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Role of microglial polarization in age-related macular degeneration

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小胶质细胞极化在年龄相关性黄斑变性中的作用

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摘要

小胶质细胞起源于卵黄囊中的原始巨噬细胞,它们既是免疫系统的防御者,又是稳态的调节者。它们主要表现为两种极化状态:M1 促炎表型极化状态和 M2 抗炎表型极化状态。小胶质细胞的极化在炎症性疾病、代谢失调和神经退行性病变的发生发展过程中起着至关重要的作用,且许多眼科疾病的病理生理过程也与之相关,如年龄相关性黄斑变性(AMD)的新生血管、炎症反应和氧化应激的过程。由于小胶质细胞的极化状态影响疾病的进展和预后,因此,在 AMD 的不同阶段调节小胶质细胞的极化表型有望成为新的个体化治疗方案。文章回顾了小胶质细胞极化在生理和病理条件下的作用,概述了其与 AMD 的相关性,并探讨了调节小胶质细胞极化治疗 AMD 的巨大潜力。

关键词:小胶质细胞极化;脉络膜新生血管;炎症;氧化应激;黄斑变性

Abstract

• Microglia, originating from primitive macrophages in the yolk sac, serves as both immune system defenders and regulators of homeostasis. These cells exhibit two primary polarization states: conventionally activated (M1) and alternatively activated (M2). The polarization of microglia plays a crucial role in influencing inflammatory disorders, metabolic imbalances, and neural degeneration. This process is implicated in various aspects of ocular diseases, especially age-related macular degeneration (AMD), including inflammation, oxidative stress and pathological angiogenesis. The distinct functional phenotypes of microglia impact disease progression and prognosis. Thus, regulating the polarization or functional phenotype of microglia at different stages of AMD holds promise for personalized therapeutic approaches. This comprehensive review outlines the involvement of microglia polarization in both physiological and pathological conditions, emphasizing its relevance in AMD. The discussion underscores the potential of polarization as a foundation for personalized treatment strategies for AMD.

• KEYWORDS: microglia polarization; choroidal neovascularization; inflammation; oxidative stress; macular degeneration

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INTRODUCTION

Microglia, crucial nervous system-specific immune cells, significantly contributes to brain development, neural environment maintenance, and responses to injury and repair, constituting 10%-15% of the total brain parenchyma cell population. As the resident macrophages of the central nervous system, microglia monitor tissue changes, produce an immune response to pathogens, and sustain tissue homeostasis by clearing pathogens, dying cells, aberrant proteins, or

debris[1]. Microglia possesses the ability to change their phenotypes and function to preserve tissue homeostasis, depending on their surroundings. They can shift to an conventionally activated (M1) phenotype for pro-inflammatory cytokine expression or transition into an alternatively activated (M2) phenotype for inflammation resolution and tissue repair[2]. Polarized M1 or M2 microglia can change their phenotype and function in answer to varied microenvironmental conditions. Although the conceptual framework for M1 and M2 is depicted as two distinct statuses, Microglia states may present a variety of unique functional characteristics that overlap as a spectrum. Nonetheless, the overall M1 and M2 classification continues to be a helpful idea to further our comprehension of the functional state of microglia as injuries advance and to help us investigate novel therapeutic approaches[3-5].

Changes between these two phenotypes may contribute to various neurodegenerative conditions, such as age-related macular degeneration (AMD), glaucoma, retinitis pigmentosa, and other fundus diseases[6-7]. AMD has become a significant public health issue and a substantial global burden, leading to severe vision loss. With a global increase in aging populations and longevity, this prevalence is predicted to reach 288 million by 2040[8]. Usually affecting those aged 55 and older, AMD impairs the high-acuity central vision needed for important tasks[9]. Clinically, AMD is classified into the nonexudative or atrophic subtype (dry AMD) and the neovascular or exudative subtype (wet AMD). In early stage, AMD is characterized by the complete loss of both macular photoreceptors and retinal pigment epithelium (RPE). In advanced stage, AMD either becomes neovascular (wet AMD) or causes progressive cell loss without any neovascular constituent (dry AMD with geographic atrophy), which can result in rapid vision loss[10].

There are mainly three types of glial cells in retina, Müller cells, astrocytes and microglia, which jointly play essential roles in normal neural conduction. In the healthy retina, microglia comprise 0.2% of all retinal cells, which existed in nerve fiber layer and two neuropil layers, named the inner plexiform and outer plexiform layers. Microglia actively contribute to the structure formation of neuronal and vascular in retina, as well as the regulating of synaptic circuits in the retinal plexiform layers[11-12]. However, abnormal angiogenesis could impair the delivery of oxygen and nutrition, which eventually lead to a dysregulation in neuronal retinal function. Recently, there is an ongoing debate that whether microglia has a significant impact on the development of retinal neovascular. In this article, we will review recent studies on microglia polarization in the development of choroidal neovascularization (CNV) to explore new therapies for AMD.

