Review

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Research Progress on Multicellular Pathogenic Mechanisms and Targeted Diagnostic and Therapeutic Innovations in Diabetic Retinopathy

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Diabetic retinopathy (DR) is among the most common microvascular complications of diabetes and is the leading cause of blindness among the working-age population. According to conventional perspectives, DR is a purely microvascular disease; however, accumulating evidence has demonstrated that it is fundamentally a complex condition characterized by coordinated multicellular injury to the retinal neurovascular unit. Under hyperglycemic conditions, retinal pericytes, endothelial cells, Müller cells, microglia, and retinal neurons display highly heterogeneous pathological mechanisms, which, through epigenetic reprogramming, metabolic dysregulation, oxidative stress, inflammation, and intercellular crosstalk, collectively drive the progression of DR from nonproliferative to proliferative stages. This review summarizes the cell-heterogeneous injury mechanisms and intercellular signaling networks involved and the clinical manifestations of DR progression from the perspective of cell and molecular medicine and, on the basis of relevant cellular damage targets, integrates current diagnostic and therapeutic strategies as well as emerging research directions, aiming to provide a theoretical foundation for precise targeting of multicellular pathological processes in DR.

Keywords: diabetic retinopathy; neurovascular unit; cellular heterogeneity; pathological mechanisms; clinical staging and complications; novel diagnosis and treatment

Introduction

Diabetes, a global epidemic, not only affects body metabolism and energy homeostasis but is also often accompanied by a series of complications, thereby attracting widespread attention. Among these, diabetic retinopathy (DR) is the most common ocular complication of diabetes [1]. The morbidity of DR exceeds 80% in patients with a diabetes duration of more than 20 years, making it the leading cause of blindness among ophthalmic diseases. By 2045, the number of individuals with DR worldwide is projected to increase to 160 million from 103 million in 2020 to 160 million [2]. The disease burden is most pronounced in low- and middle-income countries (e.g., China and India), where the prevalence rates are as high as 20.6–47.2% [3]. Owing to the high prevalence and significant pathogenic risk of DR, this disease has attracted widespread attention in the clinical field. Systemic risk factors for DR include hyperglycemia (reflected by HbA1c levels), hypertension, anemia, infection or chronic inflammation and epigenetic modifications. The underlying pathophysiological mechanism is characterized by comprehensive dysfunction of the retinal neurovascular unit (NVU) [3]. The NVU is composed of multiple cell types, each of which are involved in distinct pathogenic mechanisms and signaling pathways during the progression of DR. However, DR staging and grading systems that stratify disease severity by cell type are lacking, thereby limiting current clinical management largely to nonspecific therapeutic strategies, including anti-inflammatory and antioxidant interventions, along with glycemic and lipid control. Future research must delve deeper into the pathogenesis and clinical characteristics of DR, which will not only improve our understanding of this complex disease but also significantly facilitate the identification of more precise therapeutic targets and the development of more effective treatment strategies. This article elucidates the core pathological mechanisms of DR at the cellular and molecular levels and accordingly delineates screening, intervention, and treatment strategies targeting individual cell types, thereby establishing a comprehensive review framework with a panoramic perspective of "multicellular mechanisms to precision medicine".

Cell Types and Specific Pathological Mechanisms

Chronic hyperglycemia induces metabolic disorders, oxidative stress, inflammation, and vascular dysfunction, resulting in the disruption of NVU homeostasis and the breakdown of intercellular communication networks within the NVU. These pathological alterations constitute the direct mechanistic basis for the initiation and progression of DR. The NVU consists of a tightly coupled system of retinal neurons (including ganglion cells, horizontal cells, amacrine cells, bipolar cells, and photoreceptors), glial cells (including Müller cells, astrocytes, and microglia), and vascular cells (including pericytes and endothelial cells) [4]. Under normal conditions, the intraretinal vascular system can automatically adjust to meet the metabolic needs of neurons, with intact cellular structures and functions working together to maintain the stability of retinal blood flow, ensuring adequate delivery of oxygen and nutrients and thereby achieving neurovascular coupling [5]. Under hyperglycemic conditions, the retinal nervous system is activated, leading to changes in the secretion of matrix molecules within the NVU, which disrupts neurovascular coupling and ultimately triggers vascular lesions and hemodynamic changes. Moreover, glial cell signaling is activated, resulting in neuronal damage and synaptic dysfunction, which collectively contribute to the loss of retinal barrier function and neurodegenerative changes [6] (Fig. 1).

Pericytes—The Earliest Damaged "Vascular Scaffold Cells"

Pericytes are the first cells to undergo selective apoptosis during the pathogenesis of DR. Pericytes are located at the neurovascular interface and regulate pathophysiological processes such as angiogenesis, pathological neovascularization, and vascular leakage through physical contact and paracrine signaling [7]. In DR, elevated DNA methyltransferase 1 (DNMT1) expression leads to mtDNA hypermethylation, which triggers mitochondrial dysfunction and subsequent pericyte loss. Concurrently, hypomethylation of the matrix metalloproteinase-9 (MMP-9) promoter upregulates MMP-9 expression, thereby degrading the basement membrane and compromising barrier integrity. These epigenetic alterations synergistically drive the pathological progression of DR. Indeed, in addition to epigenetic alterations, the activation of inflammatory pathways by external risk factors represents an even more significant cause of pericyte injury. Risk factors such as hyperglycemia preferentially activate the polyol pathway, inducing sorbitol accumulation and oxidative stress. Concurrently, oxidative stress promotes the generation of advanced glycation end products (AGEs) and activates their receptor (RAGE), creating a positive feedback loop that further intensifies oxidative stress and inflammatory responses [8]. Recent studies have shown that circFAT1, a covalently closed circular RNA derived from exons of the FAT1 gene, can significantly inhibit pericyte pyroptosis by regulating the miR-802-5p/SIRT6 signaling axis, whereas its downregulation in DR promotes pyroptosis through the NLRP3/Caspase-1/GSDMD inflammasome pathway, ultimately accelerating disease progression [9]. In addition, pericytes function as antigen-presenting cells in the immune system; these cells express multiple leukocyte markers and contain abundant numbers of lysosomes, suggesting their phagocytic ability [10]. Under physiological conditions, pericytes mainly express major histocompatibility complex (MHC) class I molecules; however, in inflammatory microenvironments stimulated by proinflammatory factors such as tumor necrosis factor-α (TNF-α) and IFN-γ, they can upregulate the expression of MHC class II molecules. presenting exogenous antigens to CD4+ T lymphocytes and significantly amplifying the local immune inflammatory response [11]. Activated immune cells release large amounts of inflammatory cytokines through paracrine pathways, further stimulating pericytes and other immune cells in a positive feedback loop, ultimately forming a sustained and amplified inflammatory cascade. These pathological changes impair pericyte–endothelial signaling and compromise the integrity of the inner blood–retinal barrier (iBRB). On the one hand, this facilitates the infiltration of peripheral immune cells; on the other hand, it also facilitates the transbarrier migration of neurotoxic substances, ultimately exacerbating neurodegenerative changes [12].

Endothelial Cells—"Gatekeeper Cells"

Endothelial cells form a continuous, nonfenestrated barrier with low vesicular transport activity, constituting the core structure of the iBRB and strictly regulating material exchange between the bloodstream and retinal tissues. Endothelial cells supply oxygen and nutrients to the metabolically active retina; facilitate immune surveillance by circulating immune cells; and eliminate circulating toxins, microbes, and proinflammatory leukocytes to maintain iBRB integrity and retinal protection [13]. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway is the most critical central regulator of inflammatory responses in vascular endothelial cells. Upon activation, NF-κB upregulates the expression of downstream cytokines such as interleukin 1 β (IL-1β) and TNF-α. In turn, TNF-α and IL-1β sustain the activation of NF-κB, forming a positive feedback loop that gradually amplifies inflammation. This leads to retinal cell damage, vascular structural disruption, and ultimately vascular leakage and retinal edema [14]. Previous studies have demonstrated that under hyperglycemic conditions, hypoxia-inducible factor 1-α (HIF-1α) accumulates in the retina as a transcription factor, directly binding to hypoxia response elements on the vascular endothelial growth factor (VEGF) gene promoter to upregulate VEGF transcription levels. By binding to vascular endothelial growth

