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Novel drugs and their targets in the potential treatment of diabetic retinopathy

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Diabetic retinopathy (DR) is the most common complication of diabetes. It causes vision loss, and the incidence is increasing with the growth of the diabetes epidemic worldwide. Over the past few decades a number of clinical trials have confirmed that careful control of glycemia and blood pressure can reduce the risk of developing DR and control its progression. In recent years, many treatment options have been developed for clinical management of the complications of DR (e.g., proliferative DR and macular edema) using laser-based therapies, intravitreal corticosteroids and anti-vascular endothelial growth factors, and vitrectomy to remove scarring and hemorrhage, but all these have limited benefits. In this review, we highlight and discuss potential molecular targets and new approaches that have shown great promise for the treatment of DR. New drugs and strategies are based on targeting a number of hyperglycemia-induced metabolic stress pathways, oxidative stress and inflammatory pathways, the renin-angiotensin system, and neurodegeneration, in addition to the use of stem cells and ribonucleic acid interference (RNAi) technologies. At present, clinical trials of some of these newer drugs in humans are yet to begin or are in early stages. Together, the new therapeutic drugs and approaches discussed may control the incidence and progression of DR with greater efficacy and safety.

Key words: diabetic retinopathy • drugs • neurodegeneration • retina • oxidative stress • hyperglycemia

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Background

Diabetic retinopathy (DR) is one of the major complications of diabetes, leading to vision loss and blindness. According to a recent report by the World Health Organization (WHO), approximately 346 million people worldwide have diabetes, approximately10% of diabetic people have severe visual impairment, and 2% become blind [1]. In the last few decades a number of hyperglycemia-induced metabolic stresses (e.g., the activation of protein kinase C [PKC], poly[ADP-ribose] polymerase [PARP], and increased flux through the hexosamine pathway, and the accumulation of polyols and advanced glycation end-products [AGEs]) have been implicated in the pathophysiology of diabetes via the increased production of reactive oxygen species (ROS) [2]. The recognition of these processes and pathways has led to the investigation and development of potential targets and corresponding therapeutic agents for the prevention and treatment of DR. Other processes associated with DR include the acceleration of inflammatory responses, the upregulation of the renin-angiotensin system (RAS), and the dysregulation of growth factors, which have been discussed in a number of recent review articles [3,4].

Despite the continuous efforts of researchers toward a better understanding of the pathophysiology of the disease, the identification of potential targets for the treatments of diabetic retinopathy remains a challenge. Future therapies would likely involve the inhibition of several different pathways or the discovery of a master regulator molecule(s) and their inhibitors to be used for DR treatment. In this review, we discuss recent advances in discovering potential drug targets and their corresponding therapies that have shown great promise in the treatment of DR (Tables 1 and 2). However, clinical trials for some of these drugs are yet to begin or are in the early stages, but it is hoped that these potential drugs would be safe and effective in treatment of the DR. We anticipate that this discussion will provide a better understanding of the new treatment strategies for the control of DR.

Inhibition of Hyperglycemia-Induced Metabolic Stresses

Advanced glycation end-product (AGE) inhibitors

Numerous studies have demonstrated the pathological role of AGEs in the initiation and progression of diabetic retinopathy [5]. In diabetes, the accumulation of AGEs and their interactions with their receptors (RAGEs) are increased, adversely affecting the retinal microvasculature in patients with diabetes [6,7].

AGE inhibitors have been used in experimental studies to modulate the action of AGEs in the pathogenesis of diabetic retinopathy. Aminoguanidine, a specific inhibitor of AGE formation, prevents AGE accumulation at the branching sites of precapillary arterioles, leading to diminished pericyte drop-out, reduced progression of vascular occlusion, and inhibited abnormal endothelial cell proliferation in diabetic dogs [8]. In addition, pyridoxamine treatment, another inhibitor of AGE formation, protects against capillary drop-out, limits the upregulation of laminin protein, and limits the increase in AGEs in the retinal vasculature of diabetic rats [9]. A number of other AGE inhibitors (e.g., OPB-9195, ALT-946, ALT-711, the RAGE inhibitor LR-90, and the putative cross-link breakers N-phenacylthiazolium bromide [PTB] and alagebrium) have been developed [6,10,11]. The systematic administration of the soluble form of RAGE (sRAGE) inhibited blood-retinal barrier breakdown, leukostasis, and the expression of ICAM-1 in the retinas of diabetic mice [12].Thus, the inhibition of AGE formation, blockade of the AGE-RAGE interaction, and suppression of RAGE expression may be useful therapeutic targets for treating the complications of diabetic retinopathy.

