Clinical Ophthalmology

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REVIEW

Revolutionizing Retinal Therapy: The Role of Nanoparticle Drug Carriers in Managing Vascular Retinal Disorders

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Abstract: Vascular Retinopathy (VR), such as diabetic retinopathy, pose significant challenges to vision and overall health. Traditional treatment methods often face limitations in efficacy and delivery. Vascular retinopathy is a common and potentially blinding group of eye diseases with core pathologic mechanisms involving vascular injury, ischemia, exudation, and neovascularization. Clinical management relies heavily on etiologic control (eg, diabetes, hypertension), anti-VEGF therapy, laser therapy, and surgical intervention. Recent advancements in nanotechnology have led to the development of innovative nanoparticle drug carriers, which offer promising solutions for targeted and sustained drug delivery in the retinal environment. This review explores the application of both conventional and novel nanoparticle carriers in treating VR. We discuss various types of nanoparticles, including liposomes, polymeric nanoparticles, and metal-based carriers, highlighting their unique properties, mechanisms of action, and therapeutic benefits. Finally, we provide insights into future perspectives for nanoparticle-based therapies in retinal disorders, emphasizing the potential for improved patient outcomes and the need for further research to optimize these advanced drug delivery systems.

Keywords: vascular retinopathy, retinal therapy, nanoparticle, drug carriers, mechanism

Introduction

VR refers to retinal dysfunction due to retinal vasculopathy, which mainly includes diabetic retinopathy, hypertensive retinopathy, venous obstructive retinopathy, and central retinal artery obstruction. As an example, Diabetic Retinopathy (DR) is one of the most common complications of diabetes and the leading cause of blindness in adults.[1–3] The pathogenesis of DR primarily involves hyperglycemia-induced retinal microvascular injury, which manifests as vascular endothelial cell damage, basement membrane thickening, vascular occlusion, and neovascularization. As the disease progresses, retinal vascular leakage, capillary occlusion, and retinal edema may occur. Among these, proliferative diabetic retinopathy (PDR) results in the formation of neovascularization in the retina due to hypoxia.[4,5] These new vessels are fragile and easily broken, leading to vitreous hemorrhage and tensor retinal detachment, which are the main causes of blindness due to diabetes.

Since vascular retinopathy has a variety of causes, this creates many difficulties in treatment. Although laser photocoagulation is commonly used in the treatment of diabetic retinopathy and venous obstructive retinopathy, it can lead to side effects such as visual field defects and night blindness.[6–8] Anti-VEGF drug injections are the mainstay of treatment for retinal neovascularization and macular edema, but they require repeated injections, increasing the risk of infection and vitreous hemorrhage.[9,10] On the other hand, the eye has multiple barriers (eg, corneal, blood-retinal barrier) that limit effective drug delivery and absorption.[11,12] Traditional ophthalmic medications, such as eye drops or oral medications, often have difficulty in reaching effective retinal concentrations, compromising therapeutic efficacy. Intravitreal injections, despite their direct effect on the retina, are more invasive and prone to complications and patient discomfort.

Received: 6 November 2024
Accepted: 31 March 2025
Published: 15 May 2025

Nanoparticles are defined as particles between 1–100 nm in diameter made from organic/inorganic materials, and a nanoparticle delivery system is the combination of such particles with a therapeutic agent.[13] As nanomedicine becomes safer and more functional, nanotechnology has emerged as a promising field of medicine, offering innovative solutions for drug delivery, diagnosis and treatment.[14]

Nanoparticles are ideal candidates for targeted drug delivery due to their unique properties such as small size, large surface area to volume ratio, and tunable surface chemistry. Nanoparticles can encapsulate drugs and deliver them to specific tissues or cells within the eye, thereby increasing drug efficacy and reducing side effects. In addition, nanoparticles can be engineered to have specific optical, magnetic or thermal properties that can be used in imaging and therapeutic applications.[15,16]

As an emerging drug delivery technology, nano-delivery system overcomes many limitations of traditional therapeutic methods and shows significant advantages. Nanoparticles can effectively penetrate the eye barrier, ensuring efficient drug delivery and absorption at the retinal site. Modification and functionalization of the nanoparticle surface can enhance its targeting and reduce the distribution of the drug in other sites, thus reducing systemic side effects.[13,17] In addition, it is able to realize the slow release and sustained release of the drug, and to reduce the frequency of drug administration by protecting the drug from metabolic degradation, thus reducing the burden of treatment on patients.[18] And many carriers have good biocompatibility and degradability, which reduces local and systemic adverse effects, especially the combined delivery of multiple drugs, providing an integrated therapeutic regimen and improving therapeutic efficacy.[19] These advantages have made nanoparticle drug delivery systems a hot research topic and look forward to further development in developing applications in combination with emerging therapeutic options such as gene therapy.

