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Review: The role of microglia in diabetic retinopathy and its potential as a therapeutic target

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Diabetic retinopathy (DR) is a common and severe complication of diabetes, which poses a serious threat to vision, and its pathogenesis is complex. Inflammatory response plays a crucial role in the progression of DR, but currently, anti–vascular endothelial growth factor therapy, the preferred treatment for DR, only targets the vascular part. Therefore, determining a treatment method targeting the inflammatory response in DR is an important step in addressing DR. As immune cells within the retina, microglia play a key role in the inflammatory response in DR, which is a crucial link in its pathogenic mechanism. By regulating the inflammatory response of microglia, the progression of DR can be effectively slowed down. This review deeply explores the mechanism of action of microglia in DR by reviewing relevant research achievements and evaluates the potential of treatment strategies targeting microglia in slowing down the progression of DR. The study focuses on how to further optimize the treatment regimen for DR by regulating different pathways such as the release of inflammatory factors, the occurrence of oxidative stress, phenotypic transformation, intercellular interactions, and phagocytic activity of microglia, providing important clues for the development of novel treatment methods for DR. Through a comprehensive analysis and evaluation of the effectiveness and safety of these treatment strategies, the study aims to provide more precise and effective treatment regimens for patients with DR, so as to improve their visual prognosis and quality of life.

Epidemiology of diabetic retinopathy: Diabetic retinopathy (DR) is an ocular fundus disease characterized by specific pathological changes. As a major ocular complication of diabetes mellitus, it exerts a significant impact on global health. Over the past few decades, with the advent of more advanced diagnostic instruments and surgical adjuvant therapies—such as preoperative intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors—the rate of vision loss caused by DR has been steadily declining [1]. Nevertheless, according to current projections, the global prevalence of DR and its associated disease burden will continue to rise substantially in the coming decades. The number of people affected by DR is estimated to increase from approximately 103 million in 2020 to 130 million in 2030 and further climb to 161 million by 2045 [2]. This projected growth can be attributed to multiple factors, including the rising global prevalence of diabetes, changes in lifestyle patterns, and the extension of life expectancy, coupled with population aging worldwide [2]. The economic costs associated with DR and its complications are enormous. The disease burden of DR has surged by more than 25% within just a decade, which may further exacerbate the pressure on already overstretched health care systems and resources. No longer merely a specialized term in the medical field, DR—a chronic disease—has gradually evolved into a critical social issue that profoundly impacts public health and even the overall national economy and people's livelihoods. Its harmfulness is increasing day by day, making research on its prevention and treatment an urgent priority.

Mechanism of DR occurrence: The pathogenesis of DR is extremely complex and has not been fully elucidated to date. What is clearly established first is that persistent hyperglycemia serves as the initiating factor for DR development. In addition, the pathogenesis of DR is also associated with multiple pathological processes induced by hyperglycemia, including the accumulation of advanced glycation end products, activation of the polyol metabolic pathway, stimulation of the diacylglycerol–protein kinase C (PKC) pathway, increased oxidative stress, and enhanced inflammatory responses [3]. Inflammatory changes represent one of the important pathological features in the early stage of DR and play a crucial role throughout the entire pathogenic process of the disease [4]. Cells involved in retinal inflammation include microglia, Müller cells, vascular endothelial cells, and others. As the primary resident immune cells in the retina, the activation of microglia can trigger the release of various proinflammatory mediators, such as cytokines,

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chemokines, caspases, and glutamate. Activated microglia also exhibit increased proliferation and migration. These changes in microglia severely affect retinal neurons, leading to increased cell apoptosis, subsequent thinning of the nerve fiber layer, and ultimately the occurrence of vision loss [5]. Therefore, inhibiting the pathological activation of microglia is recognized as an effective therapeutic strategy for the treatment of retinal degenerative diseases [6].

Current status of DR treatment: Clinically visible retinal lesions related to DR, such as microaneurysms, hemorrhages, and hard exudates, are mainly the result of retinal microvascular damage. Therefore, the focus on the pathophysiology, diagnosis, and evaluation of DR has traditionally been centered on the vasculature. Precisely for this reason, the advent of VEGF drugs has become one of the landmark achievements in the treatment of DR in the early 21st century [7]. Currently, anti-VEGF drugs have achieved certain effects in the treatment of ocular fundus diseases, but limitations still exist. For instance, most anti-VEGF drugs target only a single member of the VEGF family, making it challenging to comprehensively address the complexity of diseases. Moreover, traditional anti-VEGF treatment necessitates monthly intravitreal injections, which not only increase the physiologic burden and pain sensation for patients but also incur high costs, severely affecting treatment compliance. Therefore, to overcome these limitations, we still need to explore new treatment strategies and drug targets to provide patients with more comprehensive and effective treatment options. At present, there are no therapies that selectively target the activation of microglial cells. Regulating the number, activation, and polarization state of microglial cells are the three key mechanisms for developing targeted therapies for DR microglial cells. Although studies have shown that the activation state of microglial cells is closely related to the development of DR, the specific causal relationship still needs to be further clarified [8]. Therefore, in-depth research into the specific role of microglial cells in DR and clarifying their role in the disease process are crucial for developing effective treatment strategies.

The impact of microglial activation on DR: Microglia, the resident macrophages of the central nervous system (CNS), originate from the embryonic yolk sac. As the first line of defense against pathogen invasion, they mediate innate immune responses by recognizing, sequestering, and processing antigens [9]. Microglia exist in two primary states: resting and activated. Under normal physiologic conditions, they are in a "resting" state. Although their cell bodies remain relatively stationary, resting microglia engage in extensive interactions with neighboring cells. Characterized by highly branched processes, they maintain close contact with neurons and dynamically monitor the microenvironment for potential threats via these processes—ensuring the normal function of neurons and thus sustaining physiologic functions such as vision [10]. Additionally, neurons express microglial ligand proteins (e.g., fractalkine) on their surfaces, which are specifically recognized by receptors on microglia (e.g., the fractalkine receptor CX3CR1) [10]. On one hand, this allows microglia to sense changes in neurons and rapidly respond to subtle alterations in their microenvironment; on the other hand, these interactions help regulate microglial functions. Upon activation by trauma, inflammation, or infection, microglia undergo changes in morphology, gene expression, function, and quantity. For instance, within 24 h postinjury, their cell bodies become hypertrophic and their processes retract; proliferation peaks approximately 3 days later, accompanied by upregulated expression of molecules such as CR3 [11], Toll-like receptor (TLR) 4 [12], and major histocompatibility complex class II proteins [13]. Moreover, activated microglia exhibit enhanced proliferation and migration capabilities [14]. Specific examples include the following: after optic nerve transection, microglia in the retina proliferate extensively within 7 to 21 days, with over 80% adopting a rod-like morphology. Following diffuse brain injury, microglia in the somatosensory cortex of rats form "rod-like microglial chains" through local proliferation. When the CNS sustains laser-induced damage, mechanical injury, or blood-brain barrier disruption, microglial processes migrate rapidly toward the injured site at an average speed of 1.25 ± 0.06 μm/min, forming a barrier to separate healthy tissue from damaged tissue. This migration depends on adenosine triphosphate (ATP) signaling and purinergic receptors (e.g., P2Y12); for example, local injection of ATP can mimic injury signals and induce microglial migration toward the source of ATP [9].

