

Progress of Nanotechnology in Diabetic Retinopathy Treatment

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Abstract: Diabetic retinopathy (DR) is a chronic diabetes complication that progressively manifests itself as blurred vision, eye floaters, distorted vision, and even partial or total loss of vision as a result of retinal detachment in severe cases. Clinically, patients who have undergone variations in the microcirculation of the ocular fundus are treated with laser photocoagulation to improve the circulation of retina; but for patients with macular edema, anti-vascular endothelial growth factor (anti-VEGF) drugs are generally injected to eliminate macular edema and improve vision. The worst cases are patients with fundus hemorrhage or proliferative vitreoretinopathy, for whom vitrectomy has been performed. At present, these clinical treatment methods have widely been used, providing satisfactory results. However, considering the low bioavailability and potential side effects of drugs and the inevitable risks in major surgery, DR prevention, and treatment as well as nerve tissue regeneration in the later stage have always been the focus of research. In recent years, nanotechnology has been increasingly applied in the medical field, leading to new ideas for DR treatment. This study aims to systematically review the research progress of nanotechnology in DR treatment.

Keywords: diabetes mellitus, diabetic retinopathy, nanotechnology, drug delivery

Introduction Nanotechnology

Nanotechnology is a technology to study the properties and applications of materials in the range of 0.1 nm to 100 nm. When the material reaches the nanometer size, the properties of the material will change and appear special properties. This material is composed of atoms, molecules and macroscopic materials. The difference between nanoparticles and bulk materials is mainly due to the relative increase of their surface area, that is, the surface of ultrafine particles is covered with ladder structure, which represents restless atoms with high surface energy. These atoms are easily bonded to foreign atoms and provide large surface active atoms due to particle size reduction. Nanotechnology, as a rapidly developing new discipline, is widely used in electronics, biomaterials energy, environmental science, chemistry, medicine and other aspects. Its application in medical field is mainly through the use of the special properties of nanoparticles to modify the surface of nanoparticles to form targeted, controllable release, easy to detect drug transport carriers, to provide a new method for the treatment of local lesions of the body, to open up a new direction for drug development, not only the special properties of nanoparticles also make it have an important application in disease prediction and monitoring. The application of nanotechnology in medicine has brought new prospects for

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the diagnosis and treatment of various diseases, and diabetes patients have also benefitted.

Diabetes and Complications

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia caused by multiple causes. It is a chronic disease that seriously threatens human health. The prevalence and incidence of diabetes in the world are rising sharply. According to the International Diabetes Alliance, the number of diabetes patients in the world reached 400 million in 2015 and 5 million in diabetes deaths. The total number of diabetes is expected to reach 600 million by 2040. Long-term hyperglycemia can damage all tissues and organs of the body, causing a series of complications. Acute complications include diabetic ketoacidosis, diabetic hyperosmotic coma, fungal vaginitis and many other infectious diseases. Chronic complications include diabetic foot, diabetic retinopathy, diabetic nephropathy and diabetic neuropathy. These chronic complications are often irreversible and have a huge burden on the health and economy of patients. With the hard work and unremitting efforts of researchers and medical workers, many chronic complications can be clearly diagnosed early in the disease, thus avoiding the deterioration of complications and irreversible damage to the body.

Diabetic Foot

The foot ulcers, infections, and deep tissue destruction associated with distal lower extremity neurological abnormalities and varying degrees of peripheral vascular lesions are the leading causes of diabetic non-traumatic amputees. Lauri et al are dedicated to studying radiolabeled leukocyte imaging¹ using ^{99m}Tc-hexamethylamidoxime. Positron emission tomography² is used to perform early imaging of diabetic foot complications in diabetic patients to achieve early detection of lesions.

Diabetic Neuropathy

Diabetic neuropathy includes central nervous system complications such as cerebral aging ischemic stroke and peripheral neuropathy such as distal symmetric polyneuropathy, focal single neuropathy, asymmetric multiple focal neuropathy, and multiple nerve root lesions. Chan et al in the latest research to explore the peptide-peptide co-assembly design method for the detection of biomarkers C peptides of diabetic neuropathy, desire for the diagnosis and intervention of early diabetic neuropathy

through indirect monitoring of C peptide concentrations in the blood, they used a new screening strategy: complementary peptides that can be co-assembled with C peptides can be screened by blue laser excitation based on the polypeptide sequence assembled with C peptides. The structure information and C peptide were studied by ATR-FTIR spectroscopy and CD spectroscopy. The results showed that C peptide was most strongly bound to Trp-D. The second is Lys-D and Lys-L and there is no fixed binding rate between C peptide and any current complementary peptide, they point out that co-assembly between C-peptides and current 9-mer peptides is not optimal, but their research strategies still have important guiding significance in the discovery of new and more suitable complementary peptides. And its research method is also suitable for screening complementary peptides of amyloid protein, a biomarker of Alzheimer's disease, for Alzheimer's disease effective treatment preparation research to provide help.³