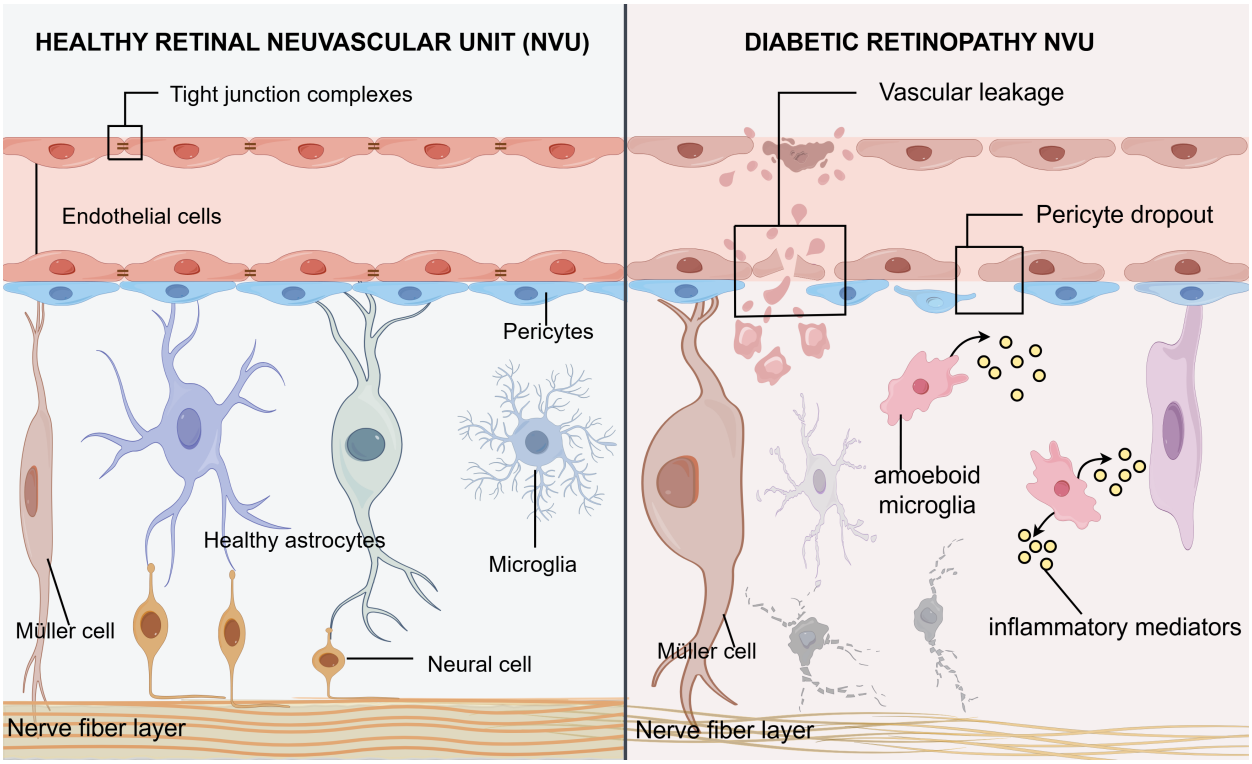

Fig. 1. Overview of NVU injury and pathogenesis in DR. A comparison of the NVU between healthy retinas and DR retinas, with emphasis on the concurrent occurrence of neurodegeneration and vascular leakage, is illustrated. The left panel shows a healthy retinal NVU with intact endothelial tight junctions, astrocytes, pericytes, and microglia. The right panel shows the NVU in DR patients, which exhibits disrupted tight junctions (vascular leakage), pericyte loss, activated microglial release of cytokines, swollen Müller cells, and thinning of the nerve fiber layer. The figure was created by the authors with Figdraw 2.0. NVU, neurovascular unit; DR, diabetic retinopathy.

factor receptor 2 (VEGFR2), VEGF promotes endothelial cell proliferation and migration and increases vascular permeability, exacerbating inflammation and vascular leakage and thereby triggering iBRB dysfunction [15]. Furthermore, hyperglycemia induces the upregulation of Intercellular adhesion molecule-1 (ICAM-1) expression in retinal microvascular endothelial cells. This activates leukocytes and promotes their adhesion to endothelial cells, triggering the release of inflammatory mediators and microvascular damage, thereby accelerating DR progression [14]. In addition to the above pathways, endothelial–pericyte crosstalk drives disease progression. Physiologically, endothelial-derived platelet-derived growth factor subunit B (PDGF-B) directs pericyte precursor migration and vascular coverage, while pericyte-secreted angiopoietin-1 (Ang-1) binds to endothelial Tie2 receptors, facilitating vascular maturation and stability. Under pathological conditions, activation of the PKCδ/p38MAPK/SHP-1 pathway induces platelet-derived growth factor receptor β (PDGFR-β) dephosphorylation, abrogating its ligand-binding capacity and consequently triggering pericyte apoptosis. Moreover, elevated Ang-2 levels competitively inhibit Ang-1/Tie2 signaling, leading to vascular wall instability [16].

Müller Cells—"Metabolic and Signaling Hub Cells"

Müller cells are the only cells that span the entire retina and maintain close contact with both retinal blood vessels and neurons. They play roles in maintaining neurotransmitter homeostasis, regulating immune and inflammatory responses, secreting VEGF and providing neuroprotection [17]. Under physiological conditions, Müller cells regulate membrane polarization and depolarization by adjusting extracellular ion concentrations, thereby maintaining the extracellular pH. They also participate in the glutamate–glutamine cycle of neurons to control neurotransmission and protect neurons from glutamate excitotoxicity [18]. Traditional studies have indicated that during the progression of DR, Müller cells contribute to neuronal dysfunction in two ways: they increase extracellular glutamate levels by reducing glutamate uptake, directly causing glutamate toxicity, and they indirectly disrupt neuronal activity by impairing K^+ uptake [19]. In recent years, novel pathological mechanisms targeting Müller cells have emerged. A study by Luo *et al.* [20] is the first to reveal an epigenetic modification positive feedback regulatory loop that drives the sustained pathological activation of Müller cells in DR. Under high-glucose con-

ditions, lactate—the glycolytic product of Müller cells—induces histone H3 lysine 18 (H3K18) lactylation, which transcriptionally activates the m6A demethylase alkB homolog 5, RNA demethylase (ALKBH5). ALKBH5, in turn, removes m6A modifications from RNF123 mRNA, reducing its stability and leading to decreased RNF123 protein levels. As an E3 ubiquitin ligase that targets PKM2, the loss of RNF123 impairs the ubiquitination and degradation of pyruvate kinase M2 (PKM2), resulting in the accumulation of PKM2, which further enhances glycolysis, thereby promoting the production of inflammatory factors. This establishes a "lactate–ALKBH5–RNF123–PKM2" positive feedback loop that drives sustained Müller cell activation, promotes gliotic responses and the massive release of inflammatory factors, and ultimately accelerates DR progression [20]. These pathological alterations compromise normal metabolic and signaling support, thereby serving as a pivotal nexus that couples vascular injury with neurodegeneration, ultimately culminating in neurovascular uncoupling and macular edema.

Microglia—"Immune Sentinel Cells"

Microglia are immune cells within the retina that finely coordinate interactions between neural and vascular tissues through intercellular communication, thereby maintaining physiological and pathological retinal functions [21]. Activated microglia exhibit two isoforms: M1 (proinflammatory) and M2 (anti-inflammatory). The M1/M2 ratio correlates with DR progression. M1-type cells, key mediators of neuroinflammation, secrete proinflammatory factors such as IL-6, IL-1β, chemokines, and tumor necrosis factor-α (TNF-α), which not only cause neuronal damage and even death but also contribute to the formation of nonperfused areas in the retina and neovascularization [22]. Conversely, M2 microglia predominantly secrete multiple anti-inflammatory and neurotrophic factors, suppressing retinal inflammation, protecting ganglion cells and photoreceptor cells, and reducing neovascularization [23]. In the early stages of DR, both activated M1-type and M2-type microglia increase in number. As the disease progresses, the proportion of M1-type cells significantly exceeds that of M2-type cells. An abnormal M1/M2 ratio induces local microglia to participate in inflammatory pathways, such as nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and Janus kinase/signal transducer and activator of transcription (JAK/STAT), accelerating the progression of DR [24]. Furthermore, fractalkine (CX3CL1), a pleiotropic molecule that functions as both an adhesion molecule and a chemokine, activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway while suppressing the NF-κB signaling cascade under physiological conditions. This sustains microglia in a quiescent surveillance phenotype, thereby conferring retinal protection against neurovascular inflammatory insult. In DR, dysregulation of this CX3CL1–CX3CR1 cytoprotective axis results in the abrogation of its protective function and paradoxically aggravates neuronal and vascular pathology [14]. More importantly, microglia are among the major cell types responsible for NLRP3 inflammasome production. The NLRP3 inflammasome is a protein complex involved in inflammatory responses. It recognizes endogenous danger signals and activates caspase-1, and activated caspase-1 cleaves pro-interleukin-1β (pro-IL-1β) and pro-interleukin-18 (pro-IL-18) into mature, highly active IL-1β and IL-18 [25]. Recent studies have shown that histone deacetylase 6 (HDAC6) is aberrantly activated in DR, where it drives inflammatory responses, neurodegeneration, and vascular dysfunction through activation of the NLRP3 inflammasome. HDAC6 is a class IIb HDAC that possesses both histone deacetylase activity and nonhistone deacetylase activity. Interestingly, this pathogenic role of HDAC6 is independent of the canonical VEGF signaling pathway, suggesting that combined administration of anti-VEGF agents and HDAC6 inhibitors may overcome the current therapeutic bottleneck in DR and offer a novel direction for optimizing clinical treatment strategies [26]. These pathological alterations trigger the massive release of inflammatory cytokines (e.g., IL-6, IL-1β, and TNF-α) and VEGF, which act synergistically to increase vascular permeability, disrupt the integrity of tight junction proteins (e.g., ZO-1 and Occludin), and consequently exacerbate iBRB dysfunction, ultimately culminating in vascular leakage, endothelial apoptosis, and pericyte loss [27].