In recent years, there has been increasing interest in utilizing nanotechnology to enhance the treatment of vascular retinal diseases. The use of nanomaterials in ophthalmology has shown great potential in the treatment of vascular retinal diseases, such as diabetic retinopathy, hypertensive retinopathy and retinal arteriovenous occlusion, which are major causes of vision impairment and blindness worldwide.[20,21] Studies have shown that nanomaterials such as gold nanoparticles and polymer nanoparticles have the potential to improve the delivery of anti-angiogenic drugs, reduce retinal inflammation, and inhibit abnormal blood vessel growth.[22–25] Despite these advances, nanomedicine still faces challenges in the clinical translation of vascular retinal diseases. Issues of biocompatibility, long-term safety, and regulatory approval need to be addressed to ensure the successful application of nanotechnology in ophthalmology.[26] Further research is also needed to optimize the design and functionality of nanomaterials for specific retinal applications.

In this review, we outline the current progress and challenges in applying nanotechnology to the treatment of vascular retinal diseases. We discuss the fundamentals of nanomaterial-based drug delivery, highlight recent advances in nanomedicine for the treatment of vascular retinal diseases, and outline future research directions in this exciting field.

Current Status of Treatment of Vascular Retinopathy

There are many challenges in the treatment of vascular retinopathy (eg, diabetic retinopathy, retinal vein occlusion, etc). One of the most critical steps is how to cross the blood-retinal barrier to deliver the drug to the retina. Retinal capillary endothelial cells form the inner barrier and retinal pigment epithelial cells form the outer barrier, which together form the blood-retinal barrier.[28] It plays an irreplaceable role in preventing the invasion of harmful substances and maintaining intraocular homeostasis.[29] (Figure 1) Because the retina is located at the back of the eye, the blood-retinal barrier makes it difficult to reach the drug by systemic administration, requiring local injections, such as intravitreal injections.[30] However, this method needs to be repeated, which increases the risk of infection and retinal detachment, as well as the inconvenience of frequent injections, which affects compliance.[31] In addition, anti-VEGF drugs may cause side effects such as intraocular inflammation and elevated intraocular pressure, and tolerance may develop with long-term use, with individual differences in response to treatment between patients.[32] Frequent injections and high drug costs also place economic pressures on patients and healthcare systems. To address these challenges, researchers and clinicians are exploring new drug delivery methods and therapeutic strategies, including long-acting injections, drug slow-release systems, gene therapy, and novel drug targets, with the aim of improving treatment outcomes, reducing treatment frequency, and enhancing patients' quality of life.

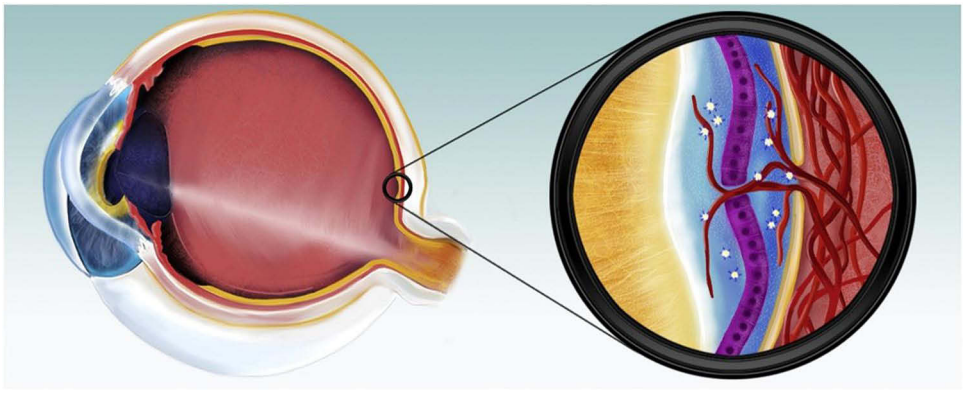

Figure 1 Diagram of the blood-eye barrier. Reprinted from *Eur J Pharm Biopharmaceut*, volume 95(Pt B), Hennig R, Goepferich A. Nanoparticles for the treatment of ocular neovascularizations. 294–306. Copyright © 2024, with permission from Elsevier B.V.[27]

