• Review Article •

Microglia in retinal vascular diseases: inflammatory mechanism and therapeutic target

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Abstract

● Retinal vascular diseases (RVDs) are leading causes of vision impairment and blindness, often associated with systemic diseases such as diabetes and hypertension. Despite treatment advancements, managing RVDs, particularly retinal vein occlusion (RVO), remains challenging due to the lack of a definitive cure and reliance on controlling complications. Microglia, the retina's resident immune cells, play a crucial role in maintaining retinal health, regulating inflammation, and modulating angiogenesis. In pathological conditions, microglia adopt heterogeneous and context-dependent activation states, contributing to both inflammatory injury and vascular repair. Studies suggest that modulating microglial activation and their secreted cytokines may provide novel therapeutic strategies for RVDs. This review examines the role of microglia in RVDs and their potential as therapeutic targets, exploring strategies such as inhibiting microglial activation, regulating pro-angiogenic factor secretion, and targeting specific signaling pathways. Future research should focus on understanding the specific roles of microglial subtypes, their contributions to disease progression, and developing targeted therapies for early diagnosis and treatment of RVDs.

● **KEYWORDS:** retinal vascular diseases; microglia; inflammation; angiogenesis

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INTRODUCTION

Retinal vascular diseases (RVDs) are major contributors to vision impairment and blindness, imposing a significant burden on global health[1-2]. A retrospective analysis of South Korea's health claims data (Health Insurance Review and Assessment, HIRA) from the past 10y, up to 2020, estimated the prevalence of RVDs to be 1.40 per 100 individuals, based on data from 140 344 patients[3]. Among these, 1963 patients were diagnosed with RVDs. These conditions, including diabetic retinopathy (DR), retinal vein occlusion (RVO), and retinal artery occlusion (RAO), are closely linked to systemic diseases such as diabetes, hypertension, and hyperlipidemia[4-5]. DR is the most common of these disorders, followed by RVO and RAO, with notable differences in their distribution by age and sex[6]. DR is more frequently observed in female, while RAO is more common in male. Key complications, such as macular edema and neovascularization, vary by age but are not significantly associated with sex[6]. Over the past decade, the incidence of retinal vascular occlusion has remained substantial, with RVO emerging as a leading cause of vision loss and blindness worldwide[3,7]. These findings underscore the importance of early detection and timely intervention. Given the strong links to systemic risk factors, effective management strategies must address both ocular and systemic conditions to mitigate vision loss and improve patient outcomes.

DR, RVO, and RAO commonly cause vascular damage through processes such as atherosclerosis and endothelial dysfunction[8]. DR results from prolonged hyperglycemia, leading to capillary damage, hemorrhage, and neovascularization[9]. In contrast, hypertensive changes contribute to RVO and RAO by increasing vascular resistance and promoting thrombotic events[10-11]. Despite advances in treatment, significant challenges persist. RVO currently has no definitive cure, and its treatment focuses on managing complications such as macular

edema and neovascularization[12]. Anti-vascular endothelial growth factor (VEGF) injections are the first-line therapy for RVO-related macular edema, but responses vary, and a subset of patients remains resistant to treatment[13]. Corticosteroids offer an alternative approach but carry risks, including elevated intraocular pressure and cataract formation. Laser photocoagulation is selectively used to prevent neovascular complications but cannot reverse vascular occlusions[14]. In DR, controlling blood glucose and blood pressure remains essential, though many patients continue to progress to advanced stages despite optimal management[15]. Given these challenges, there is a pressing need for more effective and targeted therapeutic strategies that go beyond symptomatic management to address the underlying vascular and inflammatory mechanisms driving RVDs.

The retina's complex cellular composition, which includes neurons, glial cells, and immune components such as microglia and astrocytes, plays a critical role in disease progression[16]. Dysregulation of microglia has been linked to chronic inflammation and neurovascular dysfunction, further complicating treatment outcomes. Growing evidence from both clinical and experimental studies suggests that dysregulated microglial activation is closely associated with inflammatory and immune dysfunction in various retinal diseases[16-19]. Studies have demonstrated that microglial cells not only help combat infections but also regulate the production of cytokines and growth factors, contributing to retinal repair[16-17,20]. Therefore, targeting microglial cells and controlling their activity could present a novel therapeutic approach for RVDs, potentially overcoming the limitations of current therapies and offering more effective disease management strategies for conditions such as RVO. This article reviews the latest research on microglial cells in RVDs, providing insights that may inform future treatment strategies.

A literature search was conducted in PubMed, Web of Science, and Google Scholar for English-language studies published up to 2025 using keywords related to RVDs, microglia, inflammation, angiogenesis, blood-retinal barrier (BRB) disruption, and therapeutic targeting. Relevant original studies and reviews were selected based on their relevance to microglial mechanisms and therapeutic strategies in RVDs.

