Molecular and cellular crosstalk in the pathogenesis of diabetic retinopathy

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Abstract

Diabetic retinopathy is a major cause of vision loss worldwide and arises from interconnected molecular mechanisms involving oxidative stress, inflammation, apoptosis, and angiogenesis. Chronic hyperglycaemia induces excessive reactive oxygen species production through pathways such as advanced glycation end-product formation and protein kinase C activation, leading to mitochondrial dysfunction, impaired antioxidant defences, and retinal cell apoptosis. In parallel, activation of inflammatory signalling cascades, including NF-κB–mediated cytokine release, promotes leukostasis, vascular permeability, and microvascular injury. Progressive neuronal and endothelial apoptosis further disrupts retinal integrity. At later stages, sustained hypoxia triggers VEGF overexpression and pathological angiogenesis. These processes reinforce one another, creating a self-amplifying pathogenic cycle. Effective disease control therefore requires integrated strategies that address multiple pathways simultaneously, including modulation of oxidative stress, suppression of chronic inflammation, preservation of retinal neuronal survival, and regulation of aberrant angiogenic signalling. Targeting shared upstream drivers is critical for slowing progression and limiting irreversible retinal damage.

Key words: diabetic retinopathy, oxidative stress, inflammation, apoptosis, angiogenesis.

Introduction

Overview

Diabetic retinopathy (DR) is a potentially serious ocular condition that occurs as a complication of diabetes mellitus. It is one of the leading causes of vision loss and blindness among adults worldwide [1]. DR develops when hyperglycaemia damages the blood vessels in the retina, which is the light-sensitive tissue lining the back of the eye. The retina, which plays a crucial role in transmitting visual information to the brain, is significantly affected in this disorder [2]. The epidemiology of DR shows a significant global prevalence and impact due to the increasing

incidence of diabetes worldwide [3–5]. It is a leading cause of blindness in adults aged 20–74 years worldwide which affects both type 1 and type 2 diabetes patients [6].

Non-proliferative diabetic retinopathy (NPDR) involves damages to the blood vessels in the retina. The formation of small, abnormal outgrowths called microaneurysms leads to fluid and blood leaks [7]. NPDR may not cause noticeable symptoms in its early stages, making regular eye examinations essential for early detection and intervention. In contrast, in proliferative diabetic retinopathy (PDR), areas of the retina may become deprived of adequate blood supply due to damaged vessels [8]. In response, the retina stimulates the growth of new blood vessels, a process known as neovascularisation. However, these new vessels are often weak and prone to leakage, leading to the formation of scar tissue and further complications such as retinal detachment, vitreous haemorrhage and vision loss [9].

DR is a complex disease that involves multiple pathological changes in the retina due to long-term exposure to high blood sugar levels in individuals with diabetes [10]. The exact mechanisms underlying DR are complex and involve interactions between various molecular pathways, inflammatory processes, and growth factor signalling [11]. This review comprehensively discusses the roles of oxidative stress, inflammation, apoptosis and angiogenesis that are believed to greatly contribute to DR development and progression.

Objective

The objective of this review is to critically examine the pathophysiological mechanisms underlying DR, with particular emphasis on the integration of key molecular pathways involved in disease initiation and progression, and to contextualise their relevance to therapeutic strategies from a mechanistic perspective. While recent reviews have summarized the molecular mechanisms underlying diabetic retinopathy, the present work emphasizes the dynamic crosstalk among oxidative stress, inflammation, apoptosis, and angiogenesis, and integrates these pathways within a translational framework that includes emerging epigenetic regulators and systemic modulatory axes.

Literature search strategies

A comprehensive literature search was conducted to identify relevant studies on DR, with emphasis on oxidative stress, inflammation, angiogenesis, apoptosis, retinal neurodegeneration, long non-coding RNA (lncRNA), metabolic memory, epigenetic regulation, and therapeutic targets. Electronic databases, including PubMed and Medline, were systematically searched for peer-reviewed articles published between January 2000 and December 2025.

The search strategy incorporated Medical Subject Headings (MeSH) and free-text keywords. Core terms included “diabetic retinopathy” combined with “oxidative stress”, “inflammation”, “angiogenesis”, “apoptosis”, “retinal neurodegeneration”, “long non-coding RNA”, “metabolic memory”, “epigenetic regulation”, and “therapeutic targets”. Boolean operators (AND/OR) were applied to refine and structure the search. Where appropriate, additional pathway-specific terms such as “VEGF signalling”, “NF-κB”, and “advanced glycation end products” were used to capture mechanistic studies.

Titles and abstracts were screened for relevance, followed by full-text evaluation of eligible articles. Only English-language publications were included. Reference lists of selected articles were manually screened to identify additional pertinent studies and ensure comprehensive coverage of both foundational and emerging evidence in the field.

Diabetic retinopathy and oxidative stress

Polyol pathway

Glucose is metabolised primarily by the Krebs cycle in a normal glycaemic environment, and only a small amount is metabolised via the polyol pathway. However, in the hyperglycaemic environment, the Krebs cycle is saturated, and the glucose metabolism is shifted more to the polyol pathway [12–14]. The polyol pathway is a two-step metabolic cascade. In the first step, aldose reductase (AR) reduces glucose into sorbitol by utilizing reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor [15]. This is followed by the metabolic conversion of sorbitol to fructose in the presence of sorbitol dehydrogenase that utilizes nicotinamide adenine dinucleotide (NAD^+) as a cofactor [16]. Sorbitol is highly lipophobic, causing difficulty for it to diffuse easily through cell membranes [17]. As a result, sorbitol accumulates intracellularly, and as a sugar alcohol, it increases the osmotic pressure in cells [18]. Hence, in cells, sorbitol build-up has negative consequences, including osmotic damage which causes cell death [17]. Despite the presence of AR in retinal ganglion cells, Müller glia, endothelial cells, and vascular pericytes [19], osmotic stress-induced damage was observed not to be the primary mechanism of DR because sorbitol levels in diabetic rats’ retinas are far lower than the concentration required to cause osmotic stress [12, 20, 21] (Figure 1).

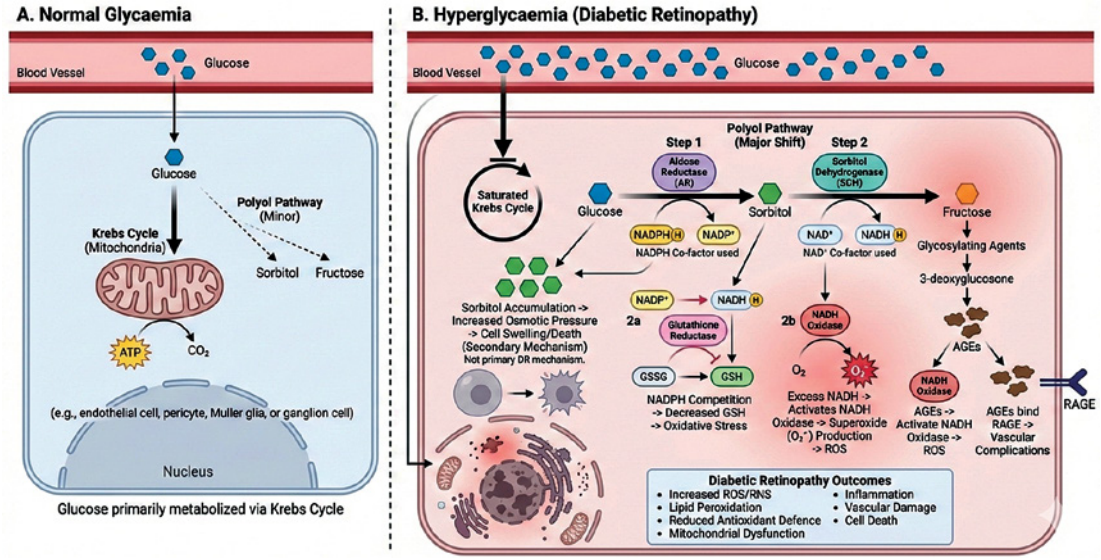

Figure 1. The polyol pathway and its role in DR-induced cellular damage. Image created with the assistance of Google Gemini

The cellular damage caused by the polyol pathway in DR is mostly associated with oxidative stress [22]. Diabetic retinas with increased polyol pathway activation were observed to have higher lipid peroxidation products [23], reactive nitrogen and oxygen species [24], and reduction of antioxidant defence [25, 26]. Several factors contribute to oxidative stress in the presence of an active polyol pathway, including AR's competitive use of NADPH, which reduces its availability for glutathione reductase, a crucial enzyme for preserving the intracellular level of GSH [27]. Lower GSH levels, an essential retinal non-enzymatic antioxidant, can lower the capacity of cells to react to oxidative stress [28]. Aside from that, sorbitol dehydrogenase's use of NAD^+ results in excess NADH, which acts as a substrate for NADH oxidase. When electron transfer is no longer capable of restoring NAD^+, the activity of the enzyme NADH oxidase is triggered, resulting in the production of superoxide radicals ($O_2^{\bullet -}$) as a by-product [29]. Fructose production via the polyol pathway also leads to increased oxidative stress levels through its phosphorylation into fructose-3-phosphate, which is further decomposed to 3-deoxyglucosone. The phosphorylation products of fructose are glycosylating agents [30, 31] that form advanced glycation end products (AGEs), which add to oxidative stress by activating NADH oxidase, resulting in a rise in reactive oxygen species (ROS) [32, 33]. The AGEs can also bind to AGE receptors (RAGEs), resulting in a wide range of vascular complications of diabetes [34]. Table I lists examples of studies investigating the mechanism of the polyol pathway in DR models [35–44].