Diabetic Nephropathy

Diabetic nephropathy is the main cause of end-stage renal failure and the main cause of death of diabetes. Satirapoj et al summarized and analyzed the potential application of renal tubulointerstitial markers in diabetic nephropathy: cystatin C is an independent predictor of CKD progression in type 2 diabetes mellitus (T2DM);^{4,5} elevated kidney injury molecule 1 (KIM-1) was negatively correlated with decreased glomerular filtration rate, independent of albumin excretion rate; neutrophil gelatinase-associated lipocalin (NGAL) in the case of diabetic nephropathy, elevated NGAL levels occur independently of decreased glomerular filtration rate, and reflects tubulointerstitial injury and inflammation,^{6,7} can also predict the progression of T2DM kidney disease.^{5,8} Angiotensinogen can be used as a potential urine biomarker for the diagnosis of diabetic nephropathy, an early biomarker of RAAS activation in diabetic nephropathy; T2DM the patient starts to have significant albuminuria, you can detect elevated levels of periostin, and causes associated renal fibrosis and inflammation,^{9,10} the proportion of urinary MCP-1 and urinary EGF/MCP-1 was independently associated with renal progression.¹¹

Diabetic Retinopathy

Hyperglycemic state due to diabetes are involved in the occurrence of DR, leading to high blood sugar levels in retinal vessels, increasing in vascular permeability,

accumulating fluid in and under the retina, and causing edema and necrosis of nerve cells. Hyperglycemia can damage the blood-retinal barrier, and the leakage of blood from the central retinal artery, ciliary vessels, and the deep retina, which triggers the ischemic changes in the surrounding retina. This ischemic state activates the body's compensatory mechanisms, thereby promoting the formation and proliferation of new vessels, resulting in retinal detachment and resultant vision loss under stretching, the role of nanotechnology in the pathogenesis of diabetic retinopathy has been represented (Figure 1). Patients with diabetes for more than 10 years suffering varying degrees of DR as a chronic complication, causing blindness in severe case scenarios.¹² According to the international clinical grading standard,¹³ DR can be classified into two categories including six stages: 1) nonproliferative diabetic retinopathy (NPDR) that includes stage I: microangioma and small bleeding points, stage II: hard exudates, and stage III: cotton-like soft exudates; 2) proliferative diabetic retinopathy (PDR) that includes stage IV: neovascularization, vitreous hemorrhage, stage V: fibrovascular proliferation, vitreous organization, and stage VI: retinal detachment and resultant blindness caused by stretching. Currently, if laser therapy is performed in a timely and appropriate manner, it can completely avoid vitreous hemorrhage and retinal neovascularization, achieving

satisfactory clinical effects. Existing drugs for DR effectively relieve macular edema in the retina, and in advanced proliferative retinal diseases, vitrectomy clears the refractive media and sucks out the debris to remove the stent on which fibrous tissues develop. The removal loosens the stretching and restores the normal anatomical relationship of the retina, thereby keeping the eyeball intact and establishing conditions for laser photocoagulation or condensation. Hence, vitrectomy is considered to be the most effective treatment method of advanced DR. However, clinical drug therapies have certain limitations like the low solubility of drugs, poor penetrability through the BRB to reach the retina, toxicity to the body, and easiness to be degraded by enzymes in the body that results in the decreased duration of drug efficacy. Nanotechnology, due to its continuous development, has been increasingly applied to the prevention and treatment of DR, addressing many problems in traditional treatments. Its main advantages include a small diameter, high penetrability through the BRB, good biocompatibility, and some nanoparticles possessing favorable physical properties that are conducive to treatment effect observation. Reduced drug degradation in the body to achieve sustained release that promises to provide a stent for nerve tissue regeneration. An increasing number of nanomaterials are being synthesized or discovered and applied in the clinical treatment of