FUNCTION AND MECHANISM OF MICROGLIA IN RETINA AND RETINAL VASCULAR DISEASES

The term "microglia" was introduced by Spanish neurologist Pío del Río-Hortega in the early 20th century following his detailed studies of glial cells[20]. He described the distribution and morphology of microglia, distinguishing them as a distinct class, separate from both neurons and other glial cells in the brain. Retinal microglial cells are specialized immune cells found in the retina, playing a crucial role in maintaining retinal health, responding to injury, and regulating inflammation[21]. Microglia originate from precursor cells in the yolk sac during early development and subsequently migrate to the retina[22]. In the healthy retina, microglia are distributed mainly in the nerve fiber layer, ganglion cell layer, inner plexiform layer, and outer plexiform layer, where they continuously survey the local microenvironment. Under homeostatic conditions, ramified microglia remove apoptotic cells and cellular debris, refine synaptic connections, secrete trophic factors, support vascular development, and help maintain neuronal and vascular integrity. These physiological functions provide a foundation for retinal homeostasis and tissue repair, bridging normal immune surveillance with responses to injury or stress[23]. Since their discovery, microglia have been extensively studied in the context of RVDs, revealing their diverse functions and highlighting their roles in various pathological conditions.

Functional Polarization of Retinal Microglia in Vascular Diseases Retinal microglia are highly specialized immune cells that exhibit distinct activation states and functional subtypes in response to various retinal conditions, particularly in vascular diseases. These activation states are crucial for regulating the retinal environment and influencing disease progression[16]. Microglia are broadly classified into pro-inflammatory (M1), anti-inflammatory and reparative (M2), and other subtypes, highlighting their complex roles in retinal pathophysiology[24-25]. In RVDs, such as DR and RVO, M1 microglia are primarily activated in response to inflammatory signals from damaged retinal tissue. These microglia release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which exacerbate neuroinflammation and further damage retinal vasculature[26-27]. This inflammatory cascade contributes to vascular leakage, retinal edema, and, in some cases, retinal cell death[28].

Additionally, M1 microglia contribute to the disruption of the BRB, exacerbating ischemic damage and promoting disease progression[24]. Conversely, M2 microglia adopt an anti-inflammatory and reparative role, helping to resolve inflammation and facilitate tissue repair in response to retinal injury. These microglia release cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which promote tissue regeneration, clear cellular debris, and support cell survival and revascularization. The M2 phenotype is particularly important during the healing stages of retinal diseases, where it mitigates damage caused by ischemia or chronic diabetes. By removing damaged cells and promoting angiogenesis, M2 microglia contribute to tissue repair and inflammation resolution[29]. The plasticity of retinal microglia allows them to adapt their functions in response to specific retinal microenvironmental signals, including cytokines,

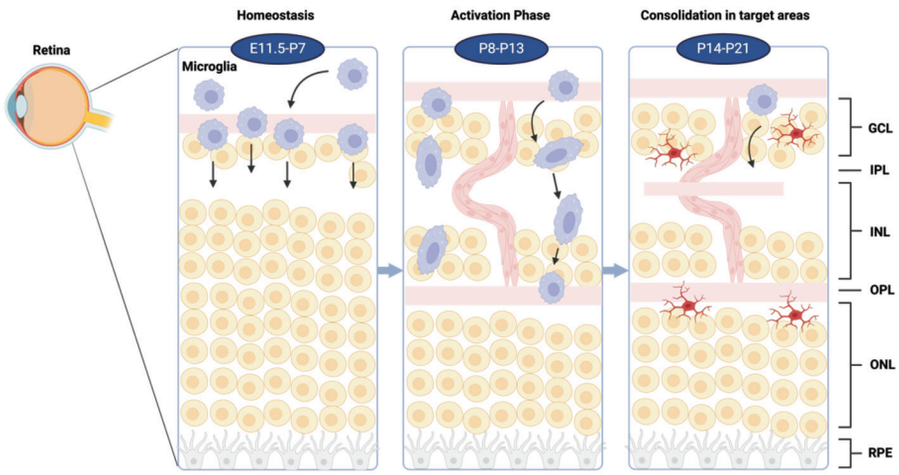

Figure 1 Spatiotemporal dynamics of microglial colonization in the developing retina Created with BioRender. GCL: Ganglion cell layer; IPL: Inner plexiform layer; INL: Inner nuclear layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; RPE: Retinal pigmented epithelium; E11.5: Embryonic day 11.5; P7–P21: Mid-postnatal stage.

growth factors, and disease-associated factors[16]. Depending on these stimuli, microglia can either exacerbate inflammation and tissue damage or engage in protective and reparative functions to restore retinal homeostasis. This adaptability highlights their pivotal role in both the progression and resolution of RVDs.

Microglial Function in Retinal Development and Healthy Retinas Microglia are among the earliest cells to populate the retina, emerging before vascular development begins[30]. In the human fetal retina, they cover the entire retinal surface by gestational week 15, whereas retinal blood vessels emerge later from the optic disc[31]. In mice, microglia have been detected in the retina as early as embryonic day 11.5 (E11.5), where they initially emerge in association with physiological cell death[32]. By E12.5, they additionally appear in peripheral retinal regions and subsequently migrate ahead of the developing vascular plexus during the first postnatal week[30]. Their migration is guided by cytokines such as IL-34, which direct microglial precursors from the yolk sac to the retina, utilizing the hyaloid blood vessels as a migration scaffold. This migration process is also influenced by the neurogenic state of the retinal tissue, where factors such as stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4 play key roles in both microglial migration and recruitment[33].