Advanced glycation end-products

The non-enzymatic reaction between the carbonyl groups of reducing sugars and the free amino groups of proteins or other carbonyl compounds is recognised as the Maillard reaction, which eventually generates AGEs [45]. This reaction is subcategorised into early, intermediate, and late stages [46, 47]. At the early stage, glucose or other type of reducing sugars react with a free amino group of organic amines to produce an unstable Schiff base, which then is rearranged to a more stable Amadori product [48]. The Amadori product reduces to a wide range of reactive dicarbonyl compounds, including glyoxal, methylglyoxal (MGO), and deoxyglucosones, via dehydration, oxidation and other chemical responses in the intermediate stage [49]. In the late stage, the reactive dicarbonyl compounds undergo further oxidation, dehydration and cyclisation reactions to produce irreversible AGEs [11, 50]. AGEs are yellow-brown, fluorescent and insoluble structures that build up on long-lived proteins. Their production is also increased in chronic hyperglycaemic conditions [51]. The dicarbonyl products formed in the intermediate stage are very reactive, and their production is enhanced in a hyperglycaemic environment, which further promotes AGE production [52, 53]. Among the above-mentioned reactive dicarbonyl products, MGO is the most studied and is shown to be associated with the pathogenesis of DR, as AGE adducts modify existing proteins through cross-linking and cause alteration in the physiological function of the proteins [54]. Substances that detoxify MGO reduce the accumulation of AGEs and reduce the retinal vascular and neuroglial lesions [55] (Figure 2).

Notably, AGE levels are higher in various ocular tissues of diabetic subjects compared to normal subjects [56–63]. The AGE formation increases in tandem with the severity and progression of DR [64]. In DR, AGEs have been shown to promote

Table I. Studies on polyol pathway in DR models/populations

Type	Study [ref.]	Model/population	Experimental system	Key findings
In vitro	Yadav, Srivastava [35]	High glucose	Human retinal endothelial cells	High glucose increased AR activity and intracellular sorbitol, leading to oxidative and osmotic stress; AR inhibition reduced cellular injury.
In vitro	Ramana *et al.* [36]	Hyperglycaemic conditions	Human lens epithelial cells	AR activation under hyperglycaemia depleted NADPH and enhanced downstream oxidative stress, contributing to pericyte dysfunction.
In vitro	Chang *et al.* [37]	Diabetes-induced retinal microglia activation	Retinal microglia	Downregulation of AR in either a pharmacological or genetic manner prevented hypoxia-induced TNF-α and VEGF expression.
In vivo	Obrosova *et al.* [38]	STZ diabetic rats	Retina and retinal vessels	Diabetes induced marked retinal sorbitol accumulation; AR inhibitors prevented early retinal microvascular abnormalities.
In vivo	Adki and Kulkarni [39]	STZ diabetic rats	Retinal capillaries	Polyol pathway activation preceded oxidative stress and mitochondrial dysfunction in retinal capillaries.
In vivo	Petrash *et al.* [40]	Diabetic mice	Retinal tissue	AR-mediated polyol flux activated PKC signalling and contributed to vascular permeability changes in DR.
In vivo (intervention)	Li *et al.* [41]	STZ diabetic rats	AR inhibitor treatment by glycine	AR inhibition significantly reduced blood glucose, plasma insulin and glutathione content.
Human (biochemical)	Reddy *et al.* [42]	T2DM with/without DR	Erythrocytes and plasma	Higher polyol metabolites were detected in patients with DR compared to diabetic controls without retinopathy.
Human (clinical)	Preston and Calle [43]	T2DM patients	Serum polyol profiling	Serum sorbitol levels correlated with DR severity, suggesting systemic polyol flux involvement.
Human (genetic association)	Kaur and Vanita [44]	T2DM patients	AR (AKR1B1) polymorphism study	Certain AKR1B1 polymorphisms were associated with increased susceptibility to DR, implicating polyol pathway genetic regulation.

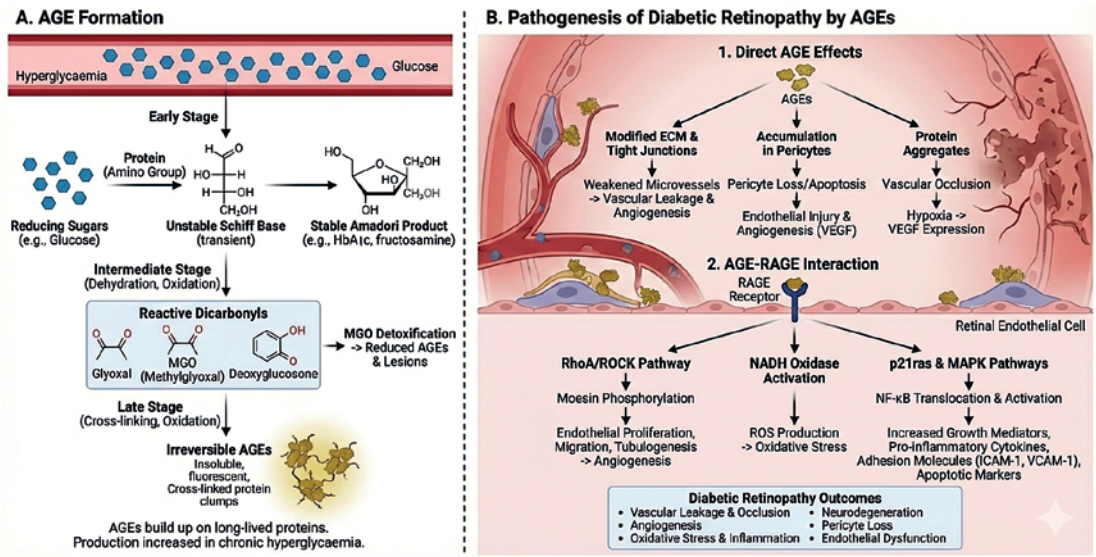

Figure 2. AGE formation and pathogenesis of DR. Image created with the assistance of Google Gemini

angiogenesis through several mechanisms [65]. AGE-modified proteins form proteinase-resistant aggregates that lead to vascular occlusion [66]. The vascular occlusion-induced hypoxic condition eventually promotes the expression of pro-angiogenic proteins such as VEGF [67, 68]. In addition, the alteration of tight junction proteins and extracellular matrix (ECM) proteins by AGEs weakens the microvascular unit that promotes vascular leakage and angiogenesis [69]. Another mechanism underlying AGE-induced angiogenesis is through accumulation of AGEs in retinal pericytes that leads to pericyte loss [70]. As pericytes are important structures in maintaining microvascular homeostasis, their loss promotes angiogenesis and endothelial cell (EC) injury through autocrine and paracrine activation of VEGF [71]. Pericyte damage and apoptosis are indicative of early retinopathy [72].

In addition to the direct modification of proteins, AGE interaction with their receptor, RAGE, induces angiogenesis, oxidative stress, chronic inflammation, and neurodegeneration in DR [73, 74]. The binding of AGEs to RAGE induces moesin phosphorylation through the RhoA/ROCK pathway, resulting in endothelial proliferation, activation, migration, and tubulogenesis, which may contribute to angiogenesis in the diabetic retina [75]. The stimulation of oxidative stress through NADH oxidase activation by AGE-RAGE interaction has been discussed above [76]. AGE-RAGE interaction also activates other downstream pathways, such as p21ras and mitogen-activated protein kinase (MAPK) pathways, resulting in nuclear factor kappa B (NF-κB) translocation [34]. NF-κB activation increases the production of growth mediators, pro-inflammatory cytokines, adhesion molecules, and apoptotic markers in DR [64, 77]. Adhesion molecules that have been reported to be upregulated in the presence of AGEs in retinal cells include intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) [69]. Table II summarizes some of the studies of AGE-related markers in DR models/populations [78–86].

Protein kinase C activation pathway

Protein kinase C consists of a group of related enzymes which act as signalling elements for various growth factors, hormones, neurotransmitters, and cytokines [87]. It contains a polypeptide chain with an N-terminal, also termed as the regulatory domain, and a C-terminal, termed as the catalytic region [88]. The physiological activation of PKC occurs via the phospholipase C (PLC)-inositol-1,4,5-triphosphate (IP_3)-DAG pathway. PLC hydrolyses phosphatidylinositol 4,5-bisphosphate (PIP2), a minor but essential constituent of plasma membranes, to modulate numerous PIP2-dependent cellular processes [89]. PIP2 cleavage products, inositol 1,4,5-trisphosphate (IP3) and 1,2-diacylglycerol (DAG), are critical second messengers mediating calcium signalling in animal cells [90]. IP3 causes the mobilisation and release of Ca^{2+} from intracellular stores, while DAG, via Ca^{2+}-catalysed reactions, activates PKC molecules [91].

Higher polyol pathway flux and increased production of AGEs in hyperglycaemia have been reported to cause enhanced generation of DAG, the biochemical activator of PKC [92]. Chronic exposure of retinal pericytes to AGEs has been shown to cause a two-fold increase in cellular DAG [93]. An increase in de novo synthesis of DAG through inhibition of glycolysis is associated with higher PKC activation [94]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), an important enzyme of glycolysis, converts glyceraldehyde-3-phosphate into 1,3- bisphosphoglycerate, which subsequently leads to pyruvate formation. In hyperglycaemia, the structure of GAPDH was observed to be modified either through nitrosation or ribosylation [95], which inactivates GAPDH. GAPDH is readily oxidised by ROS, which also leads to its loss of activity [96]. Accumulation of glyceraldehyde-3-phosphate due to GAPDH inactivity in a hyperglycaemic environment in turn causes a build-up of dihydroxyacetone-3-phosphate (DHA-3-P) [94]. More DHA-3-P is then reduced to glycerol-3-phosphate, which is further reduced to phosphatidic acid [97]. DAG is then formed through the removal of the phosphate group in the phosphatidic acid by phosphatidic acid phosphatase [92]. In addition, higher cellular DAG can be derived from the hydrolysis of the phosphatidylcholine and phosphatidyl serine [98]. Phosphatidylcholine (PC) hydrolysis in the cultured retinal capillary pericytes and endothelial cells was observed to be increased in hyperglycaemic conditions, which correlates with higher cellular DAG levels in retinal cells [99] (Figure 3).