CHOROIDAL VASCULATURE CHANGES IN AGE-RELATED MACULAR DEGENERATION

Structure, Development, and Function of Choroid The middle tunic of the eye, or the posterior portion of the uvea, is known as the choroid. In humans, the uvea develops from the mesenchyme that surrounds the two vesicles, which sprout from the embryonic forebrain at the first month and eventually becoming the eyes. The choroid is made up of melanocytes, blood arteries, immunocompetent cells, fibroblasts, and connective tissue. The choroid is histologically divided into five layers from external to internal: suprachoroidea, two vascular layers (Haller's and Sattler's), choriocapillaris, and Bruch's membrane (BrM). The BrM, which the RPE is located on, is the inner boundary of the choroid. The choriocapillaris is a highly anastomosed network of capillaries, which arise from the arterioles in Sattler's layer. The arterioles consisted to a hexagonal-shaped domain of a single layer of capillaries, which giving a patch-like structure to the choriocapillaris. Through the BrM, the choriocapillaris provides oxygen and nutrition to the outer layers of the retina, including the RPE and photoreceptors. The outer Haller's layer is with large blood vessels, and the inner Sattler's layer is with small and medium arteries which feed the capillary network and veins. The suprachoroidea is a region of transition between sclera and choroid which include melanocytes, fibroblasts, and collagen fibers[13-14].

The physiological functions of the choroid mainly rely on its vasculature, which nourishes the outer retina, the RPE, the optic nerve and the foveal avascular zone. Any disruption in the flow of oxygen from the choroid to the retina could result in ocular diseases. Additionally, the secretory cells in the choroid may modulate vascularization and scleral growth[13,15]. To form a unique capillary network for the choroidal development, the appropriate regulation of vascular development is needed. In human, the choriocapillaris forms when islets of nucleated acidophilic cells appear in the periocular stroma about 6 weeks of gestation. Hereafter, the primitive vascular plexus takes shape at 12 weeks of gestation, and intermediate choroidal vessels in Sattler's layer occur, assisting the choriocapillaris in connecting to the bigger vessels in Haller's layer. Eventually, at 22 weeks of gestation, the choriocapillaris is fully mature and has organized into a complex network[15-16]. During the development, several endothelial cell markers are found in these blood islands, such as cluster of differentiation (CD) 34, CD31, CD39, and vascular endothelial growth factor receptor (VEGFR)-2[17-18]. Moreover, in choroidal endothelial cells, several representative endothelial markers have been found, such as CA4, PV1, and RGCC[19-20].

Mechanism and Pathological Characteristics of Age-Related Macular Degeneration Any changes in choroidal structure or impaired blood flow could lead to degeneration and neovascularization, such as AMD. AMD typically progresses from early to intermediate stages, characterized primarily by RPE abnormalities and the accumulation of yellowish deposits known as drusen beneath the RPE. Subsequently, it advances to the late stage, characterized by significant damage to the retina and choroid. The pathogenesis of AMD remains elusive; nonetheless, age-related oxidative damage is widely acknowledged as a pivotal factor in the development of AMD[21]. Photoreceptors, choriocapillaris, RPE, and BrM all experience morphological and physiological

changes as a result of the cumulative impact of oxidative damage.[22]. The accumulation of lipofuscin, known as drusen, which deposited extracellularly between the interior collagenous layer of BrM and the basal lamina of the RPE, is believed to lead to the dysregulation of RPE function, and cellular damage. Lipofuscin contains more than 129 proteins, including inflammatory and complement factors[23-24]. By the age of 80, lipofuscin can constitute approximately 20% of RPE cells' cytoplasmic volume.

Drusen plays a pivotal role in activating the complement system, which critically contributes to the subsequent pathological changes in AMD. Within the choriocapillaris, the activated complement system may lead to the loss of endothelial cells, eventually lead to choriocapillaris degeneration. In addition, the accumulated oxidative damage caused by chronic inflammation drives and hypoxia irreversible damage, leading to the development of AMD[9,25]. Several studies revealed changes of choroidal vascular in early AMD. Fluorescein angiography showed decreased blood volume, abnormal blood flow and choroidal perfusion in eyes, which due to the loss of cellularity, decrease of choriocapillaris luminal diameters and thinning of the choroid[26-28].