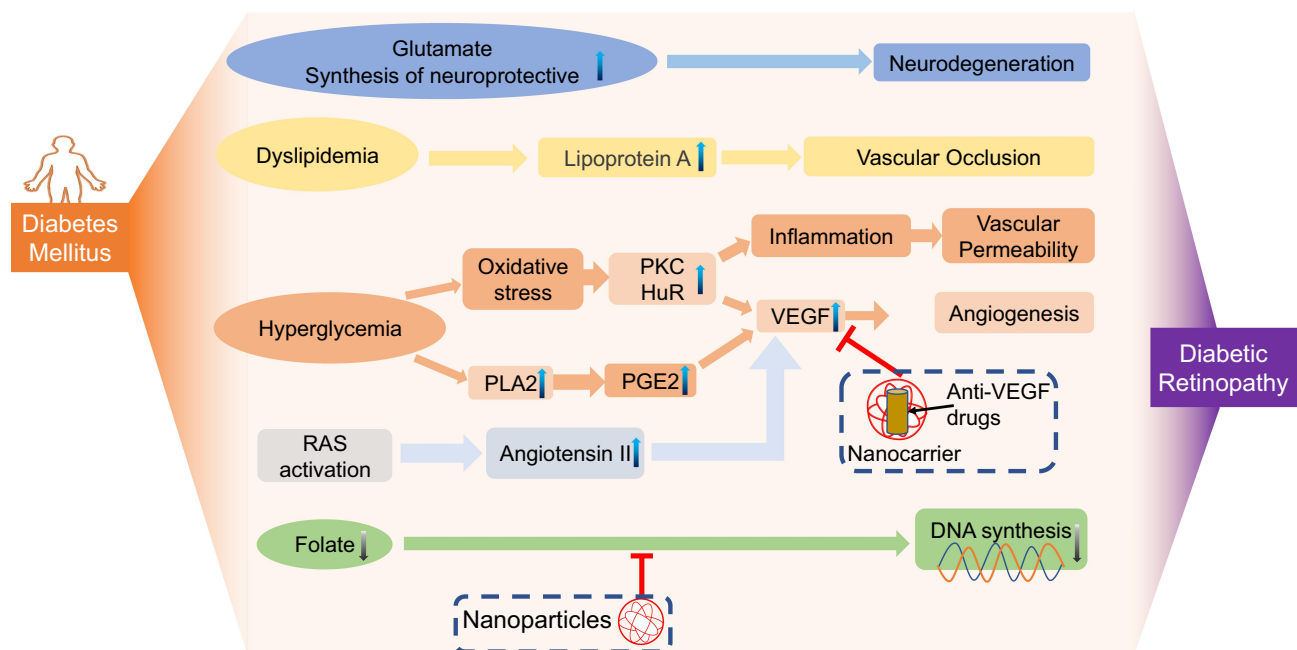


Figure 1 The role of nanotechnology in the pathogenesis of diabetic retinopathy.

Notes: Adapted from Pusparajah P, Lee LH, Abdul Kadir K. Molecular Markers of Diabetic Retinopathy: Potential Screening Tool of the Future? *Front Physiol.* 2016;7:200. Copyright © 2016 Pusparajah, Lee and Abdul Kadir. Creative Commons Attribution License (CC BY).⁸⁵

DR, contributing solutions to many problems. The application of nanotechnology in fundus examination also provides new advantages for DR prevention. However, the safety and feasibility of those new nanomaterials are still in the research stage, and investigating their application in DR treatment is of great importance. In view of these developments, this study aims to review the application and development of nanotechnology in DR treatment, exploring its contribution to the prevention and treatment of DR and its role in the regeneration of the nerve tissues damaged by DR.

Traditional Therapies for DR

Traditional therapies for DR comprising of laser therapy, vitrectomy, and conventional drugs to control hyperglycemia, hypertension, and hyperlipidemia are the points of consideration. These therapies have been widely applied to the clinical prevention and treatment of DR, delivering satisfactory efficacy and superiority in inhibiting retinal neovascularization, relieving retinal macular edema, and removing the stretching of fibrous tissues during the proliferation period for the retina. Although extensive clinical trials have proven their application value, these therapies are inevitably disturbed by certain limitations in clinical application.

Laser Therapy

Laser therapy is mainly used for proliferative retinopathy. The commonly used laser wavelengths are 532 nm and 577 nm. Beams of light are focused on the site of retinal hemorrhage to raise the temperature for protein degeneration and liposome necrosis, thereby stopping the bleeding caused by microaneurysm rupture and preventing the formation of ocular hematomas. This therapy is still used in clinical practice. Jiang¹⁴ treated 45 patients with diabetes mellitus using panretinal photocoagulation (PRP) and evaluated the efficacy, concluding that PRP can promote neovascularization, improve macular edema and vision, and prevent the deterioration of the disease. However, laser treatment is often complicated with vitreous hemorrhage, as mentioned by Bi et al¹⁵ when reviewing the progress of photocoagulation application in DR treatment, in their research, they found that the choice of delayed photocoagulation leads to a serious loss of vision of 6.5%, and timely PRP can reduce the risk of serious loss of vision to 3.8%~4.7%, significantly reduced. In the follow-up of 192 patients treated with retinal laser photocoagulation, Kleinmann et al have reported a high incidence

of 39% vitreous hemorrhage.¹⁶ Besides, this therapy may destroy some retinal cells and often results in permanent scotomas in the visual field.^{17–20} PRP can worsen night vision and delay light-to-dark adaptation.^{21–23}

Retinal laser photocoagulation mainly blocks the ischemic areas around the retina, reduces the stimulation of ischemia for vascular endothelial growth factors (VEGFs), and inhibits the diffusion of fibrovascular toward the surroundings, thereby lowering the possibility of intravitreal hemorrhage. However, it has a key limitation, as more than two surgeries are necessary to maintain a good retina.²⁴

