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## Cellular targets in diabetic retinopathy therapy

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### Abstract

Despite the existence of treatment for diabetes, inadequate metabolic control triggers the appearance of chronic complications such as diabetic retinopathy. Diabetic retinopathy is considered a multifactorial disease of complex etiology in which oxidative stress and low chronic inflammation play essential roles. Chronic exposure to hyperglycemia triggers a loss of redox balance that is critical for the appearance of neuronal and vascular damage during the development and progression of the disease. Current therapies for the treatment of diabetic retinopathy are used in advanced stages of the disease and are unable to reverse the retinal damage induced by hyperglycemia. The lack of effective therapies without side effects means there is an urgent need to identify an early action capable of preventing the development of the disease and its pathophysiological consequences in order to avoid loss of vision associated with diabetic retinopathy. Therefore, in this review we propose different therapeutic targets related to the modulation of the redox and inflammatory status that, potentially, can prevent the development and progression of the disease.

**Key Words:** Diabetic retinopathy; Oxidative stress; Inflammation; Cellular target; Diabetic macular edema

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**Core Tip:** The identification of potential therapeutic targets related to oxidative stress and low chronic inflammation induced in diabetic retinopathy (DR) may be crucial in developing therapeutic approaches for preventing the development of DR. Hence, we focus on the antioxidant role of nuclear factor erythroid 2-related factor 2, low and chronic inflammatory conditions developed in DR, modulation of lipid peroxidation,

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activation of glucagon-like peptide-1 receptor, the classical biochemical pathways altered under hyperglycemia, and epigenetic alterations.

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## INTRODUCTION

Diabetes mellitus is a metabolic disorder associated with hyperglycemia. The global prevalence of diabetes in adults 20-79 years of age, including both type 1 and type 2 diabetes, diagnosed, and undiagnosed, was estimated at 463 million in 2019. Based on the estimation, by 2045 a projected 700 million adults will have diabetes[1]. Although diabetes is a pathology with multiple systemic consequences, the loss of metabolic control in particular is not effectively controlled in many patients and that triggers the development of long-term damage of various organs, including the retina. In fact, diabetic retinopathy (DR) is the greatest cause of preventable blindness in the working age population and the most frequent ocular pathology caused by diabetes[2]. Its prevalence increases as the number of diabetic patients increases, depends on the duration of the disease, and on inadequate glycemic control. It has also been associated with the presence of hypertension, and was estimated to affect 2.6 million people in 2015 and projected to affect 3.2 million adults by 2020[2,3].

Cellular aerobic metabolism induces the physiological production of reactive oxygen species (ROS), which are molecular actors in the regulation of normal cell signaling. The production of ROS is countered by antioxidant enzymatic and nonenzymatic machinery enabling a homeostatic redox balance. However, the balance may be easily altered by a pathological condition. Glucose metabolism linked to reduction in antioxidant defenses triggers an oxidant environment in body tissues exposed to chronic hyperglycemia[4]. Although the blood-retinal barrier (BRB) makes the tissue a privileged place, as the retina is protected from the escape of circulating toxins, its cellular components are extremely sensitive to alterations in oxygen level[5]. In fact, the imbalance in redox homeostasis induced by diabetes triggers neuronal retinal cell death and pericyte cell death followed by an increase in the vascular permeability, and cumulative molecular damage leading to development and progression of DR to advanced stages[2,6-8]. Because of this, oxidative stress is considered a major cause of DR development.

The complex and extensive harmful effects of ROS contribute to the neurovascular complications observed in the retina. In this review, we focus on the main cellular targets affected by oxidative stress. The affects lead to cellular dysfunction and are potential therapeutic targets to avoid the development and progression of DR. Among hyperglycemia abnormalities closely associated with oxidative stress we highlight the key role of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and its importance in the modulation of oxidative stress, the increased accumulation of advanced glycation end products (AGEs), polyol and hexosamine pathways and protein kinase C activation, lipid peroxidation, activation of glucagon-like peptide-1 receptor (GLP1R), and alteration of the epigenetic status[2,9].

## THE IMPORTANCE OF LOOKING FOR NEW THERAPEUTIC TARGETS IN DIABETIC RETINOPATHY: ACTUAL THERAPIES

As DR is most often asymptomatic, the pathology can be significantly advanced when the patients suffer a loss of vision. Therefore, an early diagnosis is necessary to detect the first signs before the disease progresses to more serious stages[10]. In the early stages of DR, with the objective being to prevent its development or stop its progression, the only therapeutic strategy is a strict control of risk factors, mainly blood glucose and blood pressure[11]. Overall, treatment is applicable in very advanced stages of the pathology and when DR affects the macula, triggering diabetic

macular edema (DME), which is the most common cause of blindness induced by chronic hyperglycemia. The main interventions for DR and DME include ocular and systemic pharmacotherapy, with conventional laser therapy as the secondary treatment option, although it remains the first-line option when the cost and burden of drug treatment are considered, and vitreoretinal surgery[12,13]. The decision to use one or other of the treatments depends on the specific clinical situation of the patient.

### **Pharmacotherapy**

The evidence that inflammation plays a critical role when DR affects the macula, triggering DME, has opened new avenues and targets for developing new treatments. There are many anti-inflammatory therapies, such as intravitreal glucocorticoids, topical nonsteroidal anti-inflammatory drugs (NSAIDs), inflammatory molecule inhibitors, renin-angiotensin system blockers, and natural anti-inflammatory therapies that can reduce the use of anti-neovascularizing agents in the treatment of DR, but more studies are needed[6]. Despite these therapies, the most important class of drugs are those that decrease the effects of vascular endothelial growth factor (VEGF), and corticosteroids[14].