Activated microglia also show increased immunoreactivity and phagocytic activity. They are highly efficient at clearing dead and excess cells, and this phagocytic function is sustained to a certain extent [15]. Concurrently, microglia release a variety of inflammatory mediators, including cytokines, chemokines, proteases, reactive oxygen species (ROS), and reactive nitrogen species. These changes collectively indicate the transition of microglia from a resting to an activated state [16]. Traditionally, activated microglia are classified into two phenotypes: M1 (classically activated) and M2 (alternatively activated). M1 microglia exhibit strong proinflammatory properties. They secrete large amounts of proinflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and produce ROS such as nitric oxide (NO). While critical for pathogen clearance and initiating immune responses,

excessive M1 activation causes neurotoxicity, damages neurons, and is closely associated with the development and progression of neuroinflammation and neurodegenerative diseases [17-19]. M2 microglia exert anti-inflammatory and neuroprotective effects. They secrete anti-inflammatory cytokines (e.g., IL-10, TGF-β), promote tissue repair and regeneration, participate in clearing cellular debris and apoptotic cells, and regulate neural plasticity and synaptic function—playing a vital role in maintaining CNS homeostasis [20]. In reality, microglia display a broad spectrum of reactive phenotypes, each with distinct functions, morphologies, and modes of existence. Thus, the simple binary classification (M1/M2) cannot fully capture the phenotypic diversity of microglia. M1 and M2 represent two functional extremes, with transitional states between them; furthermore, disease-specific phenotypes emerge during pathological processes [21]. For example, in Alzheimer's disease (AD), a microglial phenotype is associated with amyloid-beta plaques. Dependent on apolipoprotein E and triggering receptor expressed on myeloid cells 2 (TREM2), this phenotype—linked to neurodegeneration—is termed the microglia-associated neurodegeneration phenotype. It is characterized by TREM2 signal activation and elevated apolipoprotein E expression, as well as triggered by the accumulation of cellular debris in aged mice or neurodegenerative diseases. In frontotemporal dementia, a microglial activation phenotype arises due to progranulin deficiency, which is characterized by a reactive morphology and excessive complement system activation [22]. In conclusion, from the exacerbation of inflammatory responses to the promotion of neurodegeneration and the impairment of vascular function, the activation of microglia exerts a comprehensive impact on the progression of the disease and serves as a crucial link in the pathogenesis of DR.

Potential strategies for the treatment of DR targeting microglial cells: Microglial activation contributes to the development and progression of DR through a variety of complex mechanisms, encompassing inflammatory responses, oxidative stress, vascular regulation, and intercellular interactions. These mechanisms are intertwined and collectively drive the progression of DR. Therefore, we will discuss therapeutic approaches targeting microglia for DR management from five strategies: modulation of the inflammatory response, antioxidant stress intervention, regulation of microglial phenotypes, regulation of intercellular interactions, and inhibition of the excessive activation of phagocytosis in microglia (Figure 1).

Modulating the inflammatory response: A growing body of data indicates that chronic inflammation is associated with the pathogenesis of DR, particularly in the development of pathological angiogenesis and macular edema [23,24]. Abnormal activation of microglia is the "initiator" and "amplifier" of the inflammatory cascade in DR. By targeting inflammation-related signaling pathways, excessive activation of microglia can be effectively inhibited, and inflammatory damage can be reduced.

Nuclear factor (NF)–κB is a transcription factor widely present in cells. It plays the role of a "signal hub" in the pathology of DR, and its regulation of microglia is a key link. The core triggers of DR (long-term hyperglycemia, retinal injury) can activate the NF-κB signaling pathway, prompting its key subunits (e.g., p65) to enter the cell nucleus and initiate the transcription of downstream target genes. When NF-κB is activated, it directly induces microglia to switch from the "resting state" to the "activated state." Activated microglia release inflammatory factors, which aggravate the local inflammatory response in the retina, damage nerve cells, and ultimately lead to visual impairment [25]. Therefore, regulating NF-κB–related pathways is considered one of the critical strategies for modulating microglial function.

A growing body of research has identified that certain natural compounds, endogenous substances, and potential drugs exhibit the ability to inhibit NF-κB. For example, many natural flavonoids exhibit inhibitory effects on the NF-κB signaling pathway. Kaempferol (Kae) is a flavonoid widely present in nature, and experiments have shown that it exerts multiple effects on microglia: in terms of inhibiting inflammatory responses, it reduces the expression of proinflammatory cytokines and NOS2, as well as suppresses inflammasome complexes; in the regulation of cellular signaling pathways, it prevents the nuclear translocation of p65–NF-κB and modulates the phosphorylation of mitogen-activated protein kinases (MAPKs); and in the induction of cell polarity, it increases the expression of HO-1 and Arg-1, promoting the transition of cells to the M2 anti-inflammatory phenotype, thereby playing a protective role in DR [26]. However, studies also point out that the long-term efficacy and safety of Kae as a therapeutic agent still require further in-depth research, especially regarding its impact on retinal health and overall human health under high-dose or long-term use conditions. Other flavonoids, such as baicalin [27] and galangin [28], have also demonstrated the potential to regulate microglia by inhibiting the NF-κB signaling pathway in experimental diabetes. Additionally, plant-derived components, such as chlorogenic acid [29], paeoniflorin [30], erianin [31], and sesamin [32], have also shown promise in studies on NF-κB inhibition.

Several endogenous substances also participate in the regulation of the NF-κB signaling pathway. Melatonin is a hormone secreted by the pineal gland and is also synthesized

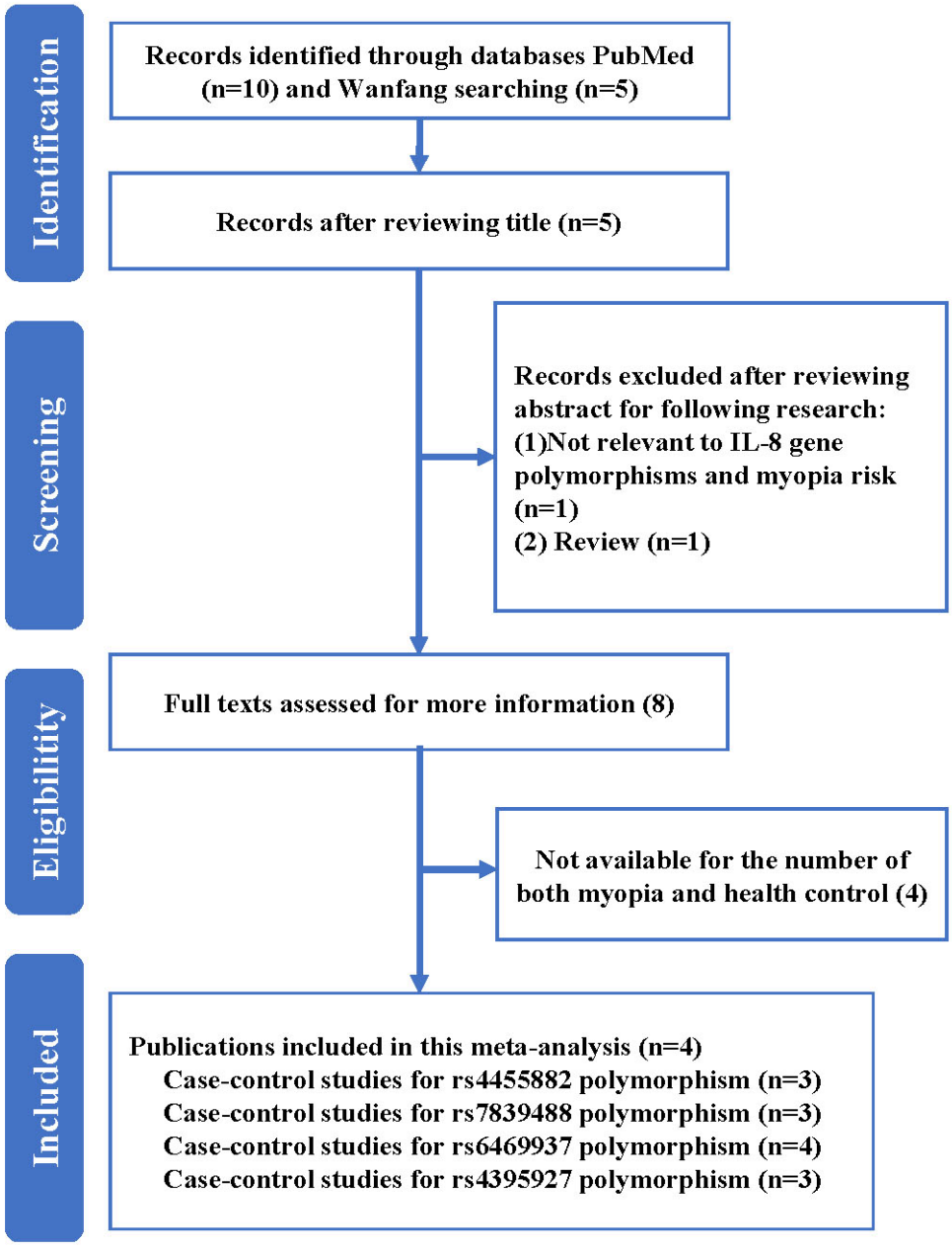

Figure 1. Five therapeutic strategies for microglia and the related research progress of each strategy.

