Am J Transl Res 2025;17(8):6262-6274
www.ajtr.org /ISSN:1943-8141/AJTR0166006

Review Article

Inflammatory mechanisms in diabetic retinopathy: pathogenic roles and therapeutic perspectives

Han-Ying Qian, Xiao-Hong Wei, Jin-Ou Huang

Department of Ophthalmology, Shengzhou People's Hospital (Shengzhou Branch of The First Affiliated Hospital of Zhejiang University School of Medicine), Shengzhou 312400, Zhejiang, China

Received May 13, 2025; Accepted July 20, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Diabetic retinopathy (DR), a leading cause of global vision impairment, represents one of the most prevalent microvascular complications of diabetes. Numerous studies have confirmed that inflammatory processes and aberrant angiogenesis constitute pivotal pathological mechanisms in DR. Elevated levels of pro-inflammatory mediators - including cytokines, chemokines, and adhesion molecules - have been consistently detected in the serum, ocular fluids (aqueous humor and vitreous), retinal tissue, and tear film of DR patients, forming an intricate molecular network that drives disease progression. Importantly, modulation of these inflammatory components demonstrates potential to attenuate both vascular abnormalities and neurodegeneration in DR. This mechanistic understanding positions inflammation as a promising therapeutic target, highlighting the need for further investigation into anti-inflammatory strategies for DR management.

Keywords: Diabetic retinopathy, inflammation, pro-inflammatory mediators, pathological mechanisms, therapeutic target

Introduction

Diabetic retinopathy (DR), a prevalent microvascular complication of diabetes mellitus (DM), affects nearly 40% of diabetic patients and is the primary cause of blindness and visual impairment among adults aged under 50 years worldwide [1]. The global burden of DR is escalating in parallel with the rising prevalence of DM, with epidemiological projections estimating 129.84 million affected adults by 2030, potentially reaching 160.50 million by 2045 [2, 3]. Disease progression correlates strongly with diabetes duration, suboptimal glycemic control, concurrent hypertension, dyslipidemia, and inflammatory activation [4]. Clinically, DR manifests initially as non-proliferative diabetic retinopathy (NPDR), characterized primarily by retinal microaneurysms, which may progress to proliferative diabetic retinopathy (PDR), developing hard exudates, cotton-wool spots, pathological neovascularization, and retinal hemorrhages [5].

In the context of hyperglycemia, retinal microglial cells undergo pathological activation and secrete a wide range of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1beta (IL-1β), interleukin-3 (IL-3), interleukin-6 (IL-6), along with other inflammatory mediators such as vascular endothelial growth factor (VEGF), reactive oxygen species, glutamate, matrix metalloproteinases (MMPs), and nitric oxide (NO). This inflammatory cascade orchestrates multiple pathogenic processes through: (1) upregulation of adhesion molecules, (2) induction of apoptotic pathways, (3) facilitation of leukocyte infiltration, and (4) disruption of blood-retinal barrier (BRB) [6]. A substantial body of research has established the synergistic interplay between inflammatory and angiogenic pathways in DR pathogenesis [7-11]. Variations in the levels of various pro-inflammatory and angiogenic mediators have been detected in biological compartments such as serum, ocular fluids (aqueous humor and vitreous), retinal tissue, and tear film of DR patients. Importantly, targeted modulation of these mediators demonstrates therapeutic potential to mitigate both vascular abnormalities and neurodegeneration in DR [12-15], positioning inflammatory pathways as promising intervention

https://doi.org/10.62347/GBF05856

targets. This review systematically examines the mechanistic contributions of inflammation to DR progression and evaluates emerging anti-inflammatory strategies with translational potential.

Inflammatory mechanisms in DR

Inflammation serves as a central pathogenic driver in DR, with inflammatory responses persisting throughout all disease stages. These processes fundamentally contribute to the two hallmark pathological features of DR-mediated visual impairment in DM: increased vascular permeability and pathological neovascularization, both in the retina [16-18]. DM induces the local or systemic upregulation of numerous inflammatory molecules implicated in DR progression, such as chemokines, cytokines, transcription factors, growth factors, and vascular adhesion molecules (VCAM-1) [19-21]. These elevated inflammatory mediators promote leukocyte activation, endothelial adhesion, and subsequent capillary sequestration [22, 23], leading to capillary occlusion, retinal ischemia, endothelial cell dysfunction, and BRB breakdown. Characteristic clinical manifestations include retinal edema, intraretinal hemorrhages, hard exudation, and microaneurysm formation [24, 25]. Concurrently, activated retinal glial cells amplify local inflammation through the secretion of pro-inflammatory mediators and the recruitment of immune cells to inflammatory foci [26, 27].

Increasing evidence suggests that retinal neurodegeneration serves as a significant pathophysiological mechanism in DR [28]. Retinal glial cells, including astrocytes, Müller cells, and microglial cells, play crucial roles in providing structural support and preserving retinal homeostasis [29, 30]. Importantly, dysfunction of these cells contributes significantly to the initiation and progression of retinal inflammation during early DR [31]. Chronic hyperglycemia potently activates retinal microglia [32]. In the early stages of DR, this activation initiates a cascade of neurodegenerative events, including neuronal apoptosis and progressive thinning of the nerve fiber layer, ultimately leading to measurable visual dysfunction and potential vision loss [33].

Inflammatory cytokines pathways in DR

Hyperglycemia induces retinal inflammation accompanied by elevated production and release of multiple inflammatory mediators [34]. This inflammatory milieu stimulates a cascade of pro-inflammatory factors, including chemokines, inflammatory cytokines, and other related molecules [35], which collectively contribute to leukocyte stasis, cellular apoptosis, and retinal capillary leakage (**Table 1**). The key pathological cascades in DR development are illustrated in **Figure 1**.

Inflammatory cytokines

Elevated levels of macrophage-derived IL-1β are consistently observed in both serum and vitreous samples from DR patients. Mechanistically, IL-1β synergizes with TNF-α to: (1) upregulate endothelial adhesion molecules via NF-κB-mediated transcription, (2) enhance IL-6 and interleukin-8 (IL-8) production, (3) activate caspase-1-dependent inflammatory pathways [36]. Additionally, IL-1β promotes: (1) accumulation of ROS through inflammatory cell recruitment, leading to mitochondrial dysfunction and retinal cell apoptosis [37], as well as (2) pathological angiogenesis via the mitogen-activated protein kinase (MAPK) cascade, promoting DR progression [38].

TNF-α, a pleiotropic cytokine, mediates multiple pathological processes in DR. First, it initiates leukocyte-endothelial adhesion and retinal vascular inflammation. Second, TNF-α activates NF-κB signaling pathways [39]. Third, TNF-α contributes to BRB disruption (demonstrated by TNF-α/epidermal growth factor receptor axis inhibition in diabetic mouse models) [40]. Additionally, TNF-α induces retinal microvascular cell loss [41].