### **Anti-VEGF treatment**

Intravitreal injections of anti-VEGF drugs are the treatment par excellence for DR and its angiogenic complications. The monoclonal antibody ranibizumab (Lucentis®), the long-acting antibody bevacizumab (Avastin®), the aptamer pegaptanib (Macugen®), and the recombinant fusion protein aflibercept (Eylea®) are the anti-VEGF agents most frequently used to treat DME. The drugs, do not affect the pathogenesis of DR and must be administered for years as frequent intravitreal injections, estimated to be around 12-15 injections in the first 3 years of treatment[15-17]. They are also associated with adverse effects such as susceptibility to the development of endophthalmitis, vitreous floaters, and transient increase in intraocular pressure[18].

### **Administration of corticosteroids**

Acknowledging the role of inflammatory processes in the pathogenesis of DR, anti-inflammatory drugs are an attractive option for the treatment of the disease[19]. Hence, the anti-inflammatory and anti-angiogenic effects associated with corticosteroids have led to their inclusion in the treatment of DR and DME. Several mediators of inflammation are upregulated in DR. The mediators, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ) and VEGF have a key role in pathogenesis and can be modulated by corticosteroids[20]. The effects of corticosteroids include the reduction of vascular permeability and the breakdown of the BRB, prevention of leukocyte adhesion to vascular walls, suppression of VEGF gene transcription and translation, and the rapid decrease of DME[21].

The main mode of administration is intravitreal injection, which avoids the limitations of BRB. However, treatment-associated adverse effects of steroids include cataracts, high intraocular pressure, and glaucoma. Less frequent side effects, such as vitreous hemorrhage, retinal detachment, and endophthalmitis are related to the injection[22,23]. Moreover, short-term effects and transient efficacy are limiting factors in the application of this treatment, and new injections it is often required at various time intervals based on the steroid half-life. Currently, DME is treated with several different steroids, including fluocinolone, triamcinolone, and dexamethasone[24]. Side effects associated with chronic use and the need for repeat injections have brought about the development of new methods of intraocular administration, such as sustained release from an intravitreal implant. Slow-release formulations are used to avoid reinjection, which allows the use small quantities of corticosteroids, which results in fewer side effects[25]. Both nonbiodegradable and biodegradable devices are available. In biodegradable devices, the polymers degrade slowly over time, thus avoiding the need for surgery to remove the implant, in contrast to the nonbiodegradable ones[26].

### **Laser therapy**

Over the past 30 years, the most successful means of delaying the progression of DR has been focal, grid, or panretinal photocoagulation (PRP) laser treatment[27]. In the treatment of proliferative DR, the use of PRP reduces oxygen requirements and decreases retinal neovascularization. PRP eliminates the hypoxic retina and/or increases the diffusion of O<sub>2</sub> found in the choroid to supplement the affected retinal circulation. Furthermore, laser therapy decreases the formation of vasoproliferative agents and inhibits neovascularization. The procedure uses scattered laser spots of

200-500  $\mu\text{m}$  in the peripheral retina, avoiding the central macula. In the case of DME, the laser spots are applied in the regions of the macular area with microaneurysms in order to decrease exudation[28].

The use of laser therapy plays an important role in controlling diabetes mellitus-related retinal disease and is generally used in situations in which the use of pharmacotherapy is contraindicated, there is poor monitoring of patient visits, if the response to anti-VEGF treatment is ineffective, or if the patient is pregnant[13]. Although PRP treatment can effectively control neovascularization and prevent blindness, it is unable to restore vision and has its own damaging effects on vision[29]. The destructive capacity of laser therapy permanently damages the cells, thus producing side effects that affect the deterioration of vision, such as loss of contrast sensitivity, decreased night vision, color vision, visual field, and the appearance of DME[30]. In certain situations, the prior use of laser photocoagulation and intravitreal anti-VEGF agents induce fibrotic changes in preexisting retinal neovascularization, causing tractional retinal detachment with the need for early surgery to avoid permanent blindness[31].

### **Surgical intervention**

Surgical intervention is used in cases that show no response to pharmacological treatment, laser, or combined therapy, as well as in the most severe cases of DME. Therefore, vitrectomy is indicated in situations such as vitreous hemorrhages that do not disappear, tractional detachment of the retina in proliferative DR, and anomalies in the vitreoretinal interface that prevent the resolution of DME[32]. To facilitate the intervention, an intravitreal injection of an anti-VEGF agent like bevacizumab, ranibizumab, or aflibercept, is included as a preoperative complement in patients with no contraindications, as they cause a rapid involution of active neovascularization[33].

Surgical vitrectomy entailing the removal of most of the vitreous body and hyaloid membrane has shown a series of benefits, such as decreased growth of fibrovascular membranes caused by the absence of proliferation in scaffolds, increased intraocular cytokine turnover, and removal of mechanical barriers that hinder the exit of metabolites and fluids and obstruct intravitreal drug delivery through intraretinal penetration[34]. However, because of individual variability in the surgical anatomy that each case presents, diabetic vitrectomy continues to be one of the most difficult conditions to treat. In addition, it has postoperative consequences such as rhegmatogenous retinal detachment, development of cataracts, proliferation of diabetic fibrovascular membranes, vitreous hemorrhage, appearance of epiretinal membranes, elevated intraocular pressure, and neurovascular glaucoma[35-37].

All these treatments are expensive, uncomfortable for the patient, have limited effectiveness because of the administration protocols, and are associated with a significant number of side effects[38]. Despite benefits in slowing the progression of DR and improving vision, damage to the retinal blood vessels the function of neuronal cells is irreversible[2]. Even after the advances made in the treatment of retinopathy, many patients still progress to advanced stages of disease. It is necessary, therefore, to investigate new therapeutic approaches capable of both delaying and preventing the appearance of the first stages of DR.

