Review

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A New Perspective on the Regulation of Microglia-Mediated Inflammation in Diabetic Retinopathy: Mechanisms of NLRP3 Inflammasome Activation and Therapeutic Strategies

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Diabetic retinopathy (DR) is among the most common complications of diabetes mellitus and is characterized by microangiopathy and neurodegeneration. Microglia constitute a resident immune population in the central nervous system (CNS) and play crucial roles in regulating retinal angiogenesis under both physiological and pathological conditions. Microglia become widely activated in DR and induce pathogenic angiogenesis by regulating the status of endothelial cells. Modulating the state of microglial activation to ameliorate neovascularization thus appears to be a promising therapeutic approach for managing DR. The NOD-like receptor protein 3 (NLRP3) inflammasome is a cytosolic multimeric complex that plays a significant role in innate immunity. After sensing injury, the NLRP3 inflammasome induces the secretion of inflammatory cytokines (including interleukin (IL)-1β and IL-18) and triggers a form of inflammatory cell death known as pyroptosis. Recently, the NLRP3 inflammasome has been found to be abundantly expressed in microglia and has been shown to play critical roles in diabetes-associated neuroinflammation. Here, we summarize the effects of diabetes on NLRP3 inflammasome activity and microglial activation. The regulatory mechanisms of NLRP3, as well as NLRP3-targeted therapeutic strategies in microglia, will be reviewed. Targeting the NLRP3 inflammasome axis might serve as a promising therapeutic approach for ameliorating microglia-mediated inflammation and pathological progression in DR.

Keywords: microglia; diabetic retinopathy; NLRP3; pyroptosis; inflammation

Introduction

Diabetic retinopathy (DR) is a retinal microvascular damage-induced fundus lesion caused by diabetes and is a common microvascular complication of diabetes. Typical symptoms include decreased vision, visual distortion, and irreversible blindness [1]. The global prevalence of DR is 22.27%, with 103.12 million cases reported by 2022, and it is expected to increase [2]. Studies indicate that the prevalence of DR is greater in women with type 2 diabetes than in men, whereas male patients experience more severe symptoms and have a greater risk of blindness [3,4]. The molecular mechanisms of DR include oxidative stress [5], inflammatory responses [6], neurodegenerative changes [7], and vascular dysfunction triggered by hyperglycemia [8]. Clinically, DR is divided into two stages: (1) nonproliferative DR (NPDR), characterized by vascular abnormalities, and (2) proliferative DR (PDR), involving pathological neovascularization. PDR typically occurs after NPDR and is more severe. Research has shown that regular screening and early diagnosis can reduce the risk of vision loss by 57.0% and lower treatment costs [9]. However, owing to its highly insidious visual manifestations, DR is often diagnosed years after the onset of diabetes. Current primary treatments for DR include intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) drugs [10], pars plana vitrectomy (PPV) [11], and laser therapy [12]. However, with repeated anti-VEGF injections, drug resistance develops, and drug efficacy diminishes over time [13]. Given these challenges, alternative methods to inhibit pathological neovascular proliferation are urgently needed.

Anatomically and developmentally, the retina is an extension of the central nervous system (CNS) and is characterized by a highly ordered structure composed of intricate networks of neurons and glial cells [14]. These cells communicate through pathways mediated by signaling molecules such as cytokines, growth factors, and metabolic intermediates. Among these, microglia, as resident immune cells in the CNS, play a crucial role in maintaining CNS homeostasis under physiological conditions by monitoring the microenvironment, clearing metabolic waste and abnormal proteins, and participating in synaptic pruning and remodeling. Studies have shown that under diabetic

pathological conditions, microglial function is impaired, the expression of tight junction proteins is suppressed, and the blood–brain barrier (BBB) is compromised [15]. In models of diabetic encephalopathy, abnormally activated microglia interact with neurons through the release of inflammatory factors, contributing to pathological processes [16,17]. Similarly, in models of diabetes combined with stroke, the aberrant response of microglia is a key factor exacerbating neural damage [18]. Similarly, under diabetic conditions, microglia in the retina become abnormally activated. These activated microglia release proinflammatory factors and toxic substances, thereby driving the breakdown of the blood–retinal barrier (BRB) and leading to vascular leakage [6].

The NOD-like receptor protein 3 (NLRP3) inflammasome is a protein complex that plays a significant role in innate immunity and inflammation-related diseases by mediating Caspase-1 activity, thereby promoting the release of proinflammatory factors such as interleukin (IL)-1β and IL-18 [19]. In the context of diabetes, the NLRP3 inflammasome in microglia is abnormally activated, contributing to the drive of neuroinflammation [20]. Studies have shown that the upregulated expression of NLRP3 under high-glucose conditions accelerates disease progression through pathways such as neuroinflammation, microglial polarization, mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum stress [21]. Additionally, increased expression of NLRP3 can promote neuronal pyroptosis, directly inducing cognitive impairment in diabetic patients [22]. Owing to the critical role of NLRP3 in mediating neuroinflammation, it has been recognized as a key pathogenic factor and a potential therapeutic target for DR [23].

This review will systematically elaborate on new perspectives on inflammation regulation mediated by microglia in DR, with a focus on the activation mechanisms of the NLRP3 inflammasome in microglia and targeted therapeutic strategies.

Microglia in the DR

Dynamic Activation of Microglia in DR

Microglia are important immune cells in the retina that are typically located in the inner retina, assisting in monitoring and clearing retinal metabolites, and are crucial for maintaining retinal homeostasis [24]. Activated microglia can generally be classified into two phenotypes: M1 inflammatory microglia and M2 anti-inflammatory microglia [25]. During the onset and progression of DR, the activation of microglia is not a simple switch but involves complex dynamic changes across disease stages. Using a db/db mouse model, Arroba et al. [26] reported that in the retinas of 5-week-old mice, activated microglia (Iba-1$^+$) colocalized with the M2 marker arginase-1, indicating that the M2 phenotype predominates at this stage and is accompanied by a systemic increase in the anti-inflammatory cytokines IL-4 and IL-13. In contrast, in the retinas of 8-week-old db/db mice, Iba-1$^+$ cells colocalized with active caspase-1, suggesting a switch toward a proinflammatory phenotype [26]. These activated M2-type microglia are primarily localized in the inner nuclear layer (INL) and ganglion cell layer (GCL) of the retina, whereas M1-type microglia are expressed in the outer segment (OS), outer plexiform layer (OPL), INL, and GCL, with their activation levels significantly increasing as the disease progresses [26]. Research has shown that in the late stages of DR, microglia shift to the secretory M1 phenotype and continuously release proinflammatory mediators, including cytokines and chemokines (such as IL-1β, IL-6, matrix metalloproteinase-9 (MMP9), and C-C motif chemokine ligand 2 (CCL2)) [27]. Thus, during the pathological process of DR, it is not a simple binary switch between M1 and M2 microglia but a complex dynamic evolution that progresses with disease stage.

Promoting the transition of microglia from the M1 to M2 phenotype and restoring immune homeostasis are promising therapeutic strategies. This process is regulated by multiple molecular pathways. For example, a study by Wang et al. [28] revealed that M2 microglial exosomes (M2-exos) reduce pericyte apoptosis and promote endothelial cell proliferation. In turn, M2-exos promote M2 polarization of retinal microglia. In summary, M2-exos reverse DR-induced microvascular damage by promoting retinal microvascular remodeling [28]. Under glucose stimulation, the expression of the circular RNA mm9_circ_014683 significantly increased, and its levels markedly increased in the retinal microglia of diabetic mice compared with those of normoglycemic mice. Although mm9_circ_014683 does not significantly affect the proliferation or apoptosis of microglia, the upregulation of mm9_circ_014683 can activate the classical nuclear factor kappa B (NF-κB) inflammatory signaling pathway. Inhibiting mm9_circ_014683 expression significantly attenuated M1 polarization and enhanced M2 polarization of retinal microglia [29]. A20, also known as tumor necrosis factor-α-induced protein 3 (TNFAIP3), is a ubiquitin-associated enzyme with notable anti-inflammatory functions. Under glucose stimulation, the level of A20 is significantly reduced. A20 can reverse glucose-mediated M1 polarization of retinal microglia [30]. Utilizing mesenchymal stem cell-derived small extracellular vesicles to deliver miR-29a-3p, which targets and inhibits high-mobility group box 1 (HMGB1), can effectively suppress M1 microglial polarization and alleviate retinal damage in diabetic rats [31]. Additionally, some strategies have been developed to directly promote M2 microglial polarization. For instance, the delivery of IL-4 via engineered extracellular vesicles [32] or the use of apoptotic cell membrane-biomimetic nanoparticles to scavenge reactive oxygen species (ROS) and regulate the mechanistic target of rapamycin kinase (mTOR) pathway [33] both effec-

tively promote the transition of microglia to the M2 phenotype, thereby reducing retinal inflammation and vascular damage. These studies indicate that regulating microglial polarization is a potentially effective strategy for DR treatment.