The process of AGE-induced retinal leukostasis and hyperpermeability has been shown to be inhibited by pigment epithelium-derived factor (PEDF), which blocks superoxide generation and NF-κB activation in AGE-exposed endothelial cells [13]. PEDF is also a potential anti-oxidative agent and anti-inflammatory factor that may block the AGE-RAGE interaction, thereby ameliorating the progression of proliferative diabetic retinopathy (PDR) [14,15].

Protein kinase C (PKC) inhibitors

The increased activities of the classic protein kinase C (PKCs) isoforms (PKC-α, β1/2, and PKC-δ) in diabetes greatly enhance the *de novo* synthesis of diacylglycerol (DAG), which has been linked to vascular dysfunction and the pathogenesis of DR [16].

Some selective PKC isoform inhibitors are likely to be able to delay the progression of diabetes-associated visual and vascular pathogenesis. One of the first PKC inhibitors, PKC412, reduced the effects of several isoforms of PKC and improved visual acuity when administered orally (100 mg/d) to patients with diabetic macular edema (DME) [17]. In the diabetic retina, the isoform PKC-β is highly expressed; thus, the selective inhibition of PKC-β by ruboxistaurin mesylate has been widely studied [18]. Eli Lilly Co., USA, has designed a specific inhibitor of the PKC-β isoform, ruboxistaurin, which has shown beneficial effects in animal models of DR [19]. The effect of ruboxistaurin in a clinical trial for Protein Kinase C beta-Inhibitor Diabetic Retinopathy Study (PKC-DRS) in patients with moderately severe to very severe non-proliferative diabetic retinopathy suggested that the drug was well tolerated and delayed the time to occurrence of moderate visual loss, but did not prevent DR progression [20]. Another clinical trial for Protein Kinase C beta Inhibitor Diabetic Retinopathy Study (PKC-DRS2) demonstrated that the drug-treated patients experienced significantly less sustained moderate visual loss [21,22]. More recently, the combined data from 2

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Table 1. An overview of the potential drugs and their targets early in the treatment of diabetic retinopathy.

Targets	Drugs	Potency	References
Inhibitor of AGE formation	Aminoguanidine	High	[8]
	Pyridoxamine	High	[9]
	OPB-9195, ALT-946, ALT-711, RAGE inhibitor, LR-90, Putative cross-link breaker N-PheracylThiazolium Bromide (PTB) and alagebrium	Fair	[6,10,11]
Protein Kinase C (PKCs) inhibitors	PKC412	Good	[17]
	Ruboxistaurinmesylate	High	[18]
	Ruboxistaurin (RBX)	High	[19–23]
Aldose Reductase Inhibitors (ARIs)	Sorbinil	High	[30]
	Tolrestat, Lidorestat, Zenarestat, Ponalrestat and Zopolrestat	Fair	[28,31]
	ARI-809	High	[28]
	Epalrestat, Fidarestat and Ranirestat	Good	[29,31,32]
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Aspirin	Good	[35,38]
	Nepafenac, Sodium salicylate and Sulfasalazine	Good	[40,41]
	Baicalein and Genistein	Fair	[44,45]
	Nepafenac, Celecoxib	Good	[40,43]

Table 2. An overview of the potential drugs and their targets early in the treatment of DR.