Other inflammatory factors, such as IL-6 and IL-8, have been found to have significant elevation in the serum, vitreous, and aqueous humor, with concentrations correlating with DR severity [42, 43]. IL-6 plays significant pathological roles. It activates retinal glial cells, induces TNF-α secretion, and initiates early BRB breakdown [44]. IL-6 and IL-8 stimulate VEGF production in fibroblasts and monocytes, thereby promoting inflammation-associated neovascularization and diabetic macular edema (DME) progression [45, 46].

Adhesion molecules and integrins

The upregulation of adhesion molecules constitutes a critical step in DR pathogenesis. Key

Table 1. Inflammatory cytokines involved in DR

Category	Mediator	Mechanism	Stage of DR Involved	Therapy	References
Inflammatory Cytokines	IL-1β	Increases ICAM-1 expression, induces reactive oxygen species formation, iNOS expression, NF-κB, MAPK activation	Increased expression in NPDR and correlated with the severity of DR	Anakinra, Canakinumab, Gevokizumab	[36-38]
	TNF-α	Mediates leukocyte adhesion, activates NF-κB	Increased expression in PDR and correlated with the severity of DR	Infliximab, Adalimumab, Golimumab, Triamcinolone acetonide, Fluocinolone, Dexamethasone	[39-41]
	IL-6	Increases vascular permeability, and disrupts the BRB	Increased expression in PDR, DME	Tocilizumab, Triamcinolone acetonide, Fluocinolone, Dexamethasone	[45, 46]
	IL-8	Promotes VEGF expression, induces angiogenesis	Increased expression in PDR, DME	Risuteganib	[47]
Adhesion Molecules	ICAM-1	Increases leukocyte adhesion, endothelial cell damage, capillary non-perfusion	Increased expression in NPDR and correlated with the severity of DR	Triamcinolone acetonide, Fluocinolone, Dexamethasone	[49-51]
	VCAM-1	Increases leukocyte adhesion and stasis, promotes inflammatory factor release	Increased expression in NPDR and correlated with the severity of DR	Triamcinolone acetonide, Fluocinolone, Dexamethasone	[49, 50]
Growth Factors	VEGF	Increases vascular permeability and neovascularization	Increased expression in PDR, DME	Ranibizumab, Aflibercept, Bevacizumab, Fariximab	[52-55]
	PIGF	Promotes angiogenesis	Increased expression in PDR	Faricimab, Conbercept, Aflibercept, Roveredimab, TB-403	[56-58]
	TGF-β	Regulates cell growth, differentiation, proliferation, and apoptosis	Increased expression in PDR	Faricimab, Aflibercept, Ranibizumab, Ozurdex®, Iluvien®	[59, 60]
Chemotactic Factors	MCP-1/CCL-2	Increases VEGF expression, enhances endothelial cell adhesion, promotes inflammatory damage	Increased expression in PDR	Ozurdex®, Iluvien®, Aflibercept, Faricimab	[61, 63]
	CXCL10	Immune stimulation	Increased expression in PDR	Ozurdex®, Iluvien®, Baricitinib, Faricimab	[60, 62, 63]
Others	iNOS	Oxidative stress, cytotoxicity	Increased expression in PDR	α-lipoic acid, Ozurdex®, dimethyl fumarate, Aflibercept	[64, 65]
	COX-2	Promotes neovascularization	Increased expression in DR	Diclofenac, Bromfenac, Celecoxib, Yutiq, Iluvien	[66, 67]
	MMP-9	Oxidative stress, promotes angiogenesis	Increased expression in DR	Ranibizumab, Aflibercept, Faricimab	[68]
	Ang-2	Promotes angiogenesis	Increased expression in PDR	Faricimab	[69]

Abbreviations: DR, diabetic retinopathy; IL-1β, interleukin-1beta; ICAM-1, intercellular adhesion molecule-1; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; NPDR, non-proliferative diabetic retinopathy; TNF-α, tumor necrosis factor-α; PDR, proliferative diabetic retinopathy; IL-6, interleukin-6; BRB, blood-retinal barrier; DME, diabetic macular edema; IL-8, interleukin-8; VEGF, vascular endothelial growth factor; VCAM-1, vascular adhesion molecule-1; PIGF, placental growth factor; TGF-β, transforming growth factor-β; MCP-1/CCL-2, monocyte chemoattractant protein-1; CXCL10, interferon-Induced Protein 10; COX-2, cyclooxygenase-2; MMP-9, matrix Metalloproteinase-9; Ang-2, angiopoietin-2.