Nanotechnology has emerged as a promising field in ophthalmology, offering innovative solutions for the diagnosis and treatment of various ophthalmic diseases.[33,34] Nanomaterials, with their unique properties and wide range of applications, show great potential in addressing the limitations of conventional ophthalmic therapies.[35]

One of the main applications of nanomaterials in ophthalmology is drug delivery. Nanoparticle-based drug delivery systems enable targeted and sustained release of therapeutic drugs, improve drug bioavailability and reduce the number of drug administrations.[36] For example, liposomal formulations of anti-inflammatory drugs developed by Xia et al have been shown to have excellent anti-inflammatory effects against ocular surface diseases such as dry eye.[37]

In addition to drug delivery, the functionality of nanomaterials in diagnostics and imaging is being explored.[38] Nanoparticles can be functionalized with targeted ligands and imaging agents to enable precise visualization of tissues and structures and have been well established in the diagnosis of tumors.[39,40] Gold nanoparticles developed by Anderson et al successfully targeted enhancement of MRI signal intensity in rabbit corneal neovascularization.[41] This raises the possibility of using nanoparticles in the early diagnosis of ophthalmic diseases. In addition, the potential of nanomaterials for regenerative medicine and tissue engineering in ophthalmology is being investigated. Scaffold-based approaches using nanofibrous materials have shown promise in promoting corneal and retinal tissue regeneration, providing new avenues for the treatment of corneal injury and retinal degenerative diseases.[42,43]

Despite these advances, challenges remain for the clinical application of nanomaterials in ophthalmology. Issues of biocompatibility, safety and long-term efficacy need to be addressed to ensure the successful application of nanotechnology in clinical practice. Nonetheless, ongoing research and development in this field holds great promise for improving the diagnosis and treatment of eye diseases, which will ultimately lead to better visual outcomes for patients.

Nanoparticle Drug Delivery Systems

Nanotechnology has revolutionized drug delivery by providing new ways to improve efficacy and reduce side effects.[44] At the heart of these advances are nanoparticles, which are particles between 1 and 100 nanometers in size. 这These nanoparticles have unique properties that make them ideal for drug delivery applications. The rationale for using nanoparticles for drug delivery lies in their ability to encapsulate drugs and deliver them to specific targets in the body.[45] This can be achieved through a variety of mechanisms, including passive targeting and active targeting. Passive targeting utilizes enhanced permeability and retention effects, which preferentially accumulate nanoparticles in tumor tissue due to vascular leakage and poor lymphatic drainage.[46] This phenomenon is particularly applicable to drug delivery to solid tumors, for which conventional drug delivery systems have limited efficacy.[47,48] On the other hand, active targeting involves modifying the surface of the nanoparticle with a ligand that allows it to bind to a specific receptor on the target cell.[49,50] This improves the specificity of drug delivery and reduces off-target effects. Common ligands used for active targeting include antibodies, peptides and aptamers.[50,51]

Nanoparticles can be classified into several categories based on their composition, structure and properties, which include polymer nanoparticles, liposomes, nucleic acid nanoparticles, inorganic non-metallic nanoparticles and metallic

nanoparticles. Each type of nanoparticle has its own advantages and limitations depending on the intended application. In addition to being able to deliver drugs to specific targets, nanoparticles can also release drugs in a controlled manner. This can be accomplished by incorporating stimuli-responsive materials into the nanoparticle matrix that respond to external stimuli such as pH, temperature, or light.[52–54] By controlling the release of the drug from the nanoparticles, a sustained concentration of drug can be achieved at the target site, minimizing systemic toxicity and improving therapeutic efficacy.

Polymer Nanoparticles

Poly(Lactic-Co-Glycolic Acid) (PLGA)

PLGA is a copolymer consisting of lactic acid (LA) and glycolic acid (GA) monomers linked by ester bonds, which can be degraded to lactic acid and glycolic acid by hydrolysis.[55] Since these metabolites can be metabolized by the body and excreted, PLGA has good biocompatibility, so PLAG was used as a raw material for biodegradable sutures in the early days.[56] In addition to this, lactic acid has been shown to have a neuroprotective effect on the retina, a harmless and beneficial property that makes PLGA an ideal vehicle for retinopathy.[25,57]