During early postnatal development, microglia initially appear in the superficial vascular layer and migrate from the ganglion cell layer to the outer plexiform layer between postnatal days 8 (P8) and 13 (P13; Figure 1)[34]. Their morphology adapts to the mechanical properties of the retinal layers: in the softer outer plexiform layer, microglia take on a ramified form, while in the stiffer outer nuclear layer, they adopt a bipolar, rod-shaped morphology and closely associate with blood vessels. As retinal vascularization progresses, microglia transition from a uniform, low-density distribution to clustering around newly formed blood vessels, particularly in the vascularized center. By the end of the first postnatal week, their density becomes evenly distributed across both central and peripheral regions. During the mid-postnatal stage (P7–P21), microglia align with endothelial sprouts, assuming a polarized shape that follows the growing blood vessels. As the retina matures (P21 and beyond), microglia become evenly spread across the retinal tissue, with a lower density in areas around the blood vessels. By adulthood, microglia constitute only 0.7% of all retinal cells and less than 10% of glial cells, yet they comprise more than 80% of the retinal immune cell population[35].

Neighboring endothelial sprouts and promote vessel fusion, contributing to the establishment of a functional vascular network[30]. In the absence of microglia, there is a reduction in the contact points between neighboring tip cells early in retinal development, which is compensated by a decrease in vessel pruning during later stages. Microglia also influence the direction of blood vessel growth, and their displacement can cause the vessels to grow abnormally. The adaptability of retinal microglia highlights their critical role in both retinal development and disease[36]. They regulate immune responses, promote vascularization, and contribute to the maintenance of retinal homeostasis and integrity throughout life.

Activation Retinal microglia are highly responsive to various stimuli, which activate them and drive their polarization into distinct states to fulfill specific functions. Traditionally, microglial polarization has been categorized into two main types: classical (M1) and alternative (M2) activation. However, recent studies indicate that the M1/M2 framework oversimplifies the complexity of microglial activation[37]. *In vivo*, microglial polarization is highly dynamic and multifaceted, with intermediate states that more accurately reflect the complexity of RVDs[38]. The microglial polarization

spectrum extends beyond the simplistic M1/M2 dichotomy, encompassing a continuum of activation states. These states range from pro-inflammatory M1-like phenotypes to anti-inflammatory M2-like phenotypes, with multiple intermediate forms exhibiting mixed characteristics[39]. These intermediate states are influenced by signals from retinal neurons, immune mediators, and environmental factors, contributing to the heterogeneity of microglial responses in retinal pathology. The complexity of microglial activation *in vivo* surpasses that observed in *in vitro* models, with distinct yet overlapping functional phenotypes reflecting the plasticity and heterogeneity of microglia within the retinal environment[23].

Under pathological conditions such as retinal ischemia, microglia often polarize toward the M1 phenotype, exacerbating inflammation and contributing to retinal damage[40]. However, as the disease progresses or following tissue injury, microglia may transition toward an M2-like phenotype, promoting tissue repair and facilitating revascularization. This transition between polarization states is regulated by various signaling factors, including the chemokine CX3CL1, endogenous cannabinoids, and the activation of the TREM2-DAP12 signaling pathway[41-42].

PATHOLOGICAL MECHANISMS BY WHICH MICROGLIA CONTRIBUTE TO RETINAL VASCULAR DISEASES

As the resident immune cells of the retina, microglia play central roles in the initiation and progression of RVDs by sensing local injury, responding to metabolic and ischemic stress, and communicating with vascular and glial cells within the retinal neurovascular unit. Given their dual role in supporting physiological vascular development while also participating in pathological vascular remodeling under disease conditions, microglia play a key regulatory function in maintaining retinal vascular homeostasis[43]. Dysregulation of microglial activity is implicated in a range of pathological conditions, such as DR, age-related macular degeneration, and retinal ischemia[17]. Microglial polarization remains an important mechanism for understanding their pro-inflammatory and reparative functions in RVDs. However, the classical M1/M2 framework alone is insufficient to explain the full spectrum of microglial responses in the retinal vascular microenvironment[44]. Recent transcriptomic and single-cell studies have shown that microglia exhibit heterogeneous and dynamic activation states depending on tissue location, developmental stage, ischemic injury, metabolic stress, and inflammatory stimulation[45]. Thus, microglia-mediated retinal vascular injury should be understood through multiple interconnected mechanisms, including M1/M2-like polarization, angiogenic dysregulation, inflammasome activation, complement signaling, metabolic reprogramming, exosome-mediated communication, and crosstalk with endothelial cells (ECs) and pericytes. In this section, we focus on the pathological mechanisms by which microglia contribute to retinal vascular injury, including abnormal vascular development and remodeling, inflammatory and metabolic stress, BRB disruption, vascular instability, and cell-cell communication within the retinal vascular microenvironment. These mechanisms provide the biological basis for understanding the dual protective and pathogenic functions of microglia in RVDs.

Angiogenesis, Vascular Development, and Pathological Neovascularization Microglia play distinct and essential roles in retinal angiogenesis and neovascularization, particularly under pathological conditions. During retinal vessel development, microglia are located close to nascent blood vessels and extend their branches to interact with pericytes and ECs. While some studies have shown that microglia inhibit vascular branching in the deep retinal vascular plexus, others have found no significant differences in branching density in the absence of microglia, suggesting that these contradictory conclusions may be due to variations in microglial polarization and function[46-47].