locally in the retina. Within the retina, melatonin is involved in regulating physiologic processes such as dopamine metabolism and redox reactions, playing a crucial role in maintaining the normal function of the retina. In experimental DR, melatonin inactivates microglia by inhibiting the PI3K/Akt/Stat3/NF-κB signaling pathway, thereby preserving the integrity of the inner blood-retinal barrier (BRB) [33]. Ursodeoxycholic acid is a bile acid with significant medicinal value. As a hydrolytic product of tauroursodeoxycholic acid, it is one of the main components of bear bile. Ursodeoxycholic acid can reduce microglial activation in the retinas of diabetic mice and downregulate the expression of proinflammatory cytokines, the adhesion molecule ICAM-1, and VEGF—all of which are associated with the NF-κB–mediated inflammatory signaling pathway. These effects collectively alleviate retinal inflammation [34]. Asiatic acid, a naturally occurring pentacyclic triterpenoid, has demonstrated important roles in DR research. It modulates microglial polarization via the

TLR4/NF-κBp65 pathway and inhibits the TLR4/MyD88/NF-κBp65 signaling pathway, thereby reducing inner BRB disruption and inflammatory responses in early-stage DR. These properties make asiatic acid a potential therapeutic agent for DR [35]. Ubiquitin-specific peptidase 25 (USP25), a deubiquitinating enzyme encoded by the USP25 gene located in the 21q11.2 region of human chromosomes, belongs to the deubiquitinating enzyme family. Intracellularly, its primary function is to participate in the deubiquitination modification of proteins: by removing ubiquitin tags from proteins, it regulates protein stability, activity, and degradation, thereby playing important roles in various biological processes. In vitro studies using high glucose (HG)-stimulated HMC3 and BV2 microglial cell lines have shown that USP25 expression is significantly upregulated, with the protein primarily localized in the cytoplasm. Knocking down USP25 can inhibit microglial activation; reduce the expression of inflammatory factors; decrease the levels of ROCK1, ROCK2, phosphorylated NF-κB, and total NF-κB; and suppress the nuclear translocation of phosphorylated NF-κB. These findings indicate that USP25 is involved in regulating the inflammatory response of microglia [36].

Additionally, some drugs originally used for treating other diseases have been found to potentially exert therapeutic effects on DR. Dextromethorphan is a central antitussive that exerts its cough-suppressant effect by inhibiting the cough center in the medulla oblongata. In recent years, studies have revealed its potential therapeutic roles in other disease areas. For instance, a phase I/II clinical trial explored the efficacy of oral dextromethorphan in treating diabetic macular edema (DME), suggesting that dextromethorphan may reduce vascular leakage in DME. However, the lack of a control group limits the reliability of this conclusion. In vitro studies have shown that dextromethorphan can act directly on microglia and inhibit the NF-κB signaling pathway, thereby reducing the production of proinflammatory factors (e.g., TNF-α, IL-1β, IL-6, and NO) by microglia and exerting neuroprotective effects [37]. In the future, large-scale randomized clinical trials should be conducted, and combination therapy may be considered to optimize treatment outcomes. Meanwhile, methods to improve the retinal bioavailability of dextromethorphan could be explored—for example, coadministration with quinine sulfate. The combination of quinine sulfate and dextromethorphan can enhance the bioavailability of dextromethorphan in the CNS, as quinine sulfate inhibits the rapid first-pass metabolism of dextromethorphan, thereby achieving better therapeutic effects. Notably, this combination has already been approved for the treatment of pseudobulbar affect. In future DME trials, this coadministration strategy could be evaluated to explore the possibility of improving the retinal bioavailability of dextromethorphan, thereby optimizing therapeutic efficacy for DME (Table 1).

Upon activation, the NF-κB signaling pathway promotes the expression of inflammatory mediators such as

Table 1. Substances targeting the NF-κB pathway for microglial regulation.

Category	Name	Mechanism
Natural compounds	Kaempferol [26]	Reducing proinflammatory cytokines and preventing the nuclear translocation of p65-NF-κB
	Baicalin [27]	Reducing the activation of NF-κB and decreasing the expression of its downstream proinflammatory cytokines (e.g., TNF-α, IL-1β, and ICAM-1)
	Galangin [28]	Inhibiting the ERK1/2-ROS-NF-κB/Egr1 inflammatory signaling pathway
	Chlorogenic acid [29]	Inhibiting the NF-κB signaling pathway
	Paeoniflorin [30]	Inhibiting the TLR4 and NF-κB pathways
	Erianin [31]	Blocking the ERK1/2-NF-κB signaling pathway and reducing TNF-α
	Sesamin [32]	Reducing TNF-α secretion and inhibiting the NF-κB pathway
Endogenous substances	Melatonin [33]	Inhibiting the PI3K/Akt/Stat3/NF-κB signaling pathway
	Ursodeoxycholic acid [34]	Reducing the expression of proinflammatory cytokines, the adhesion molecule ICAM-1, and VEGF associated with the NF-κB-Mediated inflammatory signaling pathway
	Asiatic acid [35]	Inhibiting the TLR4/MyD88/NF-κBp65 signaling pathway
	Ubiquitin-specific peptidase 25 [36]	Knocking down USP25 reduces the expression of ROCK1, ROCK2, pNF-κB, and tNF-κB, and inhibits the nuclear translocation of pNF-κB
Medicine	Dextromethorphan [37]	Inhibiting the NF-κB signaling pathway and reducing the production of proinflammatory factors (e.g., TNF-α, IL-1β, IL-6, and NO) by microglia

chemokines and cytokines. These mediators interact with each other to amplify the inflammatory response. Fractalkine (FKN) is a neuron-derived chemokine. Upon binding to its receptor CX3CR1, FKN regulates microglial activation in CNS diseases and affects the neurovascular unit. Its overexpression plays important roles in neurodegeneration, the regulation of adhesive interactions, and vascular remodeling [38]; in particular, soluble FKN (sFKN) exerts a significant effect on improving retinal pathology [39]. Retinal microglia are closely associated with capillaries and neuronal synapses. Via the FKN-CX3CR1 signaling pathway, microglia can induce capillary constriction. The transcriptome of microglia contains genes encoding vasoactive factors, and this regulatory process may be mediated through the renin-angiotensin system [40]. In experimental DR, CX3CR1 deficiency exacerbates disease progression, whereas FKN exerts a protective effect on retinal neurons. Additionally, CX3CR1 deficiency disrupts microglial homeostasis, impairing their ability to synthesize and secrete sufficient insulin-like growth factor 1 to support neuronal survival and development [41]. Exogenous FKN can inhibit microglial activation and the expression of inflammation-related cytokines in the retinas of diabetic rats. It reduces neuroinflammation and ROS production by inhibiting the NF-κB pathway and activating the nuclear factor E2-related factor 2 (NRF2) pathway. Therefore, FKN may serve as a potential therapeutic agent for DR and other neuroinflammatory diseases [42].