With further research, the simple classification of M1 and M2 phenotypes cannot truly depict the complex dynamic changes in microglia in DR. Wang et al. [34] reported genes that were differentially expressed between normal rats and diabetic rats in microglia, further dividing microglia into three new subtypes, namely, two M1 types ($Egr2^+$ M1 and $Egr2^-$ M1) and one M2 type, with corresponding gradually diminishing inflammatory effects. One study proposed that during the progression of DR, M2-type microglia gradually transition to the $Egr2^+$ M1 phenotype, whereas $Egr2^-$ M1 microglia represent an intermediate transitional form [34]. A study by Zou et al. [35] revealed a new subtype called MKI67+ microglia, characterized by high expression of genes related to lactate metabolism and proliferation, such as MKI67, PARK7, and LDHA [35]. MKI67+ microglia are significantly enriched in the glycolysis pathway and, through the secretion of phosphoprotein 1 (SPP1), interact with Integrin alpha 4 (ITGA4) on endothelial cells, directly driving pathological neovascularization in PDR [35]. The discovery of these disease-specific subpopulations provides new cellular targets for precise targeted therapies.

Mechanisms of Microglia in DR

Immune Response

In the occurrence and development of DR, microglia, which are the resident immune cells of the retina, are abnormally activated. The chronic inflammatory response mediated by the cytokines they release has been confirmed to be one of the core pathogenic mechanisms [6]. A hyperglycemic environment initiates and maintains the proinflammatory phenotype of microglia through multiple signaling pathways. Persistent hyperglycemia directly affects the mitochondrial respiratory chain of cells, leading to excessive ROS production. The generation of large amounts of ROS increases the production of cellular oxygen-free radicals, thereby activating downstream intracellular signaling pathways to activate microglia [36]. ROS and accumulated advanced glycation end products (AGEs) are core damage signals in DR. The binding of AGEs to their receptor (RAGE) can directly activate pathways such as ERK and NF-κB, inducing the transformation of microglia to the M1 proinflammatory phenotype and upregulating the expression of proinflammatory factors such as TNF-α [37]. Clinical evidence has indicated that in the aqueous humor or vitreous body of NPDR patients, the levels of multiple inflammatory cytokines, such as IL-1β, IL-6, IL-8, TNF-α, and monocyte chemoattractant protein-1 (MCP-1), are elevated [38]. Moreover, the levels of cytokines such as IL-1β and IL-33, which serve as potential biomarkers for advanced PDR, are significantly increased in the vitreous and serum of PDR patients [39]. Using single-cell sequencing, Lv et al. [40] analyzed the retinas of diabetic mice at 4 months and reported that IL-1β and TNF expression was markedly upregulated and highly enriched in activated microglia; these activated microglia also exhibited metabolic reprogramming characterized by enrichment of glycolysis, purine metabolism, and triacylglycerol synthesis pathways. In addition to releasing classical proinflammatory factors, M1 microglia also release chemokines (e.g., MMP9 and CCL2), promoting their own migration and the continuous recruitment of immune cells, thereby amplifying the inflammatory response [27]. Thus, the inflammatory response mediated by microglia plays a central role in the pathological progression of DR. Simultaneously, the inflammatory factors, toxic substances, and growth factors released by microglia directly drive core pathological processes such as BRB disruption, neuronal degeneration, and pathological angiogenesis, which will be discussed below.

Neuronal Damage

DR was initially defined as a microvascular disease. Later, because of the reduction in retinal ganglion cells (RGCs), DR was referred to as a neurodegenerative disease. During the pathological progression of DR, neuropathological changes in retinal neural tissue even precede obvious microvascular abnormalities [41]. Activated microglia play a crucial role in the neurodegenerative lesions of DR. Activated M1-type microglia exhibit enhanced proliferation and migration capabilities, releasing large amounts of proinflammatory cytokines (such as TNF-α and IL-1β), the excitatory neurotransmitter glutamate, and inducible nitric oxide synthase (iNOS), collectively creating a neurotoxic microenvironment [42,43]. These mediators ultimately activate the caspase-dependent apoptotic pathway, leading to retinal ganglion cell (RGC) loss and the death of other neurons, thereby driving the progression of neurodegeneration in DR [44]. Both the diabetic environment itself and activated microglia generate excessive amounts of ROS, causing oxidative stress and damaging neurons and photoreceptor cells42. A study has shown that in DR, RIP1-RIP3-MLKL in microglia is significantly activated, initiating necroptosis and triggering programmed cell death [45]. These necrotic microglia rupture and release large amounts of proinflammatory factors (IL-6, TNF-α, and IL-1β), further amplifying retinal neuroinflammation, exacerbating neurodegeneration, and leading to significant reductions in neuronal density and neuroretinal thickness [45]. In summary, in DR, microglia actively participate in early neurodegeneration. Diabetic metabolic disturbances trigger the sustained activation and M1 polarization of microglia, which then, through mechanisms such as the release of inflammatory factors, the induction of oxidative stress, and the initiation of necroptosis, result in the progressive loss of retinal neurons and functional impairment.

Promotion of Angiogenesis

In advanced stages, DR can progress to PDR, characterized by pathological neovascular proliferation, which can lead to severe complications such as vitreous hemorrhage and tractional retinal detachment and is the main cause of irreversible vision loss [46]. In the retinas of an oxygen-induced retinopathy (OIR) mouse model, Iba1 immunofluorescence staining confirmed the presence of proliferative and activated microglia adjacent to neovascular bundles [35,47]. These persistently activated retinal microglia play a critical role in the pathological progression of DR, directly or indirectly driving pathogenic angiogenesis through the secretion of cytokines.

The direct secretion of proangiogenic factors is a core mechanism through which microglia drive neovascularization. Vascular endothelial growth factor-A (VEGF-A), fibroblast growth factor 2 (FGF2), and platelet-derived growth factor-BB (PDGF-BB) are growth factors that play central roles in both physiological and pathological angiogenesis [48,49]. A study by Chen et al. [50] revealed in *in vivo* and *in vitro* models that microglia promote angiogenesis in retinal vascular endothelial cells through the secretion of cytokines such as IL-6, IL-8, VEGF-A, and FGF2. Another study has also investigated the upstream mechanisms, revealing that in DR, damaged ganglion cells release lysophosphatidylserine (LysoPS), which directly acts on the GPR34 receptor on microglial cell membranes, activating the GPR34-PI3K-AKT-NINJ1 signaling axis to promote cytokine secretion [50]. These results highlight the importance of neuron–microglia signaling in driving angiogenesis. SPP1, a protein expressed in microglia and macrophages, is involved in retinal neovascularization [51]. The findings of Zou et al. [35] demonstrated that high glucose levels induce significant upregulation of SPP1 mRNA in human microglia (HMCs) and that their conditioned medium markedly enhances the proliferation and migration of human umbilical vein endothelial cells (HUVECs). Furthermore, under pathological conditions such as hypoxia, the expression of IGF1 in microglia is upregulated, which can independently promote endothelial cell proliferation and migration, thereby driving pathological neovascularization, independent of the VEGF pathway [52].

In addition to directly secreting proangiogenic factors, other cytokines secreted by microglia indirectly regulate retinal vascular endothelial factors. A study by Ding et al. [53] demonstrated that in a lipopolysaccharide (LPS)-stimulated *in vitro* microglial cell model, TNF-α and IL-1β produced by activated microglia induce retinal microvascular endothelial cells to generate VEGF-A and PDGF-BB, promoting their proliferation and migration. Under hypoxic conditions, the expression of hypoxia-inducible factor-1α (HIF-1α) in microglia is upregulated, which can directly transcriptionally activate the VEGF gene [54,55]. Moreover, under hypoxic conditions, MMP-9 and MMP-2 secreted by microglia can degrade the extracellular matrix (ECM), release sequestered VEGF, and provide space for endothelial cell migration [54,56]. In summary, during the progression of DR to PDR, microglia drive pathological neovascularization by being recruited to ischemic and hypoxic regions, directly and indirectly secreting proangiogenic factors, and remodeling the extracellular matrix.