In neovascular AMD, CNV may occur, affecting various cell types such as endothelial cells, pericytes, photoreceptor cells, ganglion cells, and glial cells. These changes can lead to pigment epithelial detachment, intraretinal hemorrhages, tears in the RPE, and disciform scarring[29]. In response to ischemia-induced oxidative stress during primary capillary degeneration, the synthesis of vascular growth factors, such as VEGF, is triggered. Finally, the CNV breaks the subretinal spaces as well as BrM and then invade sub-RPE[14,30]. Generally, CNV can be classified into 3 types, type 1 CNV grow beneath the RPE (corresponds to occult lesions); type 2 CNV arises from the choroid, which proliferates in the subretinal space that between the neurosensory retina and the RPE (corresponds to classic lesions); type 3 CNV are featured by intraretinal neovascularization (analogous to retinal angiomatous proliferation)[9].

ROLE OF MICROGLIA POLARIZATION INAGE-RELATED MACULAR DEGENERATION

Microglial Roles in Shaping the Development of Choroidal Vasculature Microglia, originating from primitive macrophages in the yolk sac, plays an important role in the development of blood vessels in retina[31]. During retinal development, the precise localization of microglia to endothelial apical cells is essential for promoting vascular sprouting[32-33]. More specifically, microglia engage with sprouting endothelial cells to facilitate anastomosis between neighboring cells[34]. Depleting and subsequently restoring microglia has been shown to promote the proliferation of a homeostatic microglial pool that maintains the integrity of both neurons and blood vessels[35]. Three intraretinal vascular layers interconnect different neuronal areas within the retina. The deep plexus is found inside the outer plexiform layer, the intermediate plexus ascends into the inner plexiform layer, and the superficial plexus interleaves the ganglion cell layer. Because of their distinct locations and branching patterns, each of these artery layers is regarded as a relatively separate neurovascular unit[36-37]. Anatomically, to dynamically maintain the blood-retina barrier integrity and the neurovascular unit's appropriate function, microglia are in close contact with pericytes, which are closely linked to other adjacent components of the neurovascular unit[38-39]. In addition to the classical biological features of phagocytosis, pruning, and neuron activity monitoring, microglial have been found to involved in blood vessel development. It has been reported that microglial are crucial in the development of the retinal vascular formation and cause pathological angiogenesis in response to insults[40]. According to Checchin *et al*[41], microglial appear to be closely associated with all kinds of vascular endothelial cells during retinal development. To promote vascular sprouting and pruning during angiogenesis, the microglial congregates near neovascular tufts and engage with endothelial apical cells. It could convert vascular sprouts in the deep plexus into superficial vascular plexus, which will increase the density of the superficial retinal vascular plexus[41-42]. In previous investigations, filopodia on endothelial tip cells, which direct blood vessel formation across the tissue, are directly adjacent to microglial. Intravitreal injection of exogenous microglia restored patterning, while genetic ablation or microglia depletion decreased intraretinal vessel branching and density[41,43]. However, it is unknown exactly what molecular mechanism microglia uses to create retinal angiogenesis. There are several possible mechanisms have been explored. First, microglial release soluble substances that influence the development and branching of blood vessels. For example, CD95L stimulates CD95 on blood vessels, hence promoting vascular expansion *via* Src-family kinase and phosphoinositide 3-kinase (PI3K) signaling[44]. Additionally, lectin galactoside-binding soluble 3 binding protein (LGALS3BP), a multifunctional glycoprotein, is found involved in inflammation and immunology, which could promote angiogenesis and tumor growth by increasing VEGF-A expression[45]. Studies have shown that LGALS3BP in microglia actively contributes to angiogenesis by stimulating the expression of angiogenic proteins *via* the PI3K/protein kinase B (AKT) pathway[42]. Furthermore, it has been discovered that basigin-2, an extracellular matrix metalloproteinase inducer, promotes microglial and endothelial communication by secreting insulin-like growth factor-1 (IGF-1) *via* the PI3K/AKT signaling pathway[46]. Moreover, as a microRNA crucial in inflammation, miR-155 plays a significant role in the pathogenesis of retinal neovascularization. While forced expression of miR-155 induces endothelial hyperplasia and increases microglia count and activation, constitutive miR-155 deficiency in mice results in minor vascular abnormalities. Dysregulated expression of cysteine-rich 61 (CCN1) and miR-155 heightens the inflammatory burden and activates microglia during ischemic injury, thereby inducing abnormal angiogenic responses[47]. In addition, as one of the glial cells that maintain retinal homeostasis, astrocytes can form a

reticular network that provides a substrate for angiogenesis and vessel patterning. Furthermore, microglia can regulate the developmental death of astrocytes, indirectly modulating vascular integrity by regulating the quantity of astrocytes[48-49].