The renin-angiotensin-aldosterone system is also associated with the activation of microglia in DR. Angiotensin II (AngII) plays an important role in retinal diseases, but little is known about its effect on the activation of retinal microglia. Phipps et al. were the first to find that retinal microglia express the angiotensin type 1 receptor (AT1-R) and that AngII can directly activate microglia via this receptor. This activation leads to morphological changes, increased secretion of inflammatory factors, and recruitment of monocytes, while reducing contact with neurons. This suggests that AT1-R antagonists may be used to regulate microglial activation and limit disease progression in DR and similar conditions [43]. Aldosterone synthase has been detected in microglia, and FAD286, an aldosterone synthase inhibitor, can reduce the mRNA levels of retinal aldosterone synthase. Since aldosterone promotes microglial activation and related inflammatory responses, FAD286 can inhibit microglial activation by blocking aldosterone synthesis, thereby interrupting this proinflammatory signaling pathway [44]. Rana et al. found that inhibiting AngII and aldosterone reduces the secretion of multiple proinflammatory and proangiogenic factors by hypoxia-activated microglia, indicating that blocking both has the potential to alleviate the harmful factors released after retinal microglial activation. However, in some respects, aldosterone inhibition is less effective than AngII inhibition [45]. Upon binding of AngII to AT1-R on zona glomerulosa cells of the adrenal cortex, a series of intracellular signaling mechanisms promotes the gene expression of aldosterone synthase, increasing the synthesis and secretion of aldosterone. Changes in aldosterone levels provide feedback regulation to the AngII/AT1-R signaling pathway. When aldosterone levels rise, it can bind to mineralocorticoid receptors (MRs), partially influencing AngII synthesis and release, as well as the expression and function of AT1-R, thus maintaining the balance of the renin-angiotensin-aldosterone system in the body [45]. Therefore, blocking MR is another way to regulate microglial cells. For example, the MR antagonist finerenone can improve retinal vascular pathology and inflammation in DR. In diabetic rats, it protects the BRB and reduces VEGF levels; in oxygen induced retinopathy (OIR) mice, it exhibits antiangiogenic effects. Its mechanism is related to reducing microglia/macrophages and proinflammatory mediators, while increasing $Foxp3^+$ regulatory T cells (Tregs). $Foxp3^+$ Tregs may migrate to the retina and interact with microglia to alleviate inflammation [46]. In OIR models, increasing the number of $Foxp3^+$ Tregs has been shown to alter the activation state of retinal microglia, reducing the expression of costimulatory molecules on their surface, such as CD86, and decreasing the release of proinflammatory and proangiogenic factors like TNF-α and IL-6. The molecular mechanism may involve CTLA-4 [47]. CTLA-4 is an immune checkpoint protein belonging to the immunoglobulin superfamily, primarily expressed on activated T cells. It shares high homology with CD28 and competitively binds to B7 molecules (B7–1 and B7–2) on antigen-presenting cells. Compared to CD28, CTLA-4 has a higher affinity for B7 molecules. Upon binding to B7, CTLA-4 transmits inhibitory signals that suppress T-cell activation, proliferation, and cytokine secretion, thereby downregulating immune responses to prevent excessive immune damage and playing a crucial role in maintaining immune homeostasis. Studies show that blocking CTLA-4 partially weakens the suppressive effect of Tregs on retinal microglial activation, manifested by a reduced decrease in expression of microglial surface costimulatory molecules CD40, CD80, CD86, and activation marker CD11b, as well as a smaller reduction in proinflammatory and proangiogenic factors such as TNF-α and IL-6. This indicates that CTLA-4 plays a key role in Tregs' inhibition of retinal microglial activation. Tregs may bind to corresponding ligands on microglia through CTLA-4, transmitting inhibitory signals and thereby regulating microglial function [47]. Therefore, inhibiting AngII production or blocking its binding to AT1-R, using MR antagonists, enhancing $Foxp3^+$

Tregs, and blocking CTLA-4 all hold promise as effective new therapeutic approaches for the treatment of blinding neovascular retinal diseases such as retinopathy of prematurity, DR, and age-related macular degeneration.

In contrast to the aforementioned proinflammatory substances and pathways, adenosine can inhibit the activation of immune cells and downregulate inflammatory responses. Adenosine is an important purine nucleoside that regulates various physiologic processes through four types of G protein-coupled receptors (A1R, A2AR, A2BR, and A3R) [48]. In the retina, different cells express different adenosine receptors, and the signaling functions of each receptor vary. A1R is widely expressed in various retinal cells and has a protective effect on neurons; A2AR is mainly expressed in retinal microglia, retinal pigment epithelium cells, and vascular endothelial cells. In microglia, its activation exerts a bidirectional regulatory effect on the release of inflammatory factors. Agonists (e.g., CGS21680) can inhibit the release of proinflammatory factors (TNF-α, IL-1β) and alleviate neuroinflammation; however, under pathological conditions such as high intraocular pressure, antagonists (e.g., SCH58261, ZM241385) can also inhibit microglial activation and reduce retinal ganglion cell (RGC) death [48]. Adenosine levels are regulated by various enzymes (e.g., nucleotide-degrading enzymes, adenosine kinase, adenosine deaminase) and transporters (e.g., equilibrative nucleoside transporters, concentrative nucleoside transporters). The balance of intracellular and extracellular adenosine levels is crucial for maintaining normal retinal function [49]. Under diabetic conditions, the expression and density of A1R, A2AR, A2BR, and A3R in the retina change, and these changes vary with the duration of diabetes. Enzymes involved in the regulation of adenosine levels (e.g., nucleoside triphosphate diphosphohydrolase, adenosine deaminase, adenosine kinase) also show sensitivity in diabetic retinas, with their activity or expression levels affected, leading to changes in extracellular adenosine levels [49]. Cannabidiol (CBD) is a nonpsychoactive and nontoxic compound that has been shown to prevent diabetes- and endotoxin-induced retinal damage. Studies have for the first time demonstrated that in the retina, CBD inhibits adenosine uptake and increases the binding of endogenous adenosine to its receptors, thereby inhibiting TNF-α production and exerting anti-inflammatory effects. Additionally, CBD may reduce inflammation through other pathways, such as scavenging ROS, and its enhancement of adenosine's inhibitory effect on TNF-α is mediated by A2AR [50]. As a nonpsychoactive and nontoxic anti-inflammatory drug, CBD has significant advantages over marijuana smoking and great potential in the treatment of inflammation [51]. However, like other adenosine transporter inhibitors, long-term use of CBD may lead to tolerance issues [52]. Therefore, in-depth research on the impact of long-term CBD use on adenosine receptors is crucial, which will help comprehensively evaluate its feasibility and safety in clinical applications and provide important references for future drug development and clinical treatment [50]. In addition, studies have explored intravitreal injection of the A2AR antagonist SCH58261, finding that A2AR antagonist treatment significantly reduces the proportion of reactive microglia without significantly affecting the total number of microglia. Furthermore, detection of translocator protein (TSPO) levels revealed that diabetes increases TSPO protein levels, while A2AR antagonist treatment can restore them to normal levels, further confirming the regulatory effect of this antagonist on microglial reactivity [53]. ABT-702, an adenosine kinase inhibitor, can significantly inhibit the mRNA and protein expression levels of ICAM-1 and TNF-α in the retinas of diabetic mice. It inhibits the upregulation of A2AR and equilibrative nucleoside transporter 1, as well as prevents the downregulation of adenosine kinase in the retinas of diabetic mice. It also reduces the expression of the microglial activation marker Iba1 in the retinas of diabetic mice. In in vitro experiments with cultured retinal microglia, ABT-702 can inhibit Amadori-glycated albumin–induced TNF-α release, and its effect is more significant than that of the adenosine deaminase inhibitor erythro-9-(2-hydroxy-3-nonyl) adenine [54]. However, some research results are contradictory. In diabetic rats, adenosine can prevent osmotic swelling of glial cells by activating A1R [55]; in cultured retinal microglia, activation of A2AR can block inflammatory responses [56]. In DR research, A2AR is closely related to adenosine deaminase 2 (ADA2), and their interaction jointly affects the inflammatory state and disease progression of the retina. ADA2 can influence A2AR function by regulating adenosine metabolism. In a diabetic environment, the expression and activity of ADA2 increase, as observed in Amadori-glycated albumin–treated cells or samples from diabetic patients. ADA2 accelerates the conversion of adenosine to inosine, resulting in a decrease in extracellular adenosine concentration. Since extracellular adenosine is a key ligand for activating A2AR and initiating its anti-inflammatory signaling pathway, enhanced ADA2 activity weakens the anti-inflammatory effect mediated by A2AR, making the retina more prone to inflammatory reactions and promoting the development of DR [57]. These results indicate that the role of adenosine in DR is not unique, and its impact on the retina may depend on the target receptor, cell type, and experimental method [58]. It is worth noting that although regulatory strategies targeting adenosine receptors have achieved positive results in laboratory research, many challenges need to be overcome before these findings can

be translated into clinical treatments—for example, how to precisely regulate the expression and function of adenosine receptors to avoid potential side effects, how to determine the optimal drug dosage and treatment time window to ensure maximum therapeutic effect, and how to evaluate the safety and effectiveness of these strategies in long-term treatment. Therefore, future research should further explore the specific mechanisms of adenosine receptors and their related pathways in DR, as well as combine advanced biotechnology and clinical trials to continuously optimize treatment strategies, aiming to bring more effective treatment options to patients.