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## **RETINOCELLULAR ALTERATIONS IN DIABETIC RETINOPATHY DEVELOPMENT**

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Oxidative stress has been defined as an imbalance between the production and the removal of free radicals, which leads to their accumulation. The most common free radicals are ROS, such as the superoxide anion ( $\text{O}_2\cdot^-$ ), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), the peroxy radical ( $\text{ROO}\cdot$ ), and the hydroxyl radical ( $\cdot\text{OH}$ ). These oxygen-derived molecules are very reactive and generally toxic to cells[39,40]. Under physiological conditions, free radicals are normally and continuously produced. Low to moderate levels of free radicals support normal cellular metabolism, proliferation, differentiation, immune system regulation, and vascular remodeling[2,41]. Intracellular ROS levels are controlled by enzymes including catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) and nonenzymatic species like glutathione (GSH), thioredoxin, NADPH,  $\alpha$ -tocopherol, ascorbic acid and  $\beta$ -carotene, which constitute an antioxidant defenses system. Oxidative stress leads to the accumulation of ROS because of excessive production or inefficient removal. ROS can modify the structure of proteins, lipids, carbohydrates, and nucleic acids, thus affecting their function[2].

Oxidative stress plays a critical role in the pathogenesis of DR. The retina has high metabolic activity, high oxygen partial pressure from the blood in the choroid, and it is highly exposed to bright light. All these factors, together with the oxidative environment induced by hyperglycemia in diabetes, cause an increased level of ROS in the retina[42-44]. ROS overproduction in the retina triggers cell death, retinal ischemia, retinal neovascularization, and DME[45]. Furthermore, various mutations of detoxifying enzymes that have a significant role in DR development, such as CAT or SOD, have been reported[46]. This suggests that hyperglycemia-induced oxidative stress is one of the main causes of DR[45,47,48]. Therefore, some treatments of DR are based in the inhibition of ROS generation, neutralization of free radicals, or the reinforcement of the antioxidant defense system[39].

### **Oxidative stress and Nrf2**

Nrf2 is a transcription factor that activates the expression of various detoxifying and antioxidant defense genes in response to oxidative stress[49,50]. The functional activity of Nrf2 depends on whether it is located in the nucleus or in the cytoplasm. Under physiological conditions and in the absence of oxidative stress, Kelch-like enoyl-CoA hydratase-associated protein 1 (Keap1) sequesters Nrf2 in the cytoplasm and mediates its rapid ubiquitination and degradation, suppressing its transcriptional activity[51, 52]. When there is an accumulation of ROS, Keap1 changes its conformational structure and releases Nrf2, which then translocates from the cytoplasm to the nucleus. Once there, Nrf2 binds to the antioxidant response element of a promoter region to initiate transcription of several genes encoding heme oxygenase 1 (HO-1), NAD(P)H dehydrogenase (quinone) 1, thioredoxin reductase, peroxiredoxins, SOD, CAT, GPx, GSH reductase (GR), GSH S-transferase (GST), and glutamate-cysteine ligase (GCL). These enzymes contribute to elimination of ROS and play a critical defensive role in cell homeostasis[2,50,53]. Nrf2 is an important cellular pathway that protects against oxidative stress in the retina[54,55]. In diabetes, Nrf2 increases in the retina but so does Keap-1, which prevents Nrf2 from reaching the nucleus. Thus, Nrf2 nuclear level is decreased and the antioxidant defense system is compromised[55-57]. As a result, the activity of Nrf2-associated antioxidant enzymes like SOD, GR, GPx, and CAT in diabetes patients or glutamate-cysteine ligase in rat diabetes models[55,58,59]. Thus, the increased risk of developing DR in diabetes patients results from reduced antioxidant capability and the oxidative environment generated by hyperglycemia[2]. These studies also suggest that Keap1 knockdown would release Nrf2, which would move to the nucleus and activate the antioxidant defense system[54,55]. In addition to the regulation of the antioxidant response, Nrf2 regulates the inflammatory response in diabetes[60]. The response is mediated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and cyclooxygenase-2 (COX-2). When Nrf2 activity is reduced, there is an increase of proinflammatory cytokines because of the induction of NF-κB, which is associated with capillary cell apoptosis in diabetes *via* the overexpression of proapoptotic Bax or TNF-α[61-63]. In an experimental model of streptozotocin-induced diabetes, rutin, a flavonoid derivative of quercetin, protected against neuron damage in diabetes *via* the Nrf2/HO-1 and NF-κB signaling pathway, together with its anti-inflammatory action *via* COX-2 inhibition[2,64]. The data suggest that Nrf2 activation could be an important protective mechanism for diabetic complications, making it an especially attractive pharmacological target in the progression of DR[54]. Many studies suggest that natural compounds, including polyphenols, can reduce oxidative stress and inflammation through activating Nrf2 and the consequent antioxidant response[57].

Several publications have described the therapeutic potential of various polyphenols in diabetes, including those in green tea, resveratrol, curcumin, quercetin, and tannins[65-73]. Pterostilbene (Pter), is a phenol that been shown to prevent early DR alterations *via* Nrf2 activation in an experimental rabbit model[47]. In addition to natural antioxidants, other molecules have been shown to activate Nrf2 in DR. One example is RS9, a derivative of the triterpenoid bardoxolone methyl, which was found to delay retinal degeneration by inhibiting inflammatory responses and increasing intrinsic antioxidant enzymes *via* activation of Nrf2[74]. Another triterpenoid derivative, dihydro-CDDO-trifluoroethyl amide (dh404) has been shown to protect the retina against diabetes-induced damage through the activation of Nrf2[75].

Another therapeutic approach in the treatment of DR is, as suggested above, is the inactivation of Keap1. Triterpenoids, salvianolic acids, and sulforaphane[76-79] have been shown to inactivate Keap1 by covalently modifying its reactive cysteine residues. As a consequence, Nrf2 is activated by its translocation into the nucleus and its downstream target genes are then activated, which prevents or reverts ROS-mediated toxicity[50].