Vitrectomy

Vitrectomy is used in patients with advanced DR manifested as intravitreal hemorrhage and neovascularization, in an attempt to prevent vision loss and visual field defects. The mechanism of this therapy is to remove blood from the vitreous and prevent retinal detachment caused by internal injury,²⁵ which is still widely used in clinical practice. Owing to the advances in minimally invasive techniques, it has upgraded from the initially traditional 20G vitrectomy to the 23G minimally invasive vitrectomy, which is characterized by smaller surgical incisions and higher incising efficiency. Brănișteanu et al²⁶ performed 20G and 23G vitrectomies for two groups of patients with DR separately and followed up with them for at least 12 months. The results showed that vitrectomy was an effective therapy for DR and there was no significant difference in operational complexity and retinal repair between 20G and 23G vitrectomy. Besides, they compared the therapeutic effects of these two methods and concluded that 23G vitrectomy is likely to cause serious complications such as iatrogenic retinal break and the inherent postoperative ocular sequelae, such as cataract formation.^{27,28} Therefore, the safety of a vitrectomy has become the main problem that limits its clinical application. Naruse, Veritti et al^{29,30} followed up 185 cases who received 25G or 27G minimally invasive vitrectomy (included 64 undergoing 25G vitrectomy and 125 undergoing 27G vitrectomy) and compared the two minimally invasive vitrectomy systems. They concluded that both 25G and 27G vitrectomy systems were safe and effective for PDR treatment and promised the early recovery of vision after the operation. Nathan et al concluded from a controlled trial: In Type I diabetes, early vitrectomy resulted in visual acuity of 10/20 or better in 36% of eyes whereas deferral of vitrectomy resulted in 10/20 or better visual acuity in 12% of eyes. There was no

advantage of early vitrectomy found in Type 2 diabetes patients.³¹

Drug Therapy

Drug therapies are designed to reduce the expression of VEGF by lowering vascular permeability and abating the damage to the BRB. The methods of drug administration mainly include periocular administration, subretinal administration, and intravitreal injection.

Drugs for Microcirculation Disorders

Pancreatic kininogenase degrades kininogen in the body into kinin, which relaxes capillaries to increase capillary blood flow, activates the activity of the fibrinolytic system, and dissolves the microthrombus formed under a hypercoagulable state, thereby improving retinal blood flow, correcting hypoxia, reducing protein exudation, and eliminating hemangioma. According to the clinical research by Lin et al compound xueshuantong capsule combined with pancreatic kininogenase can effectively improve microcirculation, increase blood flow, anticoagulation, thrombolysis, and decrease blood viscosity, showing satisfactory efficacy for NPDR.³²

Drugs for Vascular Endothelium Protection

Calcium dobesilate (CaD) inhibits oxidative stress and inflammation, reduces BRB injury, and improves vascular permeability and vascular leakage. It promises to relieve DR-induced fundus diseases, improve vision, inhibit neovascularization, and delay the progress of DR. CaD can also be used as adjuvant therapy for photocoagulation.³³

Anti-VEGF Drugs

Anti-VEGF type of drug reduces the formation of retinal neovascularization mainly by inhibiting VEGF. Intravitreal injection is generally used to elevate drug concentration in the eye and prevent the formation of proliferative tissues, hence improving the efficacy of retinal detachment surgery. The anti-VEGF drugs commonly used in DR treatment include ranibizumab, bevacizumab, and infliximab. For moderate to severe DR, infliximab shows better visual recovery efficacy.³⁴

Other Anti-Angiogenesis Drugs

Squalamine³⁵ promotes visual recovery by inhibiting vascular growth factors such as PDGF and b-FGF. Moreover, it is found that AKB-9778 activates Tie2 by blocking

vascular endothelial protein tyrosine phosphatase (VE-PTP), a negative regulator of Tie2, thereby reducing vascular permeability and DR incidence.³⁶

Steroid Hormones

Triamcinolone acetonide, discovered in 1970, is currently the most effective steroid drug used for PDR.³⁷ The other two alternatives are dexamethasone sodium phosphate³⁸ that reduce the damage to the BRB by exerting its anti-inflammatory effects, and fluocinolone acetate that is injected into the vitreous to relieve bruising. However, the improvement of the bioavailability and the targeting of these drugs to the retina are critical challenges to be addressed.