The degradation rate of PLGA can be controlled by adjusting the ratio of lactic acid to glycolic acid, and in general the higher the glycolic acid content the faster the degradation rate.[58] By varying the ratio of lactic to glycolic acid, the degradation rate of PLGA can vary from days to months to accommodate different drug release requirements.[59] On the other hand, PLGA nanoparticles also have physical properties that can be adjusted according to molecular weight, such as solubility, crystallinity, and mechanical strength. This allows PLGA to protect drugs from the in vivo environment. Therefore, PLGA nanoparticles can be efficiently loaded with a variety of drugs, including small molecule drugs, proteins, peptides and nucleic acids.[60]

Due to its excellent tunable biological and physical properties, PLGA is often used as a sustained-release carrier for drugs with short half-lives that require long-term administration. For example, in a study by Zhang et al PLGA nanoparticles (PEDF34-NP) encapsulating pigment epithelium-derived factor (PEDF) exhibited significant amelioration of retinal leakage and inflammation in diabetic rats and were shown to be free of any measurable toxicity (Figure 2).[61] This mechanism of sustained release provided by PLGA nanoparticles enables PEDF to maintain its efficacy in the vitreous for at least 4 weeks, reducing the need for frequent injections. It was also found that PEDF significantly reduced VEGF and ICAM-1 expression in diabetic retinopathy (DR) and ischemic retinopathy, thereby reducing retinal inflammation and vascular leakage. In addition, the modification of PLGA nanoparticles has become a new research hotspot. Numerous researchers have verified that chitosan-coated PLGA can effectively prolong the adhesion ability of nanoparticles and promote the controlled delivery of drugs, thus improving the bioavailability of drugs.[62–65] cRGDyK peptide (RGD)-modified PLGA nanoparticles have been investigated and applied by several scholars for tumor therapy targeting VEGF.[66,67] Because VEGF is also an important targeting target in VR pathology, this provides a new idea for the targeted modification of PLGA in VR therapy. The overall stability of this surface-modified PLGA nanoparticle drug delivery system are greatly improved, which supports it as an excellent potential therapeutic system for the treatment of vascular retinopathy.[68,69]

Polyethylene Glycol (PEG)

PEG nanoparticles have emerged as a multifunctional platform in biomedical applications, especially in drug delivery systems. Polyethylene glycol (PEG) nanoparticles are widely used in cancer therapy, for example, PEGylated liposomal adriamycin (Doxil) has been successfully used in the treatment of Kaposi's sarcoma and ovarian cancer by enhancing the accumulation of the drug at the tumor site and reducing side effects.[70,71] In addition, PEG nanoparticles can be used to deliver antibiotics, such as vancomycin delivered via PEG nanoparticles, which significantly improves the stability and antibacterial effect of the drug and effectively treats drug-resistant bacterial infections.[72] PEG is a hydrophilic polymer known for its excellent biocompatibility, low immunogenicity and diverse chemical properties, making it an ideal material for nanoparticle preparation. Because PEG nanoparticles are highly biocompatible and material stable, this prolongs their circulation time in the bloodstream.[73] The hydrophilic nature of PEG confers excellent water solubility and the ability to form stable colloidal dispersions in the aqueous phase, thereby enhancing the bioavailability of hydrophobic drugs. The surface chemistry of PEG allows for the introduction of various functional groups and ligands that facilitate