BRB Destruction

Like in the blood–brain barrier, in the normal retina, vascular endothelial cells and surrounding cells are responsible for nutrient supply and the formation of the BRB, maintaining retinal homeostasis. However, during the pathological process of DR, structural and functional disruption of the BRB is the core pathological link leading to vascular leakage, retinal edema, and amplified inflammation. In addition to damage to endothelial cells and pericytes themselves, abnormally activated microglia become key effector cells driving BRB collapse. Their destructive effects are primarily achieved through the direct secretion of inflammatory mediators, the induction of oxidative stress damage, and complex interaction networks with other retinal cells. First, activated M1 microglia can secrete inflammatory factors such as TNF-α and IL-1β, which directly act on retinal endothelial cells and the retinal pigment epithelium (RPE), leading to the downregulation of key tight junction proteins such as Occludin, Claudin-5, and Zonula occludens-1 (ZO-1), thereby increasing vascular and epithelial permeability [57,58,59]. Furthermore, activated microglia are induced to produce large amounts of ROS, which subsequently cause apoptosis of cocultured pericytes, potentially disrupting the integrity of the BRB *in vivo* [60]. As key supportive cells that envelop capillaries and maintain vascular stability and barrier function, the massive loss of pericytes leads to fragile vascular wall structures and accelerates the functional collapse of the BRB. Microglia form a complex interaction network with other retinal cells, collectively amplifying damage to the BRB. For example, RPE cells release MCP-1, recruiting microglial infiltration and promoting BRB degradation [61]. Müller glial cells and astrocytes form a scaffold structure in the retina and play crucial roles in maintaining the BRB. The interactions between microglia and Müller glial cells, astrocytes, and other cells amplify the local inflammatory microenvironment and extracellular matrix remodeling, collectively exacerbating BRB destruction [62].

Alteration of Microglial Phagocytosis in DR

In addition to their secretory functions, another major role of microglia as immune cells is phagocytosis. As innate immune cells in the retina, under physiological conditions, resting microglia maintain tissue homeostasis by promptly clearing apoptotic cells and metabolic waste through basal phagocytosis. However, under pathological conditions, their phagocytic function becomes dysregulated. Studies have shown that in response to systemic inflammation,

early-stage microglia maintain blood–brain barrier integrity by expressing the tight junction protein Claudin-5 and establishing physical contact with endothelial cells. However, during chronic inflammation, microglia phagocytose astrocytic endfeet, impairing blood–brain barrier function and demonstrating a dual role [63]. In DR, the phagocytic function of microglia is similarly dysregulated and dynamic. In the retinas of OIR mice, the phagocytic rate of microglia decreases during the early hypoxic phase but increases during the late phase with pathological vascular changes [64]. An *in vitro* study revealed that under high-glucose conditions, the ability of microglia to phagocytose fluorescent microspheres was significantly lower than that in the normal group, while their migratory ability was enhanced [65]. The downregulation of early phagocytosis leads to the accumulation of toxic retinal substances and microglial infiltration. These accumulated cellular debris, which acts as endogenous damage-associated molecular patterns (DAMPs), can provide a "priming signal" for NLRP3 via the TLR/NF-κB pathway, promoting M1 microglial polarization [66]. On the other hand, activated microglia exhibit erroneous phagocytic targeting. Microglia can penetrate the BRB to directly phagocytose endothelial cells in retinal blood vessels, further exacerbating BRB disruption and causing plasma protein leakage [64,67]. Concurrently, they directly phagocytose neurons, leading to neurodegenerative changes in DR [68]. Among these, the dysregulation of CD200-CD200R signaling between Müller cells and microglia during DR is among the critical molecular mechanisms contributing to microglial overactivation and increased neuronal phagocytosis [68]. Furthermore, a study has confirmed that in neurodegenerative diseases such as Alzheimer's disease, NLRP3 inflammasome activation, through the release of IL-1β and Apoptosis-associated speck-like protein containing a CARD (ASC) specks, can further suppress microglial phagocytic function, resulting in a self-amplifying inflammatory cycle [69]. Whether NLRP3 inflammasome activation in microglia is involved in DR-associated neurodegeneration requires direct validation in appropriate models.

Alterations in the phagocytic functions of microglia are intricately regulated by multiple intracellular signaling pathways, which also serve as potential therapeutic targets. Fang et al. [65] reported that in a diabetic environment, IL-12 administration increased the number and activation of microglia, enhanced their phagocytic function, efficiently cleared dead RGCs in the retina, and prevented damage to surrounding healthy RGCs, thereby protecting retinal function and alleviating early DR. Further studies revealed that IL-12 activated the expression of STAT4 in microglia and upregulated the expression of phagocytosis-related genes, including TREM2, thereby increasing their phagocytic activity [65]. Xie et al. [67] demonstrated that under diabetic or hypoxic conditions, the phosphorylation levels of key proteins in the Src/Akt/cofilin signaling pathway in microglia were reduced, promoting their activation and pathological phagocytosis of endothelial cells. Erythropoietin (EPO) inhibits microglial activation and phagocytosis by activating this pathway, thereby protecting the BRB. Yilmaz et al. [64] revealed that in an OIR mouse model, enhancing microglial phagocytosis of apoptotic endothelial cells through the GAS6-MERTK pathway effectively limited pathological neovascularization. On the basis of this mechanism, Fan et al. [32] developed engineered extracellular vesicles targeting M1-type microglia to deliver IL-4. This strategy not only successfully induced the transformation of microglia to the M2 phenotype but also directly and specifically activated GAS6-MERTK signaling, enhancing the capacity of microglia to phagocytose abnormal blood vessels, effectively engulfing and clearing pathological vessels, and repairing the damaged BRB.

The phagocytic function of microglia in DR is characterized by complex dynamic changes. On the one hand, during the early stages of disease, the weakening or dysregulation of their ability to clear apoptotic cells leads to the accumulation of dead cell debris and chronic inflammation. On the other hand, their pathological phagocytic function toward normal endothelial cells and neurons is significantly enhanced, directly resulting in disruption of the BRB and neurodegeneration. Precise regulation of microglial phagocytic function through specific signaling pathways holds promise as a novel strategy to improve DR.

In summary, during DR progression, activated microglia, through their abnormal secretory function and disordered phagocytosis, constitute the core mechanism driving disease (Fig. 1). On the one hand, the release of various cytokines and mediators directly mediates inflammation, induces neuronal damage, and promotes pathological angiogenesis and BRB disruption. On the other hand, the dysregulation of their phagocytic function further exacerbates tissue damage and the inflammatory cycle.

Molecular Mechanisms of NLRP3 Inflammasome Activation in Microglia

As primary innate immune cells in the CNS, microglia abnormally activate the NLRP3 inflammasome, which is a central driver of neuroinflammation and the pathological progression of various diseases. The NLRP3 inflammasome is a multiprotein complex primarily composed of NLRP3, the adaptor protein ASC, and the effector protein Caspase-1. Its activation is a precisely regulated two-step process: priming and assembly activation (Fig. 2).

NLRP3 Inflammasome Targeting

The inflammasome is part of the innate immune system and can trigger an inflammatory cascade to eliminate harmful pathogens and dead cells from the system. The priming signal of NLRP3, also known as signal 1, is mediated by Toll-like receptor (TLR) ligands and cytokine