### Inflammatory response

Inflammation is a defensive process mediated by the host immune system in response to injury or stress. In DR, acute inflammation normally produces beneficial effects like tissue defense and repair. Chronic inflammation produces structural and molecular alterations in the retina that usually cause tissue damage and cell death[2]. The inflammatory response in the retina is caused by various factors like hyperglycemia, growth factors, AGEs, high levels of circulating or vitreous cytokines and chemokines, and ROS[80]. These factors induce intracellular signaling pathways, including the transcription factor NF- $\kappa$ B, which translocates into the nucleus to initiate the transcription of proinflammatory cytokines *i.e.* TNF- $\alpha$ , IL-1 $\beta$ , and IL-6; proinflammatory proteins such as COX-2 or the inducible isoform of nitric oxide synthetase (iNOS), and chemokines such as monocyte chemoattractant protein-1. The proinflammatory molecules play an important role in the recruitment and activation of monocytes and leukocytes[81,82]. Adhesion of leukocytes to the capillaries of the retina (leukostasis), together with the release of ROS and proinflammatory cytokines, leads to vascular permeability, BRB breakdown, and capillary pericyte loss. Thus, it is clear that chronic inflammation is critical for the development of DR, principally in the early stages[2,27,81,83].

Several studies have shown that there is an increase of proinflammatory molecules in the retina or vitreous humor of diabetic animals and patients. Those reported are VEGF, TNF- $\alpha$ , iNOS, COX-2, prostacyclin, insulin-like growth factor 1, NF- $\kappa$ B, placental growth factor, intercellular adhesion molecule-1, IL-1 $\beta$ , IL-2, IL-6 and IL-8[81, 84-86]. The findings highlight the key role of inflammation in the development of DR. The detailed mechanisms involved in the inflammatory response in DR are not clear, but inhibition of some of the inflammatory mediators mentioned in the previous paragraphs has been shown to block DR development in animal models of diabetes[82, 87-92]. NSAIDs, anti-VEGF, and anti-TNF- $\alpha$  agents diminish the progression of DR in humans because of their anti-inflammatory properties[93]. Systemic administration of specific COX-2 inhibitors could be a possible therapy, although COX-2 inhibitors increase the incidence of heart attack and stroke[94]. Nevertheless, in preclinical studies, topical administration was shown to reduce the signs of DR[95-97]. More studies on the beneficial effects of these molecules are needed.

Tetracyclines, such as minocycline and doxycycline, have immunomodulatory properties that include inhibiting the production of NO, COX, prostaglandins, IL-1 $\beta$ , TNF- $\alpha$ , and caspases[98-100]. In a single-center phase I/II clinical trial in five patients with DME, treatment with minocycline resulted in improved visual function, reduced central DME, and vascular leakage[101]. In another clinical trial, patients with severe nonproliferative or non-high-risk proliferative DR were treated with doxycycline, which resulted in an improvement of perimetric parameters compared with patients who received a placebo[102]. IL-6 is one of the most important proinflammatory cytokines present in the vitreous of DR patients. Various clinical studies have investigated the effect on DR of two IL-6 inhibitors, an antibody against IL-6 (EBI-031, clinicaltrials.gov ID: NCT02842541) and an antibody against the IL-6 receptor (tocilizumab, clinicaltrials.gov ID: NCT02511067) in patients with DME. Although they have not yet concluded, the studies have shown that IL-6 inhibitors can be effective in the management of non-infectious uveitis. Therefore, the roles of IL-6 inhibition could be more widely investigated in the management of retinal vascular diseases and non-uveitic DME[103]. The effect of anti-TNF- $\alpha$  therapy has also been studied in a few clinical cases but there are no conclusive data about the effects of these inhibitors in DR or DME[104]. The same is true of canakinumab, a selective IL-1 $\beta$  antibody[105].

### Alteration of biochemical pathways

It has long been accepted that hyperglycemia induces the alteration of the biochemical pathways, such as an increased flux of advanced glycation end products/receptors (AGE/RAGE), the polyol pathway, protein kinase C (PKC) activation, the hexosamine pathway, and unbalancing redox status. The induction of ROS stimulates a low chronic inflammatory state that contributes to the development and progression of neurovascular dysfunction in DR[2]. The regulation of these molecular pathways therefore offers potential targets against DR.

Glucose and products generated by carbohydrate metabolism are able to transform proteins, lipids, or nucleic acids by glycation, triggering the formation of AGEs, a synthesis that is accelerated in the presence of ROS and redox-active transition metals [106,107]. In addition, the production of AGEs stimulates increased formation of oxidative species, resulting in positive feedback that contributes to the progression of the complications of diabetes[108]. AGEs have severe effects on retinal tissue, such as

aberrant extracellular crosslinking of extracellular matrix proteins and increased vascular stiffness, which disturbs normal vascular function. AGEs also bind to various receptors in the plasma membrane (RAGE) and activate intracellular signaling cascades that trigger the release of proinflammatory cytokines and proangiogenic factors, with evident damage of neurovascular retinal structures[109]. As AGEs formation is closely related to oxidative stress, modulation of the antioxidant machinery is an attractive approach for preventing the development and progression of DR. The administration of curcumin to diabetic rats was shown to improve redox imbalance in the retina[110] and protect against effects of glycation[111]. Epigallocatechin 3-gallate, quercetin, kaempferol, and resveratrol are other examples of natural antioxidants able to diminish the production of AGEs[112-115]. In addition, drugs such as aminoguanidine have been shown to be effective inhibitors of AGE formation and to inhibit the development of DR[116,117]. However, adverse side-effects preclude their use in humans[108]. Aragonès *et al*[108] in their latest excellent paper, review the benefits of enhancing the detoxifying activity of the glyoxalase system, a main mechanism for detoxifying the intermediates and precursors of AGEs formation, to avoid glycation-derived damage in DR.