These findings suggest that microglial vascular functions are context-dependent rather than uniformly pro-angiogenic or anti-angiogenic. The interactions between microglia and ECs are also crucial for vascular development, with microglia exerting angiogenic effects through cytokines, growth factors, and matrix metalloproteinases (MMP), rather than through physical contact with ECs. Research has demonstrated that CD95L and basigin-2 stimulate angiogenesis *via* the phosphoinositide 3-kinase (PI3K) signaling pathway, promoting vascular growth and microglia-endothelial communication[48]. Additionally, TGF-β1, a key mediator of vascular growth released by microglia, is tightly regulated to ensure physiological vascularization[49]. Microglia are also involved in retinal vascular degeneration during postnatal development, with studies showing reduced vascular degeneration in microglia-deficient mice[48]. This regression function of microglia is mediated by signaling factors such as angiopoietin, macrophage colony-stimulating factor (M-CSF), and Wnt. However, microglia/macrophages can also inhibit vascular branching through the VEGF-Flt1 axis[50]. Thus, microglia participate in both vessel sprouting and vascular pruning, acting as dynamic regulators of retinal vascular remodeling. Recent studies suggest that the Tsp-1/miR-27a-5p/Smad3 axis regulates microglia-mediated anti-angiogenesis, partly through exosome production[51]. Together, these observations indicate that microglia contribute to retinal vascular remodeling through stage-dependent and context-dependent mechanisms. Under physiological conditions,

they help coordinate vessel formation and regression; under ischemic or inflammatory stress, the same regulatory functions may become maladaptive and contribute to pathological neovascularization or vascular degeneration.

Inflammation, Metabolic Stress, and Blood-Retinal Barrier Disruption Inflammation serves as a protective response to harmful stimuli, often initiated by resident immune cells. This process is characterized by the excessive release of chemokines and cytokines. In the retina, microglia, the resident immune cells, are responsible for detecting external stimuli through pattern recognition receptors (PRRs)[52]. Upon activation, microglia trigger various signaling pathways that lead to the synthesis and release of proinflammatory cytokines, such as TNF-α and IL-1β. These cytokines not only promote the activation and proliferation of microglia but also contribute to retinal neuronal damage, particularly through mechanisms like mitochondrial dysfunction. Although the release of these cytokines can be detrimental, microglia may also provide protection in some cases, such as during acute excitotoxic injury, where IL-1β may play a protective role[53]. Therefore, microglial inflammation in RVDs should be interpreted as a context-dependent response: transient activation may support tissue defense and repair, whereas sustained activation can amplify neurovascular damage. Beyond cytokines, microglia in the retina also produce other inflammatory mediators, including cyclooxygenase-2 (COX-2), nitric oxide synthase 2 (NOS2), reactive oxygen species (ROS), and nitric oxide (NO)[35]. In addition to conventional cytokine release, inflammasome activation represents another important mechanism by which microglia amplify retinal inflammation. Metabolic stress, hypoxia, and oxidative injury may activate inflammasome-related pathways, promoting IL-1β maturation, pyroptosis, and further disruption of the retinal neurovascular unit[54]. This mechanism extends microglial injury beyond the classical M1/M2 polarization framework and links metabolic stress to inflammatory cell death and BRB dysfunction. Notably, NO production contributes to retinal cell toxicity, further exacerbating inflammation. Recent research has shown that microglia also participate in neuroinflammation by shedding exosomes, which carry proinflammatory cytokines such as IL-1β, TNF-α, and miR-155[55]. These exosomes play a significant role in transmitting inflammatory signals within the retina and across the central nervous system (CNS). While exosome release is typically associated with activated microglia in inflammatory contexts, even homeostatic microglia can release exosomes that influence CNS processes like synaptic transmission. Metabolic reprogramming is another mechanism linking microglial activation to retinal vascular injury. Under hyperglycemic or hypoxic conditions, microglia may shift their energy metabolism, leading to increased glycolytic activity, mitochondrial dysfunction, ROS production, and sustained inflammatory signaling[55]. Such metabolic alterations may reinforce cytokine production, inflammasome activation, and BRB impairment, thereby connecting metabolic stress with chronic neurovascular inflammation.

More specifically, M1-like microglia may contribute to BRB disruption by directly impairing the endothelial component of the retinal neurovascular unit. Under sustained inflammatory or ischemic stimulation, microglia shift toward a pro-inflammatory phenotype and release TNF-α, IL-1β, IL-6, NO, ROS, and other inflammatory mediators[35]. These factors can act on retinal vascular ECs and activate nuclear factor (NF)-κB- and inflammasome-related signaling pathways, resulting in endothelial dysfunction and increased paracellular permeability[56]. A central event in this process is the disruption of tight-junction proteins, including zonula occludens-1 (ZO-1), occludin, and claudin-5, which are essential for maintaining the integrity of the inner BRB. In addition, M1-like microglia-derived inflammatory mediators may promote MMP-2/MMP-9 activation and VEGF-A upregulation, leading to extracellular matrix remodeling, tight-junction degradation or redistribution, and vascular leakage[57].

Overall, the activation of microglia and the subsequent release of inflammatory factors are central to retinal diseases. Sustained microglial activation can aggravate retinal injury through cytokine release, oxidative stress, inflammasome activation, pyroptosis, metabolic dysfunction, BRB disruption, and inflammatory signal transmission.

