by crossing the blood-retinal barrier. The polarization disbalance could lead to various ocular inflammatory diseases and cause potential vision loss.

ceptor retinoid-binding protein (IRBP), and recoverin have been identified in cases of autoimmune uveitis [17,18]. AIU can occur as an isolated condition or be associated with systemic autoimmune or autoinflammatory diseases, including rheumatoid arthritis, sarcoidosis, Behçet's disease, multiple sclerosis, and even aging [19–23]. In autoimmune uveitis, macrophages are among the primary immune cells infiltrating the eye, releasing pro-inflammatory cytokines and acting as mediators that exacerbate ocular inflammation. However, uncontrolled management of inflammatory response could lead to ocular tissue damage and dysfunction, causing vision loss and other ocular complications such as glaucoma, cataracts, and retinal detachment.

The activation of macrophages is a critical determinant of disease outcome, regulated by inflammatory signals from the microenvironment, including interferon-gamma (IFN-γ) from T cells [24,25]. Activated macrophages are a hallmark of autoimmune uveitis, playing a vital role in the disease's initiation and maintenance [26]. During experimental autoimmune uveitis (EAU), macrophages and microglia (resident macrophages in the retina) act as antigen-presenting cells and express major histocompatibility complex (MHC) -II [27]. Lin *et al.* [28] found elevated levels of six chemokines in active uveitis compared to controls, with monocyte chemoattractant protein 1 (MCP1) or chemokine ligand 2 (CCL2) and C-X-C motif chemokine ligand 10 (CXCL10) being particularly important for immune cell migration. Further, ribonucleic acid (RNA) sequencing and expression mapping study revealed an extensive macrophage-derived CCL2 and CXCL10 signaling network in human uveitis [28].

Experimental models of AIU have provided insights into how macrophages contribute to this condition. The disease develops when activated $CD4^+$ Th1 and Th17 macrophages infiltrate the eye, leading to the recruitment of neutrophils and macrophages and subsequent structural damage [29]. Depleting macrophage-specific proteins such as CD47 significantly reduces uveitis severity, indicating the significance of macrophages in the mediation of uveitis [30–32]. Further, Zhao *et al.* [26] have indicated that the macrophage levels are different across various EIU phases when compared to other immune cells in the retina tissue. This study also demonstrated that during the acute phase, the macrophage levels peaked and decreased during the chronic phase. Further, the change in the shift suggests a polarization of macrophages from pro-inflammatory M1 to anti-inflammatory M2 over time [26]. Glucocorticoids mediate the P38-MAPK/myocyte enhancer factor-2c axis, promoting the transition from M2 to M1 macrophages and releasing anti-inflammatory factors, inhibiting EAU and supporting tissue healing [33]. Several studies suggest that macrophage-mediated activation of Th1 and Th17 responses plays a major role in the pathology of uveitis (Fig. 2) [29–32].

Enhanced M2 macrophage polarization has been shown to be promoted by IL-33, which signals through the interleukin-1 receptor-like 1 protein receptor (ST2) receptor [34]. Further, Barbour *et al.* [35] have shown that after three weeks of EAU induction, ST2-deficient mice exhibited worse uveitis symptoms than wild-type mice. They have also shown that interleukin (IL)-33 treatment in wild-type mice improved uveitis lesions by increasing CD206 and CD273 cells, indicating that IL-

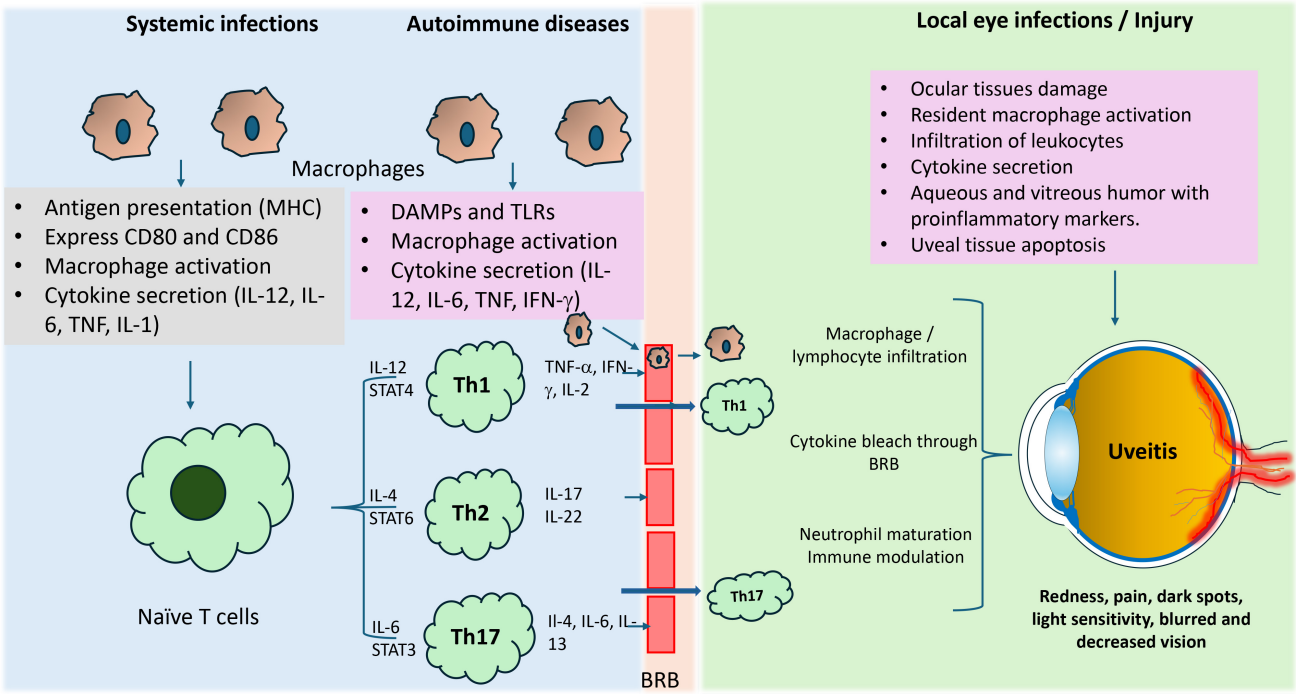

Fig. 2. Macrophage-mediated inflammatory response in uveitis. During autoimmune diseases and infections, macrophages act as antigen-presenting cells and, cause their activation and release pro-inflammatory cytokines. These cytokines activate naive T cells, which differentiate into subsets, such as Th1, Th2, and Th17. These subsets are formed based on the type of stimulated cytokines. These cell subsets release various inflammatory cytokines and further amplify immune response locally and by crossing the blood-retinal barrier internally at ocular tissues. Th1 and Th17 cell-mediated inflammatory response are well known to play a significant role in developing uveitis complications. IL-, interleukin-; TNF, tumor necrosis factor; IFN-γ, interferon-gamma; STAT, signal transducer and activator of transcription; BRB, blood-retina barrier.