PKC activation also increases oxidative stress. PKC activation has been reported to stimulate ROS-generating enzymes such as NADPH-oxidases and lipoxygenases, collectively creating a vicious cycle that further exacerbates cellular oxidative stress [100]. Among the various types of PKC isoforms, the beta isoform (PKC β) has been observed to be activated in blood vessels secondary to hyperglycaemia [101]. PKC β is associated with microvascular dysfunction by inducing ischaemia and local inflammation, leading to neovascularisation, macular oedema, and neurodegeneration in DR [102]. PKC-mediated Akt activity also plays an essential role in VEGF-stimulated angiogenesis [103] through phosphorylation of Akt [104], although conflicting results have also been reported [105]. VEGF plays an important role in retinal neovascularisation, which will be discussed further

Table II. Studies on AGE-related markers in DR models/populations

Study type	First author [ref.]	Model/ population	Experimental system	Key findings
In vitro	Wang *et al.* [78]	AGE exposure	Human retinal pigmented epithelial cells	AGE stimulation increased RAGE expression and NF-κB activation, leading to endothelial inflammation and dysfunction relevant to DR.
In vitro	Sheikpranbabu *et al.* [79]	AGE-modified proteins	Retinal pericytes	AGE–RAGE interaction induced pericyte apoptosis, contributing to early microvascular damage in DR.
In vitro	Pachydaki *et al.* [80]	AGE-BSA treatment	Müller glial cells	AGEs stimulated VEGF and ICAM-1 expression via RAGE-dependent pathways, linking AGE signalling to angiogenesis and inflammation.
In vitro	Mahmud [81]	High glucose + AGE	ARPE-19 cells	Combined high glucose and AGE exposure amplified oxidative stress and inflammatory signalling in retinal pigment epithelial cells.
In vivo	Kim *et al.* [82]	STZ diabetic rats	Retinal capillaries	AGE accumulation and RAGE activation preceded retinal microvascular lesions, implicating AGE signalling early in DR pathogenesis.
In vivo	McVicar *et al.* [83]	Diabetic mice	Retina	Blockade of AGE-RAGE interaction attenuated retinal inflammation and vascular leakage in diabetic mice.
In vivo	Berner *et al.* [84]	STZ diabetic rats	Retinal tissue	Increased retinal AGE accumulation correlated with oxidative stress and capillary degeneration in DR.
Randomised clinical trial (multicentre)	Bolton *et al.* [85]	Type 1 diabetes patients with nephropathy and retinopathy	Randomised, double-masked, placebo-controlled trial of pimagedine (aminoguanidine) for 2–4 years	Fewer pimagedine-treated patients experienced ≥ 3-step progression of diabetic retinopathy (ETDRS score) compared with placebo, supporting the concept that inhibiting AGE formation can attenuate DR progression. This is among the earliest human trials testing AGE inhibition in diabetic complications with retinopathy endpoints.
Randomised clinical trial (secondary analysis)	Freedman *et al.* [86]	Type 2 diabetes patients (retinopathy + nephropathy)	Randomised double-blind placebo-controlled aminoguanidine vs. placebo	In this large trial of 599 T2DM patients, one of the secondary outcomes was progression of retinopathy. The study provides clinical data on AGE inhibition effects; however, the primary endpoints focused on renal outcomes, and the retinopathy effect was a secondary evaluation.

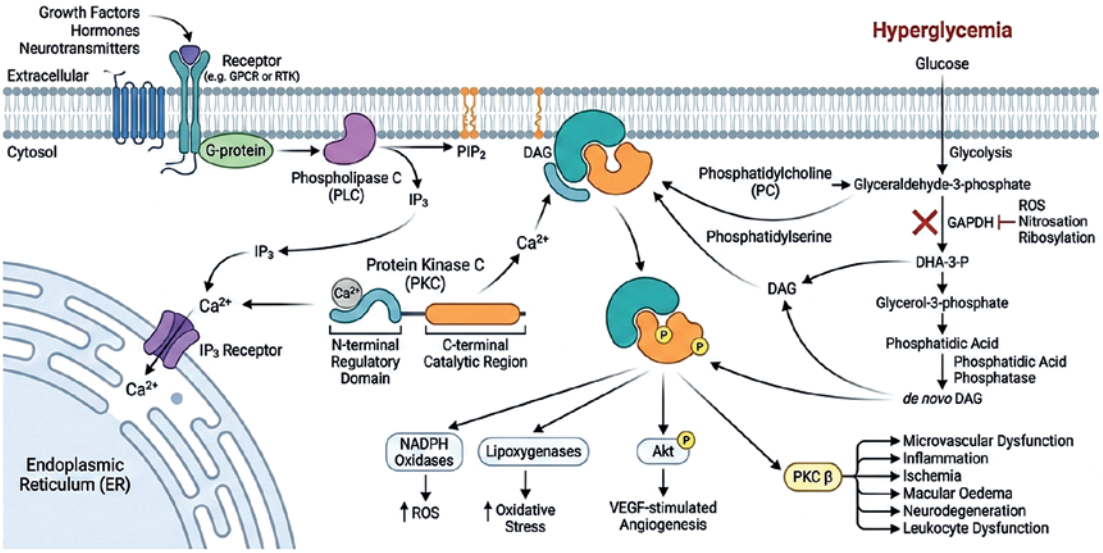

Figure 3. Schematic diagram of hyperglycaemia-related PKC activation in DR. Image created with the assistance of Google Gemini

GAPDH – glyceraldehyde-3-phosphate, -3-P – 3-phosphate, PIP2 – phosphatidylinositol 4,5-biphosphate, IP3 – inositol 1,4,5-triphosphate, DAG – diacylglycerol, PKC – protein kinase C, PLC – phospholipase-C, PLD – phospholipase-D.

under the subtopic of angiogenesis. Additionally, as briefly mentioned earlier, PKC causes dysfunction of leukocytes, leading to capillary occlusion and leukostasis [106]. Table III lists some of the studies on PKC-related markers in DR models [107–110].

Reactive oxygen species

Excessive production or deficient removal of ROS causes oxidative stress. Among the major pathways implicated in microvascular complications of DM, including DR, is hyperglycaemia-induced oxidative stress [46, 111]. Dysregulation in the mitochondrial electron-transport chain leads to overproduction of superoxide, an oxygen-free radical, which has been demonstrated to be the leading factor of oxidative stress in a hyperglycaemic state [112]. Mitochondria is a cell powerhouse [113] and uses nearly 90% of the oxygen consumption for oxidative phosphorylation and adenosine triphosphate (ATP) generation. The mitochondrial electron transport chain produces superoxide as an inevitable by-product via the transfer of electrons from reduced substrates to molecular oxygen via electron transport chain complexes I–IV, making mitochondria a target for harmful oxidants. Superoxide is released by complex I into the matrix, and by complex III on both sides of the inner membrane [114]. These free radicals, which are molecules or molecular fragments with one or more unpaired electrons

Table III. Studies on PKC-related markers in DR models/populations

Study type	First author [ref.]	Model/ population	Experimental system	Key findings
Clinical trial	Group [107]	NPDR patients	Ruboxistaurin (PKC-β inhibitor) RCT	Oral ruboxistaurin reduced risk of sustained moderate visual loss in patients with moderately severe to very severe NPDR, indicating benefit of PKC-β inhibition.
In vitro/ mechanistic (PKCδ)	Kim *et al.* [108]	STZ diabetic rats and HRMECs	Diabetic retina + HRMECs	PKC-δ activation contributed to retinal vascular hyperpermeability; inhibition of PKC-δ restored tight junction protein expression and integrity in diabetic retina and AGE-treated HRMECs.
In vivo	Amadio *et al.* [109]	STZ diabetic rats	Diabetic retina	Diabetes increased PKC-β isoforms and VEGF expression in retina; PKC-β activation linked to VEGF–HuR signalling and diabetic retinal changes.
In vivo	Abdul Ghani *et al.* [110]	STZ diabetic rats	Diabetic retina	Elevated Ang-2 and PKC gene and protein expressions in DR rats.

in molecular orbitals, are extremely reactive. Thus, oxygen, while essential for aerobic life, is not only necessary for energy metabolism and respiration but also interacts with other molecules to produce more free radicals, such as hydroxyl, peroxyl, alkoxyl, and hydrogen peroxide [115]. Increased superoxide can have long-term negative consequences by destroying mitochondrial deoxyribonucleic acid (DNA) and proteins, which can lead to changes in electron transport chain subunits that can trigger even more superoxide generation [116]. Increased production of retinal superoxide in DR derived from the impaired mitochondrial electron transport chain in retinal cells has been demonstrated in numerous animal studies [117–120]. In addition, retinal Müller glial cells were shown to produce significant quantities of higher superoxide levels in a hyperglycaemic environment *in vitro* [121, 122], retinal endothelial cells [121, 123–125], photoreceptor cells [126, 127], and retinal pigment epithelium (RPE) [128, 129]. Other than superoxide, hydrogen peroxide content is also higher in diabetic rat retinas [130]. Peroxynitrite, a potent pro-oxidant with a long half-life, is produced through a spontaneous reaction between nitric oxide and superoxide. Like other free radicals and pro-oxidants, peroxynitrite also causes lipid peroxidation and activates a cascade of events which result in DNA damage, death of endothelial retinal and neuronal cells, retinal neurodegenerative changes and breakdown of the blood-retinal barrier in experimental diabetes models [102, 131, 132]. Moreover, peroxynitrite also activates the transcriptional NF-κB, which leads to higher expression of inflammatory cytokines such as IL-1β, TNF-α, and iNOS [133–135].