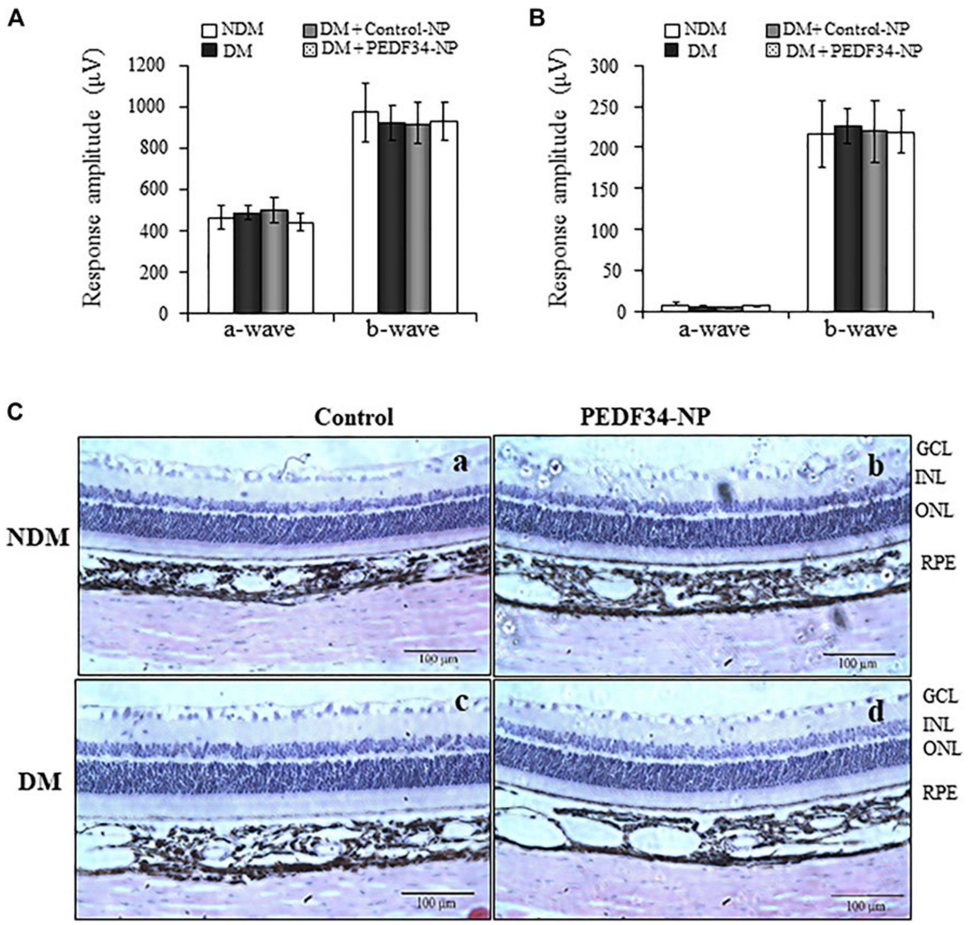

Figure 2 No changes in ERG response and retinal histology in response to PEDF34-NP injection. Scotopic and photopic ERG were recorded from six rats at 4 weeks after the intravitreal injection of PEDF34-NP and Control-NP as indicated. Amplitudes of a- and b-waves from scotopic (**A**) and photopic (**B**) ERG were averaged and compared (mean ± SD, n = 6). (**C**) Representative images of retinal section stained with H&E from non-diabetic rats (a), non-diabetic rats (NDM) injected with PEDF34-NP (b), diabetic rats (DM) (c), and diabetic rats injected with PEDF34-NP (d). Reprinted from Qu Q, Park K, Zhou K, et al. Sustained therapeutic effect of an anti-inflammatory peptide encapsulated in nanoparticles on ocular vascular leakage in diabetic retinopathy. *Front Cell Develop Biol.* 2022;10:1049678. Creative Commons.[61]

targeted drug delivery.[74] Therefore, PEG nanoparticles are often used to carry water-insoluble drugs such as apatinib which is a insoluble VEGFR-2 inhibitor exerts antiangiogenic effects. In the study by Suh et al, a PEG-coupled nanoparticle made of human serum albumin was developed to carry apatinib for the treatment of diabetes-induced retinal vascular disease and was demonstrated to have an excellent slow-release effect.[75] (Figure 3).

On the other hand, the synthesis of PEG nanoparticles allows a precise control of their size and shape, which is essential to influence biodistribution, cellular uptake and penetration of biological barriers. The PEG-loaded system prolongs the circulation time of the drug in the body and reduces the conditioning effect and clearance by the mononuclear phagocyte system.[76,77] These nanoparticles also exhibit high drug loading capacity, achieved by physical encapsulation, covalent binding, or adsorption, and are designed to degrade to non-toxic by-products, reducing long-term accumulation and potential toxicity.The biocompatibility of the PEG material ensures virtually no adverse reactions and toxicity in ocular tissues, and its ability to degrade to non-toxic by-products further enhances safety.[78] Taken together, these properties suggest that PEG nanoparticles could provide a novel and effective approach for the treatment of vascular retinopathy and improve the efficacy of ophthalmic therapies.