Retinal Neurons—Overlooked "Early Damaged Cells"

Retinal neurons are specialized nerve cells in the retina that are responsible for receiving, processing, and transmitting visual information [5]. Early pathological neuronal degeneration has been established as a key pathogenic driver of diabetic retinopathy (DR). Prior to the onset of clinically detectable microvascular lesions, apoptosis and axonal degeneration of retinal ganglion cells (RGCs) are already evident, indicating that hyperglycemia-mediated neuronal insult precedes overt vascular pathology. This neurodegenerative cascade is mediated by multiple convergent mechanisms, including hyperglycemia-induced oxidative stress, mitochondrial dysfunction, neurotrophic factor imbalance, aberrant activation of the polyol pathway, and glutamate-mediated excitotoxicity [28]. Recent research by Rao *et al*. [29] demonstrated that hyperglycemia suppresses retinal tyrosine hydroxylase (TH) expression, leading to dopamine depletion and consequent inhibition of the Nrf2/HO-1 antioxidant signaling pathway. This cascade triggers the downregulation of glutathione peroxidase 4 (GPX4) and solute carrier family 7 member 11 (SLC7A11), disrupts iron homeostasis, and promotes lipid peroxide accumulation, thereby driving ferroptosis in retinal ganglion cells (RGCs), which manifests as mitochondrial shrinkage, RGC loss, and impaired visual function [29]. Be-

yond ferroptosis, hyperglycemia also drives neuronal degeneration through multiple convergent pathogenic mechanisms, including glutamate-mediated excitotoxicity, downregulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), oxidative stress and inflammatory cascades that synergistically promote apoptosis, and epigenetic silencing of cytoprotective genes. These pathological processes culminate in retinal nerve fiber layer thinning, neuronal apoptosis, and disrupted visual signal transduction, manifesting clinically as early vision loss. Concomitantly, aberrant upregulation of glial fibrillary acidic protein (GFAP) expression in Müller cells and microglial activation progress in concert with neuronal apoptosis, collectively constituting the early pathological hallmarks of neurovascular unit impairment in DR [28].

Multicellular Crosstalk Regulatory Network

The pathological mechanism of DR is not a result of single-cell damage but rather involves pathological circuits formed by intercellular signal crosstalk (Fig. 2). First, pericyte apoptosis leads to disruption of the endothelial barrier, resulting in ischemia and hypoxia, which subsequently activate Müller cells and microglia, promoting the secretion of VEGF and inflammatory factors that further damage endothelial cells and neurons. Second, inflammatory factors released by microglia activate Müller cells, leading to the accumulation of neurotoxic substances and the induction of retinal ganglion cell (RGC) apoptosis. This causes neurovascular uncoupling, thereby exacerbating the ischemic state. Furthermore, as key cells responsible for maintaining the outer blood–retinal barrier, which participates in nutrient metabolism, metabolic waste clearance, and retinal attachment preservation, dysfunction of the retinal pigment epithelium (RPE) leads to the accumulation of metabolic waste and exacerbation of oxidative stress, ultimately amplifying damage across all retinal cell types. These pathological processes share a unified upstream pathway of "hyperglycemia–oxidative stress–epigenetics–inflammation", which triggers specific downstream effects in different cell types, ultimately manifesting as the diverse pathological phenotypes of DR. In view of the aforementioned complex pathological mechanisms, the academic community has advocated the adoption of the term "diabetic retinal disease" (DRD) in lieu of the conventional DR, aiming to more accurately delineate the complete panretinal injury spectrum of the disease. The conceptual framework of DRD encompasses not only structural pathologies involving neurons, glial cells, and the vasculature but also the preclinical phase characterized by functional deficits preceding overt vascular manifestations. Moreover, this construct integrates diverse domains, including neurodegeneration, visual function, quality of life, and systemic health, thereby underscoring the imperative need for holistic disease assessment and multifaceted intervention [3].

Clinical Manifestations

The clinical stages of DR include four stages: mild nonproliferative diabetic retinopathy (mild NPDR), moderate nonproliferative diabetic retinopathy (moderate NPDR), severe nonproliferative diabetic retinopathy (severe NPDR), and proliferative diabetic retinopathy (PDR). Each stage has characteristic pathophysiological changes and clinical manifestations, with typical symptoms including decreased visual acuity and visual field defects (e.g., scotoma formation) (see Table 1, Ref. [30–32]). Accurate staging is essential for optimizing treatment strategies in clinical practice. In addition to having typical clinical symptoms, DR patients often develop serious complications, such as ischemic optic neuropathy, vitreous opacities (floaters), and macular edema. In-depth research on their pathogenesis is crucial for optimizing DR treatment strategies. Ischemic optic neuropathy results from inadequate blood perfusion to the optic nerve, triggered by hemodynamic impairments (e.g., blood flow obstruction or reduced perfusion pressure) [30]. Floaters occur when retinal capillary rupture leads to leakage into the vitreous cavity, causing vitreous hemorrhage. In DR, vitreous hemorrhage primarily results from fragile and leaking retinal neovascularized structures [33]. Macular edema involves fluid accumulation in the macular interstitium, leading to progressive vision decline and visual distortion [34]. Glaucoma is characterized by abnormal neovascularization affecting the iris and other intraocular structures, obstructing aqueous outflow and elevating intraocular pressure, damaging the optic nerve and causing visual field defects [35].

Cell-Based Screening and Diagnosis

The fundamental limitation of current DR diagnosis lies in the reliance of the existing staging paradigm on clinically overt microvascular pathology, which precludes the detection of antecedent cellular-level insults and consequently engenders diagnostic delay. Moreover, the lack of cell type-specific molecular stratification and validated in vivo biomarkers renders current diagnostic information inadequate for guiding individualized therapeutic interventions directed against discrete cellular pathogenic pathways [36]. Currently available conventional cell type-directed diagnostic modalities for DR and potential molecular biomarkers are summarized in the accompanying table (Table 2). However, with the rapid advancement of intelligent medicine, AI-assisted screening has become a mainstream trend in current clinical practice and is capable of identifying moderate or worse DR and covering early changes in both vascular and neuronal cells. Among emerging technologies, FDA-approved AI deep learning systems can be used to detect mild or worse DR, with sensitivity and specificity exceeding 87% and 88%, respectively [37]. Handheld fundus cameras combined with AI are suitable

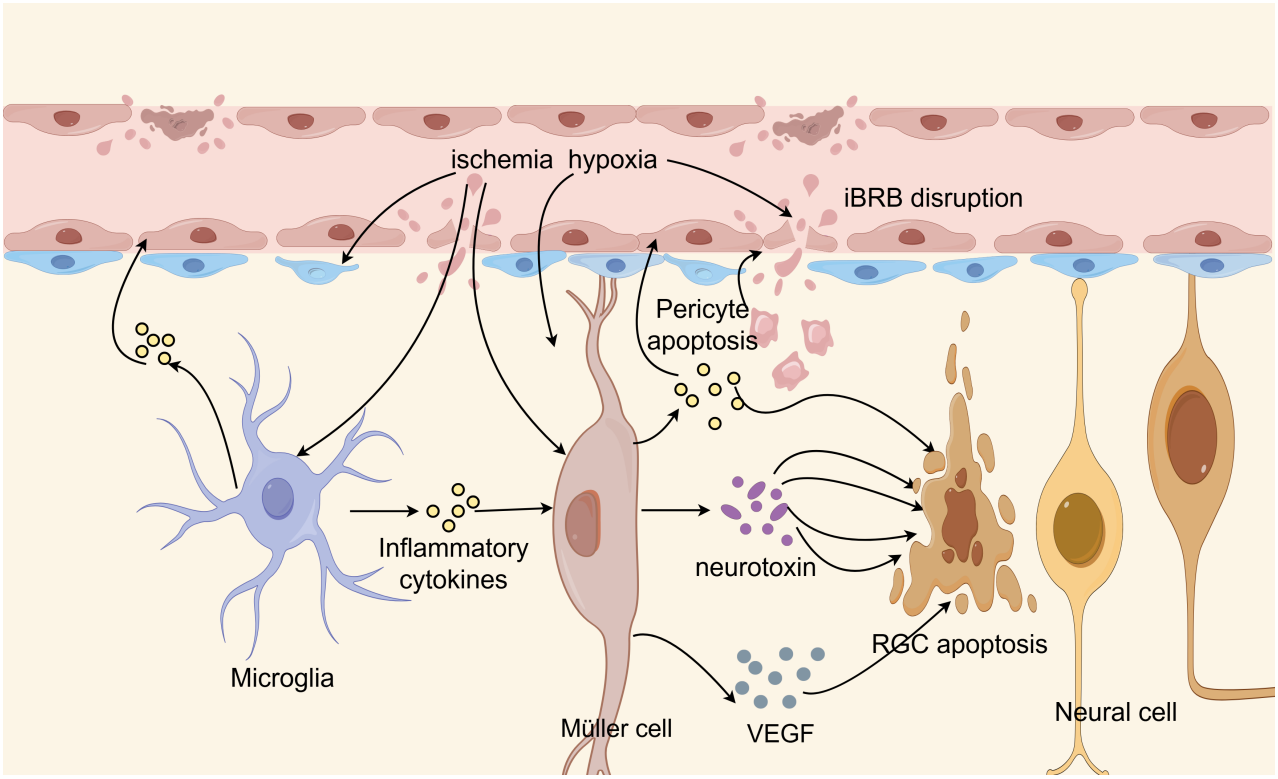

Fig. 2. Multicellular crosstalk regulation promotes the progression of DR. The figure intuitively illustrates the regulatory mechanism of multicellular crosstalk, providing a deeper appreciation of the complexity of the pathogenesis of DR. The figure was created by the authors with Figdraw 2.0. iBRB, inner blood–retinal barrier; VEGF, vascular endothelial growth factor.