33/ST2 signaling enhances M2 polarization and alleviates EAU symptoms [35]. Similarly, Huang *et al.* [36] have shown that activating the aryl hydrocarbon receptor (AhR) with 2,3,7,8-tetrachlorodibenzo-p-dioxin through the nuclear factor-kappa binding protein (NF-κB), signal transducer and activator of transcription (STAT) 1, and STAT3 pathways also induces M2 macrophage polarization. AhR negatively regulates lipopolysaccharides (LPS) -mediated inflammatory responses in macrophages and appears to inhibit M1 polarization [37]. Further, AhR-deficient mice exhibit more severe uveitis and a shift from M2 to M1 macrophages/microglia compared to AhR-sufficient mice [38]. These studies thus suggest that AhR could be a potential therapeutic target for ocular inflammatory diseases [38–40].

Interestingly, suppressors of cytokine signaling (SOCS) proteins, particularly SOCS1 and SOCS3, play crucial roles in regulating macrophage polarization and cytokine expression [41]. For example, in bone marrow-derived macrophages, SOCS3 negatively regulates granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced expression of CCL2, arginase-1 (Arg-1), and matrix metallopeptidase (MMP) 12 [42]. SOCS3-deficient mice (LysMCre/+SOCS3fl/fl) exhibit increased GM-CSF in the retina and trigger the release of CCL2 and Arg-1 from macrophages. This leads to enhanced retinal degeneration and angiogenesis due to inflammation [43]. Further, it has been shown that during the initial phase of EAU, there is an increased infiltration of neutrophils, decreased macrophages, and increased inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, IFN-γ, GM-CSF, and Arg-1 were observed in SOCS3 null mice but not in the wild-type mice. This suggests that the absence of SOCS3 fosters partial M2 polarization, contributing to angiogenesis [43]. Similarly, Arg inhibitor or its knockdown suppressed the LPS-induced increase in inflammatory markers, leukostasis, and retinal damage in an EIU mouse model [44].

In the context of Experimental Autoimmune Uveitis (EAU), the potential for therapeutics in treating uveitis has been demonstrated. For example, Chen *et al.* [45] have shown that the small molecular integrin inhibitor (GW559090) prevents the accumulation of Ly6C$^+$ macrophages and blocks the development of EAU in mice by inhibiting Th17 cell migration through the blood-retinal barrier. This leads to swift suppression of ocular inflammation and preservation of the blood-ocular barrier. Further, several studies have shown that antioxidants and small

molecular anti-inflammatory agents could prevent animal models of EAU and EIU by preventing the activation of NF-κB mediated release of inflammatory cytokines and chemokines in ocular tissues and aqueous and vitreous humor [46–49]. NF-κB is a crucial transcription factor involved in the mediation of inflammatory signaling by transcriptionally activating various pro-inflammatory cytokines and chemokines. Further, NF-κB-mediated inflammatory signaling has been shown to be critical in the pathophysiology of ocular inflammatory complications [47]. Indeed, several antioxidants and small molecular inhibitors have been shown to prevent ocular inflammatory diseases by blocking the activation of NF-κB. For example, Hwang *et al*. [48] have shown that cristacarpin prevents EIU in a mouse model. Similarly, Liu *et al*. [49] have shown that IMD-0354 (an IKK-β inhibitor) has been shown to prevent EAU in mice by preventing the activation of NF-κB. Further, Liu *et al*. [50] have shown that TD133, an inhibitor of galectin-3, prevents EIU in mice by preventing the TLR4/Myd88/NF-κB inflammatory signaling. On the other hand, regulation of macrophage polarization by various compounds has also been shown to control uveitis. For example, Qu *et al*. [51] have also demonstrated that recombination signal binding protein for immunoglobulin kappa a region (RBPJ) gene knockdown prevents EAU by promoting M2 macrophage polarization. They have also shown that N-acetyl cysteine reduces M2 polarization by regulating the Notch1 signaling. Similarly, antioxidant apigenin has been shown to prevent EAU in mice by interrupting the microglia M1 polarization [52]. In another study, Qu *et al*. [53] have also shown that miR-223-3p prevents M1 macrophage polarization via reducing Notch1 signaling in EAU. These studies suggest that inhibition of Notch1 signaling, which alters the macrophage polarization, is a potential therapeutic approach for uveitis.

3.1 Role of Macrophages in Optic Neuritis

Optic neuritis (ON) can encompass a wide range of conditions that may cause optic neuropathies. However, it is defined as an inflammatory condition that demyelinates the optic nerve and causes the loss of retinal ganglion cells (RGCs), resulting in damaged vision. ON is often studied using the experimental autoimmune encephalomyelitis (EAE) model [54]. ON is an associated effect of Multiple Sclerosis (MS), so many models aim at replicating this autoimmune condition. Funaki *et al*. [55] have found that upregulated gal-3 controls the NOD-like receptor family pyrin domain containing 3 (NLRP3) signaling in microglia/macrophages in the visual pathways during the peak of an MS flare in EAE mice. Like the retina, the brain is also an immune-privileged site. However, most immune cells in the inner environment of the central nervous system in an inflammatory state are microglial cells and macrophages responsible for most neuronal degradation [54,56].

In EAE, macrophages infiltrate the optic nerve and contribute to demyelination and axonal damage by releasing pro-inflammatory cytokines and reactive oxygen species [56]. The infiltrated macrophages could promote inflammation and help clear the myelin debris in optic nerves. Further, this intriguing dual role of macrophages regulates the immune cell dynamics between EAE and uveitis. Thus, suppression of the M1 phenotype and activation of M2 phenotype macrophages could prevent retinal inflammation and protect against optic nerve damage and RGC death.

The polarization is still a point of therapeutic interest as fatty acids (FAs), when obtained through diet, can positively impact neuronal health by modulating the macrophage phenotypes from M1 to M2 [57–59]. Further, cytokines such as IL-12 and IL-23 can significantly contribute to the progression of EAE by promoting the recruitment of M1-macrophages and the release of CXCL-10 and CXCL-11 [60–62].

3.2 Role of Macrophages in Retinitis

Retinitis is inflammation of the retina due to infections by various pathogens such as bacteria, fungi, and viruses. Herpes simplex virus (HSV), herpes zoster virus (HZV), and Cytomegalovirus (CMV) are common viral infections that can lead to retinitis [63,64]. Further, syphilis and tuberculosis bacterial infections could also lead to retinal inflammation [63]. These and additional infectious agents are known to cause visual impairment by disrupting the retina, retinal detachment, macular edema, and retinal scarring [63]. Most of these cases are also linked with uveitis complications and autoimmune diseases [65]. Macrophage infiltration is one of the major causes of retinal inflammation. Although immune cells generated cytokines play a significant role in retinal damage, the blood-retina barrier provides great support to maintain homeostasis. Yang *et al.* [66] have indicated that the damage to retinal pigmented epithelial cells could cause cell death, which is sometimes aggravated by the macrophages and T-cell mediated inflammatory response. On the other hand, Taylor *et al.* [67] have suggested that retinal pigment epithelial cells also regulate immune cells in the eye, as they can cause macrophage apoptosis and altered immune modulation. Most of the studies have shown that infectious uveitis due to viral infections causes retinal apoptosis, necrosis, and inflammation [66–68]. Viral infections in the retina, such as from CMV, HSV, or varicella zoster virus (VZV), can lead to retinal detachment by causing necrosis of retinal cells. As the virus replicates, it destroys retinal tissue, which is then replaced by scar tissue. The viral infections from CMV, HSV, and VZV could cause damage to the retina and cause retinal necrosis, leading to retinal detachment. Further, the damaged retina tissue can also inflame healthy cells, leading to their detachment from the retina. Indeed, some studies have shown that during acute retinal necrosis and CMV-

induced retinitis, the inflammatory response plays a major role in retinal detachment in retinitis [69–71]. Some viral particles, such as CMV, replicate in the eye due to the lack of functional activity of $CD4^+$ T cells, which could lead to retinal necrosis [69].