Microglial Regulation of Vascular Stability and Remodeling Microglia play a critical role in maintaining the stability and homeostasis of the retinal vasculature, especially after the vascular network is established. Under physiological conditions, microglia help regulate vessel branching, pruning, and remodeling, thereby preventing excessive or abnormal vascular growth. However, under pathological conditions, activated microglia may shift toward a pro-inflammatory and pro-angiogenic state. Activated microglia are central to this process by releasing pro-inflammatory cytokines such as IL-1β, which induce the production of VEGF from Müller cells[51]. VEGF, in turn, drives pathological angiogenesis, a key feature in DR[58]. Along with this, microglia induce oxidative stress and the production of ROS, further compromising the BRB and accelerating the progression of the disease. The interactions between microglia and the retinal vasculature are also significant, as microglia interact with capillaries and pericytes, leading to vascular constriction. This constriction can indirectly contribute to retinal neovascularization. Research by Mills *et al*[59] demonstrated that, in the early stages of RVO, activation of the fractalkine receptor CX3CR1 between neurons and microglia leads to increased vascular constriction

and reduced blood flow. Although this study did not directly link reduced blood flow to retinal neovascularization, impaired perfusion may aggravate retinal ischemia and promote pro-angiogenic signaling.

Beyond their role in promoting pathological angiogenesis, microglia are essential for maintaining vascular homeostasis in the retina. They contribute to the stabilization of the vascular network by inhibiting excessive vessel branching and ensuring proper vessel formation. Microglia expressing VEGF-C can activate VEGFR-3 on ECs, reducing endothelial sensitivity to VEGF and preventing excessive branching[58]. Additionally, microglia regulate vascular stability by expressing soluble VEGF inhibitory receptors, which limit abnormal vessel growth in the deeper retinal vasculature[31]. Thus, microglia have a dual role in RVDs: they can stabilize the vasculature under homeostatic conditions, but may promote vascular leakage, ischemia, and pathological angiogenesis when chronically activated.

Microglia-Pericyte Crosstalk and the Vascular Microenvironment Microglia play a critical role in shaping the retinal vascular microenvironment, which is essential for the formation, remodeling, and stability of retinal blood vessels. Located in close proximity to the retinal vasculature, microglia interact with ECs, astrocytes, and other retinal cells to regulate vascular development and maintain vascular homeostasis[31]. In this microenvironment, their interactions with ECs, astrocytes, Müller cells, pericytes, and neurons influence vascular remodeling, barrier integrity, and local inflammatory responses. Complement-related signaling may further amplify retinal vascular inflammation by linking activated microglia with endothelial dysfunction, pericyte injury, and BRB breakdown[60]. In the context of ischemic retinopathies, microglia accumulate in ischemic areas and sites of new vessel growth[31]. Activated microglia in these regions secrete a variety of cytokines, both pro-inflammatory and anti-inflammatory, which can modulate the local environment. These signals may influence vascular remodeling in a context-dependent manner.

Microglia-pericyte crosstalk is increasingly recognized as an important component of retinal vascular injury. Pericytes are essential for capillary stability, endothelial quiescence, and inner BRB integrity, and pericyte loss is one of the earliest pathological features of DR and other ischemic retinal vascular disorders[61]. Under hyperglycemic, hypoxic, or inflammatory conditions, activated microglia may affect pericyte survival, contractility, and detachment through TNF-α, IL-1β, ROS, complement-related signaling, and VEGF-dependent pathways. Conversely, injured or stressed pericytes may release danger-associated signals, chemokines, and angiogenic mediators that recruit and activate microglia around damaged capillaries. This bidirectional microglia-pericyte interaction may promote capillary constriction, endothelial destabilization, basement membrane remodeling, acellular capillary formation, and increased vascular permeability, thereby linking local inflammation to BRB dysfunction and capillary degeneration[62].

While much is known about the role of microglia in the early stages of vascular formation, their role in vascular remodeling and regression is less well understood. In ischemic retinopathy models like oxygen-induced retinopathy (OIR), microglia have been shown to promote angiogenesis during the early stages after vascular occlusion[63]. They achieve this through the secretion of VEGF and basic fibroblast growth factor (bFGF), which stimulate the formation of new blood vessels. However, microglia also play an important role in the later stages of the disease, when vascular clusters are being remodeled or regressed. Research using colony-stimulating factor 1 receptor (CSF1R) inhibitors, such as PLX5622, to deplete microglia has demonstrated that these cells are essential for the proper formation and regression of pathological vascular clusters[64]. Without microglia, the process of vascular pruning is disrupted, and abnormal vessel growth persists, leading to further retinal damage and visual impairment.

In summary, microglia are integral to the retinal vascular microenvironment, playing essential roles in both the formation and remodeling of retinal blood vessels. Through their interactions with ECs, pericytes, glial cells, and ischemic vascular lesions, microglia may either support vascular remodeling or aggravate inflammation, vascular leakage, and pathological neovascularization. These effects are mediated by multiple mechanisms, including cytokine signaling, complement activation, oxidative stress, exosome release, metabolic remodeling, and direct neurovascular cell-cell communication, rather than by M1/M2 polarization alone.

MICROGLIA-TARGETED THERAPEUTIC STRATEGIES FOR RETINAL VASCULAR DISEASES

Microglia play a critical role in retinal vascular development, and their dysregulation contributes to inflammation, vascular leakage, and pathological neovascularization in RVDs. Based on these mechanisms, targeting microglial activation and function holds great potential as a therapeutic strategy for treating retinal vascular lesions, particularly in conditions like RVO, where abnormal blood vessel formation and vascular instability play central roles in disease progression. Accordingly, therapeutic modulation of microglial polarization, pro-inflammatory cytokine release, and vascular signaling pathways such as VEGF, Notch, and complement activation may help alleviate pathological neovascularization and vascular degeneration[48,58,65] (Figure 2).