Under normoglycemic conditions, glucose is metabolized by the glycolytic pathway. However, in chronic hyperglycemia, excess glucose is reduced to sorbitol by the enzymatic action of aldose reductase. Sorbitol is then converted to fructose by sorbitol dehydrogenase. The two enzymes constitute an alternative route of glucose metabolism known as the polyol pathway, which is an important source of oxidative stress and AGE production[2]. In addition, sorbitol increases cellular osmolarity, triggering osmotic damage and cell death in retinal capillaries[118,119]. Although clinical trials have been inconclusive in the use of polyol pathway inhibitors to treat DR, its use as a potential therapeutic target in DR should not be ruled out[120,121]. In fact, the benefits of polyphenols for DR treatment is extended to inhibition of the polyol pathway. For example, Pter, a natural stilbene analog of resveratrol, in addition to promoting antioxidant defenses *via* Nrf2, inhibited aldose reductase and AGEs formation in a galactosemic rat model[47,122]. Another alternative route to glycolysis in hyperglycemia is the hexosamine pathway. Glutamine fructose-6-phosphate amidotransferase (GFAT) converts fructose-6-phosphate to N-acetylglucosamine-6-phosphate, which is a substrate of O-N-Acetyl-GluN transferase (OGT) and converted to uridine-5-diphosphate-N-acetylglucosamine (UDP-GlucNAc), a precursor of glycoproteins, glycolipids, proteoglycans, and glycosaminoglycans[123]. High levels of glucose and N-acetylglucosamine-6-phosphate activity inhibit glucose-6-phosphate dehydrogenase and low NADPH-dependent GSH production, triggering an increase in the level of H<sub>2</sub>O<sub>2</sub>[124]. Glucosamine administration or overexpression of GFAT also leads to H<sub>2</sub>O<sub>2</sub> accumulation, highlighting the role of the hexosamine pathway in oxidative stress[125]. Moreover, OGT activity has been associated with altered *TGFβ* gene expression, which induces NADPH oxidase (NOX) activation, suppression of the antioxidant system, and mitochondrial ROS production[126-128]. In fact, antioxidant treatment has shown beneficial effects against some adverse consequences of the hexosamine pathway[125]. Various inhibitors of the hexosamine pathway, such as the antineoplastic azaserine, the anthraquinone rhein, and the lipid-soluble thiamine derivative benfotiamine, have been evaluated in experimental animal models. In addition to the hexosamine pathway, those agents inhibit AGE formation and the PKC pathway[129-131]. However, the effectiveness of this therapeutic approach in DR has not been shown in clinical trials.

Inhibition of the PKC pathway is of interest. PKCs comprise a family of cAMP-dependent protein kinases with multiple isoforms involved in the regulation of other proteins[2]. PKCs are activated when the second messenger is bound to its regulatory domain. Phosphatidylserine, calcium, and diacylglycerol (DAG) or phorbol esters are activators of PKC- $\alpha$ ,  $\beta$ 1,  $\beta$ 2, and  $\gamma$ . Phosphatidylserine, DAG or phorbol 12-myristate 13-acetate (PMA) activate PKC- $\delta$ ,  $\epsilon$ ,  $\theta$ , and  $\eta$ , while PKC- $\zeta$  and  $\iota/\lambda$  are not activated by calcium, DAG or PMA[132]. Cysteine residues are abundant in the PKC structure which makes the regulatory domain susceptible to redox modulation[2]. In fact, hyperglycemia can activate some PKC isoforms directly through DAG, or indirectly by the oxidative stress generated through AGE production and the polyol pathway[133, 134]. PKC contributes to redox injury of retinas exposed to chronic hyperglycemia at different levels, triggering the signs of DR. For example, PKC- $\beta$  is an activator of NOX, and the overproduction of O<sub>2</sub><sup>-</sup> increases the formation of peroxynitrite to induce endothelial changes[135-137]. PKC- $\delta$  is involved in the death of capillary cells and pericytes, with subsequent formation of microaneurysms[138,139]. PKC- $\beta$  and PKC- $\zeta$  are involved in VEGF-dependent changes of the retinal barrier[140]. Moreover, PKC induces the overexpression of plasminogen activator-1 and the activation of NF- $\kappa$ B in

vascular smooth muscle and endothelial cells, pericytes, and mesangial cells[134]. Inhibition of PKC has been considered as an effective approach to treat DR. The highly selective PKC- $\beta$  inhibitor, ruboxistaurin mesylate, is one of the most studied. Initial clinical studies showed its potential in the prevention of vision loss induced by DR [141]. However, in 2007 the European Medicines Agency declared a minimum benefit in the treatment of moderately severe to severe non-proliferative DR[142]. In any case, knowledge of the role of the various isoforms of PKC is incomplete and offers another therapeutic target to be considered.

### **Lipid alterations**

Lipids play a crucial role in the maintenance and development of retinal functions. The plasma membranes of the outer segments of retina photoreceptors contain high levels of polyunsaturated fatty acids (PUFAs). The most abundant PUFAs in the retina are  $\omega$ 3-docosahexaenoic (DHA),  $\omega$ 3-eicosapentaenoic (EPA), and  $\omega$ 6-arachidonic (AA), with DHA being predominant[143-146]. The functions of PUFAs in the retina have been demonstrated in numerous studies. PUFA supplementation has protective and therapeutic effects against proliferative and degenerative retinal diseases, possibly resulting from their antioxidant and anti-inflammatory properties[147-150]. In addition, DHA deficiency has been associated with structural and functional abnormalities in the visual system[149]. ROS formed during oxidative stress can oxidize PUFAs because of the presence of susceptible carbon double bonds in the molecular structure[44,150]. The free radical chain reaction results in lipid peroxidation and acts to amplify the generation of lipid radical species, causing PUFA degradation into a variety of potentially harmful oxidation products[42,146]. The increase of ROS in DR, together with the high PUFA content in the membranes of the photoreceptors, triggers an increase of lipid peroxidation[42,44,151]. In fact, patients with DR have higher lipid peroxidation than those without retinal disease[151-153]. Moreover, a number of published papers indicate that lipid peroxidation has serious pathophysiological effects that contribute to the development of DR[149,154-158], and there is increasing evidence of the importance of products of lipid peroxidation as mediators in the development of neovascularization in DR[149,159,160].