Similarly, HSV and Epstein-Barr virus (EBV) could also result in retinal necrosis and inflammation, eventually leading to retinal detachment and visual complications [71,72]. The role of macrophages here is to respond to the infection and play a dual role by helping to clear debris and remove the virus. At the same time, the uncontrolled release of pro-inflammatory cytokines and chemokines could lead to ocular inflammation. The excessive inflammatory response leads to tissue dysfunction, scarring, and an increased risk of retinal detachment. Indeed, a recent study by Sterling *et al*. [73] demonstrated that retinal perivascular macrophages, located on post-capillary venules of the eye, play a crucial role in facilitating immune cell migration across the blood-retinal barrier by aiding $Ly6C^+$ monocyte infiltration in a mouse model of retinal inflammation. This study highlights the significance of perivascular macrophages in ocular inflammation.

Furthermore, in retinitis pigmentosa (RP), a broad collection of genetic eye conditions resulting in the deterioration of photoreceptor cells needed to see the light in the retina, microglial cells could also contribute a significant role in the degeneration [74]. This degeneration ultimately leads to a decline in visual acuity. The damage results from the loss of rods and usually starts with night blindness and gradually narrows the visual field, often resulting in tunnel vision. The genetic defects may injure multiple pathways, including apoptosis, ciliary transport, and endoplasmic reticulum stress. Like with uveitis and ON, in RP, there is a disruption in the blood-retinal barrier that results in leakage of macrophages, which play a critical role in the progression of the disease [75]. The microenvironment in RP involves the infiltration of macrophages in the retina that release pro-inflammatory factors, leading to the characteristic degeneration of the retinal photoreceptor layer [76,77]. Further, during degeneration, the macrophages and resident microglial cells could kill adjacent cells, phagocytize debris, and facilitate regeneration [78]. Thus, infiltrated macrophages in the degenerated retina help in neuroprotection and neurodegeneration.

In addition, depending on macrophage polarization state (M1 or M2), they can exacerbate retinal damage by promoting inflammation and cell death. On the other hand, M2 macrophages are involved in retinal tissue damage repair, and the removal of debris from dying photoreceptors could also contribute to retinal fibrosis. A study by Neves *et al*. [79] has shown that immune modulation between the M1 pro-inflammatory and the M2 anti-inflammatory can be achieved by using Platelet-Derived Growth Factor (PDGF)-like signaling-induced Mesencephalic Astrocyte-derived Neurotrophic Factor (MANF) for successful regeneration of the retina in flies and mice. Other studies have also found that a diet rich in FA showed benefits in RP related to shifting the macrophage polarization to M2 in mice, while the absence of FAs correlated with increased degeneration in RP [80,81]. In addition, some studies have also shown the significance of innate immune responses in retinal detachment [82,83]. Cao *et al*. [82] have demonstrated that an inhibitor of caspase-1, VX-765, inhibits microglial pyroptosis by changing the M1 phenotype to M2. They have also indicated that caspase-1 inhibition could reduce microglial pyroptosis, shift microglial phenotypes to a protective state, and preserve photoreceptor structure. Thus, the inhibition of caspase-1 could be a potential therapeutic approach for retinal detachment diseases. Similarly, Cao *et al*. [83] have also shown that P2X7-mediated microglial activation and pyroptosis are critical for photoreceptor degeneration and retinal detachment.

3.3 Role of Macrophages in Scleritis

Scleritis is an inflammatory condition of the eye, often linked to systemic infectious or non-infectious diseases. The most common underlying cause of scleritis is an autoimmune disease such as rheumatoid arthritis (RA), lupus, and Wegener's granulomatosis [84]. Scleritis can be classified into various subtypes, such as episcleritis, anterior scleritis, and posterior scleritis. Among these, the posterior scleritis is rare but more severe, potentially leading to complications such as choroiditis, retinal detachment, and optic nerve damage. On the other hand, episcleritis affects only the superficial capillaries and is less severe. Infectious agents are responsible for $<$20% of scleritis cases, and initial misdiagnosis and treatment with corticosteroids can worsen outcomes, making scleritis a potentially sight-threatening condition [84]. Loss of the injured eye is often caused by severe pain, which is secondary to the destruction of uveal and retinal tissue and sometimes perforation of the globe [85]. Blindness can also be caused by severe complications, such as scleral and corneal necrosis, keratitis, and uveitis [85]. Although the exact pathophysiology of scleritis is currently unknown, the immune system is thought to play an essential role. It has been proven that there is an increase in inflammatory cells, including T-cells of all types and macrophages, in scleritis [86]. The T-cells and macrophages invade deep episcleral tissue, leading to scleral damage. Activation of macrophages leads to their infiltration into the scleral tissue, which releases various pro-inflammatory cytokines and chemokines such as TNF-α, IL-1, IL-6, and MCP-1. These inflammatory responses are amplified by recruiting other immune cells like neutrophils and T cells, leading to redness, pain, and swelling seen in patients with scleritis (Fig. 3). Similarly, by modifying the CIA model, Nishio *et al*. [86] have successfully induced scleritis. They have shown that arthritis was followed by immune cell infiltration, predominantly $CD11b^+$ macrophages, B cells, plasma cells, and complement de-