Application Progress of Nanotechnology in DR Prevention

Regarding DR prevention, besides controlling blood pressure and sugar levels and avoiding strenuous exercise, regular fundus examination is necessary to identify DR earlier. Fluorescein angiography that emerged in the 1960s is considered as the gold standard for DR fundus examination. In the procedure, sodium fluorescein is adopted as the fluorescent dye that is quickly injected into the antebraial vein. When the agent flows into retinal vessels with blood, angiograms are obtained by photographing the fluorescent green light emitted from the dye while the blood vessels return to the eye. With the angiograms obtained, the process of the dynamic cycling of blood within the retina can be observed, thus revealing the microstructure and microcirculation changes of fundus vessels. Qian et al explored the application of polyethyleneimine which modified fluorescein sodium (PEI-NHAc-FS) nanoparticles (NPs) in fundus fluorescein angiography as well as its safety.³⁹ The research indicated that PEI-NHAc-FS NPs can effectively reduce the retention of fluorescein sodium in the body and develop retinal blood vessels, so it can be used to examine the fundus and identify the onset of DR. Moreover, PEI-NHAc-FS NPs are characterized by simple preparation methods, good biocompatibility, stable properties, and a high metabolic rate. However, similar to other fundus angiography techniques, it inevitably causes invasiveness to patients. Vadasundari Vedarethnam assumed that vanadium core-shell nanorods can be used to detect metabolic changes in DR, and to monitor the severity and make possible early detection and diagnosis of DR. Inspired by this concept, Vadasundari et al used vanadium oxide loaded on silica nanorods and

constructed a variety of vanadium core-shells that consisted of different elements and structural parameters in an attempt to assist laser desorption ionization mass spectrometry and draw plasma metabolic fingerprints of diabetic retinopathy. In the future, it is necessary to perform blood testing for patients with diabetics to identify DR earlier, which is of great benefits to the prevention and treatment of DR. Besides, the method developed by Vadanandari et al can be used to distinguish the severity degrees of non-proliferative diabetic retinopathy, delivering noticeable performance in disease grading. Therefore, it provides a new reliable and efficient blood testing strategy for DR.⁴⁰ This latest research result has been applied in clinical trials.

In addition to monitoring and auxiliary examinations, hypoxia is another factor that needs attention to prevent DR. It is the precursor stage of retinal neovascularization, so identifying hypoxic areas in retinal tissue and treating hypoxia earlier promise to delay the onset of DR. Studies have shown that Hypoxia-inducible factor-1 (HIF-1) can reduce the expression of IL-6 and TNF- α in DR⁴¹ and the expression of miR-125b-5p and miR-146a-5p in the retina,⁴² and up-regulate the expression of growth factors such as VEGF and PDGF. HIF-1 antagonists targeted to hypoxic tissues are considered to be a great way to prevent DR. Daunorubicin and doxorubicin (DXR) inhibit the transcriptional activity of HIF-1 by blocking its binding to DNA, but they have poor water solubility, precipitating on the surface of the retina after intraocular injection. Iwase et al used polysebacic acid (PSA)-polyethylene glycol (PEG) nanoparticles to continuously deliver daunorubicin to the retina and observed that after intraocular injection of a diabetic rabbit model, the antagonist was slowly released in a controlled manner for more than 105 days. Additionally, PSA-PEG nanoparticles continuously inhibit neovascularization in the retina for more than 35 days. The sustained-release of PSA-PEG is conducive to the prevention of DR, and it is non-toxic to the retina.⁴³ However, no conclusion has yet been reached as to whether PSA-PEG nanoparticles can safely play a role in the human retina as it is used in the experimental animal retina, and more clinical trials are necessary to warrant this problem.

Progress of Nanotechnology in DR Drug Treatment

Nanotechnology application to DR treatment has unique advantages. Currently, most of the nanomolecules used as drug carriers have a diameter ranging from 1 to 100 nanometers, which allows the drugs to easily pass through

the BRB barrier. Most importantly, the property of nanomolecules combining with specific receptors on retinal pigment epithelial cells allows them to reach the epithelial cells in a targeted manner, thereby achieving the goal of DR treatment. The high blood glucose levels in the retinal vessels that trigger DR have two main sources. Badr et al experimentally proved that glucose transporter 1 (GLUT1) has reduced expression in isolated retinal capillaries and the neural retina. Accordingly, the high blood glucose levels in the DR retina may be attributed to increase glucose entering into the retina through the retinal pigment epithelium (RPE)-choroid interface.⁴⁴ In subsequent studies, Ulas et al noted Streptozotocin-induced diabetes of a 2-week or 2-month duration reduced GLUT1 expression in the retina and its microvasculature by approximately 50%, but it resulted in no reduction in GLUT1 expression in cerebrum or its microvessels. The density of capillaries in retinas of diabetic animals did not change from normal, and so the observed decrease in GLUT1 expression in the retina and retinal capillaries of diabetic animals cannot be attributed to fewer vessels, they concluded that the elevated expression levels of GLUT1 and GLUT3 in the diabetic retina, which is responsible for the accumulation of glucose in the retina, thereby creating a high glucose microenvironment that induces the occurrence of DR.⁴⁵ Based on the above findings, Gao et al at Jilin University prepared hyaluronic acid nanocarriers that can target the CD44 receptor of RPE cells. Also, mouse diabetic models were established and performed controlled experiments that included a control group and a diabetic group; GLUT1 coated by hyaluronic acid nanocarriers was injected in the subretinal space of the diabetic group. Their experimental results showed that hyaluronic acid nano-particles used as a DR drug carrier can significantly control the blood sugar level in the retina of diabetic mice,⁴⁶ which further verified the inferences made by Ulas and Badr et al. In the experiment, they collected and observed the optic nerve specimens of rats, confirming that NPs also have a neuroprotective effect. According to the observation results of the thickness of the retina's outer nuclear layer, GENPs is safe and non-toxic to the retina. Hao et al prepared an amphiphilic nanosystem composed of hydrophobic polycaprolactone (PCL) and hydrophilic pluronic F68 (PF68) that was used to load hyaluronic acid (HA), a steroidal drug effective in the treatment of DR. In the experiment, HA was used as eye drops for diabetic rats. Controlled experiments suggested that PCL-PF68 NPs show optimal encapsulation efficiency for tannic