Targets	Drugs	Potency	References
Poly (ADP ribosylated) protein (PARP) inhibitors	PJ-34, 3-aminobenzamide and 1,5 isoquinolinediol	Good	[43,44,46,47]
	1,5-iso-quinolinediol (ISO) and 10-(4-methyl-piperazin-1-ylmethyl)-2H-7-oxa-1,2-diaza-benzo-[de] anthracen-3-1 (GPI-15427)	Fair	[48]
NF-κB inhibitors	Dehydroxymethylepoxyquinomicin (DHMEQ), Pyrrolidinedithiocarbamate	Good	[50,54]
Angiotensin 2 receptor blockers /angiotensin converting enzyme (ACE) inhibitors	Valsartan, PD123319 Candesartan, losartan and candesartan cilexetil	Fair Good	[57] [58–60]
	Lisinopril, Perindopril	Fair	[63,64]
Antioxidants	Alpha-lipoic, taurine, alpha-tocopherol, N-acetyl cysteine, ascorbic acid, beta carotene, Vitamin C and Vitamin E, Benfotiamine	Fair	[68–70]
Lipid lowering drugs	Fenofibrate, statins, simvastatin	Fair	[76,77]
Neuroprotective, N-methyl D-aspartate (NMDA) receptor antagonist	MK-801, Memantine	Good	[77,78]
Stem cells as a therapeutic option	Hematopoetic stem cells, bone marrow-derived mononuclear cells	Good	[92–94]
Ribonucleic acid (RNA) interference	HIF-1α siRNA, VEGF siRNA, Bevasiranib, siRNA-027 and RTP801i	Good	[97,99–102]

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clinical studies (PKC-DRS and PKC-DRS2) for ruboxistaurin treatments in diabetic retinopathy patients suggest beneficial effects on vision loss, vision gain, and reduced need for initial focal laser therapy, especially in case of diabetic macular edema [23].

Thus, inhibitors of PKCs, especially PKC-β, are likely to be potential candidates for the early treatment and management of some of the pathologies of DR.

Aldose reductase inhibitors (ARIs)

In diabetes, the polyol pathway of glucose metabolism becomes activated to produce sorbitol by the enzyme aldose reductase (AR) [24]. As a result, cells are deprived of glutathione, an endogenous antioxidant, which thus increases oxidative stress [25,26].

Numerous studies have shown that aldose reductase inhibitors (ARIs) decrease the prevalence of microaneurysms, basement membrane thickness, oxidative stress, VEGF expression, neuronal apoptosis, and gliosis in the retina in diabetic animals [27–29]. Sorbinil, the first ARI to undergo clinical trials, showed little effect in controlling or preventing the development or progression of DR [30]. Several ARIs that have been developed over the last 2 decades (e.g., tolrestat, lidorestat, and zenarestat) have been found to have hepatic and renal toxicity. Ponalrestat and zopolrestat, which have better safety profiles, also showed better potency. However, clinical studies demonstrated only a minor benefit, possibly due to insufficient inhibition of the pathway [28,31]. A new ARI, ARI-809, has a high selectivity for aldose reductase and has greater potency [28]. Other representatives of new structural classes of ARIs (e.g., epalrestat, fidarestat, and ranirestat) have been studied in diabetic animals with great success, and it is hoped that these drugs will prove useful in the treatment of diabetic retinopathy [29,31]. The oral administration of fidarestat in a streptozotocin-induced diabetic rat model reduced the expression of VEGF and retinal oxidative stress and alleviated the leukocyte-endothelial cell interactions in the retina [32]. Plant or dietary-derived active components are future potential ARI candidates that have shown good outcomes in the control and management of diabetic complications [33,34]. However, the efficiency and potency of these plant- or dietary-derived ARIs need to be validated in animals and in clinical trials in humans.

Anti-Inflammatory Drugs for the Treatment of DR

Numerous functional and molecular mediators of inflammation, including the recruitment and activation of leukocytes, have been detected in the retinas of diabetic animals. Proinflammatory cytokines and chemokines and other inflammatory markers contribute to capillary nonperfusion in DR [35]. Under the pathological conditions of DR, the inflammatory response upregulates inducible nitric oxide synthase (iNOS), nuclear factor kappa B (NF-κB), cyclooxygenase-2(COX-2), intracellular adhesion molecule (ICAM-1), vascular endothelial growth factor (VEGF), prostaglandin E2, interleukin 1β (IL-1β), and cytokines, increasing permeability and leukostasis in retinal capillaries [36,37]. The discovery of inflammatory events associated with microvascular damage in DR has led the interest in the early treatment of DR.