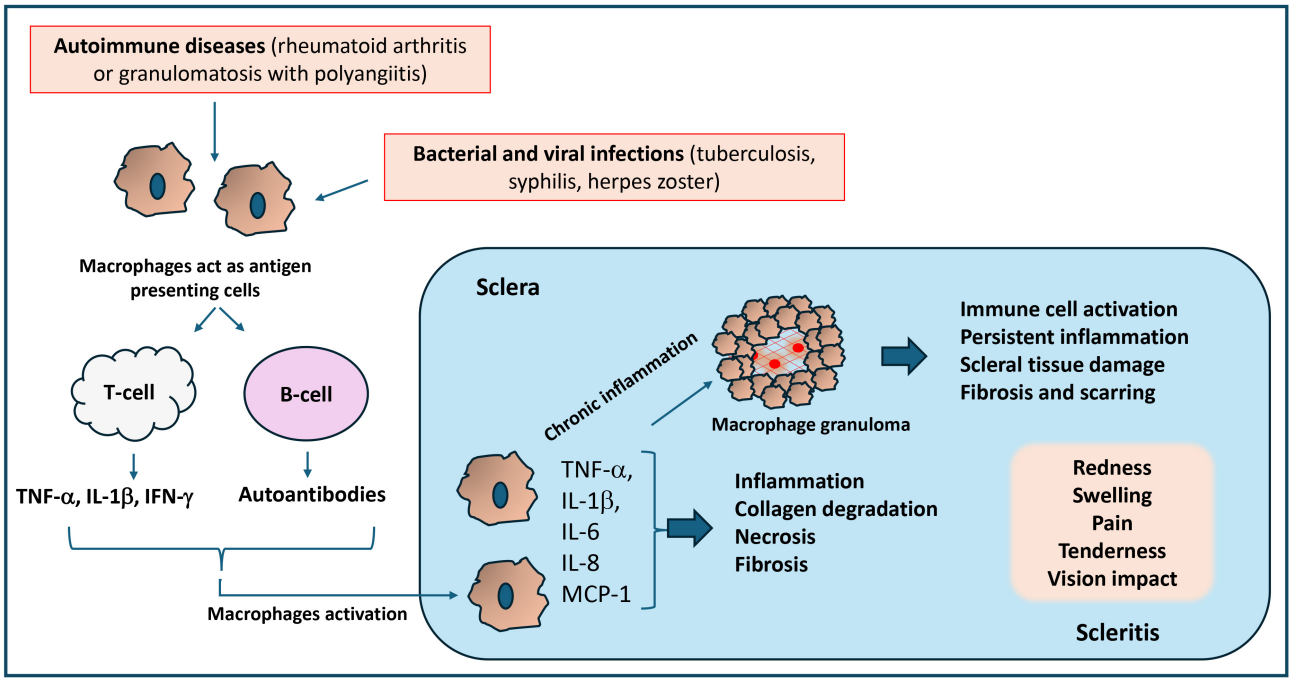

Fig. 3. Significance of inflammatory response in the pathology of scleritis. Macrophage activation during autoimmune and infectious diseases triggers an inflammatory response that can activate T-cells and B-cells, which produce inflammatory cytokines and autoantibodies that damage the sclera and cause necrosis and scleral collagen degradation. Uncontrolled and chronic inflammation could also lead to the formation of granulomas, which promote persistent inflammation, scleral tissue damage, and fibrosis. Thus, the inflammatory response caused by activated macrophages and granulomas contributes to chronic inflammation, leading to pain, swelling, and tissue damage in scleritis. MCP-1, monocyte chemoattractant protein-1.

position. These studies suggest that targeting TNF-α to suppress macrophages and focusing on B-cell suppression may be more effective for treating scleritis than targeting T cells. Further, Vergouwen *et al.* [87] have indicated the significance of proteins involved in the T-cell activation, impaired epithelial barrier, and angiogenesis could act as biomarkers for non-infectious scleritis. In addition, during autoimmune-triggered scleritis, macrophages have been shown to serve as antigen-presenting cells, which activate T cells and promote damage to the sclera [88]. Thus, the interaction between macrophages and other immune cells impairs sclera tissue and causes necrosis. Additionally, macrophage-mediated activation and release of matrix metalloproteinases could degrade basement membrane collagen and cause scleral thinning, leading to perforation [89]. Macrophages, along with other immune cells, can also form clusters of cells called granulomas. The formation of granulomas causes chronic inflammation, scleral tissue damage, and dysfunction, which is most commonly seen in granulomatous scleritis [85].

Further, Fong *et al.* [90] have found that significantly increased number of macrophages in the conjunctival epithelium of conjunctival and scleral biopsies of scleritis patients. Scleral specimens also showed an increase over controls of macrophages. This study also demonstrated that primary vasculitis plays an important role in the pathogenesis of scleritis. Scleral biopsies taken from scleritis patients showed vascular occlusions and infiltration, as well as evidence of macrophages and T cells. Further, a recent study also suggests that intraocular inflammation associated with scleritis could lead to significant visual impairment [91]. Thus, the role of macrophages in scleritis is still not completely known because of the rarity of the disease and the lack of established animal models.

3.4 Role of Macrophages in Inflammation-related Ocular Complications

Although genetic and non-genetic factors contribute to retinal diseases, innate immune responses and inflammatory responses mediated by the macrophages could play a critical role in the progression of these complications [92]. The diseases where the inflammatory response is also a contributing factor include diabetic retinopathy (DR), glaucoma, and age-related macular degeneration (AMD). Recent studies have shown that increased NLRP3-mediated release of IL-1β and IL-18 and NF-κB-mediated release of cytokines such as TNF-α, IL-6, and IFN-γ have shown in the pathophysiology of these diseases [93,94]. The innate and inflammatory responses could lead to apoptosis, pyroptosis, and necrosis in the ocular tissues, resulting in vision loss. Macrophages and other immune cells infiltrate into the retinal tissues and could interact with resident mi-

croglial cells and exacerbate the inflammatory response. In addition to hyperglycemia, aging and environmental pollutants could also trigger the progression of these diseases by increasing the oxidative and inflammatory responses. Therefore, understanding the role of macrophages and microglia is essential in targeting inflammation-associated retinal complications.

3.4.1 Diabetic Retinopathy

Diabetes mellitus is an autoimmune disease characterized by hyperglycemia resulting from improper insulin production and insulin resistance. Hyperglycemia-mediated oxidative stress and inflammation have been shown to be a major risk for developing diabetic retinopathy (DR), a secondary diabetic complication [94]. Diabetic retinopathy features microvascular retinal lesions and is the leading cause of visual impairment in the middle-aged diabetic population around the world [94]. Diabetic retinopathy is generally divided into non-proliferative and proliferative. Non-proliferative DR is seen at the initial stage, where blood vessels in the retina are weak, leading to mild visual problems. In contrast, proliferative DR is more advanced, where neovascularization is seen on the retina. Early events of diabetic retinopathy include retinal microvascular injury leading to changes in the retinal neurovascular unit and its components. Anti-angiogenic treatments have shown some therapeutic benefits in controlling DR. Ciulla *et al.* [95] have shown that diabetic macular edema treated using anti-vascular endothelial growth factor (VEGF) therapy could decrease edema and improve visual acuity. However, many patients do not respond to anti-VEGF treatment, indicating that other factors are involved in the pathogenesis of diabetic macular edema [96]. A study by Zhang *et al.* [97] found that monocyte-derived macrophages also promote diabetic retinopathy progression in mice.