Catalase, SOD, glutathione peroxidase, and glutathione reductase are antioxidant enzymes that are essential to fight against free radicals and maintain redox homeostasis throughout the retina [94]. Reduction of these enzymes in retinal tissues and serum has been reported in various diabetic animal models [136–140] as well as in diabetic patients [141–144]. The retina is also equipped with intracellular non-enzymatic antioxidant defences such as glutathione, ascorbic acid and β-carotene, for additional ROS scavenger activities [145]. Levels of serum antioxidant enzymes and non-enzymatic antioxidants were significantly lower in patients with DR compared to diabetic patients without DR [146]. The antioxidant enzymes and non-enzymatic antioxidant levels were also reduced in the retinal tissues and vitreous humour of patients with DR and animal models of diabetes [114, 147–149]. Supplementation with antioxidants in animal models reduced hyperglycaemia-induced oxidative stress, which was associated with a reduction in DR progression [150, 151]. However, contradictory findings in clinical trials have been reported, which could be due to the inevitable limitations of clinical trials, including the given dosage, concurrent diseases, other therapies, disease course and severity, and genetic and environmental influences [152]. Furthermore, ROS play a role in critical signalling cascades that are needed for optimal cellular metabolism. For instance, ROS stimulate receptor tyrosine kinases and transcriptional factors, such as nuclear factor erythroid 2-related factor 2 (NFE2L2), which then binds to the antioxidant response element (ARE) and leads to antioxidant gene expression [153]. The direct scavenging of ROS may also interact with signalling processes, which may explain the lack of efficacy of antioxidant supplementation in several human studies [149].

ROS also promote lipid peroxidation, which generates a broad range of highly reactive aldehyde species that in turn can cause a variety of disease-related responses in cells and tissues [154]. Higher lipid peroxidation was seen in the diabetic retina compared to the normal retina [155]. Mitochondria and microsomal membranes contain relatively large amounts of polyunsaturated fatty acid in their phospholipids, which makes them a target for free radical-induced lipid peroxidation [156]. The retina also has a high proportion of polyunsaturated fatty acids and a high glucose and oxygen requirement. Greater glucose oxidation in the retina compared to other tissues causes it to be more susceptible to lipid peroxidation [157]. Abnormal lipid metabolism in DM may also contribute to higher lipid peroxidation in DR [156]. Elevated lipid peroxide levels in DM could disrupt the SOD enzyme, resulting in accumulation of superoxide radicals that cause the most lipid peroxidation and tissue injuries in diabetes [158, 159]. Higher protein glycation in DM leads to higher free radical production, which causes higher lipid peroxidation [160]. In parallel to increased free radical production, a lack of antioxidant defence is also associated with higher lipid peroxidation [130].

Oxidative stress also promotes DR through the 'metabolic memory' or 'hyperglycaemic memory' phenomenon [161]. The metabolic memory term came about when clinicians and researchers observed that diabetic patients developed complications despite good glycaemic control [161, 162]. This phenomenon was observed especially in diabetic patients who started to adopt strict glycaemic control after being on poor glycaemic control for a long period previously [163]. This 'metabolic memory' was also observed in diabetic dogs, where retinopathy progressed despite the correction of hyperglycaemia [164, 165]. The sustained as well as transient episodes of poor glycaemic control result in mitochondrial oxidative disruption, which then triggers multiple signalling pathways such as PKC, NF-κB and AGEs that induce

inflammation, angiogenesis, apoptosis and oxidative stress [166]. The mitochondrial oxidative disruption was observed to be caused by protein glycation, which exacerbates the oxidative damage [167]. A discussion of how protein glycation induces oxidative stress is presented above. Another mechanism thought to be involved in metabolic memory is epigenetic modifications [168]. Epigenetic changes that occur in DNA/histone complexes during hyperglycaemic episodes modulate oxidative and inflammatory genes, resulting in persistent low-grade inflammation and the alteration of supporting cells as part of vascular remodelling [161, 169–171]. Madsen–Bouterse and Mohammad [172] observed that long periods of hyperglycaemia cause persistent damage to mitochondrial DNA, which leads to impaired mitochondrial electron transport. The failure to repair the mitochondrial DNA damage despite normoglycaemia causes the complications described in DR. DNA methylation was observed to be one of the modifications that alter DNA function, causing permanent and worsening DR complications [173]. Increasing evidence also implicates epigenetic regulators such as lncRNAs as upstream modulators of multiple pathogenic pathways, offering additional avenues for precision-targeted interventions [174]. Table IV lists some of the studies on OS-related markers in DR models [175–179].

Diabetic retinopathy and inflammation

Inflammation is a non-specific injury response of the innate immune system involving several molecular and functional mediators, including leukocyte recruitment and activation [180]. The mechanism of inflammation starts with the identification of pathogen-associated or danger-associated stimuli through their unique binding to pattern identification receptors, such as toll-like receptors (TLR) and RAGE [181]. The activation of pattern-recognition receptors activates an intracellular signalling cascade, which leads to the activation of transcription factors associated with inflammation [182]. Nuclear translocation of these transcription factors upregulates the expression of pro-inflammatory mediators such as TNF-α and interleukins (ILs) [183]. To prevent persistent and chronic inflammation, the resolution process in-

Table IV. Studies on OS-related markers in DR models/populations

Study type	First author [ref.]	Model/ population	Experimental system	Oxidative stress markers/pathways measured	Key findings
In vivo	Zhang e*t al.* [175]	STZ-induced diabetic rats	Streptozotocin diabetic rat retina	Retinal superoxide, mitochondrial dysfunction, SOD	Diabetes increased retinal superoxide levels and decreased SOD activity, supporting oxidative stress's role in early DR microvascular damage.
In vivo	Xu e*t al.* [176]	STZ diabetic mice, Nrf2 knockout	Diabetic mouse retina	NRF2, ROS, GSH	NRF2 deficiency in diabetic mice increased ROS and reduced glutathione, demonstrating NRF2's protective role in retinal oxidative stress.
Human clinical (vitreous and serum)	Brzović-Šarić e*t al.* [177]	PDR patients vs. controls	Vitreous and serum oxidative markers	MDA, LPO, SOD, GSH	PDR vitreous had increased lipid peroxidation (MDA, LPO) and altered SOD compared with controls; serum showed parallel oxidative stress alterations.
Human clinical (serum)	Hartnett e*t al.* [178]	T1DM and T2DM with/ without DR	Serum oxidative biomarker analysis	TBARS, SOD, GSH-Px	Diabetic patients had higher lipid peroxidation (TBARS) and lower antioxidant enzyme activities than controls; oxidative stress parameters were elevated in diabetes.
Human clinical (aqueous/ vitreous)	López-Contreras e*t al.* [179]	T2DM + PDR/ DM2 + no PDR	Aqueous, vitreous, serum biomarkers	8-isoprostane, SOD, CAT, GPx, TAC	Oxidative stress biomarkers (8-isoprostane) were elevated in vitreous and serum in PDR compared with non-DR controls; total antioxidant capacity was reduced.

volving resolvins, lipoxins and protectins reduces the pro-inflammatory cytokines and chemokines over time [184, 185]. Inflammation is considered as a functional defence mechanism in acute conditions but can be detrimental if it persists chronically [186].

Chronic or low-grade inflammation is thought to be involved in the onset, spread, and progression of metabolic diseases and complications such as DR [187]. The relationship between chronic inflammation and DR was noticed after a lower prevalence of DR was observed in diabetic patients taking salicylates to treat rheumatoid arthritis [188, 189]. Increasing evidence points to inflammation as a critical contributor to the development of DR. Inflammatory cytokines and chemokines are elevated in serum and ocular samples such as vitreous and aqueous humour from diabetic patients with DR [190]. Inflammatory cytokines such as IL-1β, IL-6, IL-8, TNF-α and MCP-1 have been reported to be elevated in ocular tissues from NPDR patients [180]. Interestingly, Boss and Singh [191] showed higher levels of cytokines including IL-6, IL-8, IL-1β, and TNF-α not only in the vitreous of mild to severe NPDR but also in active PDR patients [191]. The abundance of these inflammatory mediators produced by activated microglia, endothelial cells, microglia, and later neurons at an early stage of DR contributes to the pathogenesis of early neuronal cell death [192]. However, higher levels of several cytokines, such as IL-6 and MCP-1, in the vitreous humour were observed to be associated with DR progression or severity. IL-6 expression, in particular, has been shown to positively correlate with retinal macular thickness [193]. A higher level of soluble cytokine receptors, such as IL-2 receptor (IL-2R), was also observed in the vitreous sample of PDR patients [194]. However, conflicting reports have been published regarding the type of inflammatory cytokines prevalent in DR patients. This might be the reason why there are no widely accepted valid biochemical inflammatory markers used to screen DR severity or progression.

Retinal glial cell activation, also known as gliosis, was observed in diabetic patients who were yet to be diagnosed with DR [195]. Müller glial cells (MGCs) are an important source of inflammatory mediators. Therefore, this suggests that retinal glial cell activation might play a role in the early onset of the inflammatory mechanism of DR [180]. MGCs also produce ICAM-1 and monocyte chemotactic protein (MCP-2), which are involved in leukostasis, another event observed early in DR pathophysiology associated with inflammation [196, 197]. The ability of leukocytes to produce toxic metabolites and proteolytic enzymes, such as ICAM-1 and VCAM-1 via TNF receptor-associated factor and PKC-dependent NF-κB activation, is thought to enhance leukocyte adhesiveness, leading to the development of microvascular defects [198].