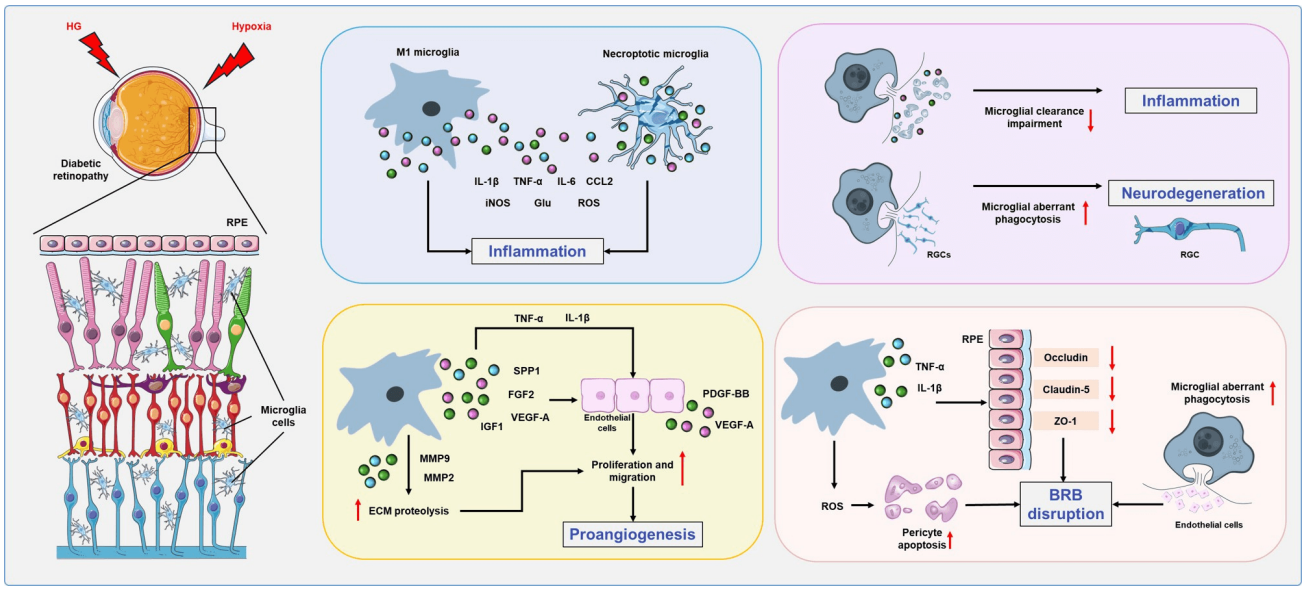

Fig. 1. Pathology mechanisms of microglia in diabetic retinopathy. In the progression of DR, activated microglia constitute a core mechanism driving disease through abnormal secretory functions and dysregulated phagocytosis. On the one hand, the release of various cytokines and mediators directly mediates inflammation, induces neuronal damage, and promotes pathological angiogenesis and BRB disruption. On the other hand, the dysregulation of their phagocytic function further exacerbates tissue damage and the inflammatory cycle. BRB, blood–retinal barrier; CCL2, C-C motif chemokine ligand 2; DR, diabetic retinopathy; ECM, extracellular matrix; FGF2, fibroblast growth factor 2; Glu, glutamate; HG, high glucose; IGF-1, insulin-like growth factor 1, IL-1β, interleukin-1 beta; MMP2/MMP9, matrix metalloproteinase-2/-9; PDGF-BB, platelet-derived growth factor-BB; RGC, retinal ganglion cell; ROS, reactive oxygen species; RPE, retinal pigment epithelium; SPP1, secreted phosphoprotein 1; TNF-α, tumor necrosis factor-alpha; VEGF-A, vascular endothelial growth factor A; ZO-1, Zonula occludens-1. The upward arrows refer to promotion, and the downward arrows refer to inhibition. Fig. 1 was created using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA).

(TNF-α) receptors. When danger signals such as DAMPs or pathogen-associated molecular patterns (PAMPs) are detected, they lead to the nuclear translocation of NF-κB, increasing the expression of proteins in the inflammasome pathway, including NLRP3, pro-caspase-1, and the precursors of IL-1β and IL-18 in the cytoplasm, thereby providing the material basis for subsequent activation [66].

In addition to the classical NF-κB pathway, Connexin43 (Cx43)-mediated abnormal cell communication has emerged as a recently highlighted upstream mechanism. Cx43 is the most abundant connexin in the CNS and is primarily distributed in astrocytes, where it participates in information exchange between cells and the external environment in the form of hemichannels (composed of six Cx43 molecules) [70]. Studies have demonstrated that in DR, CX43 forms hemichannels that release danger signals such as IL-6, IL-8, and ATP into the extracellular space, persistently amplifying inflammation [71]. Recent research has shown that under high glucose and inflammatory conditions, the expression of Cx43 in retinal and renal cells is upregulated, and the opening of its hemichannels is significantly increased, thereby accelerating and directly participating in the priming and activation processes of the NLRP3 inflammasome [72,73]. In addition, transcription factors such as signal transducer and activator of transcription 3 (STAT3) can also be activated by inflammatory factors (such as IL-6 and IFN-γ). Activated STAT3 enters the nucleus and cooperates with the NF-κB pathway, significantly upregulating the expression of TNF-α in microglia and further promoting amplification of the initiation signal [74,75].

The activation process of NLRP3 has been clearly confirmed in the clinical course of DR. Analysis of patient samples revealed that compared with individuals without diabetes or those with diabetes but no retinopathy, DR patients exhibited significantly elevated levels of IL-1β and IL-18 in the vitreous, which positively correlated with disease severity [76,77]. A study by Kuo et al. [76] confirmed that in the retinas of DR patients, microglia infiltrated the ONL, accompanied by a significant upregulation of Cx43 expression, along with elevated levels of NLRP3 and the activated form of caspase-1. These findings collectively indicate that during the development and progression of DR, the NLRP3 inflammasome is successfully primed in retinal cells such as microglia to prepare for subsequent inflammasome assembly and inflammatory responses.

Activation of the Nlrp3 Inflammasome

Activation of the NLRP3 inflammasome is a critical step in its functional execution and is regulated by signal