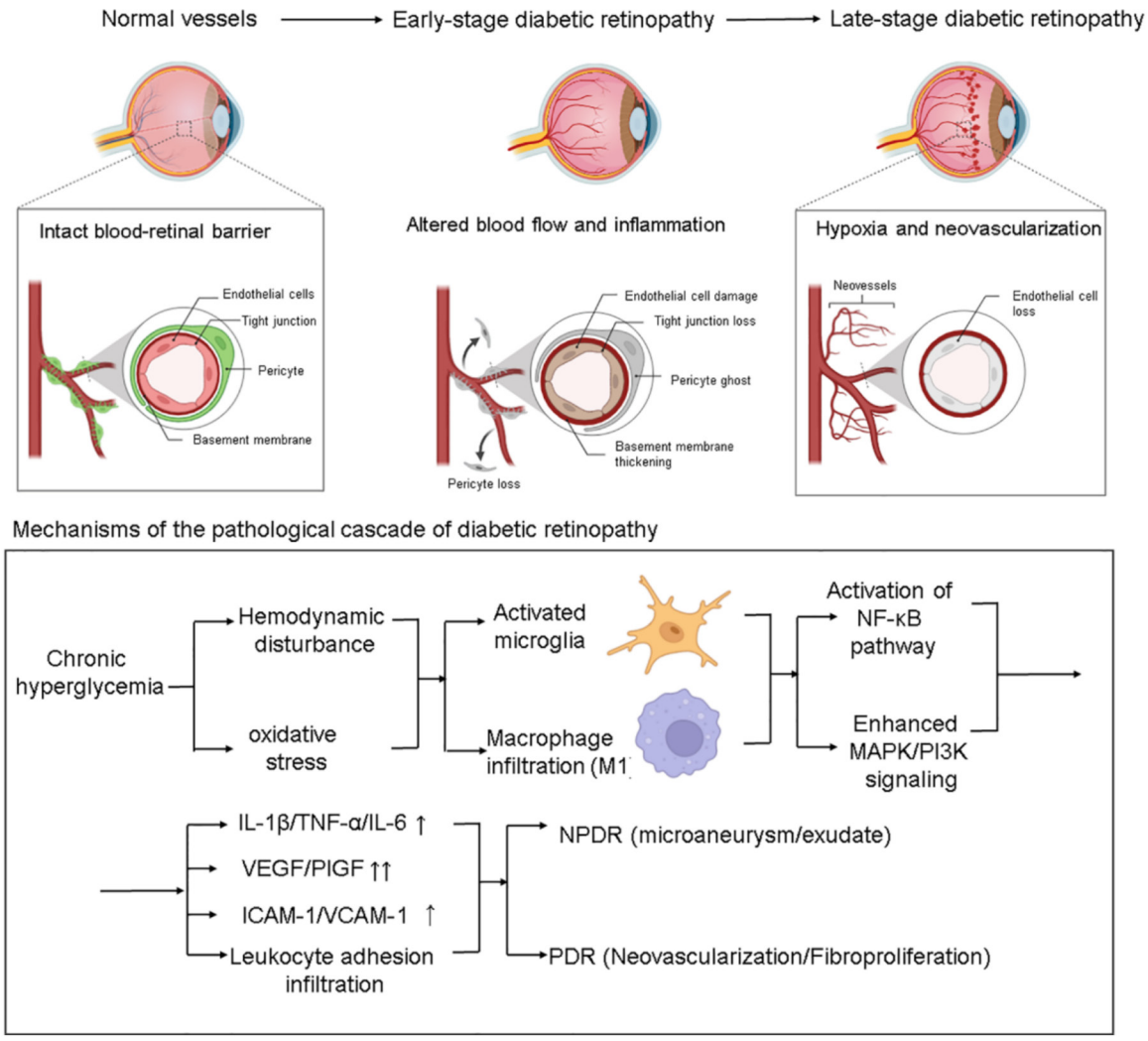

Figure 1. The mechanisms of pathological cascade of DR. Abbreviations: NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; IL-1β, interleukin-1beta; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1.

molecules include intercellular adhesion molecule-1 (ICAM-1) and VCAM-1, induced by hyperglycemia and oxidative stress during early DR. The elevated expression of these two molecules mediates leukocyte-endothelial interactions through integrins and facilitates multistep leukocyte recruitment: migration, aggregation, and adhesion, resulting in increased retinal capillary permeability and stimulated retinal neovascularization [47, 48]. Capillary occlusion can trigger the release of toxic substances (including nitric oxide synthase [NOS]) and inflammatory factors (e.g., IL-1, TNF-α), which exacerbate retinal ischemia and further stimulate ICAM-1 synthesis, forming a vicious cycle that accelerates DR progression [49].

Growth factors

VEGF serves as a potent inducer of retinal vascular permeability and angiogenesis, playing a crucial role in neovascularization in DR [50]. Under conditions of elevated glucose levels, oxidative stress, hemodynamic changes, and inflammatory mediators, VEGF expression is tightly regulated. VEGF enhances capillary permeability by phosphorylating tight junction proteins, leading to increased central subfield thickness, DME, and neovascularization [16]. Inflammatory mediators involved in DR pathogenesis can induce microvascular abnormalities, expand the avascular zone in the central fovea, and exacerbate macular ischemia [51].

These mediators further enhance VEGF expression through the upregulation of ICAM-1 in endothelial cells, which exacerbates the release of cytokines and promotes white blood cell stasis, thereby amplifying the inflammatory response. Additionally, VEGF, as a pro-inflammatory molecule, can stimulate the expression of various inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α, and IL-8. Specific inhibition of VEGF has been shown to reduce the levels of ICAM-1, TNF-α, and NF-κB in diabetic mice, which alleviates retinal leukostasis, and mitigates disruption of the BRB [52].

Placental growth factor (PlGF), a member of the VEGF family, serves as a potent pro-angiogenic factor and plays a crucial role in modulating the inflammatory response. It achieves this by stimulating tissue factor production and promoting the growth, chemotaxis, and survival of monocyte/macrophage through binding to VEGF receptor-1 [20]. Clinical studies have demonstrated elevated levels of PlGF in the vitreous humor of PDR patients [53]. Conversely, the absence of PlGF in diabetic mice has been shown to prevent BRB disruption and inhibit retinal cell apoptosis [54].

Prolonged hyperglycemia in diabetic patients induces abnormal secretion of transforming growth factor-β (TGF-β) by retinal endothelial cells and macrophages. Elevated levels of TGF-β in the bloodstream then stimulate the migration of retinal pigment epithelial cells, fibroblasts, and glial cells into the vitreous humor and subretinal space, thereby promoting the development of PDR [55]. Moreover, the fragile nature of retinal neovascularization, which is prone to rupture and leakage, enables platelets and macrophages from the bloodstream to infiltrate the vitreous humor and retina. This infiltration triggers the release of substantial amounts of TGF-β, creating a vicious cycle that accelerates the formation and progression of PDR [56].

Chemotactic factors

In inflammatory conditions, chemotactic factors such as Monocyte Chemoattractant Protein-1 (MCP-1, also known as CCL-2) and Interferon-Induced Protein 10 (CXCL10) are expressed at elevated levels in the vitreous humor of PDR patients. Furthermore, the concentrations of these factors are positively correlated with the DR severity [57, 58].

MCP-1, through signaling pathways such as phosphoinositide 3-kinase (PI3K) and MAPK, upregulates the expression of NO and VEGF, thereby promoting neovascularization in the retina. Additionally, inflammatory factors such as IL-1β, TNF-α, INF-γ, and platelet-derived growth factor (PDGF) can induce and positively regulate the expression of MCP-1. When acting in concert, these factors contribute to inflammatory damage. MCP-1 can activate adhesion molecules, strengthen the adhesion between vascular endothelial cells, and trigger retinal inflammatory responses [59]. CXCL10 plays a crucial role in the development, migration, and adhesion of T cells, and it can also activate monocytes and natural killer cells, contributing to the onset and progression of various autoimmune disorders [60]. These chemotactic factors further promote the activation and recruitment of white blood cells, leading to the leakage of fluid and neutrophils from blood vessels into retinal tissues.

Other inflammatory mediators

Inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) play significant roles in the inflammatory response during the progression of DR [61]. iNOS catalyzes the production of NO, which, under normal physiological conditions, is essential for regulating vasodilation and inhibiting platelet aggregation. However, under high glucose conditions, the overexpression of iNOS leads to excessive NO production. The reaction between NO and superoxide anions generates peroxynitrite, a potent oxidant that induces oxidative stress, impairing retinal cell function and triggering apoptosis [62]. Furthermore, NO enhances vascular permeability and promotes neovascularization through the activation of the cyclic guanosine monophosphate signaling pathway, thereby contributing to the pathological processes of DR [63].

COX-2, as a key enzyme in the inflammatory response, triggers the release of the pro-inflammatory cytokine prostaglandin E2 in the early phases of DR. This, in turn, leads to increased VEGF expression and promotes the formation

of neovascularization in the retina [64]. Research by Wu et al. [65] has shown that salidroside can directly bind to COX-2, inhibiting its expression and thereby mitigating the inflammatory response in ultraviolet-induced mouse epidermal JB6Cl41 cells and human skin keratinocytes.