Table 1. Clinical staging of DR and corresponding pathophysiological changes and clinical features.

Stage	Pathophysiological Changes	Clinical Features
Mild NPDR	Microaneurysms	Retinal edema, dot-and-blot hemorrhages
Moderate NPDR	Neovascular exudation, rupture	Blurred or distorted vision with dark or hollow spots [31]
Severe NPDR	Extensive retinal hemorrhage, microvascular abnormalities	Severe visual impairment, difficulty with daily activities [32]
PDR	Retinal detachment	Floaters (e.g., dot-like, thread-like, or cobweb-like shadows), vision loss [30]

NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

for primary care and remote areas. Ultrawidefield imaging can detect peripheral lesions and contribute to more accurate staging. Large language models can be used for report generation, patient education, and decision support. Nevertheless, these technologies still face challenges, including image quality, cost, validation of predictive value, hallucinations, bias, and regulatory hurdles [3].

Cell-Based Therapy

The treatment of DR faces three major challenges: drug tolerance, poor response in some patients, and poor treatment adherence. Although anti-VEGF biologics are the first-line therapy, they are limited by incomplete responses in some patients, the development of drug resistance, and the need for frequent intravitreal injections. Corticosteroids are effective but are restricted by side effects such as elevated intraocular pressure and cataracts. Laser photocoagulation remains an important adjunctive treatment modality; however, its application may lead to irreversible peripheral visual field defects [38]. The targeted therapies for the pathogenesis of DR and their corresponding main pathways are summarized in Fig. 3. Future endeavors should be directed toward the development of more precise and minimally injurious laser technologies, along with the identification of early interventional targets, to develop precise therapeutic strategies for DR.

Basic Therapy

On the basis of the etiology and pathological mechanisms of DR, it is necessary to control blood glucose levels, blood pressure, and blood lipid levels to mitigate the early

Table 2. Diagnostic approaches and potential molecular biomarkers for different cell types.

Cell type	Diagnostic modalities	Potential molecular biomarker
Pericytes	Adaptive optics scanning laser ophthalmoscopy (AOSLO); Optical coherence tomography (OCT) detection of microaneurysms; Assessment of exudation severity; Macular thickness measurement	PDGFR-β; Ang-1
Endothelial cells	Dilated fundus examination; Ultrawidefield fundus photography; Fundus fluorescein Angiography (FFA); OCT/OCTA	VEGF; PEDF
Müller cells	OCT (Indirect: morphological, thickness changes, glial scar)	GFAP; AQP1; AQP4
Microglia		CD5L; M1/M2
Retinal neurons	OCT (nerve fiber layer detection); Microperimetry; Visual electrophysiology	Neurofilament light chain (NFL)

OCTA, optical coherence tomography angiography; PDGFR-β, platelet-derived growth factor receptor β; Ang-1, angiopoietin-1; VEGF, vascular endothelial growth factor; PEDF, pigment epithelium-derived factor; GFAP, glial fibrillary acidic protein; AQP1, Aquaporin 1; AQP4, Aquaporin 4; CD5L, CD5 Molecule-Like; M1/M2, classically activated macrophages/alternatively activated macrophages.

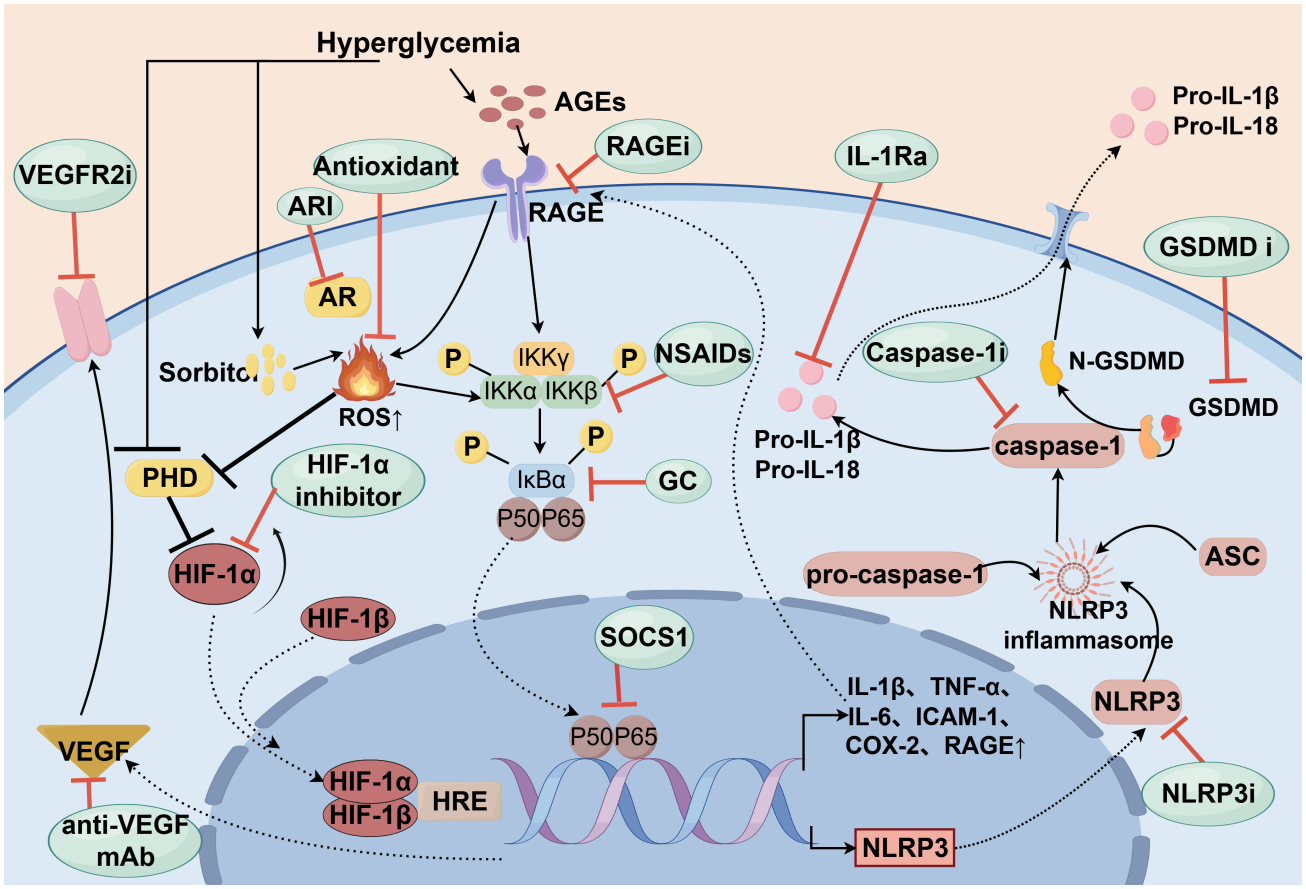

Fig. 3. Overview of NVU injury and pathogenesis in DR. This figure summarizes five key signaling pathways involved in the NVU, namely, the polyol pathway, AGEs/RAGE pathway, NF-κB pathway, NLRP3/Caspase-1/GSDMD pyroptosis pathway, and HIF-1α/VEGF pathway. Each pathway has corresponding targeted intervention strategies, including receptor antagonists, enzyme inhibitors, and product inhibitors. In-depth analysis of these pathways is crucial for the development of more promising targeted drugs for DR. The figure was created by the authors with Figdraw 2.0. AGEs, advanced glycation end products; RAGE, activates their receptor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; HIF-1, hypoxia-inducible factor 1; IL, interleukin; SOCS1, suppressor of cytokine signaling 1; ROS, reactive oxygen species.

damage induced by hyperglycemia to pericytes, endothelial cells, and neuronal cells. Additionally, the administration of antioxidant and anti-inflammatory agents can target and inhibit oxidative stress and inflammatory responses at the whole-cell level. In the context of anti-inflammatory therapy, suppressor of cytokine signaling 1 (SOCS1), a mem-

ber of the SOCS protein family, regulates cytokine signaling pathways through negative feedback mechanisms [39]. Experimental evidence has indicated that SOCS1 significantly reduces the activation level of reactive glial cells in the retina while simultaneously inhibiting the expression of proinflammatory factors such as IL-1β and IL-6 and decreasing the perivascular deposition of TNF-α [40]. Minocycline shows potential therapeutic value in DR treatment because of its ability to inhibit microglial activation, suppress the release of inflammatory cytokines, and downregulate poly ADP-ribose polymerase-1 (PARP-1) expression [41]. PARP-1 inhibitors can reduce the expression of angiogenesis-related regulators in DR; however, their high doses are associated with cytotoxicity and limited efficacy in improving vascular complications and neuroprotection. Therefore, combining them with anti-VEGF agents may achieve synergistic multitarget regulation, representing a more promising therapeutic strategy for DR [42].