In animal models of diabetes, the use of daily doses of non-steroidal anti-inflammatory drugs (NSAIDs) can protect against diabetic retinal microangiopathy and damage to the vasculature [35]. Aspirin, at doses <0.6 mmol/l, prevented the apoptosis of capillary cells and the development of acellular capillaries in a streptozotocin-induced diabetic rat model [38]. A high dose of aspirin inhibited blood retinal barrier breakdown in diabetic rats; this inhibition was accompanied by the inhibition of the retinal expression of ICAM-1, a reduction in the adhesion of leukocytes to the retinal vasculature, and lower retinal expression of eNOS and NF-κB [39]. Aspirin has also been shown to inhibit inflammatory mediators, iNOS, and the production of nitric oxide. The administration of topical nepafenac, which has unique time-dependent inhibitory properties against COX-1 and COX-2, has been shown to inhibit diabetes-induced microvascular abnormalities with no adverse effects on neuronal degeneration [40]. Salicylate drugs (aspirin, sodium salicylate, and sulfasalazine), etanercept (a soluble receptor of TNFα), and meloxicam (an inhibitor of COX-2) have been found to inhibit the loss of retinal capillaries in diabetic rats in conjunction with an inhibition of the diabetes-induced activation of NF-κB, which mediates inflammatory responses [41]. In another study, the periocular injection of celecoxib-poly-lactide-co-glycolide micro-particles was found to reduce VEGF mRNA and vascular leakage in diabetic animals [40,42,43]. Two other anti-inflammatory drugs – baicalein and genistein – suppressed diabetes-induced inflammatory processes and inhibited vascular abnormalities and neuron loss in diabetic retinas [44,45].

The topical application of the COX-2 inhibitor nepafenac (via eye drops) inhibited diabetes-induced increases in vascular lesions and PGE2, superoxide, and COX-2 production [40,43]. The oral administration of celecoxib, a potent COX-2 inhibitor, reduced VEGF mRNA and vascular leakage in animals. A phase III study evaluating celecoxib in patients with diabetic retinopathy is currently ongoing.

Poly (ADP ribose) Protein (PARP) Inhibitors

PARP is a nuclear enzyme that is generally present in the inactive form in cells but is activated in the retinas of diabetic animals, causing DNA damage and increasing oxidative and nitrosative stress [43]. PARP inhibits the activity of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), inducing the

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activation of the hexosamine pathway, protein kinase C (PKC), and AGE formation, which triggers the production of reactive oxygen and nitrogen species.

The specific PARP inhibitor PJ-34 inhibits the diabetes-induced increase in TUNEL-positive (apoptotic) cells and inhibits early vascular lesions of DR [46]. PJ-34 also inhibits diabetes-induced leukostasis in the retina [47]. Other structurally unrelated PARP inhibitors (3-aminobenzamide and 1,5isoquinolinediol) inhibit the diabetes-induced increase in VEGF expression. In diabetic rats, PARP inhibitors have been shown to inhibit the activation of NF-κB and the induction of the expression of inflammatory proteins [43]. Diabetic mice treated with PJ-34 for 6 months exhibited inhibition in both the loss of pericytes and the formation of acellular capillaries [44]. Recently, Drel et al showed that the PARP inhibitors 1,5-iso-quinolinediol (ISO) and 10-(4-methyl-piperazin-1-ylmethyl)-2H-7-oxa-1,2-diaza-benzo-[de] anthracen-3-1 (GPI-15427) reduce diabetes-induced retinal oxidative-nitrosative and endoplasmic reticulum stress and glial activation [48]. The increase in the number of TUNEL-positive nuclei in the retinas of diabetic rats was prevented by ISO and GPI-15427. Thus, the inhibition of PARP is a promising therapeutic target to inhibit the development of diabetic retinopathy.