Further, Wang *et al.* [98] have shown increased levels and density of macrophage-like cells in the DR subjects with macular edema. The macrophage-mediated inflammatory response and angiogenesis could lead to diabetic macular edema. Thus, in DR, macrophages are involved in inflammation, oxidative stress, pathological angiogenesis, and tissue healing processes. Further, the breakdown of the blood-retinal barrier during the early stages of DR allows blood immune cells to enter the retina, causing an inflammatory response mediated by macrophages. The breakdown of the blood-retinal barrier is influenced by inflammatory factors and causes vascular damage and neovascularization. Although macrophages seem to be the primary cells involved in the pathogenesis of proliferative diabetic retinopathy, they might also be responsible for capillary occlusion, acellular capillaries, retinal nonperfusion, and retinal ischemia seen in diabetes conditions. New evidence has emerged to highlight the pivotal role of macrophage polarization in the pathophysiology of diabetic retinopathy [99]. During hyperglycemia, the balance between M1 and M2 polarization is disturbed, leading to increased M1/M2 polarization. This polarization imbalance is linked to insulin resistance and poor glycemic control. However, over time, macrophages in diabetic conditions shift from protective M2a to pro-inflammatory M1 phenotypes, contributing to increased inflammation in both human and mouse models of diabetes [99]. Further, in diabetic retinopathy (DR), both M1 and M2 polarization are present at the preclinical stage, but M1 polarization dominates in later stages, where VEGF secretion drives retinal neovascularization. Whereas M2 macrophages contribute to excessive VEGF release, raising concerns about treatments that shift M1 to M2 polarization [99,100]. Thus, additional researches are required to understand macrophage/microglia polarization in the therapeutic development of DR. Additionally, macrophages are known to influence cellular proliferation through the synthesis of various cytokines and growth factors such as TNF-α, IL-1β, VEGF, PDGF, FGF, and TGF-β through NF-κB signalosome and NLRP3 inflammasome activation. These factors are released into the vitreous humor and retina of diabetic retinopathy patients, causing immune and inflammatory responses and leading to the development of diabetic retinopathy (Fig. 4). Further, NF-κB inhibition has been shown to prevent diabetic retinopathy in animal models. For example, antioxidant saponin compounds derived from the roots of plant P. notogiseng have been shown to prevent NF-κB-mediated retinal inflammation and diabetic retinopathy in rats [101]. Similarly, catechin and Resolvin D1 have been shown to prevent NF-κB-mediated inflammatory response and reduce DR in streptozotocin-induced rats [102,103]. Further, Sui *et al.* [104] have shown that NF-κB inhibition prevents retinal neovascularization by altering the macrophage polarization.

3.4.2 Glaucoma

Glaucoma is a progressive neurodegenerative disease characterized by damage and death of retinal ganglion cells and tapering of the retinal nerve fiber layer [105]. Glaucoma is one of the most frequent causes of irreversible blindness that often results from irreversible loss of retinal ganglion cells. The loss of retinal ganglion cells is caused by a rapid increase in intraocular pressure, which can lead to acute angle-closure glaucoma [106]. Damage and dysfunction of the retinal ganglion cells could be categorized as primary or secondary. Primary damage often results from direct injury to the axon or cell body, whereas secondary damage results from releasing toxic effectors from adjacent dying cells. The mechanisms leading to cell death in retinal ganglion cells of glaucoma include the activation of microglia and macrophages [106,107]. Macrophages have been shown to play a protective role in retinal ganglion cells after optic nerve injury [108]. Although the immune response has been shown to be critical for normal-tension glaucoma, recent studies suggest that neuroinflammation could be the significant factor contributing to various glau-

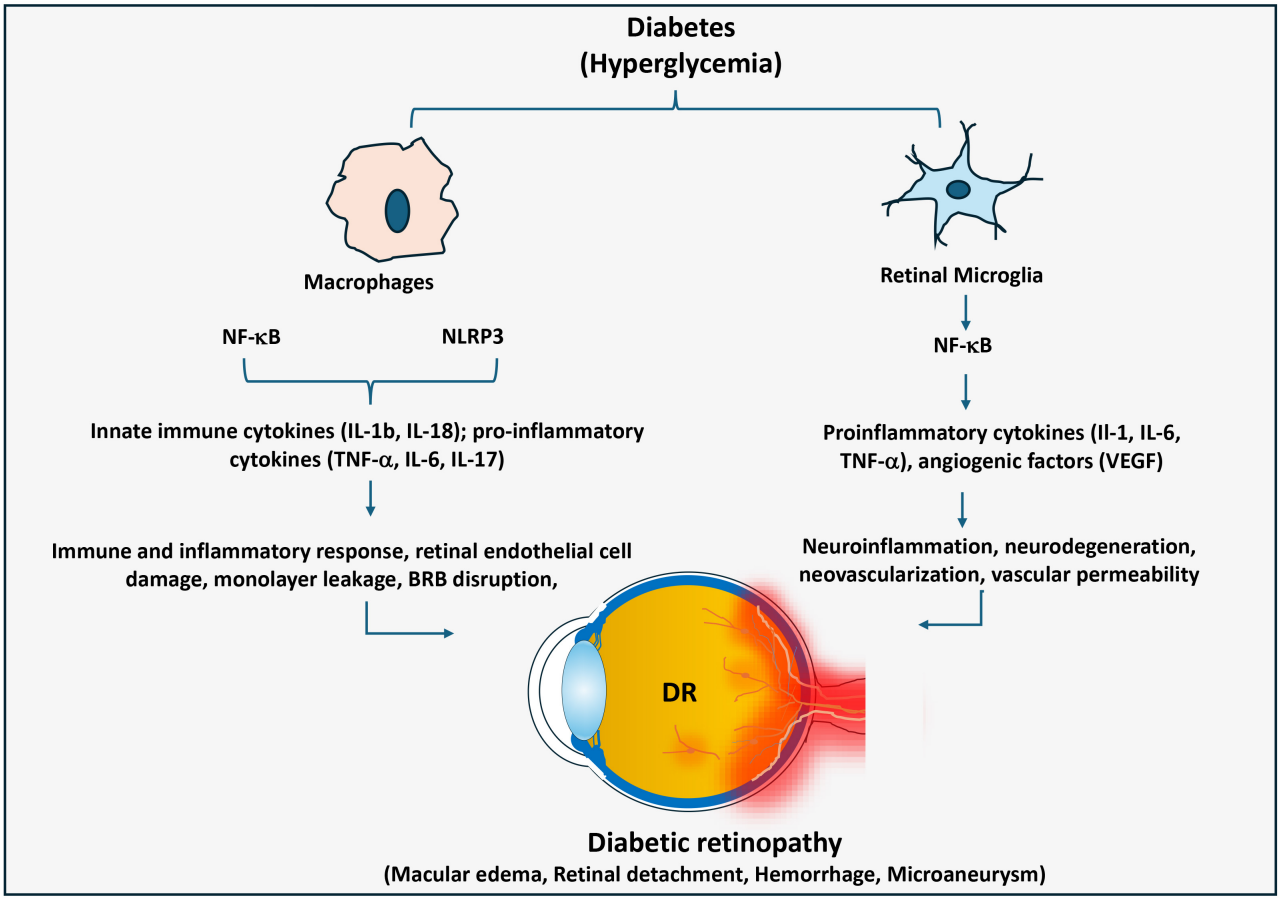

Fig. 4. Significance of macrophage-mediated inflammatory responses in diabetic retinopathy. In diabetes, macrophages and retinal microglia cells promote chronic inflammation in the retina through activating NF-κB- and NLRP3-mediated generation and release of pro-inflammatory cytokines. The macrophage-mediated inflammatory response could cause retinal endothelial cell damage, retinal monolayer leakage, and blood-retina barrier disruption. Retinal microglia also contribute to neuroinflammation, neurodegeneration, and neovascularization. The inflammatory response further leads to retinal damage, detachment, hemorrhage, macular edema, and microaneurysm in diabetic retinopathy. NF-κB, nuclear factor-kappa; NLRP3, NOD like receptor family pyrin domain containing 3; DR, diabetic retinopathy; VEGF, vascular endothelial growth factor.