Matrix metalloproteinase-9 (MMP-9) plays a dual role in DR progression by degrading extracellular matrix components and inducing oxidative stress under hyperglycemic conditions. Additionally, MMP-9 interaction with CD44 triggers TGF-β release, which contributes to neovascularization in PDR [66]. The balance between the angiopoietin (Ang) family members (Ang-1 and Ang-2) and the Ang/tyrosine kinase receptor 2 system determines vascular formation and stability. Clinical evidence demonstrates significantly elevated serum Ang-2 levels in PDR patients compared to NPDR cases. This Ang-2 upregulation drives the formation of immature and leak-prone neovessels, exacerbating retinal edema and inflammatory responses [67].

Role of inflammatory cells in DR

Retinal cell dysfunction may exacerbate inflammation in the early phases of DR. Key pathological changes, including microglial activation, Müller cell proliferation, retinal pigment epithelium secretion, endothelial cell proliferation, and pericyte loss, are associated with BRB breakdown and DME progression [68, 69]. The involvement of specific inflammatory cells in DR pathogenesis is shown in **Table 2**.

Leukocytes

Leukocyte adhesion and aggregation to the vascular endothelium represent critical early events in retinal inflammation, contributing to microcirculatory dysfunction and BRB breakdown in DR [70]. This process is mediated by mutual recognition between endothelial cells and leukocyte surface adhesion molecules. Under inflammatory conditions, VEGF and ICAM-1 expression in retinal endothelial cells is upregulated. ICAM-1 binds to its receptors, facilitating leukocyte transendothelial migration and subsequent adhesion. VEGF can induce the expression of endothelial NOS, which further promotes leukocyte adhesion.

Macrophages

Several studies suggest that macrophages are a primary driving force in PDR pathogenesis [71, 72]. In the early stages of DR, macrophages can polarize into M1 phenotype, exacerbating retinal vascular endothelial damage by secreting inflammatory factors. This increases vascular permeability, disrupts the BRB, and leads to retinal leakage, hemorrhage, microaneurysm formation, and other pathological changes such as vascular occlusion [73]. In the late stages of DR, M2 macrophages become progressively activated, inducing chemotaxis and fibrosis through the secretion of leukotrienes and fibronectin. They also influence cell proliferation by synthesizing VEGF and PDGF, promoting neovascularization and fibrovascular membrane formation [74]. Studies have shown that both in vitro and in vivo, human monocytes and macrophages are activated, with elevated levels of CD11c and iNOS in macrophages treated with high glucose, as well as in circulating monocytes from DR patients [75]. Additionally, activated macrophages release excessive inflammatory factors, including TNF-α, IL-1β, IL-6, and IL-12, through the NF-κB signaling pathway. However, their phagocytic function is impaired, suggesting that macrophage dysfunction may exacerbate DR inflammation [76, 77].

Astrocytes

Astrocytes are the primary source of VEGF and inflammatory factors in the retina [78]. In DR, retinal astrocytes are closely associated with retinal blood vessels and play a crucial role in maintaining the BRB [79]. Additionally, astrocytes contribute to the inflammatory response by producing pro-inflammatory cytokines such as IL-1β, TNF-α, and iNOS, which exacerbate damage to the retinal neurovascular unit and promote neuroinflammation [80].

Müller cells

Müller cells, the primary glial cells of the retina, provide support and nourishment to retinal neurons. They play a crucial role in maintaining retinal integrity and are involved in various pathological processes [81]. In DR, the expression of glial fibrillary acidic protein (GFAP) is increased [82], and the secretion of pro-inflammatory mediators such as IL-1β, IL-6, IL-8, VEGF,

Table 2. The role of inflammatory cells in DR

Category	Mediator	Mechanism	Stage of DR Involved	Therapy	References
Leukocyte	VEGF/ICAM-1	adhesion, aggregation, and sedimentation	causing BRB damage in early DR	Yutiq, Iluvien, Trivaris, Triesence, Ozurdex, Aflibercept, Faricimab, Ranibizumab	[70]
Macrophage	M1/M2 type	Early destruction of BRB, late promotion of neovascularization and fibrovascular membrane formation, exacerbation of DR inflammation	Increased expression in NPDR and correlated with the severity of DR	Yutiq, Iluvien, Ozurdex, INCB-8765, PLX3397, BLZ945, Pioglitazone, Glycyrrhizin	[73, 74]
Astrocyte	VEGF	Increases vascular permeability and neovascularization	Increased expression in PDR, DME	Ozurdex®, Iluvien®, Aflibercept, Faricimab	[78, 79]
Müller cells	GFAP/VEGF/ICAM-1	It is the main component of retinal astrocytes, providing support and nutrition for retinal neurons	Participate in the inflammatory process of DR	Aflibercept, Faricimab, Ranibizumab, Ozurdex®, Iluvien®, N-acetylcysteine, Epalrestat	[81-85]

Abbreviations: DR, diabetic retinopathy; VEGF, vascular endothelial growth factor; ICAM-1, intercellular adhesion molecule-1; BRB, blood-retinal barrier; NPDR, non-proliferative diabetic retinopathy; GFAP, glial fibrillary acidic protein; DME, diabetic macular edema.

and ICAM-1 is elevated. This suggests that, during the progression of diabetes, Müller cell proliferation and reactive gliosis contribute to the inflammatory response [83-85].

Therapeutic approaches for DR inflammation

Given the critical role of inflammation in the pathogenesis of DR, targeting or inhibiting inflammation is considered a potential treatment strategy. Glucocorticoids exhibit potent anti-inflammatory effects, by suppressing the expression of various inflammatory mediators, reducing retinal edema, and alleviating inflammatory responses. Local application of glucocorticoids can effectively treat vision-threatening DR [86]. Studies [87] have demonstrated that long-acting water-soluble steroid dexamethasone reduces VEGF expression. Further research indicates that dexamethasone reduces VEGF levels by inhibiting p38 MAPK activity, extracellular signal-regulated kinase activity and MMP-9 expression, thereby reducing neovascularization [88].

Anti-VEGF therapy has emerged as a novel and widely adopted approach in clinical practice in recent years. Currently available anti-VEGF drugs include Ranibizumab, Bevacizumab, Conbercept, and Aflibercept, with Conbercept injections as the primary treatment. Conbercept, a VEGF multi-target recombinant fusion protein, effectively blocks the VEGF receptor signaling pathway, thereby reducing retinal edema, promoting the absorption of hemorrhages, decreasing retinal vascular permeability, alleviating inner retinal hypoxia and ischemia, and reducing retinal nerve fiber layer thickness. These effects collectively inhibit neovascularization and retinal microvascular leakage, facilitating visual recovery and enhancing treatment efficacy [89, 90]. Study have demonstrated that 20 weeks of Conbercept intervention in diabetic mice inhibits the NF-κB signaling pathway, reduces the expression of ICAM-1, IL-1β, IL-6, and TNF-α, and improves PDR [91].