acid (TA), a hydrophobic drug, and perform noticeably well in controlling the release of HA, allowing it to exist in the retina for a longer time. The measurement results of retinal thickness also verified the safety of PCL-PF68NPs in DR treatment. After 24h exposure at the test concentration, the cell survival rates of NPBs and NPDs are both 100%, suggesting that NPBs and NPDs have good cell compatibility. This quality can well avoid the strong side effects of drugs when they are applied to DR treatment, remarkably reducing the probability of adverse reactions. Therefore, this nanosystem serves as a non-invasive and safe carrier of drugs to eye tissue,⁴⁷ but when used as a lipid carrier, it has problems such as low drug loading capacity and poor stability during storage. In recent studies, an increasing number of new nanomaterials that can be used for DR treatment have been developed, kinds of nanomaterials in DR treatment (Table 1) have been investigated.

Application of Nanotechnology in DR Drug Delivery and Monitoring

In a research article published in 2016, Amadio et al treated DR using SLN, liposomes, and a nanosystem that contains siRNA to silence HuR expression. Through STZ induction, they established a diabetic rat model, which HuR-silencing siRNA encapsulated by SLN and liposomes was injected. After measuring the expression of HuR and VEGF genes in the retina of the experimental and control groups and observing the histology of the retina, they verified the inhibitory effect of HuR-silencing siRNA on the expression of mRNA encoding VEGF gene. Also, they confirmed that nanocarriers can carry miRNA through the BRB smoothly, thereby achieving the targeted treatment of PR.⁵⁸ This cationic lipid-based non-viral carrier promises to be widely used for DR drug delivery due to its advantages of freedom from immune responses of the body, simple production, and affordable price. Based on the “host-guest” interaction between MPEG and α -CD, Zamani et al managed to release Dex and Avastin separately from the supramolecular hydrogel as a nanocarrier that is composed of methoxy polyethylene glycol/polycaprolactone (mPEG-PCL) micelles and α -cyclodextrin (α -CD), in an attempt to treat inflammatory corneal neovascularization in a rat model.⁵⁹ The results showed that 70% of Avastin was released within 5 days and 70% of Dex was released within 1 day, suggesting that DEX/Avastin play a role in inhibiting retinal neovascularization and that PEG-PCL hydrogel as a drug carrier is

effective in achieving sustained drug release. Italian scientists Amato et al developed another possible effective method for DR treatment in 2020, that is, combining the somatostatin analog octreotide (OCT) that displays important neuroprotective and anti-angiogenic properties with magnetic nanoparticles (MNPs), and injecting the combination into the eyes of the rats.⁶⁰ Results indicated that the significant effect of MNP-OCT is maintained at lower doses (100-fold in HRECs and 10-fold in retinal explants) compared to free OCT, demonstrating a strong improvement of the drug bioactivity following binding to MNPs. Besides, MNPs produced no toxicity in the rats and showed good compatibility, prolonging the release of OCT in the rat retina for several months while not affecting its efficacy. Therefore, MNPs greatly reduce the frequency of injection of anti-VEGF antibodies, making it easier to sustain an effective drug concentration.

The superiority of nanotechnology in DR treatment is not only reflected in its nano-scale that contributes to drugs smoothly passing through the BRB but also in some properties unique to nanoparticles, which provide convenience for therapeutic drug monitoring. In 2019, Shoval et al⁶¹ coated the two anti-VEGF drugs, bevacizumab and aflibercept, with carbon nanodots (C-dots) and separately injected the combinations into diabetic rats. By taking advantage of the inherent fluorescence of C-dots, they performed non-invasive monitoring of intraocular drug concentration, thereby avoiding the damage to the eyes caused by invasive monitoring. The research results showed that C-dots used as the outer envelope of bevacizumab and aflibercept can effectively prevent the degradation of the drugs before they reach the retina, thereby increasing the effective drug concentration in the retina of the eye and more efficiently inhibiting VEGF-induced neovascularization in choroidal blood vessels. Hence, the development from NPDR to PDR can be prevented, and the retinal tissue effectively protected.