comas [105,109]. However, very few studies are available showing the significance of macrophage-mediated inflammatory response leading to glaucoma [110,111]. Bell *et al.* [111] have analyzed the trabecular meshwork of patients with open-angle and acute-angle closure glaucoma and have found macrophages in the tissue. Few studies also indicate that macrophages are drawn to the trabecular meshwork of human eyes following selective laser trabeculoplasty of glaucomatous eyes [112–114]. At the same time, microglia in the optic nerve are activated and generate pro-inflammatory cytokines [112]. In a DBA/2J mouse model of glaucoma, myeloid cells such as monocytes have been shown to be accumulated at the early stages before ON damage is detectable [113]. Furthermore, increased serum levels of the MCP-1, ET-1 but not MMP9, and hs-CRP have been linked to visual field deterioration in normal-tension glaucoma patients, suggesting peripheral macrophages play a role in glaucoma development [114]. Further, Lee *et al.* [114] have also shown that CD163$^+$ macrophage infiltration is crucial for the development of glaucoma. In addition, Bell *et al.* [111] have observed that a significant increase in the number of macrophages in the retina was found to follow retinal ganglion cell loss in a rat model of glaucoma. This study also suggests that the removal of macrophages results in a reduction of retinal ganglion cell loss, suggesting that macrophages play a role in retinal ganglion cell death. Further, Bauer *et al.* [115] have analyzed various pro-inflammatory markers in aqueous humor of Fuchs uveitis syndrome (FUS) patients with secondary glaucoma. They found increased levels of TGF-β1, MMP3, and MMP2 and decreased MCP-1 and MMP9 when compared to FUS patients without glaucoma.

3.4.3 Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a retinal disease that primarily affects the central part of the

macula, which causes irreversible decline in central vision [116]. Pathologically, AMD presents with an accumulation of drusen, retinal pigment epithelium degeneration, photoreceptor atrophy, and sometimes choroidal neovascularization. Besides oxidative stress, genetic variations, and angiogenesis, ocular inflammatory response also plays a critical role in AMD pathogenesis. Here, macrophages are the primary immune cells that contribute to increased immune and inflammatory responses in AMD by releasing various pro-inflammatory factors [117]. Macrophage-mediated inflammatory response can promote neovascularization, and their interactions are essential for the pathogenesis of AMD. Blood vessels and mononuclear phagocytes are not present in the subretinal space during normal conditions in adulthood, but many macrophages are found in the subretinal spaces of AMD lesions [116]. Overall, the pathology of AMD lesions has been proven to show the infiltration of macrophages and the accumulation of inflammatory components.

Resident tissue macrophages are found adjacent to retinal pigment epithelium, which sits on Bruch's membrane, an acellular layer of connective tissue and basal lamina [118]. An inflammatory response occurs when changes occur in Bruch's membrane and the retinal pigment epithelium. Macrophages have been histologically found near AMD lesions, especially in the breakdown of Bruch's membrane and retinal pigment epithelium atrophy [118]. As this breakdown continues, retinal pigment epithelium can be lost, and the neural retina can become atrophied, resulting in dry AMD. This can then progress into wet AMD when choroidal neovascularization takes place. Generally, dry AMD is more common, with a gradual breakdown of the light-sensitive cells in the macula, while wet AMD is more severe, involving choroidal neovascularization leading to rapid vision loss [119]. Macrophages help in the clearing of yellow deposits under the retina (drusen). However, uncontrolled activation could lead to a weak inflammatory response, causing retinal damage over time. In wet AMD, macrophage-mediated release of pro-angiogenic factors such as growth factors, specifically VEGF, could increase the formation of new blood vessels, leading to retinal damage and dysfunction (Fig. 5).

Few studies also indicate that pro-inflammatory M1 macrophages induce the inflammatory response to retinal injury and accelerate AMD complications [119,120]. On the other hand, anti-inflammatory M2 macrophages are found to have a role in the early stages of inflammation and may clear the drusen. While several factors have been associated with the AMD risk, the pathogenesis of AMD is still not well known [120]. Therefore, more researches are required to define macrophages' precise protective and harmful roles in AMD pathogenesis. However, the pathology of AMD lesions proves that macrophages do play an important role in the inflammation of AMD.

4. Clinical Implications of Macrophages in Ocular Inflammatory Complications

Recently, some clinical studies have investigated the therapeutic significance of macrophage- mediated immune and inflammatory responses in ocular inflammatory diseases [121–124]. However, most of these researches are directed toward certain diseases such as uveitis, diabetic retinopathy, and age-related macular degeneration. Since inflammatory cytokines and chemokines released by macrophages and other immune cells play a role in the development of ocular inflammatory diseases, anti-cytokine inhibitors have been investigated as a potential therapy. For example, Jaffe *et al*. [121] have performed a multinational phase-3 study to examine the therapeutic efficacy of adalimumab, a TNF-α inhibitor, in non-infectious uveitis in adult patients. The results suggest that adalimumab reduced the symptoms associated with the uveitis and improved vision. Similarly, several other studies have also performed clinical studies using adalimumab in treating uveitis complications and found it to be efficacious in improving vision loss [122–124]. In addition, Greiner *et al*. [125] have treated a recombinant protein generated by fusing the p55 TNF-alpha receptor with human IgG1 (immunosuppressive as it blocks the TNF-α activation) in patients with posterior segment intraocular inflammation. They also found that by regulating the fraction of peripheral blood $CD4^+$ T cells expressing IL-10, anti-TNF-α improved the impaired vision in these patients. These studies suggest that prevention of M1-macrophages released pro-inflammatory cytokines such as TNF-α could mediate the uveitis, and inhibition of TNF-α could prevent the uveitis complications. Further, targeting macrophage migration inhibitory factor also has the potential to control uveitis complications [126]. These studies demonstrate the significance of M-1 macrophage-mediated inflammatory response in uveitis and suggest potential therapeutic use of developing drug targets against potent pro-inflammatory cytokines.

Similarly, inhibition of M2 macrophage - released VEGF has been shown to prevent diabetic retinopathy as well as AMD. Yang *et al*. [127] have investigated the effect of a bispecific fusion protein (efdamrofusp), which neutralizes the VEGF isoforms and C3b and C4b complement proteins in dry AMD patients in a phase-1 clinical study. They found that the bispecific fusion protein prevents the infiltration and polarization of macrophages into the M2 phenotype and is effective in treating neovascular AMD. Similarly, Jia *et al*. [128] have also indicated the therapeutic significance of this bispecific fusion protein in treating neovascular AMD in a phase-1b clinical trial. Another study by Chang *et al*. [129] has demonstrated that intravitreal aflibercept (VEGF-A inhibitor) prevents treatment-resistant neovascular age-related macular degeneration. Similarly, Sarao *et al*. [130] have also indicated that intravitreal injections of aflibercept reverse the pre-switching trend toward losing vision and improve sta-