NF-κB Inhibitors

NF-κB is a transcriptional factor that is activated in the diabetic retina. NF-κB subunits accumulate in the endothelial and glial cells of the epiretinal (e.g., MCP-1 and sICAM), which are involved in the pathogenesis of PDR [49,50].

The use of dehydroxymethylepoxyquinomicin (DHMEQ), an NF-κB inhibitor, attenuates the retinal expression of angiotensin II and AT1-R and other inflammatory parameters in the diabetic retina [50]. Several different antioxidants inhibit the diabetes-induced activation of retinal NF-κB [47,51]. The inhibitor DHMEQ has been shown to suppress cytokine expression *in vitro* [52] and to inhibit tumor growth and angiogenesis *in vivo* [53]. In another study, the inhibition of NF-κB led to the suppression of VEGF and ICAM-1 in the diabetic retina [50]. NF-κB inhibition with pyrrolidinedithiocarbamate led to the suppression of ischemia-induced retinal neovascularization [54]. Thus, NF-κB inhibitors may be potential agents for ameliorating the complications of diabetic retinopathy.

Angiotensin 2 Receptor Blockers/Angiotensin-Converting Enzyme Inhibitors

Hypertension has been identified as a major risk factor of microvascular complications, which are characteristic of DR. Several studies on the components of the retinal renin angiotensin system (RAS), rennin, angiotensin-converting enzyme (ACE), and angiotensin types I and II, have shown increased levels of prorenin, renin, and Ang-2 in the vitreous humor of patients with PDR and diabetic macular edema (DME), suggesting the involvement of the RAS in the pathogenesis of DR [55,56].

The RAS activates downstream inflammatory responses by upregulating VEGF, ICAM-1, MCP-1, and NF-κB. These components are being explored intensively to control the pathogenesis of DR [50,56]. The AT-I receptor antagonist valsartan and the AT-II receptor antagonist PD123319 attenuated the increase in retinal VEGF expression observed in diabetic rats [57]. A proteomics analysis revealed that the differential expression of certain proteins in the retina of diabetic mice was controlled by treatment with candesartan, an AT-I blocker [58]. Other inhibitors of AT-I (e.g., losartan and candesartan cilexetil) are undergoing clinical trials for the management of dysregulated RAS in DR [59,60].

The blockade of the RAS at the level of ACE inhibition or angiotensin reduces the increase in retinal VEGF and VEGFR-2 that occurs in diabetic rats and transgenic rats with oxygen-induced retinopathy (OIR) and attenuates vascular pathology, including the proliferation of endothelial cells, vascular leakage, angiogenesis, and inflammation [61,62]. The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus Study (EUCLID) has shown the beneficial effect of lisinopril in reducing the risk of DR progression in diabetic patients [63]. Recent work by Zheng et al. has shown the therapeutic effect of the ACE inhibitor perindopril on decreasing the VEGF-to-PEDF ratio [64]. However, both the UK Prospective Diabetes Study (UKPDS) and Appropriate Blood Pressure Control in Diabetes (ABCD) trials failed to show a benefit of ACE-inhibitor treatment in DR patients [30]. Therefore, specific RAS inhibitors remain to be discovered in efforts toward controlling DR.

Antioxidants for the Management of DR

An increased level of oxidative stress in diabetes plays an accelerative role in the progression and pathogenesis of diabetic retinopathy. Diabetes induces increased AGE formation, the activation of aldose reductase, hexosamine, the PKC pathway, altered lipoprotein metabolism, and excess levels of excitatory amino acids, all of which may lead to an increased production of reactive oxygen and nitrogen species (ROS/RNS) [65,66]. Oxidative stress creates a vicious cycle of macromolecular damage by increasing the production of more ROS/RNS, activating several metabolic pathways, which in turn dysregulate cellular and molecular mechanisms associated with DR [43,67].