Application of Nanotechnology in Retinal Regeneration

Nanoscaffolds for Retinal Regeneration

PDR causes damages to the retina that contains seven major cell types (RPE, cone cells, rod cells, horizontal cells, bipolar cells, retinal ganglion cells, and amacrine cells). Among them, RPE is the main nutritional source of the retina, so the research focuses on retinal regeneration. At present, there are two main types of nanomaterials

Table I Nanomaterials in DR Treatment

Nanomaterials	Time	Diameter	Source	Loaded Drug	Efficacy	Existing Problems	Reference
CNE	2014	N/A	N/A	Hydrophilic/protein-based drugs	The retention time of drugs in the eyeball was prolonged and the adhesion of the mucus to the retina was enhanced through the electrostatic interaction with the human eye mucosa.		[50] [48]
SLN NLC	2013	288nm	Stearic acid, castor oil	Triamcinolone acetonide	Due to the good biocompatibility of physiological lipids, PEG loading further improves drug bioavailability in the eye and reduces drug irritation to the ocular mucosa and the occurrence of intraocular rejection.	The drug loading capacity is low, and the stability is poor during storage, which may lead to particle size growth and drug degradation.	[41] [50]–[55]
SiO ₂ –CeCl ₃ nanoparticles	2014	130nm	N/A	N/A	Low-concentration silica-cerium (III) chloride (CeCl ₃) and α -crystal protein quickly form a preliminarily stable conjugate, inhibiting advanced glycation end products (AGEs) and restraining the production of intracellular reactive oxygen species as well as oxidative stress.		[42]
Silica nanoparticles	2012	N/A	N/A	N/A	Oxygen-induced abnormal retinal neovascularization is effectively reduced, and VEGF receptor-2 is induced to phosphorylate by restraining VEGF in vitro, thereby blocking the activation of ERK1/2 and inhibiting angiogenesis induced by VEGF in vitro.		[43]
AgNPS	2019	35nm	Mulberry leaf extract	N/A	AgNPS prepared by mulberry leaf extract using an environmentally friendly method have a satisfactory treatment effect on PR.	There is genotoxicity, which may be attributed to the elevated intracellular ROS induced by AgNPS and the resultant DNA damage.	[44] [56] [58]
GNP	2011	50nm	N/A	N/A	VEGFR-2 autophosphorylation induced by VEGF is suppressed, thereby inhibiting the activation of ERK1/2. No retinal toxicity is found, nor the viability of retinal microvascular endothelial cells is affected.	Cytotoxicity may occur as the particle size shrinks. A lot of experiments are needed to identify an appropriate particle size.	[39] [45]
MNP	2020	50nm	Iron oxide, ferric oxide	Octreotide	MNP has no toxicity to human retinal cells, and when combined with octreotide, it does not affect the anti-angiogenesis and anti-apoptosis effects of octreotide; MNP may be first located on the RPE and then on the entire retina.	Compared with other nanoparticles, magnetic iron oxide nanoparticles (MIONs) are less biologically toxic, but further studies are necessary to verify their safety.	[39] [57]

(Continued)

Table I (Continued).

Nanomaterials	Time	Diameter	Source	Loaded Drug	Efficacy	Existing Problems	Reference
PLGA	2012 2013	20-250nm	Lactic acid, glycolic acid	Bevacizumab or other protein/ enzyme drugs	PLGA is safe for the retina, widely used for drug delivery. PLGA nanoparticles can protect the protein from inactivation and aggregation in the presence of albumin.	The solubility in water is relatively poor, and the nanoparticles formed are large in size, so they tend to be cleared by the liver and spleen, reducing drug concentration in the retinal tissue.	[46] [47]
Chitosan-based nanoparticles	2014	N/A	N/A	N/A	Chitosan-based nanoparticles enable bevacizumab to be sustainably released in the retina, thereby inhibiting retinal neovascularization.		[49]

Abbreviations: DR, diabetic retinopathy; CNE, cationic nanoemulsion; SLN, solid lipid nanoparticles; NLC, nanostructured lipid carrier; AgNPS, silver nanoparticles; GNP, gold nanoparticles; MNP, magnetic nanoparticles; PLGA, polylactic acid-glycolic acid.

used for retinal regeneration: electrospun nanofibers and self-assembled nanofibers. The common natural polymers in electrospun nanofibers are fibrin, gelatin/chitosan, laminin, collagen, and hyaluronic acid, while the common synthetic polymers include poly(L-lactic-co-ε-caprolactone) (PLCL), PCL, poly (lactic-co-glycolic acid) (PLGA), and poly (L-lactic acid) (PLA). Under normal circumstances, there are chemical property differences between natural and synthetic polymers, which lead to natural polymers more suitable for cell attachment and biological activity. Therefore, natural nanopolymers show larger attraction for cells, but they are obscured by synthetic polymers in terms of mechanical strength and half-life. To be specific, synthetic polymers are easier to be designed and controlled in terms of biodegradation, mechanical strength, and transport properties, facilitating the acquisition of an extracellular analog matrix used for cell growth and differentiation. In 2016, Milton Wyman established a radiating nanofiber scaffold to mimic the oriented nerve fibers and found that 72% of the nerve axons grew along the scaffold.⁶² According to a research,⁶³ nanofibers in a diameter of about 200 nm can mimic the distribution of nerve fibers more accurately than those in a diameter of about 1000 nm, thereby promoting retinal regeneration. For some neurons, retinal nerve function is lost on the edge of death. Therefore, measures have to be taken to promote the regeneration of endangered neurons. In this end, a multichannel self-assembling peptide nanofiber scaffold that contains nerve growth factor (NGF) and brain-derived growth factor (BDGF) has been developed—