A variety of inflammatory mediators are activated in DR, but the signalling process involved in initiating this response is still unclear. One of the signalling pathways that plays a role in initiating inflammatory responses in DR is the NF-κB signalling pathway. NF-κB is a nuclear transcription factor that regulates cell responses to factors such as stress, cytokines, free radicals, ultraviolet irradiation, and bacterial or viral antigens [199, 200]. NF-κB was identified in B cells because of its association with the 11-base pair sequence in the immunoglobulin light-chain enhancer, but it was later found in other types of cells [201]. The inactivated NF-κB is sequestered in the cytoplasm complexed with inhibitory kappa B (IκB) proteins [202]. When IκB proteins are degraded, NF-κB is released, and in its activated form, it is free to translocate into the nucleus, where it regulates gene expression [203]. Degradation of IκB is therefore an essential step in the activation of NF-κB [203]. Multiple stimuli such as free radicals, inflammatory cytokines and growth factors can stimulate NF-κB activation [204]. Kowluru *et al*. [205] showed that NF-κB activation is a major event in the initial development of DR, which is one of the first discoveries on the function of NF-κB in DR development. NF-κB involvement in the early phase of DR is also associated with retinal neurodegeneration and ganglion cell death [206]. Activation of NF-κB in DR increases the regulation of pro-inflammatory cytokines, which could further reactivate the signalling pathway of NF-κB and aggravate the inflammation process in the retina. Other than inflammatory cytokines, activation of NF-κB also enhances the regulation of proteins that modulate cell apoptosis, neurodegeneration and angiogenesis in DR [207].

iNOS is upregulated in pathological conditions such as in the chronic inflammatory environment of DR. Several receptor molecules such as TLRs and CD14 regulate iNOS through activation of the NF-κB signalling pathway [208]. High expression of iNOS was observed in retinal cells of diabetes models [209]. Uncontrolled and excessive iNOS expression leads to higher NO levels, which may affect retinal ocular blood flow and the retinal neurovascular unit [210]. Elevated NO levels also predispose cells to higher oxidative damage through the production of peroxynitrite, a toxic reactive nitrogen species [211, 212].

Apart from the NF-κB signalling pathway, other biochemical pathways involved in augmenting inflammation in DR include the PKC, AGE and hexosamine pathways. These pathways not only promote inflammation but also oxidative stress, which results in worsening of the vascular permeability and angiogenesis in DR [207]. As an exam-

ple, PKC activation was associated with increased activation of leukocytes, basement matrix protein synthesis, endothelial cell activation and proliferation, smooth muscle cell contraction, stimulation of cytokines and endothelial permeability, and transforming growth factor-β (TGF-β) in the pathogenesis of DR [213, 214]. Table V lists some of the studies on inflammatory markers in DR models [215–220].

Diabetic retinopathy and apoptosis

In multicellular organisms, apoptosis is a process of programmed cell death. Apoptosis is necessary for the physiological maintenance of tissue in a normal cell population [221]. Apoptosis serves as a defence mechanism against noxious stimuli or disease in maintaining a normal cell population. Initially, the nucleus was thought to govern the apoptotic event, before it was discovered that enucleated cells also undergo apoptosis, implying that mitochondria control the intrinsic apoptotic cascade [222]. However, malfunctioning of the apoptotic processes is associated with the pathogenesis of multiple diseases [223].

In mammals, signalling cascades that activate apoptotic cell death can be divided into intrinsic and extrinsic pathways [224, 225]. The stimuli for the intrinsic apoptotic pathway include intracellular stressors such as oncogenes, direct DNA damage, hypoxia, and survival factor deprivation [226]. The stimuli then trigger the translocation of p53 to mitochondria, leading to the release of mitochondrial proteins such as cytochrome C and SMAC/DIABLO [227] that may involve proapoptotic B-cell lymphoma 2 (BCL-2) family proteins or mitochondrial permeability transition pore (MPTP) activation. Cytochrome C is the key factor in the development of apoptosis [228, 229]. Cytochrome C release may be caused by changes in mitochondrial dynamics such as mitochondrial fragmentation [230] or through activation of the dynamin-related protein 1 (Drp1) [231]. Once released, cytochrome C forms an 'apoptosome' complex with apoptotic protease activating factor 1 (APAF-1) and procaspase-9 [232]. In the presence of ATP or deoxyadenosine triphosphate (dATP), the apoptosome complex activates caspase-3 and caspase-7, which leads to cell apoptosis [233]. SMAC/DIABLO assists caspase-3 and caspase-7 activation by inhibiting the X-linked inhibitor of apoptosis protein (XIAP), which is responsible for caspase-9 degradation [227, 234]. Crosstalk between the intrinsic and extrinsic apoptotic path-

Table V. Studies on inflammatory markers in DR models/populations

Study type	First author [ref.]	Model/ population	Experimental system	Key findings
In vitro	de Lemos *et al.* [215]	hiPSC-derived retinal organoids (HG)	3D retinal organoid high-glucose model	High glucose induced increased IL-1β and MCP-1 expression and gliosis markers, modelling early-stage DR inflammation and neurodegeneration.
In vivo	Mugisho *et al.* [216]	NOD diabetic mice	Intravitreal IL-1β + TNF-α injection	Pro-inflammatory cytokines induced retinal gliosis, microglial activation and oedema, consistent with inflammatory DR features.
In vivo	Scuderi *et al.* [217]	STZ-induced diabetic rats	Retinal protein analysis	Hyperglycaemia increased retinal IL-1β and receptors, demonstrating IL-1 signalling involvement in diabetic retinal inflammation.
In vivo	Portillo *et al.* [218]	STZ diabetic mice	CD40 modulation	Disruption of CD40–TRAF2/3 signalling reduced ICAM-1 upregulation and leukocyte adhesion in diabetic retina, implicating inflammatory pathways in DR progression.
Human clinical (vitreous)	Yu Y *et al.* [2020]	PDR and NPDR patients	Vitreous cytokine ELISA	IFN-γ and TNF-α levels were significantly elevated and adiponectin reduced in DR vitreous compared to controls, supporting a pro-inflammatory intraocular profile.
Human clinical (vitreous)	Ucgun *et al.* [219]	PDR patients vs controls	Vitreous cytokine profiling	Multiple inflammatory cytokines (including CRP and IL-8) and adhesion molecules were elevated in PDR vitreous, showing widespread inflammatory activation in advanced DR.
Human clinical (serum)	Loporchio *et al.* [220]	T2DM with NPDR vs PDR	Serum/vitreous biomarkers	IL-6 and CRP levels were significantly higher in PDR patients versus NPDR, indicating systemic inflammatory biomarker associations with DR severity.

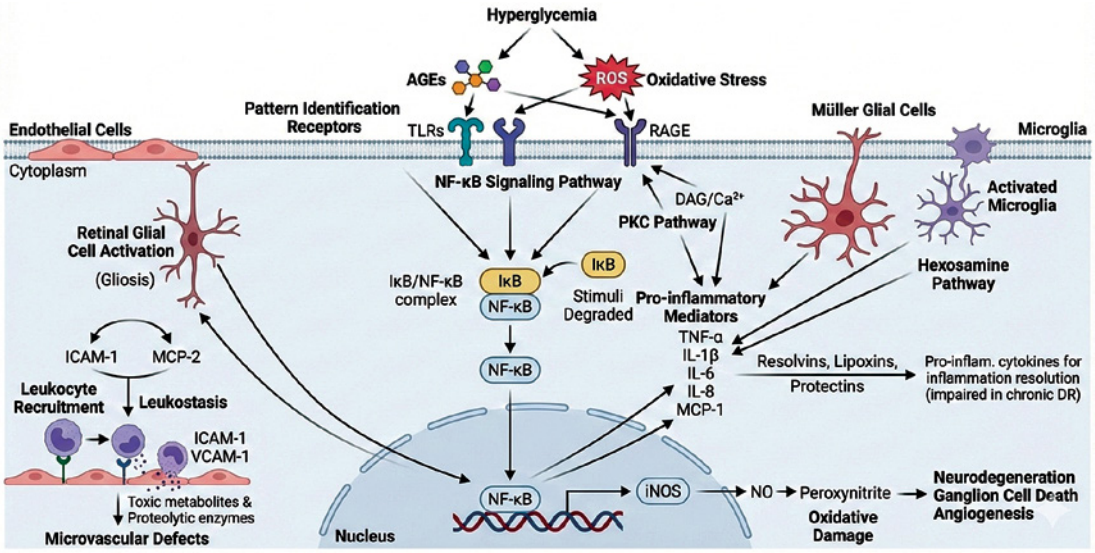

Figure 4. Inflammation pathway in DR pathogenesis. Image created with the assistance of Google Gemini

ways occurs through caspase-8 activation (Figure 4). In comparison to the intrinsic apoptotic pathway, the extrinsic apoptotic pathway stimulation in inflammation is mediated through the death receptors of the TNF receptor superfamily, which includes Fas, TNF-α, and TNF-related apoptosis-inducing ligand (TRAIL) receptors [235]. Once the TNF superfamily members/ligands interact with the death receptor, it initiates the formation of a death-inducing signalling complex (DISC) that includes the critical adaptor molecule Fas-associated death domain (FADD), which in turn stimulates caspase-8 and caspase-10 activation [236]. Caspase-8 and caspase-10 can directly activate caspase-3 and caspase-7. Activation of caspase-8 and -10 can also induce the intrinsic apoptotic