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted by intestinal L cells. In the field of diabetes treatment, GLP-1 is an important drug target. Because it can promote insulin secretion and only functions when blood glucose is elevated, thus avoiding the risk of hypoglycemia, drugs developed based on GLP-1, such as GLP-1 receptor agonists, have been widely used in the treatment of type 2 diabetes. In the BV2 microglial cell line, the GLP-1 analogue exendin 4 activates GLP-1R and promotes the production of cAMP and the phosphorylation of CREB; it can also inhibit the lipopolysaccharide (LPS)–induced increase in mRNA expression of IL-1β, IL-6, CCL2, NOS2, and so on, as well as the nuclear accumulation of NF-κBp65. Studies have shown that exendin 4 can prevent BRB disruption and inflammation caused by ischemia-reperfusion injury by inhibiting microglial activation and inflammatory responses [59]. Liraglutide is a drug commonly used in the treatment of diabetes and is a GLP-1 analog. Systemic administration of liraglutide can reduce blood glucose in db/db mice and alleviate glial cell activation and retinal cell apoptosis. Local administration of liraglutide, native GLP-1, lixisenatide, and exenatide eye drops can prevent diabetes-induced glial cell activation and apoptosis. In conclusion, GLP-1R agonists can prevent retinal neurodegeneration independently of hypoglycemic effects, and local application of GLP-1R agonists is expected to become a new method for early treatment of DR, but it needs to be verified by clinical trials [60,61]. In addition, linagliptin, used for the treatment of type 2 diabetes, increases the level of active GLP-1 in the body by inhibiting the activity of dipeptidyl peptidase 4. A study on diabetic rats found that in a hyperglycemic environment, the number of Iba-1–positive microglia in the retinal surface layer increased by 78%, while linagliptin treatment reduced this increase by 73%, making it close to the normal state. This indicates that linagliptin has an inhibitory effect on the activation of microglia in DR, and its mechanism may be related to indirectly increasing GLP-1 levels, reducing oxidative stress and methylglyoxal, and decreasing IL-1β expression [62]. To sum up, GLP-1 and its analogues in diabetes treatment not only control blood glucose by promoting insulin secretion but also show potential in reducing inflammatory responses, protecting retinal nerve cells, and preventing DR. These findings suggest that GLP-1R agonists may become pleiotropic drugs for the treatment of diabetes and its complications.

In addition, in recent years, the role of noncoding RNA in regulating microglial activation and inflammatory responses has also received extensive attention. In DR, some miRNAs such as miR-124, miR-200b, miR-146, miR-155, and miR-21 have been abnormally expressed and are related to key factors such as VEGF, NF-κB, and hypoxia-inducible factor 1, participating in the regulation of retinal microvascular damage, cell proliferation, apoptosis, and inflammatory responses [63].

MiR-124, one of the abundant miRNAs in the CNS and retina, is involved in regulating processes such as physiologic neurogenesis and neuronal development. It can modulate microglial responses in neurodegenerative and inflammatory diseases [64]. In DR, miR-124 exerts significant and complex effects on microglia. It can inhibit microglial inflammatory responses, normalize the upregulated inflammatory mediators in the retinas of diabetic rats, and prevent inflammatory damage; it can restrict microglial migration under HG conditions to maintain the stability of the retinal microenvironment; it also regulates microglial functions by downregulating the expression of PU.1 and Flot1. PU.1 is associated with microglial activation, and reduced expression of PU.1 can inhibit microglial activity. Flot1 plays an important role in vesicle transport and signal transduction, and its abnormality can hinder signal conduction. The regulation of these targets by miR-124 affects microglial functions [6]. Long noncoding RNAs can act as competing endogenous RNAs to regulate gene expression by competitively binding to miRNAs. Taking MALAT1 as an example, bioinformatics analysis and experimental verification have shown that MALAT1 contains binding sites for miR-124 and can directly bind to miR-124. In retinal cells, overexpression of MALAT1 downregulates miR-124 expression, while knockdown of MALAT1 leads to increased miR-124 levels. Moreover, MALAT1 indirectly regulates the expression of MCP-1 by "sponging" miR-124. When MALAT1 is knocked down, the inhibitory effect of miR-124 on MCP-1 is enhanced, resulting in decreased MCP-1 expression; conversely, overexpression of MALAT1 weakens the inhibitory effect of miR-124 on MCP-1, leading to increased MCP-1 expression, thereby affecting the inflammatory process of DR [65]. The development of specific inhibitors targeting MALAT1 or miR-124 mimics is of great significance for the treatment of DR.

Circular RNA (circRNA) is a significant type of noncoding RNA, forming a unique closed and continuous

circular structure through the splicing of linear precursor mRNA. It is extensively involved in regulating various cellular biological processes, including cell proliferation and differentiation. In terms of diseases, recent studies have found that its abnormal expression can lead to the progression of inflammatory diseases. For example, in DR, circRNA-ZNF532 is upregulated in DR pericytes, resulting in retinal microangiopathy [66]; the expression of circRNA DNMT3B is decreased in retinal microvascular endothelial cells, contributing to diabetic retinal vascular dysfunction [67]. Ying Chen and colleagues performed circRNA sequencing on BV2 mouse microglia treated with glucose and identified 347 differentially expressed circRNAs. Among them, mm9_circ_014683 showed increased expression after glucose stimulation and was mainly located in the cytoplasm, and its expression level rose with the increase in glucose concentration. It was elevated after M1 polarization and decreased after M2 polarization. Further studies indicated that mm9_circ_014683 can promote M1 polarization of microglia, inhibit M2 polarization, and positively regulate the classical NF-κB signaling pathway. It plays an important role in the pathogenesis of DR and may become a therapeutic target for DR [6].

In conclusion, various substances have demonstrated potential therapeutic effects in treating eye diseases. These substances exert a positive influence on DR and other ocular conditions through diverse mechanisms. However, these studies remain in the preliminary stages and necessitate additional clinical trials and research to confirm their safety and efficacy, with the goal of offering new strategies and methods for the treatment of eye diseases.

Antioxidant stress intervention: The hyperglycemic state in diabetes can cause mitochondria to produce excessive superoxide and enhance the flux of the polyol, hexosamine, and PKC pathways, leading to an increase in ROS and triggering oxidative stress responses [68]. This oxidative stress environment can activate microglia, causing them to release more inflammatory factors, forming a vicious cycle between oxidative stress and inflammatory responses, and exacerbating retinal tissue damage [69]. Activated microglia themselves can also generate large amounts of ROS due to the activation of NADPH oxidase (NOX), mitochondrial dysfunction, or abnormal opening of channels formed by connexins and pannexins (hemichannels and pannexon channels), further increasing the level of oxidative stress [69]. ROS not only directly cause oxidative damage to retinal cells but also can activate signaling pathways such as NF-κB, upregulate the expression of inflammatory factors, promote the continuous development of inflammatory responses, and induce endothelial cells to express adhesion molecules, thereby promoting leukocyte adhesion and aggravating vascular inflammation and damage [70].

The NOX system is a major source of ROS in microglia, regulating metabolic reprogramming and inflammatory responses through ROS signaling [71]. The NOX family includes seven isomers: NOX1, NOX2, NOX3, NOX4, NOX5, Duox1, and Duox2 [72]. Among them, NOX2 activates the AKT/MAPK pathway by generating ROS and promoting glycolysis and the secretion of proinflammatory factors, leading to microvascular dysfunction (e.g., increased vascular permeability and endothelial cell senescence) [73]; NOX4 promotes retinal neovascularization through the H_2O_2/VEGFR2/ERK pathway, participating in proliferative diabetic retinopathy (PDR) [74]; NOX1 damages mitochondria in retinal endothelial cells under HG conditions, triggering metabolic memory and driving the progression of DR [75]. The thioredoxin (TRX) system is an important antioxidant system, consisting of TRX, thioredoxin reductase, and peroxiredoxin. It can regulate cellular redox status and resist oxidative stress [76]. Thioredoxin-interacting protein (TXNIP) is an endogenous inhibitor of the TRX system, which is upregulated in DR. It may induce microglia to release the proinflammatory mediator IL-1β by activating the NLRP3 inflammasome, and targeting TXNIP may improve DR symptoms [77]. NRF2 is a key transcription factor that regulates the cellular antioxidant defense system and plays an important role in responding to hyperglycemia. Under normal conditions, it binds to Kelch-like ECH-associated protein 1 (KEAP1) in the cytoplasm; during oxidative stress, it dissociates from KEAP1 and enters the nucleus to regulate the expression of various antioxidant genes [78]. In DR, the redox-sensing ability of KEAP1 is altered, affecting NRF2 activity and leading to reduced glutathione (GSH) synthesis. Targeting NRF2/KEAP1/GCL/GSH signaling may correct the decrease in GSH levels in DR. In the early stage of DR, NOX2 is highly active in M1-type microglia. It inhibits phosphatase and tensin homolog by generating H_2O_2, activates the AKT signaling pathway, promotes glucose uptake and glycolysis, and simultaneously activates the MAPK cascade reaction to release proinflammatory mediators. H_2O_2 can also activate hypoxia-inducible factor 1α, further promoting the expression of glycolysis-related genes and exacerbating retinal vascular inflammation and nerve damage. When the disease progresses to the middle and advanced stages, microglia switch to the M2 type. The tricarboxylic acid cycle product citrate is isomerized to produce itaconate, which can activate NRF2, inhibit NF-κB, and reduce the production of proinflammatory mediators. At the same time, the TRX system is activated, improving the efficiency of oxidative

phosphorylation and inhibiting glycolysis. These characteristics of M2-type microglia are beneficial for the treatment of DR [79].