the NGF is immediately released from the scaffold to assist the initial stage of nerve axon regeneration, and the BDGF is constantly released to promote axon growth and myelin sheath formation.⁶⁴ Similarly, conductive polypyrrole and single-electron layer graphite nanoparticles were experimentally added into the scaffold, and the growth of retinal ganglion cells was found to have increased by up to 137% under electrical stimulation.⁶⁵ Distribution of nerves in the body using nano-scaffolds contributes to the regeneration of retinal tissues, thereby preventing the complete necrosis of nerve tissues.

Jing et al created multidomain peptide nanofiber hydrogel with sequence K2(SL)6K2, which, after entering the host retinal tissue, triggers an inflammatory response and causes the host cell to infiltrate, followed by the release of a large number of growth factors and cytokines. These growth factors and cytokines are to be diffused into the hydrogel and initiate local vascularization after degradation, thus resulting in innervation.⁶⁶ Soleimannejad et al studied the applicability of fibrin gel as a scaffold for differentiation of conjunctival mesenchymal stem cells into photoreceptor cells using scanning electron microscopy, rheology testing, biodegradation rate determination, and culture of conjunctival mesenchymal stem cells. The results of sem analysis showed that the pore structure of fibrin scaffold was good, conjunctival mesenchymal stem cells combined well in all gels, and there was good compatibility between cells and fibrin gel its physical properties can be easily adjusted to environmental^{67–69} appropriate for photoreceptor cell preparation. The

rheological properties of fibrin gels were measured by rheometer and the biodegradation rate of fibrin was determined for two weeks. The results of these tests show that the elastic modulus and constant degradation of hydrogels contribute to cell growth and proliferation. Compared with the cells cultured on the surface of tissue culture plate, the activity of conjunctival mesenchymal cells cultured on fibrin gel was significantly enhanced and had no cytotoxicity. Good biocompatibility and biodegradability.⁷⁰

Nanomaterials as Gene Delivery Devices to Reprogram Cells for Retinal Regeneration

In addition to these nanoscaffolds, nanomaterials also as gene delivery devices to reprogram cells for ocular regeneration, the first type of non-viral gene nanocarriers investigated for gene delivery for ocular tissue regeneration is liposome-protamine-DNA (LPD) complexes, they better protected the plasmid DNA from enzymatic degradation and offered higher gene expression.⁷¹ Inclusion of cholesterol as a helper lipid could further increase the in vivo transfection efficiency of the LPD nanocarriers with less need of the cationic lipids.⁷² The second type of nanocarriers that have good gene delivery potential is mesoporous nanoparticles that contain pores with diameters between 2 and 50 nm. The porous structure and high surface area of mesoporous nanoparticles enable high gene loading/encapsulation and enhanced transfection,^{73,74} Cao et al found that, based on fluorescent microscopic results, plasmid DNA encoding VEGF-loaded mesoporous iron oxide nanoparticles transfected MSCs better than free plasmid DNA.⁷⁴ Organic-inorganic hybrid nanocrystals are the third type of gene nanocarriers, the hybrid nanocarrier enhanced gene transfection and transgene expression 20 and 3 times, as compared with the non-modified inorganic carbonate apatite nanocrystals and the commercially available Lipofectamine in the mouse embryonic cells, respectively, demonstrating the great potential of the hybrid nanocarriers for stem cell reprogramming.⁷⁵

Conclusions and Future Perspectives

Nanoparticles as a carrier for preventing, monitoring, and treating DR have shown incomparable advantages, such as the early diagnosis, the non-invasiveness in treatment outcome monitoring, carrying therapeutic drugs to smoothly pass through the BRB, assisting therapeutic drugs in targeting to the retina and wrapping therapeutic drugs to avoid contact with other tissues in

the eye. Although the development of nanomedicine and the clinical application of nanomaterials is still in the initial stage, the potential of nanotechnology is to be further utilized with the progress of research. However, before clinical trial application, each aspect of nanocarriers, whether it is of safety research, pharmacokinetics, or pharmacodynamics, shall be treated with caution to avoid additional damage to the eye. Further research on nanocarrier-based individualized therapies, for developing nanocarriers with different properties to carry therapeutic drugs is of great interest for the implementation and development of personalized medicine.

Statement of Ethics

This article does not contain any studies with human or animals performed by any of the authors.

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest for this work.

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