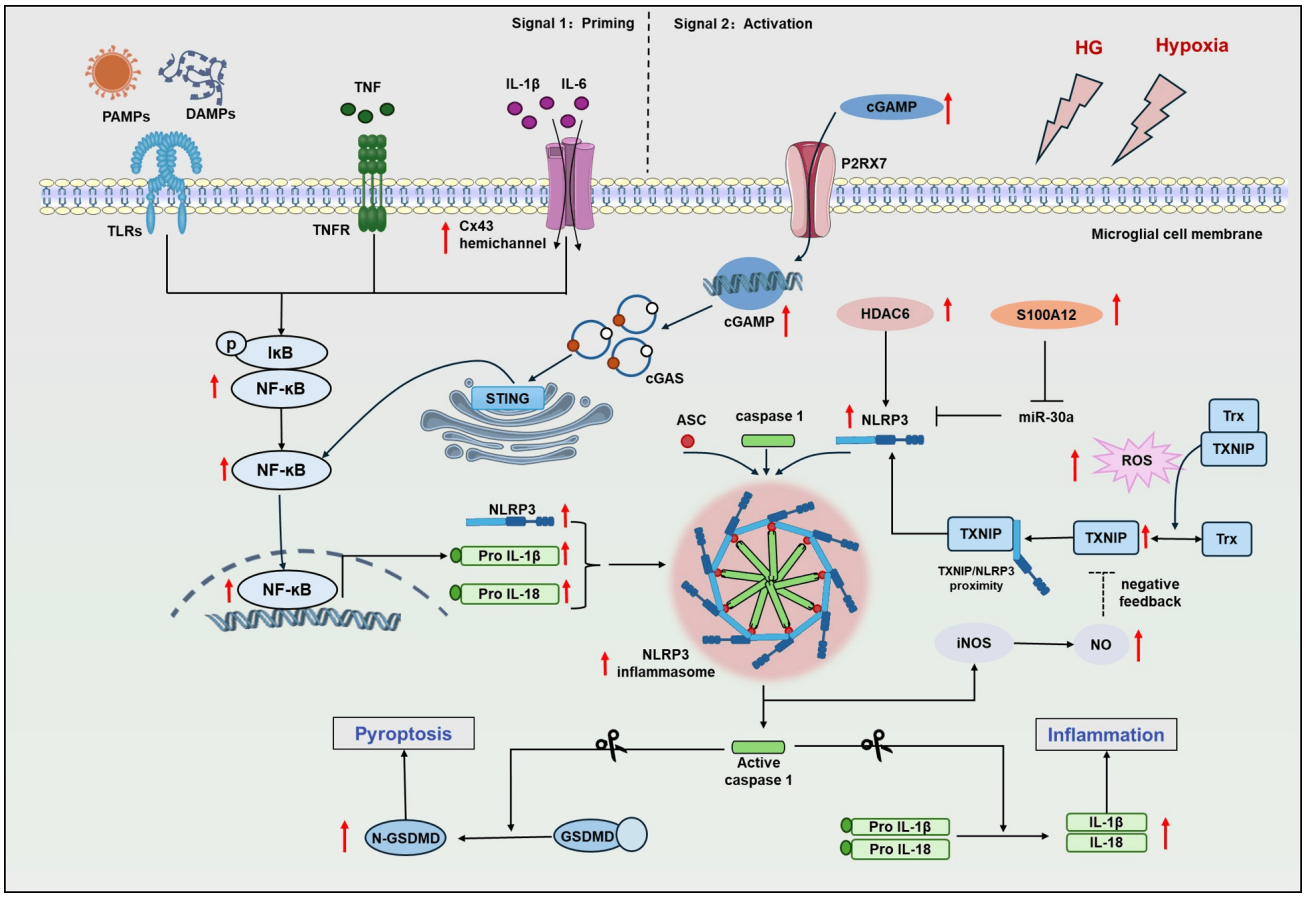

Fig. 2. Molecular mechanisms of NLRP3 inflammasome activation in microglia in diabetic retinopathy. Initial priming and activation of the NLRP3 inflammasome. Signal 1 (priming, left) is induced by TLRs, TNFR, and other receptors that can recognize danger signals such as PAMPs, DAMPs, and TNF, leading to the upregulation of NLRP3, IL-1β, and IL-18 transcription through the NF-κB pathway. In diabetic retinopathy, signal 2 (activation, right) is mediated by multiple signaling pathways, including the ROS-TXNIP axis, cGAS-STING pathway (with cGAMP entering microglia via P2RX7), S100A12/miR-30a axis, and HDAC6-mediated mitochondrial ROS production. Negative feedback: Nitric oxide (NO) suppresses TXNIP/NLRP3 signaling (dashed inhibitory arrow). Activated NLRP3 recruits ASC and pro-caspase-1 to form the inflammasome, leading to caspase-1 cleavage. Active caspase-1 processes pro-IL-1β/pro-IL-18 into mature IL-1β/IL-18 and cleaves GSDMD to induce pyroptosis. PAMPs, Pathogen-Associated Molecular Patterns; DAMPs, Damage-Associated Molecular Patterns; TLRs, Toll-like Receptors; TNF, Tumor Necrosis Factor; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; TNFR, Tumor Necrosis Factor Receptor; IκB, Inhibitor of κB; STING, Stimulator of Interferon Genes; P2RX7, Purinergic Receptor P2X 7; Cx43, Connexin 43; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; S100A12, S100 Calcium binding protein A12; ASC, Apoptosis-associated speck-like protein containing a CARD; Trx, Thioredoxin; TXNIP, Thioredoxin-interacting protein; HDAC6, Histone Deacetylase 6; GSDMD, Gasdermin D; IL-18, Interleukin-18; iNOS, Inducible Nitric Oxide Synthase; NO, Nitric Oxide; ROS, Reactive Oxygen Species. The upward arrows refer to promotion, and the downward arrows refer to inhibition. Fig. 2 was created using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA).

2. The core step involves the assembly of protein components synthesized during the priming phase to form an active inflammasome (Fig. 2). In DR, the activation of the NLRP3 inflammasome in microglia involves regulation through multiple pathways, ultimately leading to inflammasome activation via different molecular signaling mechanisms.

ROS-TXNIP Axis

Oxidative stress is among the core mechanisms involved in the pathological progression of DR. A hyperglycemic environment leads to the excessive production of ROS in retinal cells. Thioredoxin-interacting protein (TXNIP) is a ROS-responsive factor. Under normal conditions, TXNIP binds to the antioxidant protein thioredoxin (TRX). Studies by Iwasa et al. [78] and Kato et al. [79] revealed that in high glucose-stimulated mouse microglia, excess ROS cause the dissociation of TRX from TXNIP,

resulting in the release of activated TXNIP, which binds to NLRP3, triggering the assembly and activation of the inflammasome and thereby promoting the production of IL-1β. These two studies differ in the specific downstream effector molecules of this pathway. Iwasa et al. [78] reported that no activation of cleaved caspase-1 was detected in high glucose-stimulated BV2 cells, which may suggest a noncanonical activation mechanism of this pathway under specific conditions, and the detailed mechanisms remain to be further elucidated. In fact, the TXNIP/NLRP3/IL-1β pathway has been validated in various diabetic complications, such as diabetic nephropathy [80] and diabetic cataract [81], indicating that it is a common pathway for diabetes-related inflammation.

In DR, this activation pathway is subject to precise negative feedback regulation. Yang et al. [82] revealed that in DR, nitric oxide (NO), a downstream signaling molecule of this pathway, can inhibit upstream TXNIP/NLRP3 signaling. In early DR rat models, supplementation with NO donors effectively downregulated the expression of TXNIP/NLRP3 in microglia, reduced IL-1β release, and exerted neuroprotective and vasoprotective effects by increasing the expression of the neurotrophic factor GDNF and the tight junction protein Occludin [82]. These findings indicate that in DR, the ROS-TXNIP-NLRP3 axis is activated in microglia and mediates inflammatory responses and that a NO-mediated self-inhibitory loop is present.

cGAS–STING Axis

The cGAS-STING pathway is a crucial intracellular immune signaling pathway responsible for recognizing viral and bacterial double-stranded DNA (dsDNA) [83]. Upon binding to dsDNA, cGAS generates cyclic GMP-AMP (cGAMP), which subsequently activates the adaptor protein STING on the endoplasmic reticulum. Activated STING further recruits and phosphorylates TANK-binding kinase 1 (TBK1), ultimately activating the transcription factors IRF3 and NF-κB, thereby promoting the expression of type I interferons and inflammatory cytokines to enhance immune responses. In addition to defending against pathogens, chronic activation of cGAS-STING plays a pivotal role in inflammatory diseases, autoimmune disorders, and neurodegenerative diseases [84]. In the context of DR, persistent hyperglycemia and oxidative stress-induced mitochondrial damage may lead to DNA leakage in retinal cells, abnormally activating the cGAS-STING pathway and exacerbating inflammatory responses [85]. Analysis of patient datasets revealed significant upregulation of cGAS and STING expression in the retinal tissues of PDR patients, with pathway-related genes enriched in retinal myeloid cells [86]. Immunofluorescence experiments in an OIR mouse model revealed colocalization of cGAS with Iba-1+ cells near neovascular clusters, indicating that activation of the cGAS-STING pathway in microglia accelerates BRB disruption and is associated with pathological angiogenesis [86]. A study by Ge et al. [87] revealed that cGAMP levels in the aqueous humor of DR patients and the vitreous of model mice were significantly elevated. cGAMP can actively enter microglia via the P2RX7 transporter, activating STING signaling and directly causing breakdown of the BRB and neuronal degeneration. These findings demonstrate that in DR, the cGAS–STING pathway in microglia can be activated by both endogenous DNA leakage and exogenous cGAMP.

However, whether the cGAS-STING pathway directly triggers NLRP3 inflammasome activation has not yet been directly validated in DR models. Nevertheless, the upstream mechanism of NLRP3 activation has been verified in other neuroinflammatory and diabetic complications. A study by Ding et al. [88] demonstrated that in a mouse model of cerebral venous sinus thrombosis (CVST), cGAS and STING were primarily expressed in Iba-1-positive cells and mediated the activation of the NLRP3 inflammasome, leading to the production of cleaved caspase-1, which subsequently promoted the expression of IL-1β and GSDMD proteins, thereby triggering neuroinflammation and pyroptosis. The findings from Yan et al. [89] revealed that in the cardiomyocytes of diabetic cardiomyopathy mice, the cGAS-STING signaling pathway was activated, resulting in NLRP3 inflammasome activation in the hearts of diabetic mice, the release of proinflammatory cytokines (TNF-α, IFN-β, and IL-1β), and the induction of systemic inflammation. Collectively, these lines of evidence support the reasonable hypothesis that activated cGAS-STING signaling in microglia likely promotes NLRP3 inflammasome activation in DR through a similar mechanism, thereby driving neuroinflammation and pyroptosis. This hypothesis awaits direct validation in DR-specific models (e.g., using NLRP3 reporter mice or gene knockout mice) by simultaneously detecting the activation status of the cGAS-STING and NLRP3 pathways.

HDAC6

Histone deacetylase 6 (HDAC6) is a class IIb HDAC that is primarily localized in the cytoplasm and participates in histone modification. It also targets various nonhistone substrates, such as α-tubulin and heat shock protein 90, mediating acetylation and playing regulatory roles in various diseases, including cancer, neurodegenerative disorders, inflammation, and metabolic disorders [90]. In diabetic complications, inhibition of HDAC6 has been demonstrated to have protective effects against diabetic nephropathy [91] and diabetic cardiomyopathy [92]. Recent studies have indicated that in DR, HDAC6 can serve as an independent predictive biomarker and is significantly enriched in autophagy-related pathways [93]. The expression and activity of HDAC6 are upregulated in the diabetic retinas of streptozotocin (STZ)-induced rats. Inhibiting HDAC6 can alleviate diabetes-induced redox-imbalanced retinal microvasculopathy by increasing the expression of the redox

homeostasis histone deacetylase SIRT1 and reducing the expression of the senescence marker γH2AX [94]. Additionally, HDAC6 directly regulates NLRP3 inflammasome-driven neuroinflammation in microglia. Kim et al. [95] reported that inhibiting HDAC6 in both *in vivo* and *in vitro* DR models suppressed NLRP3 inflammasome activation and mitigated retinal damage. In DR, HDAC6 is not only a disease marker but also a regulatory factor for oxidative stress and inflammation. Therefore, targeting HDAC6 is expected to provide a novel multitarget intervention strategy for DR by simultaneously improving cellular metabolic homeostasis and inhibiting inflammasome activation.