Nonsteroidal anti-inflammatory drugs achieve their anti-inflammatory effects by inhibiting COX activity and reducing the formation of prostaglandins. Sodium bromfenac, as a new generation NSAID, is highly effective and safe for anti-inflammatory and analgesic purposes, primarily targeting COX-2 [92]. In a preliminary study, local application of Sodium bromfenac significantly reduced central foveal retinal thickness in DME patients, although it did not significantly improve vision [93]. Nepafenac is a prodrug that inhibits COX-1 and COX-2 activity through its active metabolite Amfenac [94]. Animal experiments have shown that topical Nepafenac significantly inhibits pro-inflammatory cytokine prostaglandin E2 content in corneal tissues, improves corneal edema symptoms, and decreases corneal neovascularization [95].

Moreover, numerous new anti-inflammatory targets are being developed to address key molecules in the inflammatory pathway, such as TNF-α, IL-1β, and IL-6, representing an emerging area of research in DR treatment. TNF-α inhibitors, including Infliximab, Adalimumab, and Golimumab [96], have demonstrated some degree of improvement in vision and retinal edema in patients [97]. Canakinumab, an IL-1β inhibitor, reduces DME and stabilizes the condition, aiding in the treatment of PDR without affecting neovascular formation [98]. IL-6 inhibitors such as Siltuximab, Sirukumab, Olokizumab, and Clazakizumab can globally block IL-6 signal transduction [99].

Conclusion and future perspectives

DR represents a major microvascular complication of diabetes, characterized by complex inflammatory pathogenesis involving multiple interrelated pathways rather than isolated factors. This review elucidates the mechanistic roles of inflammatory cells, cytokines, and associated signaling pathways in DR progression, highlighting that targeted modulation of intra- and intercellular inflammatory signaling may offer promising therapeutic strategies. While substantial advances have been achieved in understanding inflammatory mechanisms in DR, current research remains constrained by several limitations. Most therapeutic studies rely predominantly on animal models and in vitro systems, with a notable paucity of large-scale clinical trials to validate long-term efficacy and safety in human populations. In the future, the mechanism of action of multi-target inflammatory factors should be further elucidated, and research into anti-inflammatory mechanisms should be enhanced. Additionally, the development of new formulations for the anti-inflammatory treatment of DR is critical for advancing clinical treatment options.

Disclosure of conflict of interest

None.

Address correspondence to: Jin-Ou Huang, Department of Ophthalmology, Shengzhou People's Hospital (Shengzhou Branch of The First Affiliated Hospital of Zhejiang University School of Medicine), No. 666 Dangui Road, Chengnan New District, Shengzhou 312400, Zhejiang, China. E-mail: 13605855780@163.com

References

[1] Kaur A, Kumar R and Sharma A. Diabetic retinopathy leading to blindness- a review. Curr Diabetes Rev 2024; 20: e240124225997.

[2] Tan TE and Wong TY. Diabetic retinopathy: looking forward to 2030. Front Endocrinol (Lausanne) 2023; 13: 1077669.

[3] Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, Bikbov MM, Wang YX, Tang Y, Lu Y, Wong IY, Ting DSW, Tan GSW, Jonas JB, Sabanayagam C, Wong TY and Cheng CY. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. Ophthalmology 2021; 128: 1580-1591.

[4] Li H, Liu X, Zhong H, Fang J, Li X, Shi R and Yu Q. Research progress on the pathogenesis of diabetic retinopathy. BMC Ophthalmol 2023; 23: 372.

[5] Luo JX, Hu ZZ, Liu QH and Fang Y. The influence of anti-VEGF adjuvant therapy on intraocular inflammatory factor levels in proliferative diabetic retinopathy. Int J Ophthalmol 2023, 23: 827-832.

[6] Lee SJ, Noh SE, Jo DH, Cho CS, Park KS and Kim JH. IL-10-induced modulation of macrophage polarization suppresses outer-blood-retinal barrier disruption in the streptozotocin-induced early diabetic retinopathy mouse model. FASEB J 2024; 38: e23638.

[7] Tang L, Xu GT and Zhang JF. Inflammation in diabetic retinopathy: possible roles in pathogenesis and potential implications for therapy. Neural Regen Res 2023; 18: 976-982.

[8] Hu A, Schmidt MHH and Heinig N. Microglia in retinal angiogenesis and diabetic retinopathy. Angiogenesis 2024; 27: 311-331.

[9] Li J, Zhao T and Sun Y. Interleukin-17A in diabetic retinopathy: the crosstalk of inflammation and angiogenesis. Biochem Pharmacol 2024; 225: 116311.

[10] Invernizzi A, Chhablani J, Viola F, Gabrielle PH, Zarranz-Ventura J and Staurenghi G. Diabetic retinopathy in the pediatric population: pathophysiology, screening, current and future treatments. Pharmacol Res 2023; 188: 106670.

[11] Yang J and Liu Z. Mechanistic pathogenesis of endothelial dysfunction in diabetic nephropathy and retinopathy. Front Endocrinol (Lausanne) 2022; 13: 816400.

[12] Jiang Y, Zhou L and Yao L. Serum levels of interleukin-18 in diabetic retinopathy patients: a meta-analysis. Eur J Ophthalmol 2023; 33: 2259-2266.

[13] Saucedo L, Pfister IB, Schild C and Garweg JG. Association of inflammation-related markers and diabetic retinopathy severity in the aqueous humor, but not serum of type 2 diabetic patients. PLoS One 2023; 18: e0293139.

[14] Tsai T, Alwees M, Asaad MA, Theile J, Kakkassery V, Dick HB, Schultz T and Joachim SC. Increased angiopoietin-1 and -2 levels in human vitreous are associated with proliferative diabetic retinopathy. PLoS One 2023; 18: e0280488.

[15] Wen X, Ng TK, Liu Q, Wu Z, Zhang G and Zhang M. Azelaic acid and guanosine in tears improve discrimination of proliferative from non-proliferative diabetic retinopathy in type-2 diabetes patients: a tear metabolomics study. Heliyon 2023; 9: e16109.

[16] Xu C, Li H, Xu Q, Zhao K, Hao M, Lin W, Ma X, Gao X and Kuang H. Dapagliflozin ameliorated retinal vascular permeability in diabetic retinopathy rats by suppressing inflammatory factors. J Diabetes Complications 2024; 38: 108631.

[17] Vujosevic S, Lupidi M, Donati S, Astarita C, Gallinaro V and Pilotto E. Role of inflammation in diabetic macular edema and neovascular age-related macular degeneration. Surv Ophthalmol 2024; 69: 870-881.

[18] Mi XJ, Gu XY and Yu XB. Changes in intraocular cytokines in DR patients and their significance. Chin J Exp Ophthalmol 2024; 42: 750-757.

[19] Wang ZL, Zhang XY, Tan CY, Zhuang M, Zhu L, Zheng XH, Yao Y and Wei TT. FXR suppress Müller cell activation by regulating cGAS/STING pathway in diabetic retinopathy. FEBS J 2025; [Epub ahead of print].

[20] Ren FF, Chen F, Fu Q, Zhang XD, Wu GP, Yang SQ, Song YH, Li Y, Lai JJ and Yu H. Study on the correlation between disease progression in patients with diabetic retinopathy and aqueous humor cytokines. Ophthalmic New Advances 2024; 44: 464-469.