The role of lipid peroxidation in DR has been extensively studied, the determination of lipid peroxidation products, including aldehydes such as 4-hydroxynonenal (4-HNE) or malondialdehyde (MDA), and  $F_2$ -isoprostanes ( $F_2$ -IsoP) such as 8-iso-PGF<sub>2 $\alpha$</sub>  in plasma, urine, or the retina[161]. 4-HNE, an end product of nonenzymatic lipid peroxidation of  $\omega$ 6 PUFAs like linoleic acid and amino acids, has been shown to be extremely reactive with DNA, RNA, and proteins in the retina[39,162-165]. Zhou *et al* [166] reported that 4-HNE activates the canonical WNT pathway through oxidative stress in a rat model, playing a pathogenic role in the development of DR. Previous studies by that group have shown that blockade of WNT signaling attenuated retinal inflammation and neovascularization in DR in humans and animal models[167]. In fact, inhibition of the WNT pathway by peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) overexpression induced anti-inflammatory and antifibrosis effects [168]. The retinal protective role of PPAR $\alpha$  has been demonstrated both *in vitro* and *in vivo*. Chronic hyperglycemia in experimental animal models of diabetes or treatment of retinal cell lines with high glucose concentrations reduces PPAR $\alpha$  mRNA and protein expression levels. The use of PPAR $\alpha$  agonists, such as fenofibrate, have been discussed as a treatment of DR by preventing microvascular damage[169,170]. Overexpression of PPAR $\alpha$  was found to reduce ROS production, apoptosis induced by oxidative stress, and downregulation of NOX4 expression[171]. It also inhibited cell proliferation, migration, and had anti-angiogenic effects[172]. The data suggest that the WNT pathway and PPAR $\alpha$  represent a new target for therapeutic intervention of DR[167].

Other studies suggest that 4-HNE retinal damage in DR could result from the induction of p53-mediated apoptosis in retinal pigment epithelial cells[173]. It has also been shown that 4-HNE attenuated  $\beta_2$ -adrenoceptor-mediated vasodilation of rat retinal arterioles, which would contribute to the retinal vascular dysfunction observed in patients with diabetes mellitus[174].

Several studies of possible new treatments of DR have focusing on protecting effects damage associated with 4-HNE. Chiang *et al*[175] reported that fucoxanthin, a marine carotenoid extracted from seaweed, effectively protected against the effects of 4-HNE- and high glucose-induced DR in ARPE-19 human retinal epithelial cells through the antioxidant ability of this compound. Pter was also shown to reduce 4HNE levels in the retina of a rabbit model of type 1 diabetes mellitus, preventing early DR alterations [47]. MDA is a product of the peroxidative decomposition of PUFAs. It is a highly reactive molecule that forms covalent bonds with the amino acids of endogenous

proteins[42,48]. MDA possesses cytotoxic, hepatotoxic, mutagenic, and genotoxic properties, and can alter proteins, DNA, RNA, and many other biomolecules[176,177]. MDA concentration as a final product of lipid oxidation is routinely determined by thiobarbituric acid assay or chromatography-mass spectrometry[176-178]. There are no studies of its mechanism of action in DR. It has only been used as a biomarker of lipid peroxidation in biological samples.

Since its discovery, F<sub>2</sub>-IsoP has become one of the most reliable biomarkers of lipid peroxidation and oxidative stress in *in vitro* studies and in animal models[179-181]. F<sub>2</sub>-IsoP comprises a family of prostaglandin-like compounds produced by nonenzymatic peroxidation of amino acids in membrane phospholipids[181]. One of the most studied F<sub>2</sub>-IsoP is 8-iso-PGF<sub>2α</sub> (also known as 8-epi-PGF<sub>2α</sub> or 15-F<sub>2t</sub>-isoprostane), which has been shown to be involved in inflammation and immunity in various diseases[48,181]. In DR, 8-iso-PGF<sub>2α</sub> is produced by COX activity and enzymatic oxidation of PGF<sub>2α</sub>[182]. It has been shown to be a potent vasoconstrictor in the retina by increasing thromboxane A<sub>2</sub> formation through the activation of Ca<sup>2+</sup> influx[182-184].

Further research is needed to clarify the pathophysiological activity of PUFA derivatives in DR. Nevertheless, it seems that inhibition of the formation of these highly cytotoxic molecules could be a possible therapeutic strategy for the management of DR. In fact, Pter has been recently reported to be able to restore the control levels of a large group of specific neuronal and retinal lipid peroxidation markers in diabetic rabbits[185]. This suggests that this polyphenol could protect the retina, preventing early lipid peroxidation damage in DR development.

### GLP1R

In recent years, new pharmacological therapies have been developed as effective treatments for type 2 diabetes. Glucagon-like peptide 1 receptor agonists (GLP1RAs) have emerged as a safe treatment, and some agonists have been incorporated into the clinical guidelines of the American Diabetes Association and the European Association for the Study of Diabetes. Furthermore, preclinical studies have shown the benefits of GLP1R activation on diabetic vascular complications such as DR[186]. Actually, the benefits are broad. GLP1R activation, independent of homeostatic glycemic control, can reduce the harmful consequences of diabetes on the retina, such as oxidative stress, neurodegeneration, inflammation, BRB breakdown, or angiogenesis[187-190].