S100A12

S100 calcium-binding protein A12 (S100A12), also known as calgranulin C, is an important DAMP that plays a key role in various inflammatory diseases, such as primary knee osteoarthritis [96]. Under diabetic conditions, the level of S100A12 in the retina is significantly elevated. Studies have shown that the expression of S100A12 in the retinas of diabetic rats can be approximately five times greater than that in nondiabetic retinas [97]. In patients with type 2 diabetes and those with type 2 diabetes combined with DR, plasma S100A12 levels are significantly higher than those in healthy individuals and are independently associated with retinopathy in patients with type 2 diabetes [98]. These findings establish S100A12 as a critical inflammatory trigger in DR. S100A12 activates the NLRP3 inflammasome pathway by directly acting on retinal microglia. A study by Dong and Wang [97] demonstrated that in a DR rat model, S100A12 promotes the release of inflammatory factors such as IL-1β and IL-18 by activating NLRP3 in retinal microglia. The underlying molecular mechanism involves the regulation of microRNAs (miRNAs). Under physiological conditions, miR-30a negatively regulates NLRP3 protein expression by directly binding to the 3′ untranslated region (3′-UTR) of NLRP3 mRNA. However, in the DR environment, S100A12 significantly inhibits the expression of miR-30a in microglia, thereby alleviating its posttranscriptional suppression of NLRP3 activity, leading to upregulated NLRP3 protein levels and excessive inflammasome activation [97]. These results indicate that in DR, S100A12 not only serves as a biomarker reflecting disease severity but also acts as a key effector molecule driving microglial inflammatory responses through the S100A12/miR-30a/NLRP3 axis.

HIF-1α

HIF-1α is a crucial transcription factor that can bind to the β subunit to form a transcriptionally active dimeric complex. It regulates the expression of numerous downstream target genes and participates in various responses, such as hypoxia adaptation, angiogenesis, immune response, and apoptosis, and plays a significant role in multiple diseases, including diabetes [99]. Studies have shown that in high glucose-stimulated retinal microvascular endothelial cells and BV-2 microglia, a high glucose environment activates HIF-1α and promotes its nuclear translocation through mechanisms such as ROS induction, directly upregulating VEGF expression and driving angiogenesis [100,101]. Inhibiting the ERK1/2 signaling pathway can block HIF-1α activation, thereby downregulating VEGF expression and indirectly affecting the inflammatory environment [101]. Research has shown that NLRP3 expression is elevated at sites of angiogenesis, indicating that NLRP3 contributes to pathological neovascularization in late stages [102]. In CNS diseases, HIF-1α can directly regulate NLRP3 activation. In traumatic brain injury, upregulated HIF-1α promotes NLRP3 inflammasome activation and pyroptosis [103]. Conversely, in cellular models of acute ischemic stroke, HIF-1α overexpression suppressed the increase in ROS in microglia, thereby inhibiting the NLRP3 inflammasome and ultimately reducing microglial pyroptosis [104]. The regulation of NLRP3 by HIF-1α may be context- and dose dependent. In DR, although there is no direct evidence that HIF-1α independently activates NLRP3, the two exhibit strong synergistic effects on the pathological process.

Conversely, the expression of HIF-1α is regulated by NLRP3. Studies have shown that in the retinas of rats with STZ-induced diabetes, knocking down NLRP3 expression can inhibit the expression of proinflammatory factors such as IL-1β and IL-18 and downregulate the expression of HIF-1α and VEGF, thereby reducing the generation of pathological cardiovascular disease [105]. These findings indicate that the activation of NLRP3 can form a positive feedback loop through its effector molecules (e.g., IL-1β), further consolidating the activity of HIF-1α and downstream proangiogenic responses. In the progression of DR, HIF-1α and the NLRP3 inflammasome constitute a mutually reinforcing signaling network. The hypoxia adaptation and angiogenic responses driven by HIF-1α, together with the inflammatory responses mediated by NLRP3, collectively promote disease progression toward proliferative lesions. Intervening at key nodes of this cross-talk may provide new therapeutic strategies to simultaneously inhibit neovascularization and neuroinflammation.

Potential Therapeutic Strategies Targeting the NLRP3 Inflammasome in Diabetic Retinopathy

Direct Targeting of NLRP3

In DR, NLRP3-mediated inflammatory responses play pivotal roles in the onset and progression of the disease. Currently, targeting NLRP3 is a promising avenue for DR treatment. First, certain small molecules can directly target the NLRP3 protein to modulate its activity or bind to its mRNA to inhibit translation (Table 1, Ref. [106,107,108,109,110,111,112,113,114,115,116,117,118,119]).

Table 1. Summary of therapeutic agents targeting the NLRP3 inflammasome in diabetic retinopathy.

Agents	Model type	Effects	Mechanism	Ref.
MCC950	STZ-induced diabetic mouse	Reduces retinal vascular damage; decreases IL-1β production; attenuates vascular leakage; protects against hyperglycemia-induced histological changes	Direct NLRP3 inflammasome inhibition	[106]
OLT1177	PDR patient proliferative membranes; OIR mouse model	Inhibits retinal neovascularization; attenuates microglial inflammation; protects retinal neurons; preserves astrocytic template; improves retinal function	Selective NLRP3 inflammasome inhibition	[107]
Methylene Blue	STZ-induced diabetic rat model	Attenuates retinal layer thinning and BRB permeability; reduces NLRP3, ASC, caspase-1, IL-1β, IL-18.	Inhibits NLRP3 inflammasome activation	[108]
Vitamin D3	STZ-induced diabetic rat model; High glucose-exposed HRMECs	Reduces retinal vascular permeability and apoptosis; decreases VEGF expression	Downregulates ROS/TXNIP/NLRP3 axis	[109]
Minocycline	STZ-induced diabetic rat model; High glucose-exposed HRMECs	Decreases retinal vascular permeability and apoptosis; reduces inflammatory cytokines (IL-1β, IL-18)	Downregulates ROS/TXNIP/NLRP3 axis	[110]
Hydrogen Sulfide (H_2S)	High glucose-induced human RPE cells	Protects RPE cells from high glucose-induced damage; reduces expression of IL-1β and IL-18	Inhibits ROS formation and subsequent NLRP3 inflammasome activation.	[111]
Tilianin	STZ-induced diabetic rat model	Lowers blood glucose; improves insulin sensitivity; exerts antioxidant and anti-inflammatory effects; ameliorates retinal morphology.	Activation of the Nrf2-HO-1 axis, and inhibition of ROS/TXNIP/NLRP3 axis.	[113]
Spermidine	High-glucose treated human RPE (ARPE-19) cells	Attenuates cytotoxicity and apoptosis in RPE cells; reduces release of IL-1β and IL-18	Inhibits ROS production and NF-κB signaling, TXNIP/NLRP3 inflammasome	[112]
Tonabersat	A spontaneously hyperglycemic strain of SD rats	Reduces gliosis (GFAP, Iba-1) and improves retinal function	Inhibits CX43	[114]
Salidroside	STZ-induced diabetic rat model	Protects retinal ganglion cells from pyroptosis; improves retinal pathological structure	Modulation of Nrf2/NFE2L2, NF-κB/NFKB1, and NLRP3 pathways	[115]
Oridonin	STZ-induced diabetic mouse; HG-stimulated hRECs	Alleviates visual impairment & retinal lesions; protects neuroretinal structure; reduces systemic & retinal inflammation; inhibits pyroptosis.	Inhibits NF-κB signaling; blocks NEK7-NLRP3 inflammasome	[116]
miR-22-3p	STZ-induced rat; AGEs induced BV2 cell	Inhibits NLRP3 inflammasome activation, suppresses microglial activation, decreases inflammatory cytokines levels	Binds to NLRP3 mRNA 3′-UTR to inhibit its expression	[117]
miR-192	High glucose-induced human RPE cells	Inhibits pyroptosis of RPE cells by suppressing NLRP3 inflammasome activation	Targets FTO to reduce NLRP3 expression	[118]
miR-128-3p	High glucose-induced human retinal endothelial cells	Reduces inflammatory injury (TNF-α, IL-1β) in retinal endothelial cells	Targets KDM3A to repress NLRP3 transcription	[119]

Notes: STZ, streptozotocin; PDR, proliferative diabetic retinopathy; OIR, oxygen-induced retinopathy; HG, high glucose; HRMECs, human retinal microvascular endothelial cells; RPE, retinal pigment epithelium; BRB, blood–retinal barrier; IL-1β, interleukin-1 beta; VEGF, vascular endothelial growth factor; ROS, reactive oxygen species; TXNIP, thioredoxin-interacting protein; NLRP3, NOD-like receptor protein 3; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; FTO, fat mass and obesity-associated protein; KDM3A, lysine-specific demethylase 3A; AGEs, advanced glycation end products; NEK7, NIMA-related kinase 7.