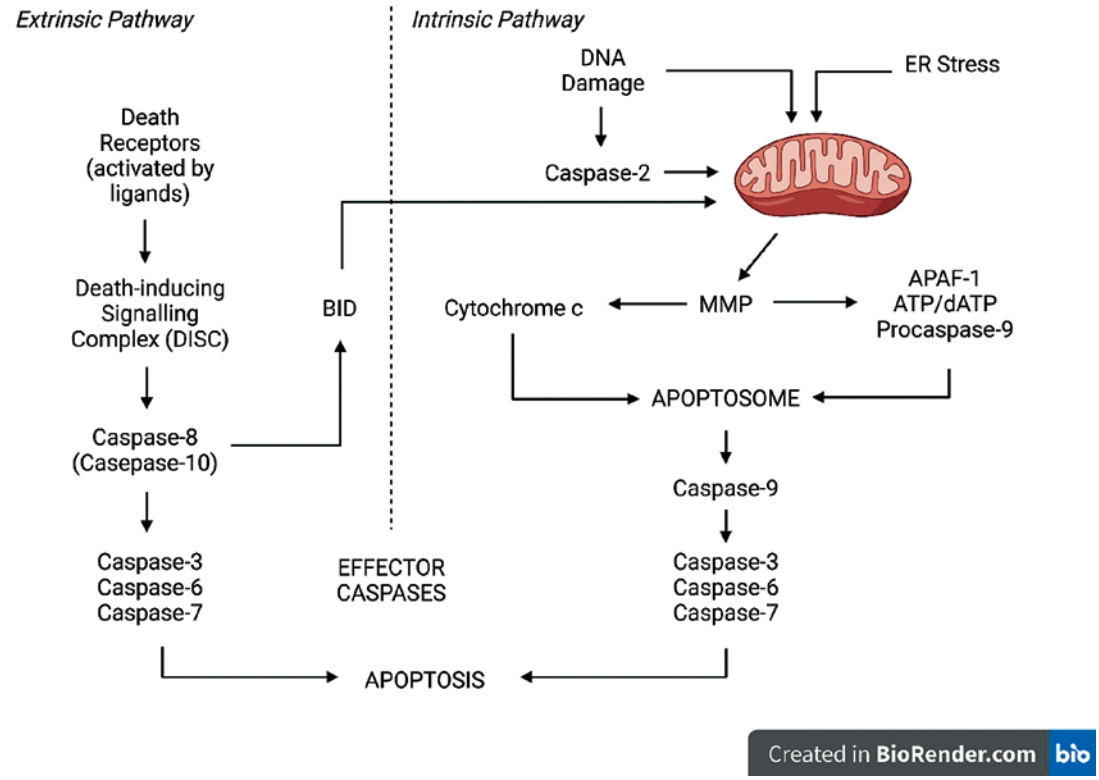

Figure 5. Crosstalk between the intrinsic and extrinsic apoptotic pathways

BID – BH3-interacting domain; ER – endoplasmic reticulum; MMP – matrix metalloproteinase; APAF-1 – apoptotic protease activating factor-1; ATP – adenosine triphosphate; dATP – deoxyadenosine triphosphate.

pathway through cleavage of full-length (p22) BH3 interacting domain (BID), which causes cytochrome C release [237]. Figure 5 presents a schematic representation of intrinsic and extrinsic apoptotic pathways in DR.

Apoptosis is activated by factors such as Fas receptors and caspases, while apoptosis is inhibited by members of the BCL-2 protein family, as previously mentioned [238, 239]. BCL-2 family proteins such as BCL-2, BCL-XL, BCL-W, MCL-1, and BFL-1/A1 are considered to be anti-apoptotic, whereas effector proteins such as BAX, BAK, and BOK are considered to be pro-apoptotic [240].

The diabetic retina has a greater number of apoptotic cells, indicated by the reduction of the overall number of cells remaining in the retina after a long duration of diabetes [241, 242]. Retinal vascular endothelial cells treated with glucose showed higher mitochondrial fragmentation, altered membrane potential heterogeneity, reduced oxygen consumption rate, increased extracellular acidification, and cytochrome C release that promotes apoptosis [243]. This proved that mitochondrial dysfunction involving structural changes mediates the retinal vascular cell death in a hyperglycaemic environment. The apoptotic changes described above also correspond with higher expression of pro-apoptotic retinal protein markers such as caspase-3 and BAX and lower expression of anti-apoptotic protein markers such as BCL-2 [244, 245]. Reduction in the total number of cell bodies of the retinal ganglion cell layer was also accompanied by a reduction in the thickness of the inner plexiform and inner nuclear layer [246]. The thickness of the outer nuclear layer (ONL), on the other hand, remained unchanged, implying that more cells were lost in the inner retina than in the outer retina [247]. The selective thinning of inner retinal layers observed in diabetic patients with minimal retinopathy compared with healthy controls corroborates the concept that early DR involves neuronal apoptosis [248].

Oxidative stress and inflammation are known to be intracellular stressors responsible for activating the intrinsic apoptotic pathway in the diabetic retina [249]. Additionally, glutamate excitotoxicity is responsible for triggering retinal cell apoptosis in DR [250, 251]. Glutamate excitotoxicity, causing uncontrolled continuous depolarisation of neurons, occurs in the hyperglycaemic environment, as glutamate uptake and metabolism are compromised [252]. Proinflammatory cytokines, which were increased in the hyperglycaemic environment, prevented glutamate from being cleared from the synaptic cleft by interfering with glutamate uptake [253] or by inactivating the glutamate converting enzyme known as glutamine synthetase [254]. In diabetic neural retinal cells, excess glutamate induces an unregulated intracellular calcium response by opening the voltage-dependent anion channels, which enhances the mitochondrial membrane permeability and eventually activates cell apoptosis [255]. Higher expression of the mitochondrial Ca^{2+} uniporter also contributes to increased mitochondrial Ca^{2+} influx through the loss of mitochondrial membrane potential [256]. Corresponding changes were noted in visual-behaviour responses, suggesting associated neurocognitive decline secondary to retinal neurodegeneration in an STZ-induced model [257].

Retinal cell apoptosis and microglial activation are features of neurodegeneration. Retinal glial cells, such as macroglia (Müller cells and astrocytes) and microglia, act as a communication channel between retinal blood vessels and neurons in the retina [258]. In a normal environment, microglia are in a 'resting' state, whereas in an inflammatory condition, microglia become overly activated [259]. Neurodegeneration has now been acknowledged as an important early process involved in the pathogenesis of DR that leads to microvascular abnormalities [260–263]. A higher number and activity of microglial cells were observed in DR retinal tissues, as evidenced by increased expression of the macrophage markers OX42 and iba1 [264]. Due to chronic exposure to chemokines and cytokines, activated microglia cause morphological and functional changes in their structure, which leads to the release of microglial products that promote blood-retinal barrier breakdown [265]. Aside from the changes in cellular morphology and function, activated microglia can produce cytotoxic substances such as the cytokine TNF-α, ROS, proteases, and excitatory amino acids, which promote neuronal degeneration [266]. Chronic microglial activation also leads to changes in macroglial function such as an increase in the Müller cell population and glial fibrillary acidic protein expression, as well as a decrease in the astrocytic population, which may be attributed to increased vascular permeability in DR [267]. Neurotrophins (NTs), a group of specific growth factors that maintain neuronal function, were found to be higher in NPDR and PDR patients [191]. This may represent an attempt by glial cells to rescue compromised neurons in DR. Table VI lists some of the studies on apoptotic markers in DR models [268–273].

Diabetic retinopathy and angiogenesis

Angiogenesis is the development of new blood vessels as a result of proliferation of existing endothelial cells that lack fully developed tunica media [274]. Persistent, uncontrolled neovascularisation is a significant pathological feature of microvascular complications of diabetes including DR. Angio-

Table VI. Studies on apoptotic markers in DR models/populations

Study type	First author (year)	Model/ population	Experimental system	Key findings
In vitro and *in vivo*	Hu *et al.* [268]	Human retinal microvascular endothelial cells (HG-treated) + STZ diabetic mice	HRMEC hyperglycaemia and diabetic retina	Dapagliflozin reduced HG-induced apoptosis in HRMECs and diabetic mouse retina; decreased ROS, BAX/Bcl-2 ratio, and cleaved caspase-3, via ERK1/2/ cPLA2/ROS pathway.
In vivo	Martin *et al.* [269]	STZ-induced diabetic mice	Experimental DR retina	Diabetes increased retinal neuronal apoptosis (ganglion layer) shown by TUNEL and active caspase-3 in diabetic mouse retina.
In vivo	Sadikan *et al.* [270]	STZ-induced diabetic rats	Retina	Caspase-3 activation increased in diabetic rat retina, indicating apoptosis of retinal vascular cells; antioxidant treatment reduced activation.
In vivo	Yang *et al.* [271]	STZ-induced diabetic rats	Retina	Caspase-3 activity increased in diabetic rat retina over time, supporting apoptosis in DR microvascular cells.
In vivo	Goh *et al.* [272]	STZ-induced diabetic rats	Retina	Higher retinal expression of caspase-3 and Bax protein but lower Bcl-2.
In vitro (pericytes)	Suarez *et al.* [273]	Human retinal pericytes	High glucose culture	High glucose induced apoptosis in human retinal pericytes via enhanced caspase-3 activity; blocking Siah1/ GAPDH interaction reduced apoptosis.
Human tissue (postmortem)	Barber *et al.* [250]	Human diabetic donor retinas	Postmortem retina	Increased TUNEL-positive apoptotic cells in inner retina of human diabetic donor eyes compared with non-diabetic controls.

genesis progression is controlled by a counterbalance between endogenous angiogenic stimulators and angiogenic inhibitors [274]. There are several angiogenesis stimulators such as VEGF, tumour growth factor-alpha (TGF-α), TGF-β, epidermal growth factor, IGF-1, platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), and angiopoietin-II (Ang-II), as well as inflammatory cytokines such as IL-1α and IL-8. Among them, the most well-known angiogenesis stimulator associated with DR is VEGF [275]. In contrast, angiogenic inhibitors such as thrombospondins-1 and -2, vasohibin, chondromodulin, pigment epithelial-derived factor, platelet factor 4, endostatin and angiostatin, play a role in maintaining the balance of angiogenic process [276].