[21] Sabaner MC, Akdogan M, Doğan M, Oral AY, Duman R, Koca T and Bozkurt E. Inflammatory cytokines, oxidative and antioxidative stress levels in patients with diabetic macular edema and hyperreflective spots. Eur J Ophthalmol 2021; 31: 2535-2545.

[22] van der Wijk AE, Hughes JM, Klaassen I, Van Noorden CJF and Schlingemann RO. Is leukostasis a crucial step or epiphenomenon in

the pathogenesis of diabetic retinopathy? J Leukoc Biol 2017; 102: 993-1001.
[23] Herdade AS, Silva IM, Calado Â, Saldanha C, Nguyen NH, Hou I, Castanho M and Roy S. Effects of diabetes on microcirculation and leukostasis in retinal and non-ocular tissues: implications for diabetic retinopathy. Biomolecules 2020; 10: 1583.
[24] Hu A, Schmidt MHH and Heinig N. Microglia in retinal angiogenesis and diabetic retinopathy. Angiogenesis 2024; 27: 311-331.
[25] Yao X, Zhao Z, Zhang W, Liu R, Ni T, Cui B, Lei Y, Du J, Ai D, Jiang H, Lv H and Li X. Specialized retinal endothelial cells modulate blood-retina barrier in diabetic retinopathy. Diabetes 2024; 73: 225-236.
[26] Spencer BG, Estevez JJ, Liu E, Craig JE and Finnie JW. Pericytes, inflammation, and diabetic retinopathy. Inflammopharmacology 2020; 28: 697-709.
[27] Mazzeo A, Arroba AI, Beltramo E, Valverde AM and Porta M. Somatostatin protects human retinal pericytes from inflammation mediated by microglia. Exp Eye Res 2017; 164: 46-54.
[28] Barresi C, Chhablani J, Dolz-Marco R, Gallego-Pinazo R, Berni A, Bandello F and Borrelli E. Retinal neurodegeneration in age-related macular degeneration. Eur J Ophthalmol 2024; 34: 624-630.
[29] Zhang Q, Qi S, You J and Wang C. The role of retinal glial cells and related factors in macular edema. Biochem Biophys Res Commun 2024; 695: 149415.
[30] Li X and Li XH. The association between retinal glial cells and proliferative vitreoretinopathy. Chin J Exp Ophthalmol 2022; 40: 1197-1201.
[31] Chen Z, Wang ZP and Li H. The role of microglial cells in the retinal neurovascular unit in diabetic retinopathy. Int J Ophthalmol 2024; 24: 731-736.
[32] Douglass JD, Ness KM, Valdearcos M, Wyse-Jackson A, Dorfman MD, Frey JM, Fasnacht RD, Santiago OD, Niraula A, Banerjee J, Robblee M, Koliwad SK and Thaler JP. Obesity-associated microglial inflammatory activation paradoxically improves glucose tolerance. Cell Metab 2023; 35: 1613-1629, e8.
[33] Li Y, Kong E, Ding R, Chu R, Lu J, Deng M, Hua T, Yang M, Wang H, Chen D, Song H, Wei H, Zhang P, Han C and Yuan H. Hyperglycemia-induced Sirt3 downregulation increases microglial aerobic glycolysis and inflammation in diabetic neuropathic pain pathogenesis. CNS Neurosci Ther 2024; 30: e14913.
[34] Tan TE and Wong TY. Diabetic retinopathy: looking forward to 2030. Front Endocrinol (Lausanne) 2023; 13: 1077669.
[35] Semeraro F, Morescalchi F, Cancarini A, Russo A, Rezzola S and Costagliola C. Diabetic retinopathy, a vascular and inflammatory disease: therapeutic implications. Diabetes Metab 2019; 45: 517-527.
[36] Fang M, Wan W, Li Q, Wan W, Long Y, Liu H and Yang X. Asiatic acid attenuates diabetic retinopathy through TLR4/MyD88/NF-κB p65 mediated modulation of microglia polarization. Life Sci 2021; 277: 119567.
[37] Peng Y, Hu L, Xu H, Fang J and Zhong H. Resveratrol alleviates reactive oxygen species and inflammation in diabetic retinopathy via SIRT1/HMGB1 pathway-mediated ferroptosis. Toxicol Appl Pharmacol 2025; 495: 117214.
[38] McDermott EP and O'Neill LA. Ras participates in the activation of p38 MAPK by interleukin-1 by associating with IRAK, IRAK2, TRAF6, and TAK-1. J Biol Chem 2002; 277: 7808-7815.
[39] Götz L, Rueckschloss U, Reimer A, Bömmel H, Beilhack A, Ergün S and Kleefeldt F. Vascular inflammaging: endothelial CEACAM1 expression is upregulated by TNF-α via independent activation of NF-κB and β-catenin signaling. Aging Cell 2025; 24: e14384.
[40] Liu Y, Li L, Pan N, Gu J, Qiu Z, Cao G, Dou Y, Dong L, Shuai J and Sang A. TNF-α released from retinal Müller cells aggravates retinal pigment epithelium cell apoptosis by upregulating mitophagy during diabetic retinopathy. Biochem Biophys Res Commun 2021; 561: 143-150.
[41] Behl Y, Krothapalli P, Desta T, DiPiazza A, Roy S and Graves DT. Diabetes-enhanced tumor necrosis factor-alpha production promotes apoptosis and the loss of retinal microvascular cells in type 1 and type 2 models of diabetic retinopathy. Am J Pathol 2008; 172: 1411-1418.
[42] Thazhe Poyil NJ, Vadakkekuttical RJ and Radhakrishnan C. Correlation of periodontal inflamed surface area with glycated hemoglobin, interleukin-6 and lipoprotein(a) in type 2 diabetes with retinopathy. World J Diabetes 2024; 15: 686-696.
[43] Wu J, Zhong Y, Yue S, Yang K, Zhang G, Chen L and Liu L. Aqueous humor mediator and cytokine aberrations in diabetic retinopathy and diabetic macular edema: a systematic review and meta-analysis. Dis Markers 2019; 2019: 6928524.
[44] Valle ML, Dworshak J, Sharma A, Ibrahim AS, Al-Shabrawey M and Sharma S. Inhibition of interleukin-6 trans-signaling prevents inflammation and endothelial barrier disruption in retinal endothelial cells. Exp Eye Res 2019; 178: 27-36.
[45] Wang Y, Zhai WL and Yang YW. Association between NDRG2/IL-6/STAT3 signaling pathway and diabetic retinopathy in rats. Eur Rev Med Pharmacol Sci 2020; 24: 3476-3484.
[46] Hu KK, Tian CW, Li MH, Wu T, Gong M, Wei XL, Du YR, Hui YN and Du HJ. Differential analysis