Microglia Polarization in Age-Related Macular Degeneration The microglial can be classified into two main categories based on their immune responses and phenotypes: conventionally activated (M1) and alternatively activated (M2). M1 microglia, characterized by surface markers including human leukocyte antigen DR (HLA-DR), CD80, CD86, and CD197, release significant amounts of pro-inflammatory cytokines upon activation, including tumor necrosis factor (TNF)-α and interleukins (IL-1, IL-6, IL-12, IL-18, IL-23). Several characteristics of M1 and M2 microglia are summarized and compared in Table 1. Moreover, the response also includes the activation of NLRP3 inflammasome complex or production of reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS)[50-51]. M1 microglia may eliminate pathogens but concurrently causing tissue damage. Conversely, M2 macrophages release anti-inflammatory molecules to alleviate this damage. In addition, they produce angiogenic factors, such as epidermal growth factor (EGF), VEGF, and transforming growth factor (TGF)-β, which facilitate resolution of inflammation and quicken the healing of wounds. Nevertheless, abnormal hyperplasia, such as pathological angiogenesis, may arise precisely because the overproduction and activation of these factors[52-54](Figure 1).

The diverse phenotypes and functions enable microglia to perform crucial roles in resistance of pathogen, inflammation, remodeling and repair of tissue, and regulation of autoimmune. The plasticity of microglia polarization is influenced by the tissue microenvironment and has been documented in ocular conditions, including sympathetic ophthalmia[55], uveitis[56], and diabetic retinopathy (DR)[57]. Microglia have been described as exerting both protective and detrimental effects on local tissues in AMD[58-59]. M1 microglia are involved in the early phase of CNV, whereas the M2 phenotype plays a crucial role in the intermediate and advanced stages of CNV development and remodeling[60-61]. In a laser-induced model of neovascular AMD, expression profiling indicated that microglia infiltrating into CNV lesions exhibited the expression of M2-type markers, while M1-type markers were not induced following the laser injury[62]. The upregulation of IL-4-STAT6-PPAR-γ signaling activity induced polarization of microglia towards the M2 phenotype, subsequently resulting in the inhibition of inflammatory cytokines and the spontaneous regression of neovascular tufts in the oxygen-induced retinopathy (OIR) model[63]. The differences in microglial polarization direction and the occurrence of CNV may be closely associated with the timing of the research.

MECHANISMS OF MICROGLIAL POLARIZATION IN AGE-RELATED MACULAR DEGENERATION

Microglial polarization plays a pivotal role in ocular diseases such as DR[53] and AMD, participating in processes such as inflammation, oxidative stress, and pathological angiogenesis. The functional phenotype of microglia significantly impacts the progression and prognosis of AMD (Table 2). Therefore, modulating the polarization or functional phenotype of microglia at different stages of AMD may offer novel therapeutic strategies for AMD.

Inflammation AMD emerges from a complex interplay of metabolic, functional, genetic, and environmental factors. This intricate network of elements sets the stage for the gradual and enduring structural alterations within the macular region, affecting the choriocapillaris, BrM, RPE, and photoreceptors[73-74]. Drusogenesis, degeneration of RPE/photoreceptors, disruption of BrM, and the onset of CNV are consequences of localized inflammation. Inflammation is also a significant outcome of both oxidative and non-oxidant stress. Consequently, inflammation is considered an important contributor to the pathogenesis of both dry and neovascular AMD (nAMD)[74]. The retinal microglia are believed to play a crucial role in initiating retinal inflammation[75]. Abnormal microglial activity has traditionally been linked to AMD[76]. In the mouse model of laser-induced nAMD, amoeboid microglia and mononuclear phagocytes are recruited to the neovascular lesion. The number of these cells changes according to the severity and nature of the lesion, whether it is fibrotic or leaking, indicating the dynamic nature of these cells[77-78]. In AMD, microglia activation is evident in retina, with a significant imbalance between M1 and M2 cell populations, along with the presence of deformed and enlarged microglial cells near RPE cells associated with drusen. This suggests a potential role of microglia in the pathological processes of AMD. In mouse laser induced CNV models, activation of the AKT2 pathway in microglia induces M1 polarization, subsequently activating neutrophils and triggering early RPE