Strategies to prevent the deleterious effects of oxidative stress or free radicals have been considered as potential treatments

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of this disease. However, antioxidants have not effectively controlled diabetic retinopathy in clinical trials. Antioxidant therapy in combination with other treatments may have a role in slowing the progression of diabetic retinopathy. The increased levels of VEGF in the retinas of diabetic rats were attenuated by 2 antioxidants, alpha-lipoic acid and taurine. The administration of a mixture of antioxidants also inhibits the activation of NF-κB, which is involved in the regulation of a large number of genes. Feeding rats a diet supplemented with several antioxidants, including alpha-tocopherol, N-acetyl cysteine, ascorbic acid, and beta-carotene, inhibited the increase of caspase 3 activity. The administration of vitamin C and vitamin E prevented the inhibition of enzymes such as glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase. Clinical studies have shown that high doses of vitamin E can apparently reverse some of the changes in retinal vessels that occur in DR [68]. Benfotiamine (vitamin B1), a lipid-soluble thiamine derivative, blocked major hyperglycemia-induced pathways and prevented experimental diabetic retinopathy [69]. A combination of oral benfotiamine and alpha-lipoic acid reduced AGE and ROS formation in animal studies [70]. The administration of antioxidants in a study of type 2 diabetic patients with non-PDR maintained the antioxidant plasma status levels with decreased oxidative plasma activity as measured by oxidative malonyldialdehyde (MDA) and total antioxidant status (TAS) [71]. The use of PEDF as a therapeutic option to block pathways that lead to the production of ROS are being extensively studied and remain to be validated for human use [72]. Therefore, antioxidant therapy may be useful as an adjunct treatment in combination with other treatments for the prevention of retinal damage.

Lipid-Lowering Drugs

There is a growing body of evidence suggesting that serum lipid and fatty acid composition, concentration, and tissue distribution contribute to the development and severity of DR [73]. High levels of lipids and fatty acids are associated with increased oxidative stress, an inflammatory response, and an altered physiological metabolic profile in the retina and vitreous humor, leading to the progression of DR [74,75].

The therapeutic use of lipid-lowering drugs such as fibrates and cholesterol-lowering drugs have been found to have a great potential in the treatment of DR. Both the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial have shown the reduced need for laser treatment in patients with DR who received these therapies [76]. Statins, (ie, 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) have also been evaluated in the treatment of DR. The combination of fenofibrate with simvastatin reduced the rate of progression of DR compared with simvastatin alone [77]. In diabetic rats, the administration of simvastatin protected against oxidative damage by scavenging free radicals and restoring the nonenzymatic and enzymatic antioxidant systems [78]. Derivatives of polyunsaturated fatty acids such as lipoxins possess anti-inflammatory actions and suppress the production of interleukin-6, TNF-α, and VEGF. More recently, Das [79] proposed that lipoxins could be of significant benefit in the prevention and management of diabetic macular edema and retinopathy. Thus, these drugs can act as potential lipid-lowering therapeutic treatments in preventing retinal complications in the management of DR [80].

Neuroprotection

Neurodegeneration is well established in the early stage of diabetic retinopathy, which involves the retinal ganglion cells and cells of the inner plexiform layers [81]. Increasing evidence suggests that dysregulated level of metabolites (e.g., glutamate, homocysteine, and branched chain amino acids) in the diabetic retina may cause excitotoxicity to neurons. Neuroprotective treatments have attracted significant interest as therapies for DR, and considerable attention has been given to discovering neuroprotective drugs/agents that could possibly repair vision loss and damage to ganglion cells.

The intraocular administration of MK-801, an N-methyl D-aspartate (NMDA) receptor antagonist, has been shown to protect against neurodegenerative conditions [82]. Another NMDA receptor antagonist demonstrated a neuroprotective effect in RGCs when exposed to glutamate [83]. In another study, memantine treatment in animal models of diabetes exhibited neuroprotection in addition to reduced vitreoretinal VEGF protein levels and reduced BRB breakdown [84]. Recently, Smith et al showed that a specific sigma receptor-1 ligand, pentazocine, protected neurons in an *in vivo* model of retinal degeneration, suggesting that sigma ligand may be a potential therapy for neurodegenerative diseases of the retina [85]. In one of our studies, we found that gabapentin (Neurontin) administration to diabetic rats reduced caspase-3 activity and reduced the increased levels of ROS in the diabetic retina, suggesting these agents may protect neuronal cells [86].