of aqueous humor cytokine levels in patients with macular edema secondary to diabetic retinopathy or retinal vein occlusion. Int J Ophthalmol 2023; 16: 1041-1046.
[47] Ekelund C, Dereke J, Nilsson C and Landin-Olsson M. Are soluble E-selectin, ICAM-1, and VCAM-1 potential predictors for the development of diabetic retinopathy in young adults, 15-34 years of age? A Swedish prospective cohort study. PLoS One 2024; 19: e0304173.
[48] Siddiqui K, George TP, Mujammami M, Isnani A and Alfadda AA. The association of cell adhesion molecules and selectins (VCAM-1, ICAM-1, E-selectin, L-selectin, and P-selectin) with microvascular complications in patients with type 2 diabetes: a follow-up study. Front Endocrinol (Lausanne) 2023; 14: 1072288.
[49] Loporchio DF, Tam EK, Cho J, Chung J, Jun GR, Xia W, Fiorello MG, Siegel NH, Ness S, Stein TD and Subramanian ML. Cytokine levels in human vitreous in proliferative diabetic retinopathy. Cells 2021; 10: 1069.
[50] Shaw P, Dwivedi SKD, Bhattacharya R, Mukherjee P and Rao G. VEGF signaling: role in angiogenesis and beyond. Biochim Biophys Acta Rev Cancer 2024; 1879: 189079.
[51] Nagasato D, Muraoka Y, Tanabe M, Nishigori N, Osaka R, Mitamura Y, Tabuchi H, Kadomoto S, Murakami T, Ooto S, Suzuma K and Tsujikawa A. Foveal thickness fluctuation in anti-VEGF treatment for branch retinal vein occlusion: a long-term study. Ophthalmol Retina 2022; 6: 567-574.
[52] Zhou Y, Zhao C, Shi Z, Heger Z, Jing H, Shi Z, Dou Y, Wang S, Qiu Z and Li N. A glucose-responsive hydrogel inhibits primary and secondary BRB injury for retinal microenvironment remodeling in diabetic retinopathy. Adv Sci (Weinh) 2024; 11: e2402368.
[53] Zhang X, Wu J, Wu C, Bian AL, Geng S and Dai RP. Comparison of aqueous humor levels of PlGF and VEGF in proliferative diabetic retinopathy before and after intravitreal conbercept injection. Diabetes Res Clin Pract 2020; 162: 108083.
[54] Huang H, He J, Johnson D, Wei Y, Liu Y, Wang S, Lutty GA, Duh EJ and Semba RD. Deletion of placental growth factor prevents diabetic retinopathy and is associated with Akt activation and HIF1α-VEGF pathway inhibition. Diabetes 2015; 64: 200-212.
[55] Sripathi SR, Hu MW, Turaga RC, Mikeasky R, Satyanarayana G, Cheng J, Duan Y, Maruotti J, Wahlin KJ, Berlinicke CA, Qian J, Esumi N and Zack DJ. IKKβ inhibition attenuates epithelial mesenchymal transition of human stem cell-derived retinal pigment epithelium. Cells 2023; 12: 1155.
[56] Callan A, Jha S, Valdez L, Baldado L and Tsin A. TGF-β signaling pathways in the development of diabetic retinopathy. Int J Mol Sci 2024; 25: 3052.
[57] Song S, Yu X, Zhang P and Dai H. Increased levels of cytokines in the aqueous humor correlate with the severity of diabetic retinopathy. J Diabetes Complications 2020; 34: 107641.
[58] Pan X, Tan X, McDonald J, Kaminga AC, Chen Y, Dai F, Qiu J, Zhao K and Peng Y. Chemokines in diabetic eye disease. Diabetol Metab Syndr 2024; 16: 115.
[59] Wang S, Bao N, Li M, Liu D and Tao L. Ets2 exacerbates diabetic retinopathy by aggravating the proliferation of endothelial cells and inflammatory response. Biochem Genet 2024; [Epub ahead of print].
[60] Hu HL and Luo M. The influence of exogenous chemotactic factors on the function of human umbilical vein endothelial cells in a high glucose environment. Int J Ophthalmol 2020; 20: 773-777.
[61] Tang L, Xu GT and Zhang JF. Inflammation in diabetic retinopathy: possible roles in pathogenesis and potential implications for therapy. Neural Regen Res 2023; 18: 976-982.
[62] Yang FY, Su J, Wang L, Wang LH and Zhang M. Protective mechanism of reduced glutathione regulating Nrf2/iNOS signaling on the retina of DR rats. J Transl Med 2022; 11: 36-41.
[63] Hernández-Ramírez E, Sánchez-Chávez G, Estrella-Salazar LA and Salceda R. Nitrosative stress in the rat retina at the onset of streptozotocin-induced diabetes. Cell Physiol Biochem 2017; 42: 2353-2363.
[64] Zhang QL, Zhao N and Li ZJ. The impact of rhodiola glycoside on diabetic rat retinopathy through the COX-2/PGE2/VEGF pathway. Journal of China Medical University 2023; 52: 731-735.
[65] Wu D, Yuan P, Ke C, Xiong H, Chen J, Guo J, Lu M, Ding Y, Fan X, Duan Q, Shi F and Zhu F. Salidroside suppresses solar ultraviolet-induced skin inflammation by targeting cyclooxygenase-2. Oncotarget 2016; 7: 25971-25982.
[66] Ritu, Goyal RK, Narwal S, Bhatt A, Sehrawat R, Devi P, Gulati M and Singla RK. Role of MMP-9 and NF-κB in diabetic retinopathy: progression and potential role of bioflavonoids in the mitigation of diabetic retinopathy. Curr Med Chem 2024; [Epub ahead of print].
[67] Wang Y, Fang J, Niu T, Xing X, Wang H, Shi X, Liu Y, Liu X, Chen C and Liu K. Serum Ang-1/Ang-2 ratio may be a promising biomarker for evaluating severity of diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol 2023; 261: 49-55.
[68] Wang Y, Yang X, Li Q, Zhang Y, Chen L, Hong L, Xie Z, Yang S, Deng X, Cao M, Yi G and Fu M. Single-cell RNA sequencing reveals the Müller