Targeting Microglial Signaling Pathways Microglia, as the resident immune cells of the retina, play an essential role

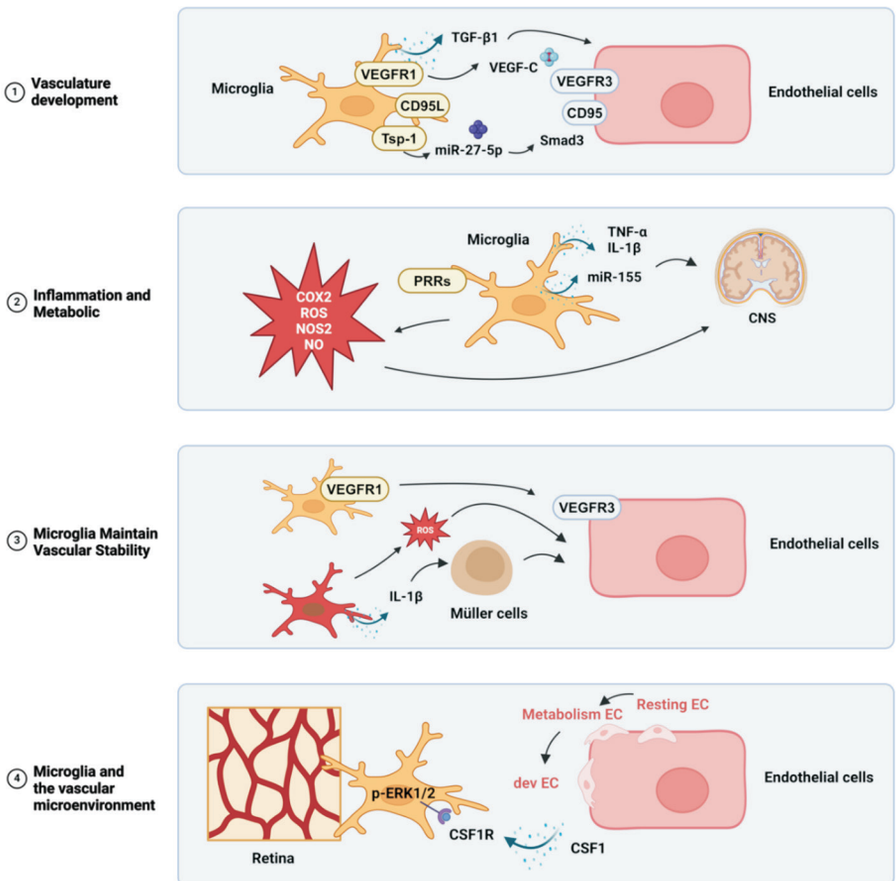

Figure 2 Microglia as a potential target for treatment of retinal vascular diseases Created with BioRender. VEGFR: Vascular endothelial growth factor receptor; PRRs: Pattern recognition receptors; CNS: Central nervous system; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin-1 beta; COX2: Cyclooxygenase-2; ROS: Reactive oxygen species; NOS2: Nitric oxide synthase 2; NO: Nitric oxide; CSF: Colony-stimulating factor; EC: Endothelial cell; p-ERK: Phosphorylated extracellular signal-regulated kinase.

in the pathogenesis of RVDs, particularly in conditions like RVO. These cells are involved in a complex interplay of inflammatory and neuroprotective responses that can both exacerbate and ameliorate disease progression. In retinal diseases, microglial activation is a key event that often leads to pathological changes such as neovascularization and inflammation, which are characteristic features of advanced disease stages. Given their central role, targeting microglia represents a promising strategy to halt or slow the progression of RVDs (Table 1)[64,66-73].

Several therapeutic strategies targeting microglia are under investigation. CSF1R inhibitors are among the most widely explored options for depleting microglia. CSF1R, the receptor for the colony-stimulating factor 1 (CSF1), is critical for microglial survival and activation[64]. Additionally, CSF1/CSF1R-mediated crosstalk between choroidal vascular ECs and macrophages plays a significant role in promoting choroidal neovascularization[66]. Although complete microglial depletion may reduce pathological angiogenesis in some models, this approach requires caution because microglia also support vascular remodeling and retinal homeostasis. Another promising target is the CX3CL1–CX3CR1 signaling axis. CX3CL1, or fractalkine, plays a critical role in modulating microglial activity[69]. The interaction between CX3CL1 and its receptor, CX3CR1, helps regulate microglial migration and activation. In experimental models of retinal diseases, CX3CL1 has shown neuroprotective effects by reducing microglial activation and promoting photoreceptor survival. However, CX3CL1 also has a dual role, as it can stimulate angiogenesis in certain contexts. This highlights the complexity of microglial signaling and the need for careful modulation of this pathway to achieve optimal therapeutic outcomes. The CD200–CD200R pathway is another area of interest in targeting microglial function[67]. CD200, a glycoprotein expressed on retinal neurons, interacts with its receptor CD200R on microglia to inhibit excessive activation and reduce neuroinflammation. In models of retinal diseases, activating the CD200R pathway has been shown to mitigate retinal degeneration and reduce microglial activation, suggesting that CD200R agonists could be effective in treating RVDs.