Oxidative stress plays a key role in the pathogenesis of DR, providing a theoretical basis for antioxidant therapy. Flavonoids such as quercetin significantly increase the body's antioxidant defense capacity, downregulate the expression of proinflammatory cytokines, alleviate reactive gliosis, and inhibit programmed cell death in retinal ganglion cells [43]. As members of the carotenoid family, lutein and zeaxanthin can accumulate in retinal tissues, with particularly high concentrations in choroid and retinal pigment epithelial cells. These compounds suppress choroidal neovascularization via anti-inflammatory mechanisms, including scavenging free radicals, downregulating the expression of inducible nitric oxide synthase, and filtering blue light, which may induce phototoxic damage to photoreceptor cells [44]. Melatonin is a unique antioxidant possessing both lipophilic and hydrophilic properties, allowing it to easily penetrate various biological barriers. Studies have demonstrated that melatonin helps maintain the expression of superoxide dismutase (SOD) and maintains reactive oxygen species (ROS) at low levels, thereby protecting ocular tissues from oxidative stress-induced injury [45].

Pericyte-Targeted Therapy

Targeting pericytes to protect vascular scaffolds is an important therapeutic strategy for DR. Administration of reductase inhibitors and RAGE inhibitors can reduce pericyte apoptosis, and intensive glycemic control can delay pericyte loss and stabilize early-stage DR [46,47]. Protecting or replacing pericytes through the modulation of signaling pathways such as Ang-1 and PDGF represents a potential new direction for DR therapy. The combination of anti-PDGF therapy (e.g., Fovista) and anti-VEGF agents can enhance the vascular regression effect of anti-VEGF treatment by eliminating pericytes; however, given the intrinsic protective role of pericytes, its long-term safety requires careful evaluation [16].

Endothelial Cell-Targeted Therapy

The first-line therapy targeting endothelial cells is anti-VEGF treatment, which specifically reduces VEGF expression levels and decreases vascular leakage. Currently used anti-VEGF agents include mainly monoclonal antibodies targeting VEGF-A; fusion proteins targeting VEGF-A/VEGF-B/placental growth factor (PlGF); agents targeting VEGF-A/angiopoietin-2 (Ang-2), such as faricimab; and novel inhibitors targeting VEGF-C/VEGF-D (OPT-302 and KSI-301). These agents have excellent tissue penetration and bioavailability, enabling rapid and effective reduction of intravitreal VEGF levels [48]. The mechanistic innovation of faricimab lies in its dual-target inhibition strategy, which simultaneously targets Ang-2 and VEGF-A. Through this mechanism, faricimab achieves more comprehensive vascular stabilization, theoretically enabling longer dosing intervals and superior anatomical improvements [49]. A recent study has shown that introducing gene sequences encoding anti-VEGF proteins into target cells allows for stable and long-lasting expression of therapeutic proteins, opening new avenues for sustained DR treatment [50]. However, the incomplete response to anti-VEGF therapy observed in a subset of patients with diabetic macular edema is attributable to the complex and interconnected pathological network of DR, which can sustain retinal damage via non-VEGF-dependent pathways. Concurrently, the "metabolic memory" phenomenon perpetuates hyperglycemia-induced epigenetic alterations and mitochondrial dysfunction, collectively mediating substantial resistance to anti-VEGF therapy [38].

An adjunctive therapy targeting endothelial cells is retinal laser photocoagulation, which, on the basis of the thermal effect of laser energy, induces dense photocoagulation spots on the retinal surface to selectively destroy abnormal neovascularization and leakage foci. The advantage of this technique lies in its ability to precisely target pathological regions while preserving normal retinal function. However, potential complications, including iatrogenic vitreous hemorrhage, permanent visual field defects, and irreversible visual impairment, must be considered [51]

Müller Cell- and Microglia-Targeted Therapy

Targeting Müller cells and microglia to inhibit inflammation and edema represents a therapeutic strategy for DR. Glucocorticoids exert anti-inflammatory effects through multiple mechanisms, including inhibiting the synthesis of inflammatory mediators, enhancing the production of anti-inflammatory cytokines, suppressing the migration of inflammatory cells, and regulating immune responses. Commonly used intravitreal glucocorticoid implants include triamcinolone, dexamethasone, and fluocinonide preparations [52]. Nonsteroidal anti-inflammatory drugs (NSAIDs) selectively inhibit cyclooxygenase (COX) activity, blocking the biosynthesis of prostaglandin proinflammatory mediators, with representative drugs including

bromfenac and diclofenac [53]. In refractory diabetic macular edema (DME), the combination of anti-VEGF therapy and corticosteroids can improve treatment outcomes.

In addition to the above treatments, many novel therapeutic strategies are currently under investigation. Given the pivotal regulatory role of lipid metabolism in the pathogenesis of DR, the potential therapeutic value of PCSK9 inhibitors (such as alirocumab, evolocumab, and inclisiran) for DR has gradually been recognized. Evolocumab exerts anti-inflammatory effects on retinal Müller cells by regulating the TLR-4/NF-κB signaling pathway. Lipid-lowering agents, including fenofibrate, have been shown to reduce the need for laser treatment and slow disease progression in patients with DR, suggesting that lipid-lowering therapy may also improve the prognosis of DR [38].

As a key regulator of the NLRP3 inflammasome, HDAC6 promotes retinal inflammation and neurodegeneration in DR, indicating the important role of epigenetic regulation in the pathogenesis of DR. HDAC6 expression is significantly upregulated in the retinas of diabetic mice, whereas knockout of HDAC6 or its specific inhibitors can alleviate retinal vascular leakage and maintain retinal structure, suggesting that selective inhibition of HDAC6 may represent a novel therapeutic strategy for DR [38]. Given that the pathogenic role of HDAC6 in DR is independent of the VEGF signaling pathway, the combination of HDAC6 inhibitors with anti-VEGF agents may theoretically produce complementary or synergistic effects, thereby substantially enhancing overall therapeutic efficacy. This combination strategy therefore holds considerable clinical promise [26].

In the therapeutic landscape of DR, epigenetic intervention is emerging as a novel strategy of interest. By administering DNMT/HDAC inhibitors and miRNA mimics, this approach can effectively reverse the persistent cellular damage mediated by "metabolic memory", thereby offering a new avenue for intervening in disease progression at its source [8].

Neuron-Targeted Therapy

Neurotrophic factors play crucial roles in the development and functional maintenance of the nervous system and participate in pathophysiological processes by promoting neuronal growth, differentiation, and neurovascular interactions [54]. Studies have shown that neurotrophic factors such as brain-derived neurotrophic factor (BDNF), insulin and its analogs (insulin-like growth factor 1, IGF-1), and glucagon-like peptide-1 (GLP-1) are important in the neuroprotective mechanisms of DR [55]. Among these, BDNF primarily protects the optic nerve and inhibits pathological angiogenesis in a hyperglycemic microenvironment by suppressing oxidative stress. Insulin and its receptor signaling pathways not only regulate blood glucose homeostasis but also maintain the normal physiological state of retinal neurons. Erythropoietin (EPO), a glycoprotein hormone, significantly reduces hyperglycemia-induced retinal ganglion apoptosis by inhibiting the activation of the c-Jun N-terminal kinase (JNK) signaling pathway [56]. In addition, somatostatin analogs (e.g., octreotide) increase neuronal autophagy activity by activating signaling pathways such as adenosine monophosphate-activated protein kinase (AMPK), thereby inhibiting neuronal apoptosis under hyperglycemic conditions and exerting significant neuroprotective effects in DR [57].

In addition, peroxiredoxin-4 (PRDX4) protects against DR-related retinal damage by scavenging hydrogen peroxide and promoting endoplasmic reticulum protein folding [58]. PRDX4 deficiency exacerbates retinal neurodegeneration, endoplasmic reticulum stress, mitochondrial dysfunction, and oxidative stress in diabetic mice, indicating that enhancing PRDX4 expression may serve as a potential therapeutic approach for DR.

Other Therapies

Beyond the aforementioned cell-targeted therapeutic strategies, emerging modalities such as surgical interventions, traditional Chinese medicine (TCM) techniques, and cell-based therapies have likewise demonstrated considerable promise, thereby offering multidimensional therapeutic options for the comprehensive management of DR.