Neurotrophins such as brain-derived neurotrophic factor (BDNF) are important for the survival of RGCs [87]. Several studies have evaluated the therapeutic merits of BDNF supplied either exogenously or by injection in diabetic mice for treating neurodegeneration in the diabetic rat retina [88,89]. Treatment with BDNF in combination with ciliary neurotrophic factor (CNTF) has been shown to rescue photoreceptors in retinal explants, conveying its neuroprotective effects [90]. Thus, neurotrophins could be active therapeutic agents to protect against neurodegeneration in DR.

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Stem Cells as a Therapeutic Option for DR

Stem cells have the potential to participate in the formation of normal-appearing intraretinal vascularization. It has been demonstrated that hematopoietic stem cells isolated from bone marrow can differentiate into all hematopoietic cell lineages, including endothelial cells, astrocytes, and retinal pigment epithelial cells, and provide a repair function [91]. One promising therapy might be the use of hematopoietic stem cells to preferentially form intraretinal capillaries. Recently, it has been reported that the intravitreal administration of hematopoietic stem cells selectively prevented blood vessel loss and promoted blood vessel growth. The feasibility and safety of transplanting mononuclear cells derived from autologous bone marrow has successfully been demonstrated in a human eye with advanced atrophy of the retina and optic nerve caused by DR [92]. Such intravitreal injection of autologous bone marrow-derived mononuclear cells in patients with retinitis pigmentosa, cone-rod dystrophy, and early DR has shown promising results in a phase I trial without any adverse effects [93]. Studies of the potential applications of stem cells are opening new avenues for maintaining normoxia and subsequently reducing the induction of retinal neovascularization, resulting in the management of DR [94].

Ribonucleic Acid (RNA) Interference (RNAi)

RNAi is a powerful tool that allows the production of double-stranded RNA molecules that can specifically inhibit the production of a particular gene product [95]. RNAi in the form of short interfering RNA (siRNA) targeting VEGF inhibited VEGF production in human RPE cells. In addition, siRNA attenuated the production of VEGF, IL-6, IL-8, TGF-β, and MCP-1 in ARPE cells [96]. HIF-1α siRNA and VEGF siRNA specifically downregulated HIF-1α and VEGF mRNA and protein levels in human umbilical vein endothelial cells (HUVECs) and in the mouse retina in an ischemic retinopathy model [97,98]. siRNAs reduced the production of angiogenic molecules in patients with macular degeneration and diabetic retinopathy [99]. The intravitreal injection of specific siRNAs targeting VEGF has been shown to prevent retinal and choroidal neovascularization in mice [100]. Bevasiranib is an siRNA against VEGF, developed by Acuity Pharmaceuticals. A Phase III, randomized, double-masked clinical trial evaluating the efficacy of bevasiranib in patients affected by wet age-related macular degeneration (AMD) was recently terminated [101]. However, results from randomized clinical trials evaluating the use of bevasiranib in the treatment of diabetic macular edema are pending. Another molecule, siRNA-027, developed by Sirna Therapeutics, was well tolerated with a single intravitreal dose in patients with choroidal neovascularization (CNV) resulting from neovascular AMD [102].

Conclusions

All of the newer drugs/strategies discussed here have been tested primarily in laboratory investigations, which may be useful in controlling disease progression if carried out at early stages of the disease in humans. However, most of these drugs are still awaiting clinical trials to demonstrate their efficacy and safety in humans. Some of these new therapeutic drugs and approaches may control the incidence and progression of DR with greater efficacy and safety. Future research may delineate several different pathways, and specific therapies will likely target the master regulatory molecules or pathways involved in DR.

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