Table 1 Markers, stimulations and secretions of M1 and M2 microglia

Phenotypes	Markers	Stimulation	Secretion
M1	HLA-DR, CD80, CD86, CD197	IFN-γ, LPS	TNF-α, IL-1, IL-6, IL-12, IL-18, IL-23
M2	CD206, CD209, CD301, CD163	IL-4, IL-13, TLR, IL-1R, LPS, IL-10, TGF-β, glucocorticoids, open-loop steroid hormones	TNF-α, TGF-β, Arg-1, IL-10, IL-1, IL-6

M1: Conventionally activated; M2: Alternatively activated; HLA-DR: Human leukocyte antigen DR; IFN-γ: Interferon - gamma; TLR: Toll-like receptor; IL: Interleukin; LPS: Lipopolysaccharide; TGF-β: Transforming growth factor-beta; TNF-α: Tumor necrosis factor-alpha.

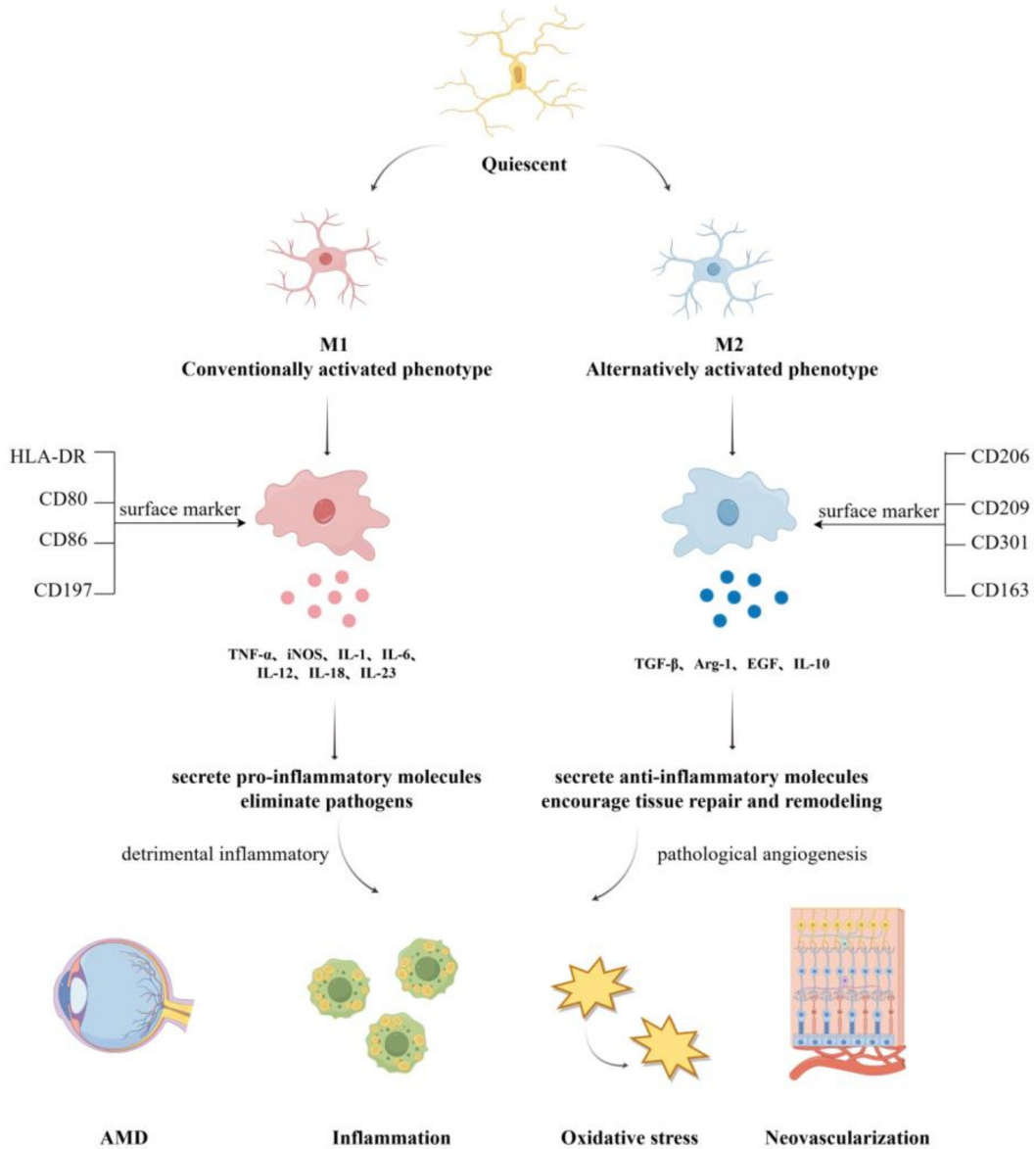

Figure 1 Microglia polarization in age-related macular degeneration. Microglial polarization plays a pivotal role in age-related macular degeneration, participating in processes such as inflammation, oxidative stress, and pathological angiogenesis. Modulating the polarization or functional phenotype of microglia at different stages of age-related macular degeneration may offer novel therapeutic strategies for age-related macular degeneration.