The AKT pathway is a target of GLP1R activation and is essential for retinal neuroprotection in early DR development[188]. AKT phosphorylates a number of heterogeneous substrates including E2 ubiquitin ligases, transcription factors, protein and lipid kinases, metabolic enzymes, *etc.*, showing that AKT not only regulates a physiological process, but also controls multiple cellular functions. The first AKT substrate reported was GSK3[191]. Inactivation of GSK3 by AKT-phosphorylation has been shown to regulate transcription factors such as Nrf2, which is needed for DR development[192]. Moreover, *in vitro* and *in vivo* studies have demonstrated the ability of GLP1 to protect neurons from aggregation by β-amyloid peptide and against AGEs, as well as being able to reduce hyperphosphorylation of the *tau* protein by regulating GSK3β. It is believed that the mechanism of action of GLP1 is the activation of the PI3K/AKT signaling pathway, which is capable of phosphorylating and inactivating GSK3β[193]. Although further studies are needed to understand the importance and possible modulation of PI3K/AKT/GSK3β/Nrf2 pathway by GLP1R, these observations allow us to develop hypotheses of the key effects that modulation of Nrf2 by GLP1R agonists have on DR development.

### Epigenetic modifications

Although glycemic control may be achieved, chronic hyperglycemia during the first few months may be enough exposure to develop stable and heritable epigenetic modifications capable of altering gene expression and becoming a potential major factor of DR development[194]. The alterations occur on chromosomes without changes in the DNA sequence and are the basis of the known “metabolic memory”. The identified molecular mechanisms underlying these long-term effects act at different levels that include DNA methylation, post translational modifications of histones or regulation by noncoding (nc)RNAs[195]. For example, the low retinal histone acetylation of H3 induced by hyperglycemia for 6 mo did not recover after 6 mo of good glycemic control[196]. Likewise, euglycemia was unable to recover the DNA hypomethylation and unusual gene expression induced by hyperglycemia[197].

DNA methylation status is controlled by the activity of DNA methyltransferase (DNMT) enzymes that catalyze the transfer of a methyl group from S-adenosyl-L-methionine, and DNA demethylases. Imbalanced activity in diabetes, induces alterations in specific genes that triggers aberrant expression related to DR. For

example, chronic hyperglycemia in the retina stimulates the binding of DNMT1 and the DNA demethylase ten-eleven-translocation (TET) 2 to the promoter of Ras-related C3 botulinum toxin substrate (Rac1)[198]. Methylation induced by DNMT1 is rapidly reversed by TET2, triggering hypomethylation of the promoter and allowing Rac1 transcription, which induces NOX, and relevant effectors in DR development[199]. In fact, the mitochondrial damage initiated by NOX-2 activation has been associated with early DR development while its inhibition protects endothelial retinal cells from diabetes-induced apoptosis[200].

Although diabetes induces a global state of DNA hypomethylation, different states of methylation for specific CpG islands are closely related to DR development. An increase in the expression and activity of DNMTs has been observed in DR[201-203]. Based on that, inhibition of DNMTs can be a possible protective therapy against the development of DR. For example, 5-aza-2'-deoxycytidine, a nonselective inhibitor of DNMTs, re-establishes the expression of genes hypermethylated by hyperglycemia and related to DR development, such as SOD2 and glutathione S-transferase theta 1 (GSTT1), which protects against oxidative stress[203].

Changes in the pattern of acetylation and methylation are the most studied post translational modifications of histones. Overall, the acetylation of histones H3 and H4 and di or tri-methylation of H3K4 are related to euchromatin status. Low acetylation and high methylation levels are associated with silent heterochromatin. Experimental models of DR have provided contradictory results for histone acetylation. For example, Zhong and Kowluru[196] revealed reduced global acetylation, but Kadiyala *et al*[204] observed augmented histone acetylation in diabetic retinas. So far, *in vivo* experimental results for histone acetylation in DR remain contradictory[194,205].

Histone methylation is associated with transcriptional activation or repression depending on the type of residue and the number of methyl groups. Hence, the methylation of H3K4, H3K48, and H3K79 have been considered activation marks, while that of H3K9 and H3K27 are associated with transcriptional repression[206]. For example, decreased levels of H3K4me1 and H3K4me3 at the GCL promoter in diabetic rats compromised Nrf2 binding, triggering low transcription of the enzyme and reduced levels of GSH in the retina[207]. Moreover, the overexpression of matrix metalloproteinase-9, a proapoptotic enzyme in the development of DR, is caused by a decrease in H3K9me2 and an increase in acetyl H3K9, which facilitates the binding of NF- $\kappa$ B p65[208].

Thus, hyperglycemia-induced differential histone methylation or acetylation appears to regulate expression of several genes in cellular pathways that contribute to the development of diabetic retinopathy. In fact, the polyisoprenylated benzophenone derivative garcinol, prevents histone acetylation involved in the metabolic memory in DR[209]. In that sense, histone deacetylase inhibitors like resveratrol, curcumin, and genistein are also being considered as targets for treatment of DR[210].

A low percentage of cellular transcribed RNA is ncRNA, RNA sequences with different but important cell functions. Long ncRNA and small ncRNA, such as circular RNA, or miRNA, are essential in the pathological processes of diabetic complications, including atherosclerosis, microvascular dysfunction, and DR[211]. The most well-studied are miRNAs[212], sequences of approximately 18-25 nucleotides partially complementary to mRNAs able to block their translation and activate their degradation in collaboration with the ribonucleoprotein complex RNA-induced silencing complex[213]. There are numerous examples of the importance of their role in DR. Experimental models of DR have shown that downregulation of miR126, miR-146a, and miR200b is associated with retinal neovascularization through increased VEGF production[214]. The expression of miR-20b-5p, a modulator of cell proliferation, apoptosis, differentiation, and angiogenesis, is upregulated in the retinal endothelial cells of diabetic rats and patients with DR, inducing a decrease in tight junction proteins that increases BRB permeability and the microvascular leakage observed in DR[215]. Although the expression and physiological function of circular RNA is not yet fully elucidated, the molecules serve as miRNA or RNA-binding protein sponges to modulate expression or translation of regulatory proteins[216]. Circular DNMT3B, a reducer of the expression of miR-20b-5p, is downregulated in diabetes and its overexpression improves the vascular dysfunction induced in diabetic retinas, an interesting potential strategy for treatment of DR[215]. The possibility of using siRNAs to target some miRNAs mentioned above has also been considered. However, no methods are currently available for *in vivo* treatments[209]. In addition, double-stranded miRNA mimics and anti-mRNA antisense oligodeoxyribonucleotide are being used to target specific miRNA in other diseases, and therefore can also be studied for the treatment of DR[210].