While these strategies hold promise, the development of effective microglia-targeting therapies for retinal diseases

Table 1 Therapeutic strategies targeting microglia in retinal vascular disease

Strategy	Target	Agents	Effects	Refs
Targeting microglia	Depleting or modulating microglial activation	CSF1R inhibitors (*e.g.*, PLX5622)	Inhibits microglial survival and activation, reduces angiogenesis and inflammation in retinal diseases	[64]
	Modulating microglial migration and activity	CX3CL1-CX3CR1 signaling modulation (Fractalkine)	Reduces microglial activation and promotes neuroprotection, though it may stimulate angiogenesis in certain contexts	[66]
	Inhibiting microglial activation and inflammation	CD200-CD200R signaling pathway	Activates CD200R receptor to reduce neuroinflammation and microglial activation, protecting retinal neurons	[67-68]
Decreasing activated microglia	Reducing microglial activation	Anti-VEGF agents (aflibercept, ranibizumab)	Reduces microglial activation and hyperreflective foci, promotes clearance of neovascular tufts in RVO models	[69]
	Reducing microglial activation	Melatonin	Regulates senescent macrophage/microglial polarization and attenuates choroidal neovascularization in aging-related ocular neovascular models; indirect supportive evidence for ocular neovascular modulation, not direct RVO evidence	[70]
	Microglia depletion and replenishment	Diphtheria toxin, CSF1R antagonists	Depletes microglia, followed by replenishment from healthy donors, reduces angiogenesis and vascular damage while protecting neurons	[64]
Inhibiting angiogenic cytokine secretion	Inhibiting pro-inflammatory cytokine release	Triamcinolone acetonide (TA), corticosteroids	Reduces microglial-derived pro-inflammatory cytokines (IL-1β, TNF-α), suppresses neovascularization and inflammation in RVO models	[71]
	Reducing microglial cytokine secretion	Omega-3 PUFAs, GLP-1 receptor agonists	Reduces TNF-α release, alleviates inflammation, and improves retinal health by targeting microglial activation and pyroptosis	[72]
	Inhibiting transcriptional activation of pro-angiogenic factors	Chlorogenic acid, Erianin, Celastrol	Inhibits HIF-1α and VEGF-A expression, reduces retinal angiogenesis and inflammation	[73]

CSF1R: Colony-stimulating factor 1 receptor; PUFAs: Polyunsaturated fatty acids; GLP-1: Glucagon-like peptide-1; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor-alpha; RVO: Retinal vein occlusion; VEGF: Vascular endothelial growth factor; HIF-1α: Hypoxia-inducible factor 1 alpha.

faces several challenges. One of the main hurdles is achieving selective modulation of microglial activity without affecting their protective roles in healthy tissues. Furthermore, designing drug delivery systems capable of specifically targeting retinal microglia while avoiding off-target effects in other areas of the CNS is a critical challenge. Therefore, rather than simply suppressing all microglial activity, a more nuanced approach is needed to selectively target pathogenic microglia and preserve their beneficial functions in retinal homeostasis. Further research into microglial biology, along with the development of more precise therapeutic agents, is essential to advancing treatment strategies for RVDs like RVO.

Decreasing Activated Microglia The activation and increased density of microglia are widely associated with pro-angiogenic effects in retinal diseases, particularly in conditions like RVO. Several studies have explored the influence of different therapeutic agents on microglia activation and their potential role in controlling pathological neovascularization in RVO[69,74-75]. An acute intraocular inflammation model was utilized to investigate the impact of anti-VEGF treatments on microglial activation[31]. Concerns have been raised that repeated anti-VEGF injections, commonly used in retinal disease treatments, might inadvertently modulate microglial activation, contributing to some of their therapeutic effects. Notably, the anti-VEGF drug, aflibercept was shown to decrease hyperreflective foci in patients with RVO, indicating a deactivation of retinal microglia. In an OIR model, aflibercept promoted the clearance of neovascular tufts by modulating microglia activity and increasing the proportion of ramified resting microglia[13]. Similarly, ranibizumab, another anti-VEGF agent, was also found to reduce the activation of microglia in ischemic retinopathy models, further highlighting the therapeutic potential of modulating microglial function to control neovascularization[69].

In addition to anti-VEGF agents, several compounds have been investigated for their potential to modulate microglia-related inflammatory and angiogenic responses in ocular neovascular diseases. Melatonin, a hormone involved in circadian regulation, has been reported to attenuate choroidal neovascularization in aging-related ocular neovascular models by regulating senescent macrophage/microglial polarization. However, because this evidence is derived from choroidal neovascularization rather than RVO, melatonin should be considered indirect supportive evidence for microglial modulation in ocular neovascular pathology rather than direct evidence for RVO treatment[70]. Its effects are partly attributed to the regulation of senescent macrophage/microglial polarization and the shift of activated microglia/macrophages toward a less inflammatory state. Therefore, melatonin should be regarded as supportive evidence for microglial modulation in ocular neovascularization, rather than direct evidence for RVO treatment. Another compound, 5Z-7-oxozeaenol,

a selective inhibitor of TAK-1, has been demonstrated to attenuate retinal neovascularization by decreasing the number of activated microglia in the OIR model[74]. Additionally, drugs like diphtheria toxin and CSF1R antagonists can deplete microglia, which, when followed by replenishment from healthy donors, has been found to ameliorate RVO-associated angiogenesis and vascular damage while offering protective effects to neurons[64]. Other potential therapeutic agents that alter microglia activation include cyanidin-3-O-glucoside (C3G), a type of anthocyanin, which has been shown to alleviate inflammation and microglia activation in RVO models[75]. Additionally, the hypoxia-inducible factor (HIF)-1α inhibitor KC7F2 and the Chinese herbal compound Magnolol have been reported to suppress retinal neovascularization by reducing microglial activation[76].