Table 2 Signaling pathways related to polarization

Pathological processes	Polarization phenotypes	Signaling pathways
Inflammation	M1	NF-κB-STAT3[63]; HIF-1α/VEGF/VEGFR-2[64]; AKT 2[65]; C1q and the classical pathway[66]; ROS/NF-κB[67]
Oxidative stress	M1	ROS/NF-κB[67]; TLR4/ROS[68]; TSPO/Nrf2[69-70]
Angiogenesis	M2	PI3K/AKT[42]; RhoA/ROCK[71]; HIF-1α/HIF-2α/NF-κB[72]

M1: Conventionally activated; M2: Alternatively activated; NF-κB: Nuclear factor kappa B; STAT: Signal transducer and activator of transcription; HIF: Hypoxia-inducible factor; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; AKT: Protein kinase B; ROS: Reactive oxygen species; TLR: Toll-like receptor; TSPO: Translocator protein; Nrf2: Nuclear factor erythroid 2-related factor 2; PI3K: Phosphoinositide 3-kinase; RhoA: Ras homolog family member A; ROCK: Rho-associated protein kinase.

degeneration[65]. M1 microglia can also induce the occurrence and development of CNV by promoting the secretion of IL-6 and TNF-α[66]. Additionally, microglia may trigger the activation of the NLRP3 inflammasome in RPE cells, leading to an increase in pro-inflammatory cytokines, including IL-1β[79]. The activation of both NLRP3 inflammasomes and

non-NLRP3 inflammasomes within macrophages/microglia at locations where CNV develops is likely to contribute to the progression of nAMD[80]. Regarding microglial polarization, it is not only observed in nAMD, but also in the early stages of OIR models, where the NF-κB-STAT3 signaling pathway is activated. This leads to an upregulation of M1 microglial polarization in the NV tufts of both central and peripheral retina, resulting in increased expression of inflammatory cytokines, including TNF-α, IL-6, and IL-1β. In the later stages, M2 microglial polarization takes over, inhibiting inflammatory cytokines through activation of the IL-4-STAT6-PPAR-γ signaling pathway, thereby promoting spontaneous regression of NV tufts[63]. Research has also shown that in the OIR mouse model, medication can switch microglia polarization from the M1 phenotype to the M2 phenotype and alleviate the inflammatory response by blocking the ROS/NF-κB pathway[67].

Oxidative stress The retinal tissue is highly vulnerable to oxidative stress, attributed to factors such as exposure to light, intense metabolic activity, elevated oxygen consumption, and the accumulation of lipofuscin[81]. Oxidative stress induced by aging are primary contributors to early AMD-related dysfunction in the RPE and eventual degeneration of RPE, leading to CNV in late AMD[22]. The studies on patients with nAMD have revealed a notable rise in total oxidant status in the serum accompanied by reduced levels of total antioxidant status[82]. Free radicals generated during oxidative stress also regulate the inflammatory pathway by enhancing the expression of pro-inflammatory genes. This, in turn, amplifies oxidative stress, creating a cycle of amplification that contributes to additional pathological events and further progresses AMD[83]. Microglia has the capability to generate ROS using NOX2, mitochondrial oxidative phosphorylation, and the Fenton reaction involving iron. These ROS function as signaling molecules, playing a vital role in mediating pathways essential for microglial functions[84]. For instance, lipopolysaccharide (LPS) stimulation activates toll-like receptor 4 (TLR4) in microglial BV-2 cells, leading to the production of nitric oxide (NO), increased expression of iNOS, and elevated intracellular ROS levels[68]. Research indicates a polarization response of macrophages following light damage. During the early stages of degeneration, pro-inflammatory M1 activation appears to predominate, while M2 responses seem to more prominently characterize the chronic post-exposure period[85]. Translocator protein (TSPO) serves as an indicator of neuroinflammation or the activation of microglia[86]. In a laser-induced neovascular AMD mouse model, TSPO gene knockout or treatment with XBD173 can prevent subsequent neovascularization and vascular leakage[69]. The TSPO ligand can enhance the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathway in RPE cells, protecting them from cellular damage caused by inflammation and oxidative stress[70]. Collectively, the results from clinical investigations substantiate the existence of oxidative biomarkers in AMD and underscore the significant role of oxidative stress in AMD pathology.