subtypes and inner blood-retinal barrier regulatory network in early diabetic retinopathy. Front Mol Neurosci 2022; 15: 1048634.
[69] Gelat B, Rathaur P, Malaviya P, Patel B, Trivedi K, Johar K and Gelat R. The intervention of epithelial-mesenchymal transition in homeostasis of human retinal pigment epithelial cells: a review. J Histotechnol 2022; 45: 148-160.
[70] Joy SS and Siddiqui K. Molecular and pathophysiological mechanisms of diabetic retinopathy in relation to adhesion molecules. Curr Diabetes Rev 2019; 15: 363-371.
[71] Wang W, Sun G, Xu A and Chen C. Proliferative diabetic retinopathy and diabetic macular edema are two factors that increase macrophage-like cell density characterized by en face optical coherence tomography. BMC Ophthalmol 2023; 23: 46.
[72] Jia Y and Zhou Y. Involvement of lncRNAs and macrophages: potential regulatory link to angiogenesis. J Immunol Res 2020; 2020: 1704631.
[73] Wang D, Su ZH, Gao JH and Jiang F. Analysis of the influence of ranibizumab on the expression of pro-inflammatory cytokines in M1 macrophages of patients with severe proliferative diabetic retinopathy. Western Medicine 2024; 36: 1849-1853.
[74] Yao Y, Li J, Zhou Y, Wang S, Zhang Z, Jiang Q and Li K. Macrophage/microglia polarization for the treatment of diabetic retinopathy. Front Endocrinol (Lausanne) 2023; 14: 1276225.
[75] Torres-Castro I, Arroyo-Camarena ÚD, Martínez-Reyes CP, Gómez-Arauz AY, Dueñas-Andrade Y, Hernández-Ruiz J, Béjar YL, Zaga-Clavellina V, Morales-Montor J, Terrazas LI, Kzhyshkowska J and Escobedo G. Human monocytes and macrophages undergo M1-type inflammatory polarization in response to high levels of glucose. Immunol Lett 2016; 176: 81-89.
[76] Yao Y, Li J, Zhou Y, Wang S, Zhang Z, Jiang Q and Li K. Macrophage/microglia polarization for the treatment of diabetic retinopathy. Front Endocrinol (Lausanne) 2023; 14: 1276225.
[77] Al-Rashed F, Sindhu S, Arefanian H, Al Madhoun A, Kochumon S, Thomas R, Al-Kandari S, Alghaith A, Jacob T, Al-Mulla F and Ahmad R. Repetitive intermittent hyperglycemia drives the M1 polarization and inflammatory responses in thp-1 macrophages through the mechanism involving the TLR4-IRF5 pathway. Cells 2020; 9: 1892.
[78] Linnerbauer M, Wheeler MA and Quintana FJ. Astrocyte crosstalk in CNS inflammation. Neuron 2020; 108: 608-622.
[79] Dharmarajan S, Carrillo C, Qi Z, Wilson JM, Baucum AJ 2nd, Sorenson CM, Sheibani N and Belecky-Adams TL. Retinal inflammation in murine models of type 1 and type 2 diabetes with diabetic retinopathy. Diabetologia 2023; 66: 2170-2185.
[80] Patani R, Hardingham GE and Liddelow SA. Functional roles of reactive astrocytes in neuroinflammation and neurodegeneration. Nat Rev Neurol 2023; 19: 395-409.
[81] Lai D, Wu Y, Shao C and Qiu Q. The role of Müller cells in diabetic macular edema. Invest Ophthalmol Vis Sci 2023; 64: 8.
[82] Sarusie MVK, Rönnbäck C, Jespersgaard C, Baungaard S, Ali Y, Kessel L, Christensen ST, Brøndum-Nielsen K, Møllgård K, Rosenberg T, Larsen LA and Grønskov K. A novel GFAP frameshift variant identified in a family with optico-retinal dysplasia and vision impairment. Hum Mol Genet 2024; 33: 2145-2158.
[83] Nagayach A, Patro N and Patro I. Astrocytic and microglial response in experimentally induced diabetic rat brain. Metab Brain Dis 2014; 29: 747-761.
[84] Wang Y, Yu H, Li J, Liu W, Yu S, Lv P, Zhao L, Wang X, Zuo Z and Liu X. Th22 cells induce Müller cell activation via the Act1/TRAF6 pathway in diabetic retinopathy. Cell Tissue Res 2022; 390: 367-383.
[85] Wang K, Zhu MH, Chen LL, Tu YY, Wang GM and Liang SZ. The effect of long non-coding RNA MEG3 regulating miR-34a on Müller cell activation and inflammatory cytokine secretion in diabetic retinopathy. Ophthalmic New Advances 2021; 41: 42-47.
[86] Chinese Diabetes Society. Chinese type 2 diabetes prevention and treatment guidelines (2020 edition). Chinese Journal of Diabetes 2021; 13: 315-409.
[87] Hollborn M, Stathopoulos C, Steffen A, Wiedemann P, Kohen L and Bringmann A. Positive feedback regulation between MMP-9 and VEGF in human RPE cells. Invest Ophthalmol Vis Sci 2007; 48: 4360-4367.
[88] Hsiao CC, Chang YC, Hsiao YT, Chen PH, Hsieh MC, Wu WC and Kao YH. Triamcinolone acetonide modulates TGF-β2-induced angiogenic and tissue-remodeling effects in cultured human retinal pigment epithelial cells. Mol Med Rep 2021; 24: 802.
[89] Li J and Li JM. Comparative study on the effects of laser photocoagulation combined with anti-VEGF drugs at different time points in patients with diabetic retinopathy. Chinese Medicine Guide 2021; 2021: 85-86.
[90] Zhang Y. The therapeutic effect of anti-VEGF regimen on diabetic retinopathy patients and its impact on inflammatory factors. Medical Forum 2024; 45: 1759-1763.
[91] Xia JP, Liu SQ and Wang S. Intravitreal conbercept improves outcome of proliferative diabet-

ic retinopathy through inhibiting inflammation and oxidative stress. Life Sci 2021; 265: 118795.
[92] Gabr AF, Kamel MF and Elbarawy AA. Topical bromfenac as adjunctive treatment with intravitreal ranibizumab for diabetic macular edema. Int Ophthalmol 2023; 43: 3219-3226.
[93] Pinna A, Blasetti F, Ricci GD and Boscia F. Bromfenac eyedrops in the treatment of diabetic macular edema: a pilot study. Eur J Ophthalmol 2017; 27: 326-330.
[94] Bezatis A, Georgou I, Dedes J, Theodossiadis P and Chatziralli I. Nepafenac in cataract surgery. Clin Exp Optom 2022; 105: 263-267.
[95] Liu Y, Zhang X and Su J. Study on the effect of Nepafenac on prostaglandin E2 in corneal tissues. Journal of Modern Medicine in China 2017; 27: 7-12.
[96] Mitoma H, Horiuchi T, Tsukamoto H and Ueda N. Molecular mechanisms of action of anti-TNF-α agents - comparison among therapeutic TNF-α antagonists. Cytokine 2018; 101: 56-63.
[97] Sfikakis PP, Markomichelakis N, Theodossiadis GP, Grigoropoulos V, Katsilambros N and Theodossiadis PG. Regression of sight-threatening macular edema in type 2 diabetes following treatment with the anti-tumor necrosis factor monoclonal antibody infliximab. Diabetes Care 2005; 28: 445-447.
[98] Lanka N, Acharya P, Virani S, Afreen S, Perthiani A, Sangster E and Arcia Franchini AP. Safety and efficacy of Canakinumab for the prevention and control of type 2 diabetes mellitus and its complications: a systematic review. Cureus 2024; 16: e67065.
[99] Sharma S. Interleukin-6 trans-signaling: a pathway with therapeutic potential for diabetic retinopathy. Front Physiol 2021; 12: 689429.