Surgical Treatment

Vitrectomy is effective at controlling DR progression and improving visual function by clearing pathological products such as vitreous hemorrhage and proliferative membranes while achieving anatomical reattachment of the retina. Clinical practice indicates that the combination of vitrectomy and retinal laser surgery produces synergistic effects, effectively clearing vitreoretinal interface pathologies while suppressing retinal neovascularization [59]. ERM peeling employs a minimally invasive vitrectomy system to precisely strip proliferative membranes composed of myofibroblasts and extracellular matrix (ECM) from the retinal surface [60]. Trabeculectomy, as the standard surgical treatment for DR-induced neovascular glaucoma, involves the establishment of an aqueous outflow pathway that diverts fluid from the anterior chamber to the subconjunctival space for absorption by surrounding tissues, effectively reducing intraocular pressure. Scleral buckling addresses DR-related tractional retinal detachment by applying external indentation to reattach the detached retina while simultaneously sealing retinal breaks and promoting anatomical adhesion between the detached retinal tissue and the pigment epithelium [30].

Traditional Chinese Medicine

Research on the use of TCM in the treatment of DR has attracted increasing attention. Current evidence suggests that the active components of TCM exert therapeutic effects via multitarget and multipathway mechanisms,

including the regulation of the NF-κB and Nrf2 signaling pathways. Recent studies have focused mainly on exploring the pharmacological mechanisms of TCM monomers and compound preparations, such as astragaloside IV, curcumin extract, berberine, and *Lycium barbarum* polysaccharide [61]. For example, curcumin alleviates retinal inflammation by inhibiting the p38 mitogen-activated protein kinase (p38 MAPK)/NF-κB signaling pathway and suppresses angiogenesis by blocking the VEGF/VEGFR2 signaling axis, thus exerting therapeutic effects on DR [62]. In addition to having anti-inflammatory and antiangiogenic effects, puerarin downregulates the expression of Bcl-2-associated X protein (Bax) and caspase-3, inhibits reactive oxygen species (ROS) production, and reduces the release of inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) induced by N-methyl-D-aspartate (NMDA), thereby exerting antiapoptotic and antioxidative effects [63]. TCM treatment not only acts on specific molecular targets but also exerts overall regulatory effects through multiple targets and pathways.

In response to the low bioavailability of TCM, recent investigations have focused on the development of drug delivery systems—including biomimetic nanoparticles and ozonated liposomes—aimed at improving the efficiency of ocular delivery of bioactive TCM constituents. Zingale *et al*. [64] developed a curcumin-loaded self-nanoemulsifying drug delivery system (SNEDDS) for topical ocular administration in DR. This system demonstrates favorable physicochemical properties following optimization and provides substantial protection of curcumin against hydrolysis, photodegradation, and thermal degradation. Further modification with cationic lipids (e.g., DDAB) enhances ocular surface retention, suggesting the potential for transscleral delivery to the retina and enabling targeted therapeutic intervention [64].

Cell Therapy

As a major breakthrough in precision medicine, stem cell therapy has significant advantages in DR treatment. The pathological progression of DR involves damage to multiple cell types within retinal tissue. Therefore, stem cell replacement therapy has become a current research focus. Multiple clinical studies have systematically evaluated the therapeutic effects of mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), and induced pluripotent stem cells (iPSCs) [65]. Experimental studies have shown that intravitreal injection of MSCs in DR model rats results in significant improvement in retinal function, accompanied by a marked reduction in vascular leakage and perivascular apoptosis [66]. EPCs exhibit unique advantages in repairing damaged vascular systems because of their potential to differentiate into endothelial cells and promote angiogenesis through paracrine actions [67].

Significant progress has been made in miRNA-targeted therapy. Extensive experimental data confirm that the expression of multiple miRNAs changes specifically during DR progression. Inhibitors or agonists developed for these miRNAs have promising therapeutic potential [68]. Studies have shown that miR-124 exerts neuroprotective effects by suppressing microglia-mediated inflammatory responses [69] and that miR-138-5p exerts protective effects against early-stage DR by regulating the expression of neuro-oncology ventral antigen 1 (NOVA1) [70]. miR-155 is located on human chromosome 21 and exerts multiple biological effects, including the regulation of microglial activation, lymphocyte proliferation, and immune cell function. By specifically binding to the 3′ untranslated region (3′UTR) of the mRNA encoded by SH2 domain-containing inositol polyphosphate 5-phosphatase 1 (SHIP1), miR-155 can downregulate the expression of SHIP1. This downregulation further activates the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway, which ultimately facilitates angiogenesis in retinal neovascularization. Owing to its dual regulatory roles in immunomodulation and angiogenesis, miR-155 has been identified as a potential therapeutic target for pathological neovascularization in DR [71].

Conclusion

DR is a disease involving synergistic multicellular injury within the retinal neurovascular unit, with highly heterogeneous mechanisms. Pericyte apoptosis initiates pathology, endothelial barrier disruption leads to edema, Müller cells and microglia drive inflammation and neovascularization, and neuronal degeneration causes early visual impairment. Cell–cell interactions form an irreversible pathological loop, while epigenetic activity and metabolic stress amplify this damage. Current treatments (anti-VEGF, corticosteroids, and laser, surgery) target mainly vascular and inflammatory pathways but lack neuroprotection, pericyte repair, and RPE reconstruction abilities. Future DR management should shift toward multicellular targeted strategies, enabling earlier screening, combined neurovascular protection, and reversal of epigenetic/metabolic memory, ultimately establishing a novel theranostic system of "precise subtyping—cell-targeted therapy—full-course intervention". To advance DR diagnosis and treatment, future efforts should proceed on multiple fronts. First, a new cell damage-based staging system should integrate neural, vascular, functional, quality-of-life, and systemic health dimensions. Second, AI and digital health can enable universal screening, individualized risk prediction, and decision support. Third, the combined application of the aforementioned novel drugs and integrated primary screening is expected to reduce the risk of disease onset in patients and decrease the occurrence of complications. Novel therapeutics should include gene therapy, tyrosine

kinase inhibitors, sustained-release devices, and non-VEGF pathway agents. Preclinical-stage interventions such as neuroprotection, RBP3, GLP-1, and insulin sensitization also warrant attention. Cross-complication research should draw on the framework developed for diabetic kidney disease. Finally, strengthening health education for diabetic patients to enhance disease awareness and self-management is crucial for preventing DR. Furthermore, promoting increased physical exercise and healthy diets among patients and the public is not only fundamental for disease prevention but also an essential measure that cannot be overlooked during treatment.

Availability of Data and Materials

Not applicable.

Author Contributions

JLJ and MRQ conceived the study; JLJ, MRQ and WLD designed the framework; MRQ and WLD drafted the initial manuscript. MRQ, WLD, YML and ML performed the literature search and data collection; JLJ, YML and ML provided critical revision of the manuscript for important intellectual content. 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.

References

[1] Li H, Liu X, Zhong H, Fang J, Li X, Shi R, *et al*. Research progress on the pathogenesis of diabetic retinopathy. BMC Ophthalmology. 2023; 23: 372. https://doi.org/10.1186/s12886-023-03118-6.

[2] Chong DD, Das N, Singh RP. Diabetic retinopathy: Screening, prevention, and treatment. Cleveland Clinic Journal of Medicine. 2024; 91: 503–510. https://doi.org/10.3949/ccjm.91a.24028.

[3] Sivaprasad S, Wong TY, Gardner TW, Sun JK, Bressler NM. Diabetic retinal disease. Nature Reviews. Disease Primers. 2025; 11: 62. https://doi.org/10.1038/s41572-025-00646-x.

[4] Alarcon-Martinez L, Shiga Y, Villafranca-Baughman D, Cueva Vargas JL, Vidal Paredes IA, Quintero H, *et al*. Neurovascular dysfunction in glaucoma. Progress in Retinal and Eye Research. 2023; 97: 101217. https://doi.org/10.1016/j.preteyeres.2023.101217.

[5] Zhou J, Chen B. Retinal Cell Damage in Diabetic Retinopathy. Cells. 2023; 12: 1342. https://doi.org/10.3390/cells12091342.

[6] Oshitari T. Neurovascular Impairment and Therapeutic Strategies in Diabetic Retinopathy. International Journal of Environmental Research and Public Health. 2021; 19: 439. https://doi.org/10.3390/ijerph19010439.

[7] van Splunder H, Villacampa P, Martínez-Romero A, Graupera M. Pericytes in the disease spotlight. Trends in Cell Biology. 2024; 34: 58–71. https://doi.org/10.1016/j.tcb.2023.06.001.

[8] He W, Tang P, Lv H. Targeting oxidative stress in diabetic retinopathy: mechanisms, pathology, and novel treatment approaches. Frontiers in Immunology. 2025; 16: 1571576. https://doi.org/10.3389/fimmu.2025.1571576.

[9] Huang C, Qi P, Cui H, Lu Q, Gao X. CircFAT1 regulates retinal pigment epithelial cell pyroptosis and autophagy via mediating m6A reader protein YTHDF2 expression in diabetic retinopathy. Experimental Eye Research. 2022; 222: 109152. https://doi.org/10.1016/j.exer.2022.109152.

[10] Alarcon-Martinez L, Yemisci M, Dalkara T. Pericyte morphology and function. Histology and Histopathology. 2021; 36: 633–643. https://doi.org/10.14670/HH-18-314.

[11] Zhang ZS, Zhou HN, He SS, Xue MY, Li T, Liu LM. Research advances in pericyte function and their roles in diseases. Chinese Journal of Traumatology = Zhonghua Chuang Shang Za Zhi. 2020; 23: 89–95. https://doi.org/10.1016/j.cjtee.2020.02.006.