The changes in the retinal vessels resulting from neurodegeneration, oxidative-nitrosative stress and inflammation in diabetes lead to damaged and abnormal vessels which give rise to non-perfusion or hypoxia of retinal tissue. The hypoxic environment in the retina stimulates hypoxia-inducible factor 1 (HIF-1), the primary mediator in the homeostasis of cellular oxygen promoting change to hypoxia [277]. Activated HIF-1 binds to the hypoxia response element (HRE) and modulates gene transcription. HIF-1 activation in hypoxic retinal cells was associated with higher VEGF expression [278]. The human VEGF gene has been discovered to have a 28-base sequence of HIF-1α promoter [279]. Activation of HIF-1α is initiated by proteasomal degradation of HIF-1α complex [280]. This process is promoted in a hypoxic environment, which then leads to the binding of activated HIF-1α to HRE and modulates gene transcription [281]. HIF-1α activation is associated with increased ROS accumulation [282], consistent with the observation that VEGF was elevated in an environment of increased oxidative stress [283, 284].

VEGF is considered to play a critical role in angiogenesis development in DR [285, 286]. Removal of the VEGFR-1 gene reduced neovascularisation in DR by up to 86% [287, 288]. During hypoxia, VEGF-A is upregulated transcriptionally and alternative mRNA splicing generates several VEGF-A isoforms [289, 290]. In vascular endothelial cells, the binding of VEGF-A to vascular endothelial growth factor receptor 2 (VEGFR2) triggers multiple signal transduction such as the mitogen-activated protein kinase cascade and the phosphatidyl inositol 3-kinase (PI3K)/Akt cascade, thus enhancing cell proliferation and relocation, thereby stimulating angiogenesis [291]. Furthermore, the VEGF-A-VEGFR2 signal causes vascular hyperpermeability and fluid extravasation by

disrupting endothelial cell adherens and tight junctions [291]. The VEGF-A-VEGFR2 response is therefore essential for retinal angiogenesis and vascular leakage in DR [292]. VEGF promotes angiogenesis by enhancing vasodilation and vascular permeability, inhibiting endothelial apoptosis, and attracting inflammatory cells through the growth and recruitment of progenitor cells [293].

Inflammation promotes and contributes to neovascularisation in DR. In inflammatory conditions, the VEGFR1 signal in macrophages and monocytes [294] correlates with increased VEGF-B and placental growth factor (PlGF) in DR [295]. Higher levels of cytokines such as macrophage inflammatory protein (MIP-1), IL-1, and IL-3, were observed in tandem with angiogenesis in DR [264, 296].

Increased vitreous levels of the above-mentioned cytokines along with growth factors, including VEGF, PDGF, IGF-1, basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF), have been documented in patients with PDR [297]. Beside growth factors, other key regulators of migratory and tissue remodelling phenomena – matrix metalloproteinases (MMPs) – are also important in the angiogenic process in DR [298, 299]. Upregulated MMP expression was observed in PDR (194) (Figure 6). Table VII lists some the studies on angiogenic markers in DR models [125, 270, 300–303].

Emerging role of lncRNAs as epigenetic regulators

lncRNAs are defined as transcripts longer than 200 nucleotides that do not code for proteins but regulate gene expression through diverse mechanisms, including chromatin remodelling, miRNA sponging, and modulation of transcriptional networks. In DR, several original research studies have demonstrated that lncRNAs contribute to key pathological processes such as retinal endothelial dysfunction, inflammation, oxidative stress, apoptosis, and angiogenesis, thereby linking them mechanistically to classical DR pathways.

One of the most studied lncRNAs in DR is MALAT1 (metastasis-associated lung adenocarcinoma transcript 1). In streptozotocin-induced diabetic rodent models, MALAT1 expression is significantly upregulated in retinal tissue, and its knockdown ameliorates microvascular abnormalities including pericyte loss, capillary degeneration, and retinal inflammation, implicating MALAT1 in pathological angiogenesis and endothelial cell dysfunction through p38 MAPK signalling and cell cycle regulation [304]. Furthermore, MALAT1 has been shown to modulate antioxidant defence by interacting with Keap1 to suppress nuclear factor erythroid-2-related factor 2 (Nrf2) activity, thereby inhibiting antioxidant gene transcription in retinal endothelial cells exposed to high glucose; knockdown of MALAT1 restores Nrf2-mediated transcription and protects against oxidative damage [305]. A separate line of work found that MALAT1 aggravates retinal angiogenesis in DR via the miR-320a/HIF-1α axis, demonstrating direct pro-angiogenic effects in retinal endothelial and Müller cells under hyperglycaemic stress [306]. These studies highlight MALAT1 as a multifunctional regulator that integrates oxidative stress, angiogenesis, and neurovascular dysfunction in DR.

MIAT (myocardial infarction-associated transcript) has also been directly implicated in DR pathogenesis. Plasma MIAT levels are elevated in

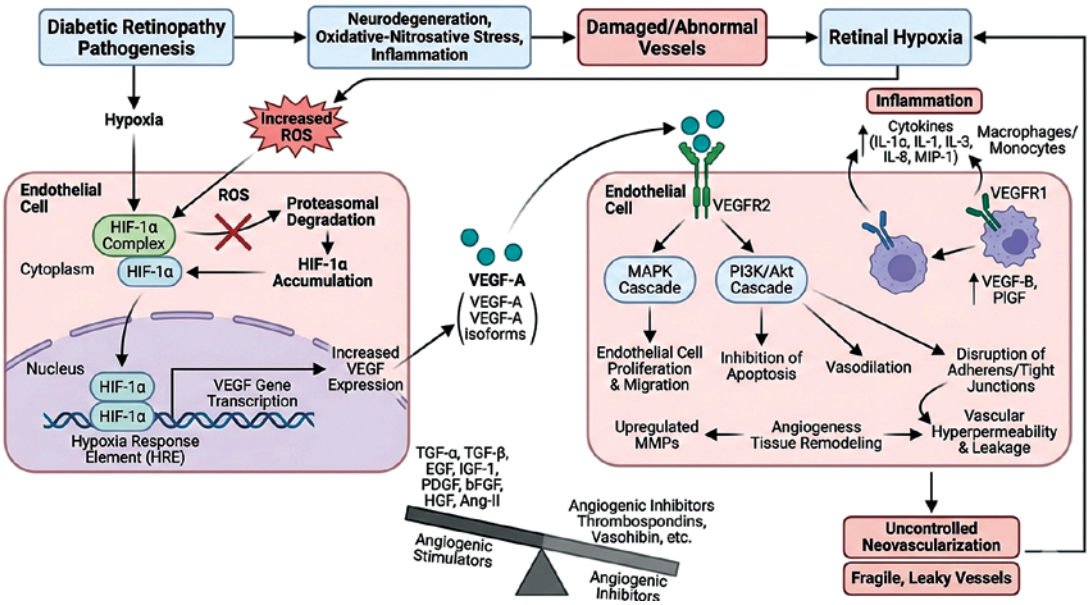

Figure 6. Angiogenesis pathways and DR pathogenesis. Image created with the assistance of Google Gemini

Table VII. Studies on angiogenic markers in DR models and populations

Study type	First author [ref.]	Model	Experimental system	Key angiogenesis findings
In vitro	Wang e*t al.* [300]	Human retinal vascular endothelial cells (HRMECs)	High glucose *in vitro* DR model	High glucose increases HRMEC proliferation, migration, and tube formation with elevated VEGF expression in hyperglycaemic conditions.
In vitro and *in vivo*	Kida e*t al.* [125]	Retinal cells and STZ-induced mice	High glucose and animal model	Hyperglycaemia increases ROS and VEGF in retinal cells; rapamycin reverses VEGF/ROS effects; supports angiogenic role of VEGF in diabetic retina.
In vivo	Gong e*t al.* [301]	STZ-induced diabetic rats	DR progression model	STZ diabetes increases retinal VEGF, VEGFR1/2 expression and new vessel formation in diabetic rat retina.
In vivo	Sadikan e*t al.* [270]	STZ-induced diabetic rats	DR and treatment with tocotrienol-rich fraction	TRF reduced retinal VEGF and HIF-1α expression and inhibited retinal angiogenesis in diabetic rats.
Human clinical trial	Wells e*t al.* [302]	Diabetic macular oedema (DME) patients	Multicentre RCT	In DME, all anti-VEGF agents improved vision and inhibited pathological VEGF-driven angiogenesis; aflibercept showed greater efficacy in worse baseline vision.
Human clinical trial	Gross e*t al.* [303]	Proliferative DR patients	Randomised clinical trial	Intravitreal ranibizumab was non-inferior to panretinal photocoagulation (PRP) for visual acuity outcomes at 2 years; supports anti-VEGF control of neovascularisation.

patients with DR compared to diabetic patients without retinopathy and healthy controls, and high glucose exposure induces MIAT expression in retinal pigment epithelial cells; MIAT overexpression *in vitro* reduces cell viability and promotes TGF-β1 signalling, linking MIAT to inflammatory and apoptotic pathways relevant to retinal neurovascular injury [307]. Additional mechanistic studies suggest that MIAT can act as a competing endogenous RNA, sequestering specific miRNAs and thereby influencing VEGF-mediated angiogenic responses, although targeted investigations in retinal endothelial cells remain ongoing.