Angiogenesis Pathological angiogenesis is the primary cause of irreversible blindness in patients with nAMD, in which both microglia and macrophages play a part in this process. Microglia also contributes to the production of pro-angiogenic cytokines and growth factors, such as VEGF and placental growth factor (PIGF). nAMD development is positively impacted by VEGF, and its receptors, VEGFR1 and VEGFR2, appear to have differing effects on the recruitment and accumulation of retinal microglia in the subretinal region[87]. PIGF could also strongly promote the survival of microglia, production of pro-inflammatory cytokine, and monocyte chemotaxis. Animal experiments have shown that in murine models of nAMD, necrotic RPE accelerates the PFKFB3-driven glycolysis in microglia, leading to the activation of HIF-1α/HIF-2α and NF-κB pathways. This subsequently induces the expression of M1/M2 markers and pro-angiogenic cytokines, ultimately promoting the reprogramming of microglia towards a pro-angiogenic phenotype and facilitating the development of CNV. The PFKFB3 inhibitor AZ67 inhibits the activation of HIF-1α/HIF-2α and NF-κB pathways, thereby suppressing laser-induced CNV in mice[72]. The soluble lectin galactoside-binding protein 3 (LGALS3BP), belonging to the scavenger receptor cysteine-rich (SRCR) domain protein family, triggers the elevation of angiogenesis-related factors (HIF-1α, MMP-9, MMP-2, and VEGF-A) *via* the PI3K/AKT pathway, subsequently fostering angiogenesis in microglia within the retina[42]. Another study demonstrated that melatonin modulated the polarization of macrophages/microglia from the M2 phenotype to the M1 phenotype by inhibiting the Ras homolog family member A/Rho-associated protein kinase (RhoA/ROCK) signaling pathway in a mouse model of CNV. This modulation resulted in the attenuation of CNV, reduction of vascular leakage, and inhibition of vascular proliferation[71].

Cross Talk between Microglia and Macroglia Moreover, investigations have explored the intricate interactions between microglia and macroglia, such as Müller cells and astrocytes. Müller cells, a subtype of neuroglia cells, are responsible for upholding the normal functioning of retinal neurons, regulating innate inflammatory responses, and upholding the stability of the retinal structure. Previous studies have shown that the activation of Müller cells could activate microglia through the ATP/P2X7 receptor pathway in mice retina. This microglial activation results in a significant increase in pro-inflammatory factors such as TNF-α and IL-6. These inflammatory factors, operating in a positive feedback loop, further enhance the expression of pro-inflammatory factors in Müller cells[88]. The activation of Müller cells also has the potential to expedite the advancement of AMD by causing harm to neurons and blood vessels. Consequently, the intercommunication between microglia and Müller cells assumes a significant role in maintaining retinal homeostasis, and this interplay is intricately regulated[89].

ROLE OF MICROGLIA IN THE TREATMENT OF AGE-RELATED MACULAR DEGENERATION

Existing anti-VEGF-A treatments effectively restrain CNV in a specific subset of nAMD patients. However, the extended use of such anti-VEGF-A therapies might compromise the physiological roles of the choriocapillaris and retina, both of which depend on VEGF-A. Furthermore, continuous anti-VEGF-A treatment may not prevent disease progression in some cases. Therefore, there is an urgent demand for innovative therapies for nAMD that selectively target disease-related mechanisms without hindering the growth factors and cellular pathways essential for the normal functioning of the retina and choroid. Hence, a potential therapeutic approach involves reprogramming pro-inflammatory microglia into a more anti-inflammatory, non-angiogenic phenotype, which is pivotal in the pathophysiology of AMD[90].