[12] Sheng X, Zhang C, Zhao J, Xu J, Zhang P, Ding Q, *et al*. Microvascular destabilization and intricated network of the cytokines in diabetic retinopathy: from the perspective of cellular and molecular components. Cell & Bioscience. 2024; 14: 85. https://doi.org/10.1186/s13578-024-01269-7.

[13] Moccia F, Dragoni S. The Calcium Signalling Profile of the Inner Blood-Retinal Barrier in Diabetic Retinopathy. Cells. 2025; 14: 856. https://doi.org/10.3390/cells14120856.

[14] Yue T, Shi Y, Luo S, Weng J, Wu Y, Zheng X. The role of inflammation in immune system of diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. Frontiers in Immunology. 2022; 13: 1055087. https://doi.org/10.3389/fimmu.2022.1055087.

[15] Li J, Lu X, Wei L, Ye D, Lin J, Tang X, *et al*. PHD2 attenuates high-glucose-induced blood retinal barrier breakdown in human retinal microvascular endothelial cells by regulating the Hif-1α/VEGF pathway. Inflammation Research. 2022; 71: 69–79. https://doi.org/10.1007/s00011-021-01518-2.

[16] Arboleda-Velasquez JF, Valdez CN, Marko CK, D'Amore PA. From pathobiology to the targeting of pericytes for the treatment of diabetic retinopathy. Current Diabetes Reports. 2015; 15: 573. https://doi.org/10.1007/s11892-014-0573-2.

[17] Bringmann A, Pannicke T, Grosche J, Francke M, Wiedemann P, Skatchkov SN, *et al*. Müller cells in the healthy and diseased retina. Progress in Retinal and Eye Research. 2006; 25: 397–424. https://doi.org/10.1016/j.preteyeres.2006.05.003.

[18] Bringmann A, Grosche A, Pannicke T, Reichenbach A. GABA and Glutamate Uptake and Metabolism in Retinal Glial (Müller)

Cells. Frontiers in Endocrinology. 2013; 4: 48. https://doi.org/10.3389/fendo.2013.00048.

[19] Li X, Lv J, Li J, Ren X. Kir4.1 may represent a novel therapeutic target for diabetic retinopathy (Review). Experimental and Therapeutic Medicine. 2021; 22: 1021. https://doi.org/10.3892/etm.2021.10453.

[20] Luo S, Sun Y, Hu Y, Xu Y. Lactylation-induced ALKBH5 targets RNF123 to worsen retinal Müller cell activation through PKM2-regulated Glycolysis in diabetic retinopathy. Journal of Translational Medicine. 2025; 23: 1105. https://doi.org/10.1186/s12967-025-07129-3.

[21] Cserép C, Pósfai B, Szabadits E, Dénes Á. Contactomics of Microglia and Intercellular Communication. Advances in Neurobiology. 2024; 37: 135–149. https://doi.org/10.1007/978-3-031-55529-9_8.

[22] Kinuthia UM, Wolf A, Langmann T. Microglia and Inflammatory Responses in Diabetic Retinopathy. Frontiers in Immunology. 2020; 11: 564077. https://doi.org/10.3389/fimmu.2020.564077.

[23] Wang X, Xu C, Bian C, Ge P, Lei J, Wang J, *et al*. M2 microglia-derived exosomes promote vascular remodeling in diabetic retinopathy. Journal of Nanobiotechnology. 2024; 22: 56. https://doi.org/10.1186/s12951-024-02330-w.

[24] Yao Y, Li J, Zhou Y, Wang S, Zhang Z, Jiang Q, *et al*. Macrophage/microglia polarization for the treatment of diabetic retinopathy. Frontiers in Endocrinology. 2023; 14: 1276225. https://doi.org/10.3389/fendo.2023.1276225.

[25] Chen TY, Wu N, Sun X. Complement, Inflammasome, and Microglial Crosstalk in Glaucoma: From Neurodegeneration to Immune-Based Precision Therapy. Life (Basel, Switzerland). 2026; 16: 368. https://doi.org/10.3390/life16030368.

[26] Kim JS, Jun JH, Lee J, Park S, Kim E, Hwang SJ, *et al*. HDAC6 mediates NLRP3 inflammasome activation in the pathogenesis of diabetic retinopathy. Metabolism: Clinical and Experimental. 2025; 164: 156108. https://doi.org/10.1016/j.metabol.2024.156108.

[27] Yang L, Yao Y, Zheng W, Zheng X, Xie M, Huang L. Nitric oxide mediates negative feedback on the TXNIP/NLRP3 inflammasome pathway to prevent retinal neurovascular unit dysfunction in early diabetic retinopathy. Free Radical Biology & Medicine. 2025; 233: 279–291. https://doi.org/10.1016/j.freeradbiomed.2025.03.050.

[28] Callan A, Jha S, Valdez L, Tsin A. Cellular and Molecular Mechanisms of Neuronal Degeneration in Early-Stage Diabetic Retinopathy. Current Vascular Pharmacology. 2024; 22: 301–315. https://doi.org/10.2174/0115701611272737240426050930.

[29] Rao S, Xiao K, Chen X, Sun X. Dopamine Alleviated Diabetic Retinal Neurodegeneration through Protecting Retinal Ganglion Cells from Ferroptosis via the Nrf2/HO-1 Signaling Pathway. ACS Omega. 2025; 10: 30397–30410. https://doi.org/10.1021/acsomega.5c02063.

[30] Mishra S, Vishwakarma PK, Tripathi M, Ojha S, Tripathi SM. Diabetic Retinopathy: Clinical Features, Risk Factors, and Treatment Options. Current Diabetes Reviews. 2024; 20: e271023222871. https://doi.org/10.2174/0115733998252551231018080419.

[31] Lai C, Su T, Cao J, Li Q, Du Z, Wang Y, *et al*. Retinal Neurovascular Impairment in Full-Course Diabetic Retinopathy: The Guangdong Diabetic Retinopathy Multiple-Omics Study. Investigative Ophthalmology & Visual Science. 2024; 65: 20. https://doi.org/10.1167/iovs.65.14.20.

[32] Lee DH, Vitale S, Agrón E, Keenan TDL, Cukras CA, Chew EY. Visual Field Changes in Diabetic Retinopathy: Natural History and after Pan-Retinal Photocoagulation in the Diabetic Retinopathy Study and the ETDRS. Ophthalmology. Retina. 2025; 9: 1071–1080. https://doi.org/10.1016/j.oret.2025.04.021.

[33] Gan J, Ding X, Ploumi I, Romano F, Overbey KM, Garcia MD, *et al*. Association of predominant peripheral lesions with retinal microvasculature and risk of vitreous hemorrhage in proliferative diabetic retinopathy. Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie. 2025; 263: 3105–3112. https://doi.org/10.1007/s00417-025-06864-z.

[34] Haydinger CD, Ferreira LB, Williams KA, Smith JR. Mechanisms of macular edema. Frontiers in Medicine. 2023; 10: 1128811. https://doi.org/10.3389/fmed.2023.1128811.

[35] Tang Y, Shi Y, Fan Z. The mechanism and therapeutic strategies for neovascular glaucoma secondary to diabetic retinopathy. Frontiers in Endocrinology. 2023; 14: 1102361. https://doi.org/10.3389/fendo.2023.1102361.

[36] Sinclair SH, Schwartz S. Diabetic retinopathy: New concepts of screening, monitoring, and interventions. Survey of Ophthalmology. 2024; 69: 882–892. https://doi.org/10.1016/j.survophthal.2024.07.001.

[37] Lin KY, Hsih WH, Lin YB, Wen CY, Chang TJ. Update in the epidemiology, risk factors, screening, and treatment of diabetic retinopathy. Journal of Diabetes Investigation. 2021; 12: 1322–1325. https://doi.org/10.1111/jdi.13480.

[38] Seo H, Park SJ, Song M. Diabetic Retinopathy (DR): Mechanisms, Current Therapies, and Emerging Strategies. Cells. 2025; 14: 376. https://doi.org/10.3390/cells14050376.

[39] Wen M, Wu R, Xie JF, Chen XM, Wen NL, Huang S. miRNA-19a-3p Exacerbates Tube Formation by Targeting SOCS1 to Regulate JAK2/STAT3/VEGF in Diabetic Retinopathy. Annals of Clinical and Laboratory Science. 2025; 55: 19–27.

[40] Hernández C, Bogdanov P, Gómez-Guerrero C, Sampedro J, Solà-Adell C, Espejo C, *et al*. SOCS1-Derived Peptide Administered by Eye Drops Prevents Retinal Neuroinflammation and Vascular Leakage in Experimental Diabetes. International Journal of Molecular Sciences. 2019; 20: 3615. https://doi.org/10.3390/ijms20153615.

[41] Rodríguez ML, Millán I, Ortega ÁL. Cellular targets in diabetic retinopathy therapy. World Journal of Diabetes. 2021; 12: 1442–1462. https://doi.org/10.4239/wjd.v12.i9.1442.