To address the damage caused by oxidative stress to retinal microglia, we can explore therapeutic strategies for DR from the following aspects. For NOX system inhibitors, Jiao et al. used GKT137831 to inhibit the activity of NOX4. Experimental results showed that after treating cells with GKT137831, compared with the HG group, intracellular ROS levels, cell death, and caspase 3 activity were significantly inhibited. This indicates that NOX4 plays a key role in HG-induced damage to human retinal endothelial cells, and the inhibition of NOX4 by GKT137831 can alleviate related damaging effects [80]. It has been reported that another novel NOX inhibitor, GLX7013114, has improved pharmacological properties in terms of efficacy and specificity for inhibiting NOX4. As a new type of NOX4 inhibitor, GLX7013114, administered via local eye drops, can effectively treat early pathological events of DR, including oxidative stress, neuronal damage, neuroinflammation, and vascular lesions. It has neuroprotective, anti-inflammatory, and vascular protective properties and is expected to become a new candidate drug for early DR treatment, but further preclinical studies are still needed for verification [81]. Diphenyleneiodonium can inhibit excessive ROS production in pericytes induced by microglia in a coculture system of LPS-activated microglia and retinal pericytes, reduce pericyte apoptosis, and thus protect retinal microvessels [82]. As a NOX inhibitor, apocynin can inhibit the activity of NOX (especially NOX2 and NOX4) in the retina and reduce the production of ROS, such as superoxide, thereby alleviating oxidative stress–induced damage to retinal cells [83]. As a potential therapeutic target for diabetic microvascular complications, existing studies have shown that various drugs, specific inhibitors, and natural food components can reduce oxidative stress and tissue damage by inhibiting NOX activity or expression [84]. In TRX system agonists, TXNIP mainly exerts its effect by inhibiting TRX activity. In diabetes and insulin resistance, hyperglycemia induces its overexpression, making cells vulnerable to oxidative stress and apoptosis [85]. Verapamil is a type of calcium channel blocker that can inhibit TXNIP expression in pancreatic β cells and cardiomyocytes. In animal experiments and clinical studies, it has been shown to improve insulin sensitivity, promote β-cell survival, improve glucose homeostasis, and also have beneficial effects on complications such as DR, neuropathy, and nonalcoholic fatty liver disease. Moreover, it has positive significance in the treatment of hypertensive patients with diabetes [77,85]. For NRF2 pathway agonists, in studies on diabetes-induced vascular lesions, the NRF2 activator dh404 can improve endothelial dysfunction in diabetic mice. In the diabetic Akita mouse model, after dh404 activated NRF2, it reduced the vascular contractile response to phenylephrine, decreased the expression of inflammatory genes (e.g., VCAM-1, ICAM-1, p65, IL-1β) and pro-oxidant genes (e.g., NOX1, NOX2), and lowered systemic and vascular oxidative stress levels. In in vitro cultured human aortic endothelial cells derived from diabetic patients, dh404 can also upregulate the NRF2-responsive genes NQO1 and HO-1, reduce the expression of oxidative stress markers and inflammatory genes, and weaken leukocyte–endothelial cell interactions. This indicates that NRF2 plays an important role in the prevention and treatment of diabetic vascular complications. Activating NRF2 may become a new strategy to improve diabetes-related endothelial dysfunction and prevent diabetic complications. However, due to its complex role in cardiovascular diseases (e.g., controversies in atherosclerosis), factors such as dosage need to be carefully considered when regulating its activity with drugs [86]. Curcumin, the main monomer component in the rhizome of *Curcuma longa*, has various biological activities with few side effects. It is one of the activators of NRF2 and has potential therapeutic effects on various oxidative stress–related diseases, including DR [87], which is worthy of further research.

It is worth noting that although these antioxidants and small-molecule compounds have shown inhibitory effects on oxidative stress–related microglial activation in in vitro and animal models, caution is required in their clinical application. This is because the physiologic environment and pathological conditions in the human body are far more complex than those in in vitro models and animal models, and the efficacy and safety of drugs need to be verified in strictly controlled clinical trials. Therefore, future research should pay more attention to evaluating the efficacy and safety of these antioxidants and small-molecule compounds in clinical applications, so as to provide strong support for the development of effective therapeutic strategies targeting microglia in DR.

Regulation of microglial phenotypes: Microglia play a complex role in DR, and the regulation of their phenotypes has become a key strategy for treating DR [88]. Hyperglycemia can directly activate the JNK and ERK signaling pathways in microglia. Phosphorylated JNK/ERK further promotes the nuclear translocation of NF-κB. As a core transcription factor for M1 polarization, NF-κB can bind to the gene promoter regions of proinflammatory factors such as TNF-α and IL-1β, drive their transcription and release, and ultimately induce the conversion of microglia to the M1 phenotype [89]. By targeting and regulating signaling pathways, adjusting metabolic status, and inhibiting the release

of proinflammatory factors, microglia can be promoted to transform into the M2 type (anti-inflammatory type), thereby controlling inflammatory responses and oxidative stress at the source and alleviating retinal damage [89]. Therefore, the regulation of microglial phenotypes provides new ideas and methods for the treatment of DR.

Studies have found that mesenchymal stem/stromal cells (MSCs) can reverse the imbalance between M1 and M2 phenotypes, promote M2 polarization, inhibit the release of inflammatory factors, and enhance the secretion of anti-inflammatory factors. In both in vitro and in vivo experiments, MSCs reduce the expression of proinflammatory factors such as TNF-α, MCP-1, and IL-6, as well as M1 markers, including inducible nitric oxide synthase (iNOS) and CD16, while increasing the expression of anti-inflammatory factors, such as TGF-β1, IL-4, and IL-10, along with M2 markers such as Arg-1 and CD206 [90]. MSC transplantation has shown therapeutic effects in various inflammatory diseases; however, direct MSC transplantation faces issues such as low stem cell survival rate and immune rejection. Future research needs to explore their paracrine effects to optimize treatment. In addition to MSCs, the natural compound Schisandrin B has also been found to regulate microglial phenotypes. As the main active component of *Schisandra chinensis* extract, Schisandrin B can reverse LPS-induced M1 polarization of BV2 microglia (reducing markers such as iNOS, TNF-α, and IBA-1) and promote M2 polarization (increasing markers such as IL-10 and Arg-1) by upregulating miR-124 and inhibiting the NF-κB/TLR4/MyD88 signaling pathway and MAPK signaling pathway (especially p38 phosphorylation). This restores the M1/M2 balance, thereby alleviating neuroinflammation [91]. Furthermore, a recombinant protein drug modified with polyethylene glycol (PEG), pegylated arginase 1 (PEG-Arg1), plays an important role in microglial phenotype switching. PEG-Arg1 exerts therapeutic effects on DR through mechanisms such as regulating macrophage/microglial polarization by reducing iNOS expression and increasing polyamine production, as well as inhibiting the mTORC pathway [92]. Both Arg1 and iNOS use L-arginine as a substrate [93]. Arg1 hydrolyzes L-arginine to produce urea and L-ornithine; when Arg1 activity is relatively insufficient, iNOS activity increases. Under normal physiologic conditions, the activities of these two enzymes are balanced. However, this balance is disrupted under pathological conditions. In DR, macrophages and microglia are activated, leading to upregulated iNOS expression, which consumes large amounts of L-arginine to produce reactive substances such as NO, thereby exacerbating oxidative stress and inflammatory responses [94]. Systemic administration of PEG-Arg1 significantly inhibited the increase in the cell body size of Iba1-positive perivascular macrophages/microglia, indicating that their phenotype was reversed from a proinflammatory phenotype to a reparative phenotype, which can alleviate the progression of DR. The key role of the interaction between Arg1 and iNOS in DR suggests that regulating their competitive relationship for L-arginine can interfere with disease progression. The metabolic balance of L-arginine has an important impact on retinal inflammation and oxidative stress, providing potential targets for the development of new therapeutic drugs. Future research can delve deeper into these mechanisms to identify more potential therapeutic intervention points, such as exploring how to more precisely regulate the polarization state of macrophages/microglia to reduce retinal inflammation.