MCC950 directly and specifically binds to the NACHT domain of the NLRP3 protein. Research by Ge et al. [106] revealed that intravitreal injection of MCC950 can alleviate retinal vascular damage, reduce IL-1β levels, and improve vascular leakage in DR mice, further supporting the feasibility of using NLRP3 as a therapeutic target. OLT1177 is a novel, highly selective inhibitor targeting the NLRP3 inflammasome but does not act on AIM2 or NLRC4 inflammasomes. Its mechanism of action involves directly binding to the NLRP3 protein and inhibiting its ATPase activity, thereby blocking the assembly of the inflammasome upstream [120]. Wu et al. [107] demonstrated that in the proliferative membranes of PDR patients and in an OIR mouse model, NLRP3 is primarily activated in microglia. The inhibitor OLT1177 not only significantly suppressed retinal neovascularization but also reduced microglial inflammatory responses and exhibited notable neuroprotective effects. These small-molecule inhibitors work by directly binding to the NLRP3 protein, hindering the activation of the NLRP3 inflammasome and thereby alleviating DR.

In addition to small molecule-specific inhibitors, some drugs that have been used clinically for many years have been shown to inhibit the NLRP3 inflammasome and alleviate DR. For example, methylene blue has been demonstrated to alleviate retinal layer thinning and BRB disruption in a streptozotocin (STZ)-induced diabetic rat model. Its protective effects are closely associated with the downregulation of NLRP3, ASC, caspase-1, and the downstream inflammatory factors IL-1β and IL-18 [108]. These findings indicated that the protective effects of methylene blue were not achieved by reducing oxidative stress, suggesting that methylene blue may interfere with NLRP3 inflammasome activation through other unknown pathways, and the specific mechanisms require further elucidation. These findings suggest that systematic screening of existing drug libraries based on the NLRP3 pathway may be an effective strategy for rapidly identifying potential therapeutic agents.

Regulation of Upstream Signaling Pathways

In addition to directly targeting the NLRP3 protein or mRNA to inhibit inflammasome activation, targeting the pathways upstream of NLRP3 activation also plays a role in improving DR (Table 1). The activation of NLRP3 is precisely regulated by various upstream signals, among which the ROS-driven TXNIP/NLRP3 axis has been identified as one of the key pathways in DR. Directly alleviating oxidative stress is the most straightforward strategy to inhibit the TXNIP/NLRP3 axis in DR. For example, minocycline, vitamin D3, and hydrogen sulfide (H2S) significantly reduce ROS generation in cells and retinal tissues under high-glucose conditions, thereby inhibiting TXNIP expression and NLRP3 inflammasome activation and reducing the release of inflammatory factors such as IL-1β and IL-18 [109,110,111]. Vitamin D3 also has additional antiangiogenic effects by reducing VEGF expression and the apoptosis rate, ultimately alleviating diabetes-induced retinal vascular damage and increasing vascular permeability [109]. In high glucose-induced retinal pigment epithelial cells, Bang et al. [112] reported that the natural polyamine spermidine effectively inhibits mitochondrial ROS generation induced by high glucose and blocks the activation of NF-κB signaling, thereby downregulating the expression of TXNIP, NLRP3, ASC, and caspase-1; suppressing inflammasome assembly; and reducing the release of IL-1β and IL-18, ultimately protecting retinal pigment epithelial cells from high glucose damage [112]. These findings suggest that simultaneously targeting both ROS and NF-κB, two critical upstream nodes, may be a more effective strategy for inhibiting NLRP3-driven inflammatory responses.

In addition to directly inhibiting ROS, regulating the body's antioxidant function is another strategy for suppressing the TXNIP/NLRP3 axis. A study has shown that the plant extract tilinaryin can significantly activate Nrf2 and its downstream antioxidant enzyme-encoding genes, such as HO-1, effectively inhibiting the expression of TXNIP, NLRP3, ASC, caspase-1, and IL-1β; blocking the assembly and activation of the NLRP3 inflammasome; and slowing changes in the retina of diabetic rats [113]. Research by ElSayed et al. [121] revealed that memantine, which is used to treat Alzheimer's disease, exhibited significant neuroprotective and vascular protective effects in a DR mouse model. The mechanism involves the role of memantine as an NMDA receptor antagonist, which inhibits glutamate signaling, thereby downregulating the ROS/TXNIP/NLRP3 pathway, ultimately reducing the release of inflammatory mediators such as IL-1β and improving retinal histopathological and ultrastructural damage [121].

Blocking abnormally opened intercellular communication channels is another emerging upstream intervention pathway. Tonabersat is a CX43 hemichannel blocker. Oral administration of Tonabersat can effectively inhibit the expression of CX43, GFAP, and Iba-1 in the retinas of diabetic SD model rats, improving retinal dysfunction by suppressing inflammatory responses [114]. These findings indicate that targeting CX43 hemichannels to prevent the release of danger signals is an effective strategy for intervening in upstream activation events of NLRP3.

These findings demonstrate that upstream strategies for NLRP3 activation involve inhibition of the ROS/TXNIP axis and CX43 hemichannels through two distinct pathways: metabolic stress and cellular communication. These studies provide clear directions and experimental evidence for the development of drugs aimed at blocking the early activation stages of the NLRP3 inflammasome.

Multitarget Regulation Strategies

DR is a complex disease characterized by the interplay of metabolic disorders, oxidative stress, and chronic inflam-

mation. Strategies targeting a single pathway often fail to fully reverse the pathological network. Therefore, the use of a single compound to synergistically regulate multiple key nodes to systematically restore retinal homeostasis has emerged as a highly promising strategy. Such strategies are typically discovered and validated through methods such as network pharmacology. A study by Zhang et al. [115] revealed through bioinformatics analysis that the protective effect of the natural product salidroside on DR involves a complex molecular network. The mechanism was validated *in vivo*, demonstrating enhanced endogenous antioxidant defenses (activation of Nrf2), inhibition of classical proinflammatory signaling (suppression of NF-κB), and direct intervention in NLRP3 inflammasome activation [115]. Another study revealed that oridonin not only inhibits the upstream NF-κB signaling pathway but also directly blocks the protein interaction between NIMA-related kinase 7 and NLRP3, thereby suppressing NLRP3 inflammasome function at both the transcriptional activation and complex assembly levels [116]. This multitarget, multipathway synergistic mechanism may provide fundamental advantages in inhibiting neuroinflammation and protecting the retinal neurovascular unit, suggesting a way to develop DR therapeutics.

Epigenetic Regulation

In addition to interventions targeting NLRP3 protein function and its upstream activation signals, novel strategies for regulating NLRP3 gene expression at the epigenetic level have been proposed. miRNAs are a class of single-stranded RNA fragments that are 21–25 nucleotides in length and serve as post-transcriptional regulators that are widely present in eukaryotes. Their primary function is to bind to mRNA and regulate its translation. A study by Chen et al. [117] demonstrated that mesenchymal stem cell (MSC)-derived small extracellular vesicles (sEVs) can be used to deliver miR-22-3p to diabetic rats. miRNAs directly bind to the 3′-UTR of NLRP3 mRNA, inhibiting NLRP3 inflammasome activation, thereby suppressing microglial activation, reducing retinal inflammatory factor levels, and ameliorating DR. This highlights the potential of miRNA-based therapies utilizing emerging delivery systems to directly target NLRP3.