In recent years, a variety of strategies targeting microglia, such as depletion, reprogramming, and effector blockade, have emerged, potentially expanding the avenues for treating CNV. The use of drugs switched the microglia polarization from pro-angiogenic M2 phenotype to anti-angiogenic M1 phenotype has been shown to improve mouse laser-induced CNV leakage and reduce the CNV area by downregulating the HIF-1α/VEGF/VEGFR2 pathway[64]. Studies have demonstrated that the molecular inhibitor of colony-stimulating factor receptor (CSF1R), PLX5622, can eradicate up to 100% of retinal microglia within 1 to 2 weeks. Administration of PLX5622 treatment resulted in rapid regression of laser induced CNV lesions in mice[91]. Minocycline can lead to a decrease in retinal microglial cells, accompanied by an increase in avascular areas in the OIR model[92]. The cytokine TGF-β exerts anti-inflammatory effects on microglia, downregulating MHC class II and inhibiting the production of IL-1, IL-6, and TNF, offering potential benefits for patients with cone degeneration[93]. Targeting the downstream of microglia directly is another tactic to retard degeneration in the eye caused by cells, including the inhibitors of pro-inflammatory cytokines like IL-1, TNF, and complement component 1q[66]. Recently, there are several novel treatments reported. MMP inhibitor called SB-3CT could decrease lesion size and vascular leakage in laser-induced CNV mice by modulating the expression of microglial[94].

Ongoing clinical trials are investigating treatment by targeting microglia for diseases such as Parkinson disease, Alzheimer disease and schizophrenia. Table 3 provides a comprehensive overview of preclinical evidence concerning the therapeutic effects by targeting microglia for ocular diseases, sourced from the official government website of clinical trial maintained by the U. S. National Library of Medicine, National Institute of Health. Several ocular diseases, especially associated cystoid macular edema, such as retinal vein occlusion, diabetic macular edema and retinitis pigmentosa, have been studied[95-100]. Researches indicate that inflammation might be a cause. It has been suggested that microglia, which are resident immune cells, activated during inflammatory processes have a contribution. It often leads to macular edema, a swelling of the retina which is a common source of vision loss. Minocycline is a drug which could help prevent cells involved in inflammation from becoming activated. Studies revealed that, oral minocycline might be a potentially useful therapeutic strategy in the treatment of retinitis

Table 3 Recent interventional clinical trials of microglia (ongoing and completed)

NCT number	Disease	Phases	Study design	Age(years)	Enrollment	Interventions	Completion date
NCT01468831	Branch retinal vein occlusion	Phase 1 Phase 2	Randomized	≥18	9	100 mg of minocycline in a pink opaque capsule; Placebo pill with inactive ingredients in a pink opaque capsule; 1.25 mg bevacizumab injection	March 2021 (Completed)[97]
NCT01468844	Central retinal vein occlusion	Phase 1 Phase 2	Randomized	≥18	6	100 mg pink opaque Minocycline capsule; Placebo; 1.25 mg bevacizumab injection	May 2015 (Completed)[98]
NCT01441102	Diabetic macular edema	Phase 1 Phase 2	N/A	≥18	7	60 mg Dextromethorphan hydrobromide capsules orally two times a day for 24 months	December 2015 (Completed)[96]
NCT01120899	Diabetic macular edema	Phase 1 Phase 2	N/A	≥18	6	100 mg minocycline pills twice daily for 24 months	February 2013 (Completed)[95]
NCT05904717	REM sleep behavior disorder	Phase 2	Randomized	50-80	40	PXS-4728 (A): Participants will receive once daily for period of 12 weeks; matching Placebo (B): Participants will receive once daily (QD) for period of 12 weeks	January 2025 (Ongoing)[100]
NCT02140164	Retinitis pigmentosa	Phase 1 Phase 2	N/A	≥12	7	Oral dose of 100 mg (or appropriate weight-adjusted pediatric dose) of minocycline twice daily for 12 months	June 2016 (Completed)[99]

pigmentosa-associated cystoid macular edema[99,101]. As a approved cough medicine, studies showed, dextromethorphan administration could decrease vascular leakage and treat diabetic macular edema[96,102]. Despite these encouraging preclinical findings, treatment by targeting microglia for AMD has yet to be clinically tested. Further high-quality research is necessary to conclusively demonstrate the clinical therapeutic efficacy of drugs targeting microglia to treat AMD. Continued research efforts should contribute to a deeper understanding of microglia's potential benefits and ensure its safe and effective utilization in clinical practice.

CONCLUSION

Microglia, as one of the primary phagocytes in the retina, plays pivotal roles in various biological functions, including phagocytosis, pruning and immune surveillance. Microglia can transition between M1 and M2 phenotypes and is crucial for maintaining retinal homeostasis and visual function. Various therapeutic approaches targeting microglia polarization, such as the CSF1R inhibitor PLX5622, cytokine TGF-β, MMP inhibitor SB-3CT, and drug delivery system C18PGM, have shown promise in treating CNV. In the future, microglia polarization may remain a focal point of research and emerge as a significant therapeutic target for CNV treatment.

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