In conclusion, a growing body of evidence suggests that targeting microglia activation plays a crucial role in managing RVO and its associated pathological angiogenesis. Anti-VEGF agents like aflibercept and ranibizumab, along with other compounds such as Melatonin, 5Z-7-oxozeaenol, and C3G, offer promising strategies to modulate microglial activation and suppress retinal neovascularization. However, these approaches should be interpreted according to disease model and disease stage, because microglia may have both pathogenic and reparative functions.

Inhibiting Angiogenic and Inflammatory Cytokine Secretion The activation of microglia and their release of inflammatory mediators are central to retinal inflammation, particularly in conditions such as RVO. In RVO, microglial-driven inflammation plays a critical role in driving pathological retinal neovascularization, making the modulation of microglial activation a promising strategy for managing retinal inflammatory diseases. Targeting microglia to inhibit their activation and reduce the release of pro-inflammatory cytokines, such as IL-1β and TNF-α, can significantly mitigate retinal inflammation and subsequent vascular damage. Recent studies have identified several therapeutic strategies aimed at modulating microglial function. One of the most studied approaches involves the use of corticosteroids like triamcinolone acetonide (TA). Studies have demonstrated that intravitreal injection of TA-conjugated nanoparticles can significantly reduce microglial cytokine release, suppressing the progression of neovascularization in retinal disease models[77]. This therapeutic strategy targets microglial-derived pro-inflammatory cytokines, thereby alleviating inflammation and vascular instability.

In addition to corticosteroids, other pharmacological interventions have shown promise in modulating microglial activity. Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) and glucagon-like peptide-1 (GLP-1) receptor agonists, for instance, have been found to reduce the secretion of TNF-α, a key inflammatory cytokine, and improve retinal health by targeting inflammation and microglial pyroptosis[72]. These compounds not only reduce microglial activation but also help maintain the balance of retinal vascular homeostasis. Natural compounds have also emerged as effective modulators of microglial function. Chlorogenic acid, erianin, and celastrol have demonstrated the ability to attenuate retinal angiogenesis and inflammation by inhibiting the transcriptional activation of HIF-1α and reducing microglia-derived VEGF-A expression[73,78]. Celastrol inhibits pathological neovascularization in oxygen induced retinopathy by targeting the miR-17-5p/HIF-1α/VEGF pathway, further enhancing its potential as a therapeutic agent for retinal diseases like RVO[79]. The findings from these studies suggest that therapies aimed at modulating microglial cytokine secretion, whether through corticosteroids, dietary interventions, receptor agonists, or natural products, offer promising strategies for inhibiting retinal angiogenesis, reducing inflammation, and preserving vision in patients with RVDs. Future studies should further clarify whether these agents directly target microglia or act indirectly through ECs, Müller cells, macrophages, or other components of the retinal vascular microenvironment.

SUMMARY AND PROSPECTS

Microglia play a crucial role in RVDs, particularly in their involvement in the inflammatory processes that drive the progression of conditions such as RVO. These resident immune cells exhibit a dual role: on one hand, they can exacerbate angiogenesis by secreting pro-angiogenic factors, and on the other hand, they can promote neovascularization regression through mechanisms such as inducing EC apoptosis or physically clearing neovascular tufts. This functional complexity of microglia within the retinal microenvironment highlights the heterogeneous nature of their populations and their diverse contributions to retinal pathology. Microglial activation and migration are often observed in the early stages of RVDs, even before noticeable vascular changes occur.

Early activation and morphological alterations in microglia have been reported in RVO, suggesting that microglia may serve as potential biomarkers for early diagnosis. These findings open up new avenues for developing microglia-targeted approaches for diagnosing RVDs at their onset. Additionally, microglial activation and polarization mechanisms are essential for understanding their role in these diseases and could provide insights into new therapeutic strategies. Current treatments targeting inflammatory pathways, such as anti-VEGF therapies, influence microglial activation and function. However, challenges remain in designing microglia-based therapies for RVDs. One significant challenge is selectively targeting activated microglia in the

retina while preserving their protective functions in healthy tissues. Furthermore, developing drug delivery systems that can specifically target retinal microglia without affecting those in other regions of the CNS is a critical hurdle. A key question for future research is identifying the triggers and regulatory mechanisms of microglial activation in RVDs. Understanding the precise role of microglia in disease progression is another critical gap. Although early microglial activation is commonly observed in RVO, it remains unclear whether it directly contributes to disease progression or if it is merely a response to retinal injury. This distinction is vital for developing therapeutic strategies that effectively modulate microglial activity without impairing their essential functions.

A comprehensive understanding of microglial functions and their interactions within the retinal microenvironment is essential for advancing therapeutic strategies. Future research should focus on identifying specific microglial subtypes involved in RVDs, developing therapies that modulate microglial activity in a targeted and safe manner, and exploring their potential as biomarkers for early detection. Addressing these challenges will be critical in the development of effective treatments for these complex and debilitating retinal conditions.

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