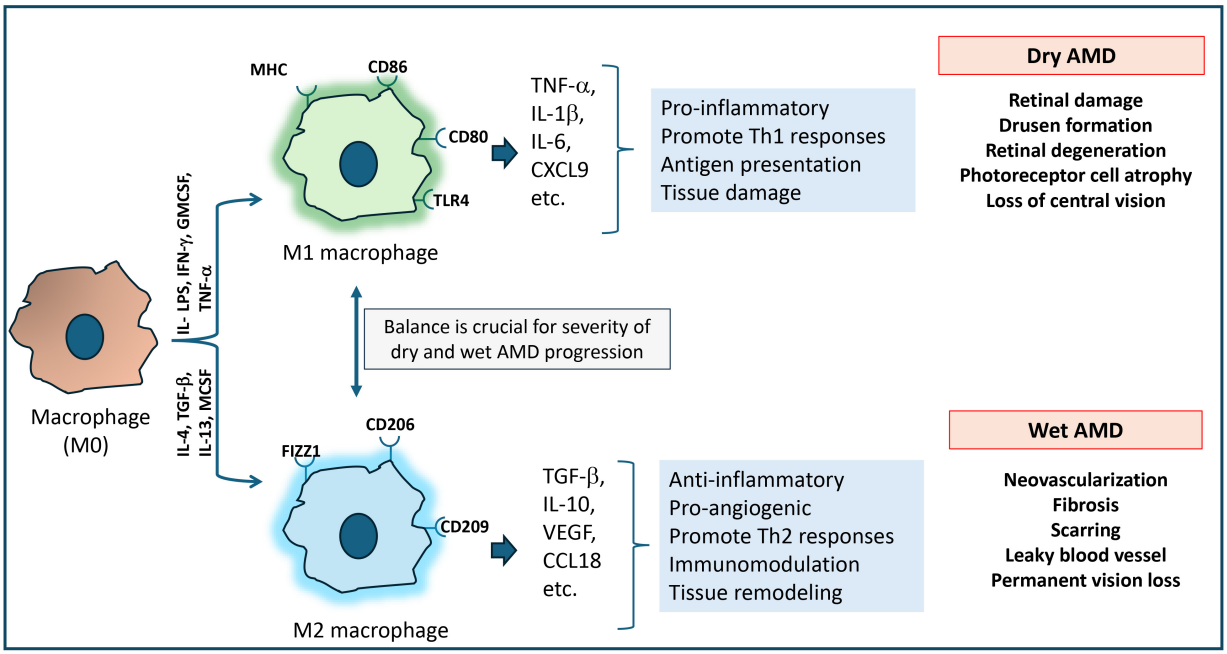

Fig. 5. Macrophage-mediated inflammatory response in the development of dry and wet AMD. In age-related macular degeneration (AMD), macrophage polarization into M1 and M2 phenotypes contributes to two different forms of AMD. M1 phenotype macrophages are pro-inflammatory in nature. They release Th1 cytokines that cause chronic inflammation and tissue damage, leading to dry AMD. Meanwhile, M2 phenotype macrophages are anti-inflammatory in nature. They promote Th2 response, tissue remodeling and could contribute to angiogenesis, leading to wet AMD. The balance between M1 and M2 macrophage activity could play a critical role in the progression of both dry and wet AMD.

ble visual acuity for up to 12 months in patients with nAMD who are not responding to ranibizumab. In addition, several recent studies also suggest the significance of anti-VEGF therapies to control AMD [131–133].

Further, several studies have also suggested the use of anti-VEGF treatment to control proliferative diabetic retinopathy and macular edema in patients [134–136]. For example, in a randomized recovery trial, Wykoff *et al.* [134] have shown that alibercept prevents retinal nonperfusion in patients with proliferative diabetic retinopathy. Similarly, a long-term prospective study conducted by Chatziralli *et al.* [135] has shown that intravitreal treatment of ranibizumab, a VEGF-A inhibitor, prevents proliferative diabetic retinopathy in patients with coexistent macular edema. In addition, intravitreal injection of farcimab improves vision in patients with diabetic macular edema [136]. In addition, several anti-cytokine therapies, such as TNF-α, IL-6, IL-1β and IL-17, are still under clinical trials for uveitis and DR. Although current clinical trials are limited to understanding anti-cytokine therapy, additional clinical studies are required to understand how macrophage polarization plays a significant role in therapeutics. However, this is a difficult task as macrophage behavior alters based on different ocular complications. Further, macrophage behavior changes with the local ocular tissue environment and generalized treatment may not be beneficial in all cases. In addition, the development of nanoparticle-based treatments could direct the drugs to specific ocular tissues and improve the outcome with minimal off-target effects. However, such nanoparticle-based studies are now limited to pre-clinical animal studies. Further, recent immune checkpoint inhibitors therapies for the cancer treatment have shown to aggravate or induce ocular inflammatory complications such as posterior uveitis, anterior uveitis and DR and AMD [137–139]. Further, some studies indicate that patients taking immune checkpoint inhibitors could lead to insulin deficiency resulting in the development of auto-immune diabetes and complicated type-1 diabetes [139–141]. Few studies have also shown that PD-1 inhibitors could worsen the type-2 diabetic complications [142–145]. Therefore, use of immune checkpoint inhibitors to control diabetic retinopathy is not a good option [143]. Similarly, in AMD and other ocular inflammatory diseases, immune checkpoint inhibitors have been shown to increase or cause the symptoms rather prevents the symptoms [144,145]. Thus, treating ocular inflammatory diseases with immune checkpoint inhibitors is not recommended and additional studies are required.

5. Conclusions and Future Perspectives

Macrophages have multifaceted functions in the development of ocular inflammatory complications, such as uveitis, optic neuritis, scleritis, DR, and AMD

Table 1. Significant role of macrophages in ocular inflammatory complications.