In contrast to MALAT1 and MIAT, MEG3 (maternally expressed gene 3) appears to have protective functions. MEG3 expression is suppressed under high glucose conditions in retinal epithelial cells, and forced expression of MEG3 alleviates inflammation and apoptosis by regulating the miR-34a/SIRT1 axis, inhibiting NF-κB signalling and restoring anti-apoptotic balance [308]. Although most MEG3 studies have been performed *in vitro*, these findings suggest that MEG3 downregulation in DR may release inhibitory control over inflammatory pathways and contribute to retinal cell loss.

Transcriptome analysis of diabetic retinopathy samples has identified additional lncRNAs differentially expressed in patient serum and retinal cells, including novel species such as MSTRG.15047.3 and FRMD6-AS2, which correlate with retinopathy status and may serve as potential biomarkers or components of regulatory networks [309]. These data indicate that lncRNA dysregulation in DR is not limited to a few canonical transcripts but reflects broader transcriptomic remodelling of non-coding RNA networks during disease progression.

Beyond individual functional roles, lncRNAs also intersect with epigenetic regulation and metabolic memory. Persistent hyperglycaemia induces stable changes in chromatin states and gene expression in retinal cells, and lncRNAs have been implicated in sustaining these alterations through interactions with chromatin regulators and miRNAs, thus promoting ongoing oxidative and inflammatory gene expression even after glycaemic normalization. Collectively, current original research supports a model in which dysregulated lncRNAs contribute mechanistically to multiple pathogenic axes in DR, including oxidative stress, inflammation, apoptosis, and angiogenic signalling. Targeting pathogenic lncRNAs or restoring protective lncRNA expression may therefore represent a promising adjunctive strategy alongside existing anti-VEGF and anti-inflammatory therapies in diabetic retinopathy management (174) (Figure 7).

Future perspectives and emerging therapeutic strategies

Future DR research should focus on integrative therapy targeting the networked pathways of oxidative stress, inflammation, apoptosis, and angiogenesis. Such combination therapy treatment

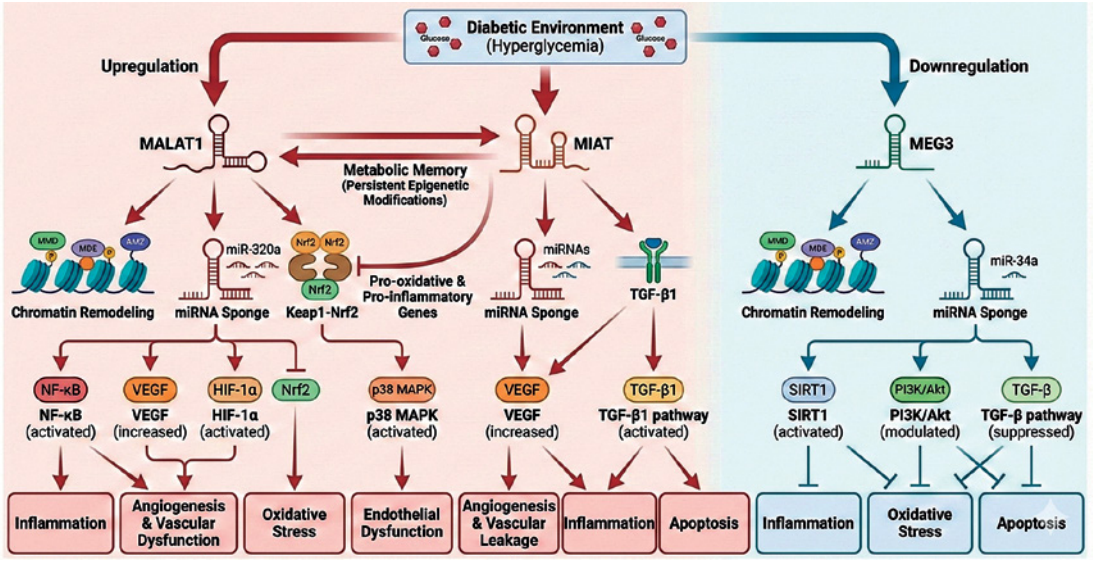

Figure 7. The epigenetic regulatory role of lncRNAs in DR pathogenesis. Image created with the assistance of Google Gemini

targeting these pathways simultaneously may ultimately yield greater therapeutic benefit than isolated single-target approaches [310]. Of the most interest would be mitochondrial-targeted antioxidants with the goal of reducing oxidative retinal damage through targeting the key source of ROS. In addition, there is growing interest in exploring non-VEGF anti-angiogenic agents, such as the angiopoietin-Tie2 pathway or hypoxia-inducible factor targets, to overcome the shortcomings of existing anti-VEGF treatments. Therapeutic induction of inflammation resolution by endogenous lipoxins and resolvins may offer a novel method for restoring immune homeostasis in the retina. Moreover, neurovascular protective strategies, such as the use of neuroprotective peptides, gene therapy, immunotherapy, nanoparticles, liposomes and stem cell-derived exosomes, present a promising avenue for preservation of retinal function and form [311–314]. Biomarker-guided, personalised anti-inflammatory, oxidative, or imaging pattern-based therapy could enhance the precision and efficacy of treatment. Additionally, the gut-retina axis and its modulation by the microbiome represent a newly developing frontier in DR studies, where regulation of systemic metabolism is linked to retinal health. It will be essential to ensure long-term safety and cost-effectiveness of new drugs, including gene-based and biologic therapies, for clinical translation [314].

In parallel with therapeutic advances, artificial intelligence (AI)-assisted screening has emerged as a transformative tool for the early detection and management of diabetic retinopathy. Deep learning algorithms, particularly convolutional neural networks trained on large-scale retinal fundus image datasets, have demonstrated high sensitivity and specificity in detecting referable DR, often comparable to expert ophthalmologists. Several landmark studies have validated the clinical performance of automated DR screening systems, leading to regulatory approvals for autonomous AI platforms in primary care and community settings [315]. AI-based screening enables rapid, standardised, and cost-effective identification of early retinal changes, facilitating timely referral and intervention before irreversible vision loss occurs. Importantly, large population-based studies indicate that AI-assisted screening can significantly improve screening coverage and adherence, particularly in underserved or resource-limited settings where access to retinal specialists is constrained [316, 317]. Emerging evidence further suggests that systemic factors beyond ocular imaging, including alterations in the gut-retina axis, may influence DR risk and progression, as diabetes-associated gut dysbiosis can modulate systemic inflammation, oxidative stress, and circulating metabolites that affect retinal vascular and neuroglial homeostasis [318, 319]. Integration of AI-based image analysis with systemic and microbiome-related data therefore represents a promising direction toward more comprehensive risk stratification and personalised management of DR.

Study highlights

DR remains a major cause of preventable vision loss worldwide, particularly among working-age populations, reflecting its substantial socioeconomic burden. DR pathogenesis is driven by interconnected molecular mechanisms, including oxidative stress, inflammation, apoptosis, angiogenesis, retinal neurodegeneration, and epigenetic dysregulation. Oxidative stress

represents a central initiating event in DR, arising from chronic hyperglycaemia-induced overproduction of reactive oxygen species and impaired antioxidant defence, thereby amplifying downstream inflammatory and apoptotic signalling. Sustained inflammatory activation, mediated through pathways such as NF-κB and pro-inflammatory cytokine release, exacerbates microvascular dysfunction and promotes blood-retinal barrier breakdown. Hyperglycaemia-induced apoptosis of retinal endothelial cells, pericytes, and neural elements contributes to capillary dropout, neurovascular unit disruption, and progressive visual decline. Hypoxia-driven angiogenesis, primarily mediated by VEGF and related pro-angiogenic factors, results in pathological neovascularization and advanced-stage retinal ischemic damage. Retinal neurodegeneration occurs early in DR and may precede overt microvascular lesions, underscoring the need to consider DR as a neurovascular disorder rather than solely a microangiopathy. Emerging evidence implicates metabolic memory, epigenetic regulation, and long non-coding RNAs as upstream modulators that sustain pathogenic gene expression despite glycaemic control. A comprehensive, multi-targeted therapeutic strategy addressing oxidative stress, inflammation, angiogenesis, apoptosis, and epigenetic alterations is likely required to effectively delay or prevent DR progression. Identification and validation of novel therapeutic targets, including epigenetic and RNA-based interventions, remain critical priorities for future translational research.

Conclusions

DR is a leading cause of vision loss in individuals with diabetes, resulting from sustained hyperglycaemia-induced damage to the retinal microvasculature. The disease is driven by interconnected pathophysiological processes, including oxidative stress, chronic inflammation, apoptotic cell loss, and aberrant angiogenesis, which collectively accelerate retinal injury and progression from non-proliferative to proliferative stages. These mechanisms underlie clinically significant structural and functional retinal changes, underscoring the critical importance of early detection and timely intervention to preserve vision. Understanding the molecular basis of DR provides a vital translational framework for mechanism-based therapeutic strategies, enabling more targeted and effective management. Increasing evidence also implicates epigenetic regulators such as lncRNAs as upstream modulators of multiple pathogenic pathways, offering additional avenues for precision-targeted interventions. When combined with advances in ocular drug delivery and pharmacological innovation, this insight holds significant promise to improve clinical outcomes and reduce the global burden of DR-related visual impairment.

Declaration on the Use of Generative AI

The authors used ChatGPT 5.0 model to improve the readability and language of the manuscript. The AI model was used with oversight and control by the authors, which was then carefully reviewed and edited to ensure the integrity and scientific accuracy of the content. Additionally, Google Gemini 3.5 Flash was used to assist in the preparation and refinement of the conceptual mechanism figure. The authors reviewed, verified, and approved the final figure and take full responsibility for its scientific accuracy.

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Data availability

The authors declare that the data supporting the findings of this study are available within the paper.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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