Regulation of intercellular interactions: Inflammatory responses are not limited to microglia themselves; they can also activate other glial cells. For example, inflammatory factors released by activated microglia can induce reactions in Müller cells, prompting them to release more inflammatory mediators. This exacerbates neuroinflammatory responses, forming a vicious cycle that sustains inflammation and continuously aggravates damage to retinal tissues [95].

Regulation of the interaction between Müller cells and microglia: There is a synergistic interaction between microglia and other glial cells, such as astrocytes and Müller cells. For example, in DR, Müller cells secrete exosomes containing long noncoding RNA OGRU, which are delivered to microglia. OGRU binds to miR-320–3p, miR-221–3p, and miR-574–5p in the form of competing endogenous RNA, regulating the expression of AR, PFKFB3, and GLUT1 in microglia, respectively. This further promotes the polarization of microglia toward the M1 proinflammatory phenotype and participates in the pathological process of DR [96]. Inhibiting the release of harmful inflammatory factors by microglia can reduce Müller cell gliosis [97]. In vitro coculture experiments have shown that under hypoxic conditions, there is a significant interaction between Müller cells and microglia. Compared with separate cultures, coculture results in increased production of NGF by microglia, altered expression of TSPO and IL-1β, and changes in the polarization state of microglia, with a decrease in M1-polarized cells and an increase in M2-polarized cells. This indicates that Müller cells can regulate the function and phenotype of microglia, and there is a direct interaction network between them, which jointly participates in the regulation of the retinal microenvironment [98]. Moreover, the DBI-TSPO signaling pathway plays a key connecting role between Müller cells and microglia. DBI secreted by Müller cells can act on microglia through TSPO, affecting their inflammatory state

and neuroprotective function, inducing microglial responses related to neuroprotection and anti-inflammation, and promoting their M2 polarization [98]. This suggests that this signaling pathway is one of the important mechanisms by which the Müller–microglia network functions in the process of retinal pathology, reflecting the existence and function of the network at the molecular signaling level. In the progression of retinal pathology in diabetic Ins2 mice, the PEDF derivative PEDF78–121 can prevent microglial activation and the loss of RGCs. This neuroprotective effect is related to the upstream anti-inflammatory mechanism and the regulation of vascular signals in Müller glial cells [99]. This indicates that the activation of microglia affects the subsequent development of the disease, including vascular function and neuronal survival, through interaction with Müller glial cells.

Regulation of the interaction between pericytes and microglia: Pericytes exert a significant influence on the recruitment, activation, and function of microglia through active secretion of inflammatory mediators, participation in immune regulation, and indirect modification of the microenvironment. This interaction plays a key role in the progression of neuroinflammation in DR [100,101]. As a STAT3 inhibitor, Stattic can directly suppress IL-1β–induced activation of STAT3 in pericytes, thereby reducing the secretion of proinflammatory factors and chemokines by pericytes, which in turn weakens the recruitment and activation of microglia and ultimately alleviates retinal inflammation [102]. β-Adrenergic receptor agonists exert a prosurvival effect on pericytes by activating Akt in them, reducing the inflammatory signals released by pericytes due to injury or apoptosis, and thus mitigating inflammatory responses such as microglial activation [103]. In addition, fenofibrate, a peroxisome proliferator–activated receptor α agonist, has been found to reduce pericyte depletion in DR, improve the formation of acellular capillaries in the retina, and lower inflammatory responses by maintaining pericyte function [104,105]. Retinal pericytes possess multidirectional differentiation potential similar to mesenchymal stem cells. Transplantation of adipose tissue–derived pericytes can protect the retina by maintaining vascular support function, reducing inflammation and vascular lesions caused by pericyte loss, and providing a new direction for the treatment of inflammation in DR [106]. Pericyte loss is a core link in the breakdown of the BRB, increased vascular permeability, and exacerbated inflammation in DR [107]. Studies have shown that the 60% ethanol extract of *Ulmus davidiana* (U60E) and its main component, catechin 7-O-β-D-apiofuranoside (C7A), can prevent HG- and TNF-α–induced pericyte apoptosis by inhibiting the activation of p38 and JNK in DR, thereby restoring the expression of the endothelial tight junction protein ZO-1 and reducing endothelial permeability [108]. Activation of the p38 and JNK pathways can prompt microglia to release inflammatory factors, triggering neuroinflammation [109]. U60E and C7A can indirectly affect the activation state of microglia and the release of inflammatory factors by inhibiting the p38 and JNK pathways, thereby regulating the function of microglia. Therefore, protecting retinal pericytes helps restore the stable state of the BRB and ameliorate the adverse effects caused by microglial activation [107]. The activation of microglia also has a significant impact on pericytes. Somatostatin is an important neuroprotective factor synthesized in the retina. In the inflammatory environment mediated by microglia, somatostatin can reverse the increased expression of pericyte apoptosis–related molecules (e.g., normalizing the expression of FasL, active caspase-8, tBid) and restore the expression of survival-related factors (e.g., BclxL and pAkt), thereby correcting the imbalance between pericyte apoptosis and survival signals, alleviating pericyte damage and subsequent inflammatory amplification effects. This indicates that somatostatin can affect the communication between microglia and pericytes [110]. The drug-free peptidyl nanohybrid (P12) is modified with gold nanoparticles and hexapeptide. In DR mice, it can be efficiently delivered to the retina through intravitreal injection and is mainly taken up by microglia and endothelial cells. By inhibiting the NF-κB, JNK, and P38 MAPK signaling pathways downstream of TLR4, it reduces the release of inflammatory factors (e.g., IL-1β, IL-6) and adhesion molecules (e.g., ICAM-1, VCAM-1) and blocks the endosomal acidification process, thereby improving vascular leakage and pericyte loss in STZ-induced diabetic mice [111]. In conclusion, in-depth analysis of the interaction mechanism between microglia and pericytes will open up new avenues for the treatment of DR and provide an important reference for understanding the common mechanisms of neurodegenerative and inflammation-related diseases.

Influencing the communication between neurons and microglia: Microglia maintain a close bidirectional communication relationship with neurons [112]. In DR, neuronal stress can activate microglia to release inflammatory factors such as TNF-α. These inflammatory factors can induce Müller cells to produce VEGF, indirectly triggering pathological angiogenesis [113,114]; meanwhile, the inflammatory factors released by microglia can also affect neuronal functions, interfere with the normal electrical activity and signal transmission of neurons, further disrupt the balance of the neurovascular unit, and promote the occurrence and development of DR [114]. Lysophosphatidylserine (LysoPS), a lysophospholipid formed by the action of phosphatidylserine phospholipase A on the membranes of activated or apoptotic cells, is mainly released by damaged or apoptotic cells [115].

In the retina, ganglion cells release LysoPS when damaged. LysoPS interacts with the GPR34 receptor on microglia; activates the GPR34-PI3K-AKT-NINJ1 signaling axis; upregulates the expression of inflammatory cytokines such as IL-6, IL-8, VEGFA, and fibroblast growth factor 2; and promotes angiogenesis in retinal vascular endothelial cells [116]. Therefore, research on ganglion cell–derived LysoPS and its related signaling pathways, such as the development of drugs targeting LysoPS receptors or signaling pathways, may provide new targets and strategies for the treatment of retinal vascular diseases. In addition, GSK-3β inhibitors (e.g., ginsenoside Rg1 [117], liraglutide [118]) can inhibit abnormally activated GSK-3β in RGCs and reduce excessive phosphorylation of tau protein and degradation of β-catenin, thereby improving mitochondrial function and synaptic integrity of RGCs, as well as alleviating damage and degeneration of RGCs [117,119,120]. The alleviation of RGC damage will reduce the release of damage-associated molecular patterns (e.g., cell debris, inflammatory signals), thereby reducing the activation stimulus to microglia, decreasing the levels of proinflammatory factors (e.g., TNF-α, IL-1β) and ROS secreted by microglia, and indirectly inhibition of the excessive activation of phagocytosis in microglia and their damage to the neurovascular unit [121]. Therefore, the functional state of microglia can be affected by regulating the signal molecules released by neurons, inhibiting their excessive activation, and thus protecting the retina from damage [122].