Disease	Role of macrophages	Reference
Uveitis	• Macrophages release pro-inflammatory cytokines such as TNF-α, IL-6, IFN-γ, contributing to tissue inflammation and uveal damage.	[12,16]
	• Macrophages are activated by T cells which polarize from M1 to M2 in uveitis disease phases.	[24,32]
	• Macrophage-derived CCL2 and CXCL10 signaling are essential for immune cell migration.	[28]
	• Depleting macrophage-specific proteins (CD47) reduces uveitis severity.	[30]
	• Glucocorticoids promote macrophage M2 polarization, helps in inflammation resolution and prevent uveitis.	[33]
	• IL-33, AhR by promoting M2 polarization prevents uveitis.	[34,35]
	• NF-κB inhibitors and antioxidants could prevent uveitis.	[46,47]
Optic Neuritis	• Macrophages in the optic nerve release cytokines leading to demyelination and axonal damage.	[54,55]
	• Activation of M2 phenotype macrophages supports retinal protection.	[56]
	• Diet-derived fatty acids could promote M2 polarization, beneficial for neuronal health.	[57–59]
	• M1 macrophages exacerbate inflammation through cytokine release (IL-12, IL-23) in EAE models, contributing to optic nerve damage.	[60,62]
Retinitis	• Macrophages respond to viral and bacterial infections by releasing pro-inflammatory cytokines and damage the retina.	[66]
	• Excessive macrophage activity can cause retinal necrosis and detachment.	[64–66]
	• HSV, CMV, and HZV infections cause immune-driven retinal apoptosis and necrosis.	[69–72]
	• In retinitis pigmentosa, macrophages contribute to photoreceptor degeneration but may aid in neuroprotection and regeneration.	[74–76,78]
	• Inhibition of caspase-1 prevents microglial pyroptosis by altering M1 and M2 polarization.	[82]
Scleritis	• Macrophage released cytokines (TNF-α, IL-1, IL-6) could amplify inflammatory responses in sclera.	[84,86]
	• Macrophages act as antigen-presenting cells, activating T cells and promote scleral damage.	[88]
	• Matrix metalloproteinase (MMP) release by macrophages leads to scleral thinning and perforation.	[89]
	• In scleritis, macrophages often form granulomas, causing chronic inflammation and tissue damage.	[85]
DR	• Hyperglycemia-mediated activation of macrophages release inflammatory cytokines and chemokines, causing inflammatory response and retinal damage.	[94–97]
	• Increased immune cells including macrophages through breaching the blood-retinal barrier cause vascular damage and neovascularization.	[98,99]
	• Hyperglycemia promotes macrophage polarization M1/M2 leading to insulin resistance and exacerbates DR.	[99]
	• Anti-VEGF therapies target macrophage-driven neovascularization to control DR progression.	[95,100]
	• NF-κB inhibition prevents DR by preventing the inflammatory response.	[101–105]
Glaucoma	• Macrophages and microglial cells contribute to retinal ganglion cell death by interacting with other cells.	[106]
	• Intraocular macrophages accumulate in the trabecular meshwork, worsening inflammation in glaucomatous eyes.	[111,112]
	• Peripheral blood macrophage levels ($CD163^+$), linked to visual field loss, suggest systemic immune involvement in glaucoma.	[114]
	• Increased inflammatory markers in aqueous humor is associated with secondary glaucoma in Fuchs uveitis syndrome patients.	[115]
AMD	• Macrophages promote inflammatory responses that accelerate AMD progression.	[116,117]
	• M2 macrophages in early AMD may help clear drusen and cause inflammation when dysregulated.	[118,120]
	• Anti-VEGF therapy targeting M2 macrophage-driven neovascularization shows efficacy in managing wet AMD.	[127,128]

CCL2, chemokine ligand 2; CXCL10, C-X-C motif chemokine ligand 10; CD, cluster of differentiation; AhR, aryl hydrocarbon receptor; EAE, experimental autoimmune encephalomyelitis; HSV, herpes simplex virus; CMV, Cytomegalovirus; HZV, herpes zoster virus.

(Table 1, Ref. [12,16,24,28,30,32–35,46,47,54–60,62,64–66,69–72,74–76,78,82,84–86,88,89,94–106,111,112,114–118,120,127,128]). Understanding the role of macrophages will shed light on developing novel immunomodulatory manipulation of macrophages for future therapeutic advancements for ocular diseases. Further, a better understanding and manipulation of macrophages is also required to associate immune and inflammatory responses with other

processes, such as oxidative stress and angiogenesis, which are involved in the progression of ocular inflammatory complications. Few studies also indicate the importance of macrophage polarization in these diseases [32–34]. Generally, macrophages can adopt pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes depending on their environment. M1 macrophages secrete TNF-α, IL-1β, IFN-γ and amplify the immune response in uveitis, AMD, and DR. On the other hand, M2 macrophages, by secreting IL-10 and TGF-β could resolve the inflammation. Future treatments could also focus on reprogramming these cells from one phenotype to another, which could help reduce ocular inflammation while promoting tissue repair. This may be more beneficial in conditions like uveitis, DR, and AMD, where controlling macrophage M1 phenotype changes could prevent tissue damage and dysfunction and improve vision. For example, glucocorticoids have been shown to promote M2 to M1 transition leading to inhibition of uveitis [33]. Identification of additional drugs that modulate phenotype changes could help in advancing treatment options for ocular inflammatory complications.

It is now well known that external and internal stimuli could activate macrophages locally or systemically. The activation of macrophages triggers immune and inflammatory responses, which drive inflammation in various ocular tissues by releasing cytokines such as TNF-α, IL-1β, IL-6, IL-17, and VEGF. These inflammatory cytokines, chemokines, and growth factors released by macrophages reach bleach through the blood-retinal barrier and cause damage to the ocular tissues. Further, recent next-generation sequencing technologies and genomics researches could help identify pathways through which macrophages mediate ocular inflammatory complications and control these diseases. In certain cases, combinational treatments may help improve vision. For example, combining anti-angiogenic drugs with drugs that target macrophage-mediated inflammatory pathways could enhance treatment effectiveness and improve rapid vision loss during wet-AMD, and DR. Some studies have also suggested that macrophages may promote the growth of abnormal blood vessels [3,6,7]. Therefore, future treatments could be directed at modulating macrophage activity to prevent neovascularization. Similarly, using engineered macrophages or drugs that modulate macrophage-mediated immune function could hold promise for treating autoimmune-initiated uveitis and optic neuritis. Further, understanding how specific gene expressions and their functions in macrophage subpopulations will help to identify the significance of macrophage heterogeneity in ocular diseases. In addition, gene-edited macrophages could offer precise immunomodulation responses and prevent ocular inflammatory diseases. CRISPR-Cas9 tools could modify the genetic makeup of macrophages and be helpful for targeted therapies. Gene-edited macrophages could also enhance M2 polarization, help resolve inflammation, and improve tissue repair mechanisms. However, additional studies are needed in this direction to optimize as well as examine the safety of gene-edited macrophages in the eye.

In summary, recent studies suggest that macrophages could play an important role in the pathophysiology of ocular inflammatory diseases. They can act either independently or in conjunction with other immune cells and modify oxidative and inflammatory responses, leading to ocular tissue damage. Understanding macrophage activation, phenotype change, and immune cell modulation could help control immune and inflammatory responses, promote tissue repair, and improve vision. Developing novel therapeutic targets related to macrophages may hold great potential for improving vision problems associated with ocular inflammatory complications.

Declaration of AI and AI-assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used ChatGPT for spelling, grammar checks and language improvements. Afterward, the content was thoroughly reviewed and edited, with the authors take full responsibility for the publication and noting where AI was utilized.

Abbreviations

AMD, Age-related macular degeneration; AIU, Autoimmune uveitis; AhR, aryl hydrocarbon receptor; Arg-1, arginase-1; CD4, clusters of differentiation 4; EAU, experimental autoimmune uveitis; EAE, experimental autoimmune encephalomyelitis; EBV, Epstein-Barr virus; CMV, cytomegalovirus; DR, diabetic retinopathy; HSV, herpes simplex virus; IL-1β, interleukin-1beta; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MCP1, monocyte chemoattractant protein 1; NF-κB; nuclear factor kappa binding protein; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NOS, nitric oxide synthase; ON, optic neuritis; RA, rheumatoid arthritis; RP, retinitis pigmentosa; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; VZV, varicella zoster virus.

Author Contributions

SM wrote the initial draft, edited; TS wrote the initial draft, edited. KVR edited the final draft, conceptualized the idea on the topic. SM, TS and KVR also contributed to acquisition, analysis and interpretation of the literature and editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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