**Table 1 Summary of alterations, targets, and novel therapies**

Contributors in DR development	Retinal alterations	Targets	Possible novel therapies
ROS accumulation	Low nuclear levels of Nrf2, antioxidant enzymes activities, and GLP1R expression. Retinal cell death, retinal ischemia, retinal neovascularization, DME	Nrf2 activation, Keap1 knockdown, inhibition and/or neutralization of ROS generation, GLP1R activation, reinforcement of the antioxidant defense system	Green tea polyphenols, resveratrol, curcumin, quercetin, tannins, pterostilbene, GLP1R agonist, RS9, dh404, triterpenoids, salvianolic acids, sulforaphane
Synthesis of proinflammatory molecules	Vascular permeability, BRB breakdown, capillary pericyte loss, neovascularization	Inhibition of inflammatory pathways	COX-2 inhibitors, tetracyclines (minocycline and doxycycline), IL-6 inhibitors (EBI-031 and tocilizumab), anti-TNF- $\alpha$ therapy, canakinumab (selective IL-1 $\beta$ antibody), fenofibrate (PPAR $\alpha$ agonist)
Increased production of AGE/RAGE	Aberrant extracellular crosslinking of extracellular matrix proteins, increased vascular stiffness, release of proinflammatory cytokines and proangiogenic factors	Low the production of AGEs	Curcumin, epigallocatechin 3-gallate, quercetin, kaempferol and resveratrol
Activation of the polyol pathway	Retinal capillary osmotic damage and cell death	Inhibition of the polyol pathway	Pterostilbene
Increased flux through the hexosamine pathway	Neuro-vascular dysfunctions	Inhibition of the hexosamine pathway	Azaserine (antineoplastic), rhein (anthraquinone), benfotiamine (lipid-soluble thiamine derivative)
Activation of the PKC pathway	Endothelial alterations, cell demise of capillary cells and pericytes, formation of microaneurysms, VEGF-dependent retinal barrier alterations	Inhibition of PKC pathway	Ruboxistaurin mesylate (PKC- $\beta$ inhibitor)
Lipid peroxidation	Generation of lipid radical species, apoptosis in retinal pigment epithelial cells, retinal vascular dysfunction, development of neovascularization	Inhibition of the formation of lipid peroxides in the retina	Fucoxanthin, pterostilbene
DNA methylation	Increased expression and activity of DNMTs	Inhibition of DNMTs	5-aza-2'-deoxycytidine
Histone methylation and acetylation	Decreased levels of H3K4me1 and H3K4me3 at glutamate-cysteine ligase promoter or decreased levels of H3K9me2 and increased levels in acetyl H3K9	Regulation of histone methylation/acetylation	Garcinol, resveratrol, curcumin, genistein
Regulation by ncRNA (miRNA and circular RNA)	Downregulation of miR126, miR-146a, and miR200b; retinal upregulation of miR-20b-5p, neovascularization and microvascular leakage	Modulation of miRNAs expression, overexpression of circular DNMT3B	siRNAs, double-stranded miRNA mimics and anti-mRNA antisense oligodeoxyribonucleotide

AGE/RAGE: Advanced glycation end products/receptors; BRB: Blood-retinal barrier; COX-2: Cyclooxygenase-2; dh404: Dihydro-CDDO-trifluoroethyl amide; DME: Diabetic macular edema; DNMT: DNA methyltransferases; GLP1R: Glucagon-like peptide-1 receptor; IL: Interleukin; Keap1: Kelch-like enoyl-CoA hydratase associated protein 1; miRNA: microRNA; ncRNA: noncoding RNAs; Nrf2: Nuclear factor erythroid 2-related factor 2; PKC: Protein kinase C; PPAR $\alpha$ : Peroxisome proliferator-activated receptor  $\alpha$ ; ROS: Reactive oxygen species; TNF- $\alpha$ : Tumor necrosis factor  $\alpha$ ; VEGF: Vascular endothelial growth factor.

With the increase in evidence on the importance of epigenetic modifications in DR, a better understanding of their effects has great potential for establishing new targets against this pathology. Fortunately, advances are being made in the use of mimics and inhibitors in different chronic diseases and cancer that will undoubtedly contribute to a better understanding of the role of epigenetic changes in DR.

## CONCLUSION

With the global increase in the prevalence of diabetes, an increase in associated complications such as DR is expected. Although in recent decades considerable advances have been made in the treatment of the disease, current therapeutic approaches focus on advanced stages in which the retina can present irreparable

damage at the neuronal and vascular level. Furthermore, the recommended treatments for DR have serious limitations such as long-term side effects, the high cost involved, or patient discomfort. Hence the need for the development of new therapeutic approaches (Table 1). Considering the current state of knowledge, treatments for diabetic retinopathy should go beyond acting on a single etiological cause such as neovascularization. New treatments should present a set of advantages that facilitate their administration without the need for special facilities. Ideal treatments would be noninvasive, effective, affordable, and accessible to the global population. Recognizing the importance of redox imbalance in the development and progression of DR offers a new direction for tackling the condition. One such option that should be explored is action directed at cellular targets that participate in modulating or altering the pathology, so that the progression of the disease can be delayed or even prevented.

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