Inhibition of the excessive activation of phagocytosis in microglia: The phagocytic function of microglia relies on specific cell surface receptors and downstream signaling pathways, mainly including TLRs, TREM-2, and P2Y6 [123]. TLRs can recognize pathogen-associated molecular patterns and damage-associated molecular patterns, as well as regulate phagocytosis through MyD88-dependent and MyD88-independent pathways. TREM-2 is a polyanionic pattern receptor, primarily located on the surface of microglia in the CNS and osteoclasts in bones. TREM-2 binds to DAP12 to mediate the clearance of apoptotic neurons and inhibit inflammatory responses. P2Y6, a member of the G protein-coupled receptor family, is activated by nucleotides such as uridine diphosphate and triggers phagocytosis-related signaling pathways to promote the phagocytosis of cellular debris. It is crucial to study specific drugs that inhibit the excessive phagocytic activity of microglia, preventing their overphagocytosis of neurons and synapses and thereby protecting retinal neural function.

In experiments with BV2 cells and primary mouse microglia, activation by LPS increases the number of phagocytic cells. However, pretreatment with GLP can significantly reduce the incidence of phagocytic events. A concentration of 1 μg/ml GLP shows a marked inhibitory effect on BV2 cells, while 0.1 μg/ml GLP is effective for primary microglia, indicating that GLP can efficiently suppress excessive phagocytosis [124]. Lehrman et al. found that in the retinal-geniculate system, CD47 is enriched during the peak pruning period (postnatal day 5 and postnatal day 10) in the dorsolateral geniculate nucleus of the thalamus and colocalizes with RGC synaptic markers, suggesting its involvement in regulation at critical stages and locations. In vitro experiments confirmed that neuronal CD47 interacts with microglial SIRPα, and CD47 can act as an instructive signal to regulate microglial phagocytosis of different synapses. This indicates that the CD47-SIRPα signaling pathway plays a key role in inhibiting excessive pruning, preventing microglia from overphagocytosing synapses [125]. Erythropoietin (EPO) is a glycoprotein with important physiologic functions, playing a key role in erythropoiesis and various disease processes. Studies have found that compared with a normal oxygen environment, hypoxia leads to a significant reduction in the phosphorylation levels of Src, Akt, and cofilin in the Src/Akt/cofilin signaling pathway. EPO can reverse this trend, indicating that it can activate the Src/Akt/cofilin signaling pathway and thereby exert a key regulatory effect on microglial phagocytosis. Further experimental verification showed that after treating cells with Src and Akt activators, the ratios of p-Akt/actin and p-cofilin/actin were significantly increased compared with untreated hypoxic cells, and the phagocytic activity of microglia was significantly reduced. This fully confirms the central role of this signaling pathway in microglial phagocytosis [126]. Although EPO has been clinically used to treat anemia and has neuroactive properties, its application in treating CNS and peripheral nervous system diseases is limited due to issues such as its large molecular weight and erythropoiesis-promoting activity [127]. Nanoparticle-formulated EPO and neuro-EPO may have better blood-brain barrier penetration or more targeted neuroprotective effects, thereby improving the therapeutic efficacy for neurologic diseases. In summary, microglial phagocytosis is crucial in CNS diseases and is regulated by various receptors and environmental factors. Although the specific mechanisms require further investigation, regulating phagocytosis may become a potential therapeutic strategy for retinal pathologies. Drugs or biologic agents targeting relevant receptors or signaling pathways can be developed to enhance or inhibit microglial phagocytosis for treating different neurologic diseases (e.g., promoting efficient clearance of pathogenic proteins by microglia in neurodegenerative diseases and inhibiting tissue damage caused by overactive microglial phagocytosis in inflammatory diseases). In addition, regulating microglial

functions using gene editing technology or cell therapy also has potential research and application value.

Summary and future perspectives: Exploring the therapeutic strategies targeting microglia in DR has revealed the complex interactions between microglial activation and the retinal neurovascular unit. It is evident that numerous compounds exhibit multiple biologic activities such as anti-inflammation, antioxidation, and regulation of microglial polarization. The classification in this study aims to deepen the understanding of the strategies targeting microglia, rather than intending to provide a strict functional definition. Although the crucial role of microglia in the pathogenesis of DR has been fully recognized, several key gaps and challenges in this field require further research. For instance, the majority of contemporary literature concentrates on the dichotomy between the M1 and M2 microglial states. While this binary classification offers a simplified framework for understanding microglial functions, it fails to encompass the full spectrum of microglial phenotypes and their dynamic responses to the retinal microenvironment. This oversimplification may obscure the subtle roles played by microglia at different stages of DR and under different metabolic conditions. The functions of microglia are directional, and drugs that inhibit or activate microglia without targeting specificity cannot fully repair the retinal damage caused by microglia. Therefore, developing targeted drugs is the primary principle for inhibiting the damage caused by microglia. Another unresolved issue is the long-term impact of regulating microglial activity on retinal health. Although shifting microglial polarization toward the M2 phenotype shows promise in reducing inflammation and promoting neuroprotection, the chronic inhibition of the M1 phenotype raises concerns about potential unintended consequences, such as impaired immune surveillance and response. Therefore, future research should aim to develop strategies to achieve a more balanced regulation of microglial activity, maintaining their protective functions while mitigating their harmful effects. Moreover, the complexity of microglial responses is influenced by numerous signaling pathways such as NF-κB, fractalkine-CX3CR1, and the renin-angiotensin system, indicating that a broader perspective is needed to fully understand their functions and therapeutic potential in DR. The combined use of multiple drugs to regulate the pathological mechanisms from multiple dimensions seems to be the right approach to solve the problems of DR.

Moreover, there is a substantial disparity in translating preclinical findings into clinical applications. Numerous promising therapeutic strategies have been demonstrated to effectively regulate microglial polarization and decrease retinal inflammation in experimental models. However, the clinical translation of these findings is limited. The differences between animal models and human pathophysiology, coupled with the challenges of delivering targeted treatments to the retina, highlight the need for innovative delivery systems and clinically relevant DR models. At the same time, researchers also need to strive to address the inconsistencies in the reported results of various interventions. For example, some reports suggest that inhibiting the adenosine receptor A2AR in the retina of diabetic mice can reduce the inflammatory response, while other reports believe that activating A2AR can block the inflammatory response. Such contradictory results may be caused by differences in experimental conditions, the selection of animal models, and the timing and duration of therapeutic interventions. Therefore, it is particularly important to establish a standardized experimental framework and unified evaluation criteria, which will help to reduce the inconsistencies in the results and improve the reproducibility of the research. Moreover, the majority of basic research primarily concentrates on localized bodily changes, such as the effects of drugs on the retinal structure, often overlooking the systemic functional alterations that drugs may induce. For instance, while some studies have documented notable enhancements in retinal function and structure following the administration of drugs such as EPO, other research has highlighted the potential systemic risks, including erythropoiesis and thromboembolic events [128]. This variability emphasizes the necessity of standardized protocols and comprehensive evaluations of efficacy and safety in therapeutic trials.

Looking ahead, the research prospects in this field are expected to benefit from the advancements in genetic and molecular therapies. The potential of gene editing technology to selectively regulate microglial functions offers a promising approach for precisely targeting the molecular pathways involved in DR. Additionally, the development of biomarkers that can track the activation status of microglia and the therapeutic response in real time can significantly enhance the personalization of therapeutic strategies.

In conclusion, although significant progress has been made in understanding the role of microglia in DR, numerous challenges persist. Future research should aim to address these gaps by gaining a more comprehensive understanding of microglial biology, improving the translation pipeline from the laboratory to the bedside, and exploring innovative therapeutic modalities. By doing so, the field can move toward the development of effective, safe, and personalized treatment methods for DR, which can alleviate neurovascular damage and protect vision.

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