[42] Pöstyéni E, Gábriel R, Kovács-Valasek A. Poly (ADP-Ribose) Polymerase-1 (PARP-1) Inhibitors in Diabetic Retinopathy: An Attractive but Elusive Choice for Drug Development. Pharmaceutics. 2024; 16: 1320. https://doi.org/10.3390/pharmaceutics16101320.

[43] Saikia L, Barbhuiya SAA, Saikia K, Kalita P, Dutta PP. Therapeutic Potential of Quercetin in Diabetic Neuropathy and Retinopathy: Exploring Molecular Mechanisms. Current Topics in Medicinal Chemistry. 2024; 24: 2351–2361. https://doi.org/10.2174/0115680266330678240821060623.

[44] Tuzcu M, Orhan C, Muz OE, Sahin N, Juturu V, Sahin K. Lutein and zeaxanthin isomers modulates lipid metabolism and the inflammatory state of retina in obesity-induced high-fat diet rodent model. BMC Ophthalmology. 2017; 17: 129. https://doi.org/10.1186/s12886-017-0524-1.

[45] Monteiro KKAC, Shiroma ME, Damous LL, Simões MDJ, Simões RDS, Cipolla-Neto J, *et al*. Antioxidant Actions of Melatonin: A Systematic Review of Animal Studies. Antioxidants (Basel, Switzerland). 2024; 13: 439. https://doi.org/10.3390/antiox13040439.

[46] Naruse K, Nakamura J, Hamada Y, Nakayama M, Chaya S, Komori T, *et al*. Aldose reductase inhibition prevents glucose-induced apoptosis in cultured bovine retinal microvascular pericytes. Experimental Eye Research. 2000; 71: 309–315. https://doi.org/10.1006/exer.2000.0882.

[47] Kim J, Kim CS, Sohn E, Lee YM, Jo K, Kim JS. KIOM-79 pro-

tects AGE-induced retinal pericyte apoptosis via inhibition of NF-kappaB activation in vitro and in vivo. PloS One. 2012; 7: e43591. https://doi.org/10.1371/journal.pone.0043591.

[48] Koksaldi S, Karti O, Saatci AO. Anti-vascular endothelial growth factor therapies in ophthalmology. Medical Hypothesis, Discovery & Innovation Ophthalmology Journal. 2025; 14: 107–135. https://doi.org/10.51329/mehdiophthal1526.

[49] Wykoff CC, Abreu F, Adamis AP, Basu K, Eichenbaum DA, Haskova Z, *et al*. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet (London, England). 2022; 399: 741–755. https://doi.org/10.1016/S0140-6736(22)00018-6.

[50] Gelfman CM, Grishanin R, Bender KO, Nguyen A, Greengard J, Sharma P, *et al*. Comprehensive Preclinical Assessment of ADVM-022, an Intravitreal Anti-VEGF Gene Therapy for the Treatment of Neovascular AMD and Diabetic Macular Edema. Journal of Ocular Pharmacology and Therapeutics: the Official Journal of the Association for Ocular Pharmacology and Therapeutics. 2021; 37: 181–190. https://doi.org/10.1089/jop.2021.0001.

[51] Liu Y, Wu N. Progress of Nanotechnology in Diabetic Retinopathy Treatment. International Journal of Nanomedicine. 2021; 16: 1391–1403. https://doi.org/10.2147/IJN.S294807.

[52] Gao L, Zhao X, Jiao L, Tang L. Intravitreal corticosteroids for diabetic macular edema: a network meta-analysis of randomized controlled trials. Eye and Vision (London, England). 2021; 8: 35. https://doi.org/10.1186/s40662-021-00261-3.

[53] Stark AK, Penn JS. Prostanoid signaling in retinal cells elicits inflammatory responses relevant to early-stage diabetic retinopathy. Journal of Neuroinflammation. 2024; 21: 329. https://doi.org/10.1186/s12974-024-03319-w.

[54] Ramos H, Simó-Servat O. Neuroprotection in Diabetes Retinal Disease: An Unmet Medical Need. International Journal of Molecular Sciences. 2026; 27: 901. https://doi.org/10.3390/ijms27020901.

[55] Zhu M, Li N, Wang Y, Gao S, Wang J, Shen X. Regulation of inflammation by VEGF/BDNF signaling in mouse retinal Müller glial cells exposed to high glucose. Cell and Tissue Research. 2022; 388: 521–533. https://doi.org/10.1007/s00441-022-03622-z.

[56] Qi YX, Su XJ, Wei LL, Zhang J. Erythropoietin inhibits apoptosis of retinal ganglion cells induced by high glucose through JNK signaling pathway. Journal of Biological Regulators and Homeostatic Agents. 2021; 35: 547–557. https://doi.org/10.23812/20-646-A.

[57] Amato R, Catalani E, Dal Monte M, Cammalleri M, Cervia D, Casini G. Morpho-functional analysis of the early changes induced in retinal ganglion cells by the onset of diabetic retinopathy: The effects of a neuroprotective strategy. Pharmacological Research. 2022; 185: 106516. https://doi.org/10.1016/j.phrs.2022.106516.

[58] Huang Y, Zhang Y, Liu Y, Jin Y, Yang H. PRDX4 mitigates diabetic retinopathy by inhibiting reactive gliosis, apoptosis, ER stress, oxidative stress, and mitochondrial dysfunction in Müller cells. The Journal of Biological Chemistry. 2025; 301: 108111. https://doi.org/10.1016/j.jbc.2024.108111.

[59] Shaikh N, Kumar V, Ramachandran A, Venkatesh R, Tekchandani U, Tyagi M, *et al*. Vitrectomy for cases of diabetic retinopathy. Indian Journal of Ophthalmology. 2024; 72: 1704–1713. https://doi.org/10.4103/IJO.IJO_30_24.

[60] Fung AT, Galvin J, Tran T. Epiretinal membrane: A review. Clinical & Experimental Ophthalmology. 2021; 49: 289–308. https://doi.org/10.1111/ceo.13914.

[61] Ai X, Yu P, Hou Y, Song X, Luo J, Li N, *et al*. A review of traditional Chinese medicine on treatment of diabetic retinopathy and involved mechanisms. Biomedicine & Pharmacotherapy. 2020; 132: 110852. https://doi.org/10.1016/j.biopha.2020.110852.

[62] Zhou YM, Cao YH, Guo J, Cen LS. Potential prospects of Chinese medicine application in diabetic retinopathy. World Journal of Diabetes. 2024; 15: 2010–2014. https://doi.org/10.4239/wjd.v15.i10.2010.

[63] Zhou YX, Zhang H, Peng C. Puerarin: a review of pharmacological effects. Phytotherapy Research: PTR. 2014; 28: 961–975. https://doi.org/10.1002/ptr.5083.

[64] Zingale E, Masuzzo S, Lajunen T, Reinisalo M, Rautio J, Consoli V, *et al*. Protective Role and Enhanced Intracellular Uptake of Curcumin in Retinal Cells Using Self-Emulsifying Drug Delivery Systems (SNEDDS). Pharmaceuticals (Basel, Switzerland). 2025; 18: 265. https://doi.org/10.3390/ph18020265.

[65] Iliadis I, Pechnikova NA, Poimenidou M, Almaliotis DD, Tsinopoulos I, Yaremenko TV, *et al*. Applications of Modern Cell Therapies: The Latest Data in Ophthalmology. Life (Basel, Switzerland). 2025; 15: 1610. https://doi.org/10.3390/life15101610.

[66] LIU X, SUN X, YANG J, ZHU D, WANG Y. Effect of human umbilical cord derived mesenchymal stem cells on apoptosis of rat retinal ganglion cells under high glucose and on the regulation of p38MAPK pathway. Chinese Journal of Experimental Ophthalmology. 2022; 40: 21–28.

[67] Altabas V, Marinković Radošević J, Špoljarec L, Uremović S, Bulum T. The Impact of Modern Anti-Diabetic Treatment on Endothelial Progenitor Cells. Biomedicines. 2023; 11: 3051. https://doi.org/10.3390/biomedicines11113051.

[68] Chen J, Zhang J, Li C, Wang L, Tao L, Xue S, *et al*. Targeting microRNAs in diabetic retinopathy: from pathogenic mechanisms to therapeutic potentials. Frontiers in Endocrinology. 2025; 16: 1664604. https://doi.org/10.3389/fendo.2025.1664604.

[69] Chen Y, Schlotterer A, Kurowski L, Li L, Dannehl M, Hammes HP, *et al*. miRNA-124 Prevents Rat Diabetic Retinopathy by Inhibiting the Microglial Inflammatory Response. International Journal of Molecular Sciences. 2023; 24: 2291. https://doi.org/10.3390/ijms24032291.

[70] Bao XY, Cao J. MiRNA-138-5p protects the early diabetic retinopathy by regulating NOVA1. European Review for Medical and Pharmacological Sciences. 2019; 23: 7749–7756. https://doi.org/10.26355/eurrev_201909_18984.

[71] Lampsas S, Agapitou C, Chatzirallis A, Papavasileiou G, Poulakis D, Pegka S, *et al*. MicroRNA (miRNA) in the Pathogenesis of Diabetic Retinopathy: A Narrative Review. Genes. 2025; 16: 1060. https://doi.org/10.3390/genes16091060.