More complex regulatory networks involve the regulation of epigenetic modification enzymes by miRNAs, thereby indirectly affecting NLRP3 transcription. A study by Gu et al. [118] demonstrated that in high glucose-induced retinal pigment epithelial cells, the expression of miR-192 was significantly downregulated. The overexpression of miR-192 directly targeted and inhibited the demethylase FTO, thereby reducing the degree of NLRP3 mRNA demethylation, ultimately downregulating NLRP3 expression at the posttranscriptional level and inhibiting inflammasome assembly and pyroptosis [118]. Wen et al. [119] revealed another pathway of NLRP3 transcriptional regulation by miRNA in retinal endothelial cells: the miR-128-3p/KDM3A/NLRP3 pathway. In high glucose-induced retinal endothelial cells, the downregulation of miR-128-3p led to the upregulation of its target gene KDM3A. KDM3A, a histone demethylase, removes the inhibitory histone marker H3K9me2 in the promoter region of the NLRP3 gene, thereby alleviating the suppression of NLRP3 transcription and promoting its expression and inflammasome activation. Conversely, overexpression of miR-128-3p reverses this process by inhibiting KDM3A to maintain H3K9me2 levels, ultimately suppressing NLRP3 expression at the transcriptional level and alleviating cellular inflammatory damage [119].

In summary, intervening in the expression of NLRP3 through miRNAs (such as miR-22-3p, miR-192, and miR-128-3p) and their regulatory epigenetic networks (such as m6A modification and histone methylation) is a potential strategy for the precise regulation of NLRP3 inflammasome expression.

Clinical Translation Challenges

Although preclinical studies of the above therapeutic strategies have shown potential for inhibiting the NLRP3 inflammasome and alleviating retinal damage, the translation of these findings into clinical applications still faces multiple challenges.

Blood-Retinal Barrier Penetration Limitations

The retina is located in the posterior segment of the eye, and the BRB is the primary anatomical barrier restricting drug entry into the retina. Consequently, systemically administered NLRP3 inhibitors cannot achieve effective therapeutic concentrations in the retina, which directly limits the routes of administration for DR treatment. Most of the effective preclinical studies mentioned above employed intravitreal injection (e.g., MCC950 or OLT1177) [106,107], and current clinical standard therapies (e.g., anti-VEGF agents) also rely on intravitreal administration. However, intravitreal injection is an invasive procedure that has risks of serious adverse events, including intraocular infection, non-infectious immune reactions, lens injury, retinal tear/detachment, and fundal hemorrhage, and it demands high technical skills and a well-controlled environment [122]. The development of targeted drug delivery systems that utilize nanoparticles, liposomes, or extracellular vesicles to overcome ocular physiological barriers and improve drug bioavailability represents a promising strategy. For example, the aforementioned use of engineered extracellular vesicles to deliver miR-22-3p or IL-4 [32,119] has demonstrated the feasibility of targeted therapy via novel delivery systems. Currently, clinical studies using stem cell-derived EV-containing eye drops for dry eye disease are ongoing (NCT04213248: https://clinicaltrials.gov/study/NCT04213248, NCT05738629: https://clinicaltrials.gov/study/NCT05738629) [123]. Fur-

thermore, structural modification of existing inhibitors to enhance BRB penetration is another promising approach. For instance, the existing HDAC6 inhibitor tubastatin A has low oral bioavailability and cannot cross the BRB. Kim et al. [95] performed structural optimization of tubastatin A, retaining its hydroxamate zinc-binding group, and obtained a new derivative with improved oral bioavailability and HDAC6 selectivity that can cross the BRB and significantly suppress NLRP3 expression. In a diabetic mouse model, oral administration of this new derivative (50 mg/kg) significantly ameliorated retinopathy, pathological neovascularization, and vascular leakage and restored cell numbers in the inner and outer nuclear layers. Mechanistically, compared with the parent compound tubastatin A, the new derivative markedly inhibited NLRP3 inflammasome activation in the retina, downregulated NLRP3 and GSDMD-NT protein expression, and reduced the levels of IL-1β, IL-6, and TNF-α, with superior efficacy across all measured parameters [95].

Long-Term Safety and Toxicity Risks

NLRP3 is an essential component of innate immunity, and long-term systemic inhibition may increase the risk of infection. Although intravitreal administration can achieve local effects and reduce systemic exposure, the safety of systemic or long-term local use of NLRP3 inhibitors remains unclear for DR, a disease closely associated with systemic metabolic status. Current DR animal models cannot fully recapitulate the long disease course and complex pathological features of human DR. In humans, the long-term safety, optimal dosage, and potential synergy with other standard DR therapies (e.g., anti-VEGF agents and lasers) need to be confirmed through rigorous clinical trials. Taking MCC950 as an example, its pharmacokinetic and toxicokinetic properties have limited its clinical development [124]. In an interventional study on diabetic kidney disease, MCC950 not only failed to confer renal protection but also exacerbated renal inflammation and fibrosis, accompanied by elevated liver enzymes (e.g., ALT/AST), suggesting hepatotoxicity [125]. Although MCC950 has shown significant efficacy in various DR animal models, its potential hepatotoxicity limits its clinical translation. These findings underscore the importance of assessing the safety of NLRP3 inhibitors and the need to develop next-generation molecules. In addition, the long-term safety of biologics targeting downstream products of NLRP3 deserves attention. Canakinumab, an anti-IL-1β monoclonal antibody, has completed an exploratory clinical trial in patients with PDR. Eight PDR patients who received 150 mg of canakinumab subcutaneously every 8 weeks for three doses were included in this study. The results showed acceptable tolerability, with no progression of neovascularization observed over 24 weeks and some regression of diabetic macular edema (NCT01589029: https://clinicaltrials.gov/study/NCT01589029). However, this trial was an open-label exploratory study with a small sample size and no control group; the efficacy conclusions need to be validated by large-scale randomized controlled trials. Moreover, the risk of infections associated with the long-term use of such biologics requires systematic evaluation in future studies.

Summary and Future Perspectives

The NLRP3 inflammasome, as a key molecular platform that integrates various danger signals, such as oxidative stress and hypoxia, plays a direct role in driving the abnormal activation of inflammatory mediators such as IL-1β and IL-18, as well as pyroptosis in DR. We have summarized the activation mechanisms of the NLRP3 inflammasome in microglia in DR. Based on these mechanisms, intervention strategies have expanded from directly inhibiting NLRP3 to targeting its upstream activation pathways, regulating its expression through epigenetic means, and employing multitarget drugs for systemic modulation.

Currently, most research remains in the preclinical stage. Future efforts should focus on enhancing clinical translation by utilizing retinal organoids, humanized animal models, and other approaches to more accurately simulate the pathological environment of human DR and validate drug efficacy. Concurrently, exploring the applicability of existing NLRP3 inhibitors (such as OLT1177, which is in the clinical stage) in DR patients is essential. Utilizing biomarkers (e.g., IL-1β, HDAC6, and S100A12) for patient stratification will enable personalized treatment. Given that DR is a progressive disease involving multiple pathological pathways, such as metabolism, inflammation, and angiogenesis, single-target intervention may not be sufficient to completely halt disease progression. Combination therapy, such as oral metformin combined with intravitreal injection of MCC950, represents a potential direction [126].

Future research could integrate traditional Chinese medicine concepts to systematically screen active ingredients from natural medicinal plants. For instance, the natural plant Plumbago zeylanica L. has demonstrated hypoglycemic and antioxidant effects in diabetic models [127]. Whether it exerts retinal protective effects by modulating the NLRP3 pathway warrants further investigation. In addition to chemical drugs and biologics, nonpharmacological interventions are also noteworthy. For example, studies have indicated that electroacupuncture stimulation can downregulate NLRP3 inflammasome components and downstream cytokines in pain models, suggesting the potential of electroacupuncture as a physical therapy for regulating neuroinflammation [128].

Conclusion

This review systematically elaborates on the new perspective of microglia-mediated neuroinflammation in DR and focuses on the central role of the NLRP3 inflamma-

some in this process. The pathological mechanism of DR involves not only simple microvascular lesions but also a complex network encompassing metabolic disorders, chronic inflammation, pathological angiogenesis, and neurodegeneration. Activated microglia are key effector cells that mediate disease progression, and their functional dysregulation is manifested primarily through two processes. On the one hand, the release of various cytokines and mediators directly mediates inflammation, induces neuronal damage, and promotes pathological angiogenesis and BRB disruption. On the other hand, the dysregulation of their phagocytic function further exacerbates tissue injury and inflammatory cycles.

Availability of Data and Materials

Not applicable.

Author Contributions

CLF: Conceptualization, Data curation, Writing – original draft; LMQ: Methodology, Investigation, Validation, Writing – review & editing; NM: Conceptualization, Supervision, Project administration, Writing – review & editing. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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