It is worth mentioning that PEGylated PLGA nanoparticles have also been developed for the treatment of retinal diseases.[79,80] These nanoparticles have longer circulation time and targeted delivery capabilities, and the presence of PEG increases their water solubility and reduces immune clearance, while PLGA can link various targeting molecules to enhance targeted therapeutic effects. In addition, PEG-PLGA nanoparticles are physically and chemically stable in

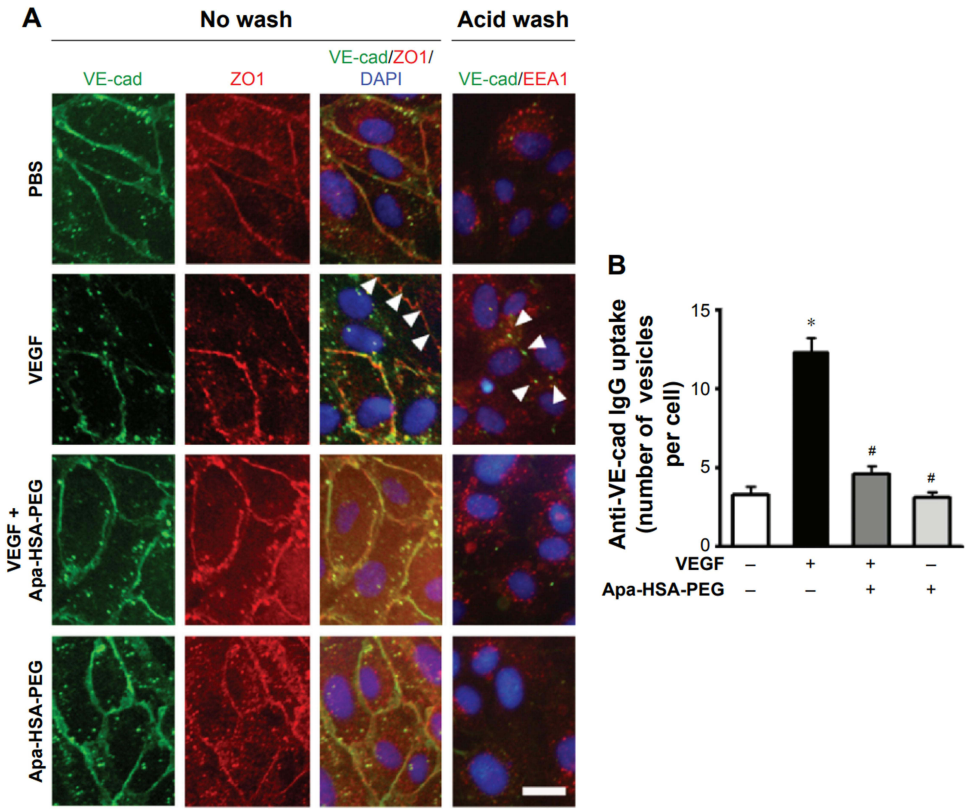

Figure 3 Apa-HSA-PEG nanoparticles prevent VEGF-induced internalization of VE-cadherin. Reprinted with permission from Dove Medical Press. Jeong JH, Nguyen HK, Lee JE, Suh W. Therapeutic effect of apatinib-loaded nanoparticles on diabetes-induced retinal vascular leakage. *Int j Nanomed*. 2016;11:3101–3109, reprinted by permission of Informa UK Limited, trading Taylor & Francis Group https://www.tandfonline.com.[75]

Notes: (**A**) Representative immunofluorescent images of VE-cadherin. (**B**) Quantification of internalized VE-cadherin in HRMECs (means ± SEM, *P<0.05 vs PBS, #P<0.05 vs VEGF, n=4). Arrowheads in the no wash image indicate the disappearance of VE-cadherin (green) at endothelial junctions that were stained positively for anti-ZO1 IgGs (red). Arrowheads in the acid wash image indicate internalized VE-cadherin (green) in endosomes that were stained positively for EEA1 (red). Nuclei are shown in blue (DAPI). Scale bars =25μm.

Abbreviations: Apa-HSA-PEG, apatinib-loaded human serum albumin-conjugated polyethylene glycol; EEA1, early endosome antigen 1; VEGF, vascular endothelial growth factor; VE, vascular endothelial; HRMECs, human retinal microvascular endothelial cells; SEM, standard error of the mean; PBS, phosphate-buffered saline; rhVEGF, recombinant human VEGF; DAPI, 4′,6-diamidino-2-phenylindole; VE-cad, VE-cadherin.

different environments, are less likely to aggregate or precipitate, and can be chemically modified to introduce a variety of functionalities to further expand their applications.

Nucleic Acid Nanoparticles

Nucleic acid nanoparticles show remarkable potential in vascular retinopathy therapy, especially in gene regulation and drug delivery. Its high stability, biocompatibility and programmability enable it to load siRNAs to target and inhibit genes associated with angiogenesis (eg, VEGF), effectively inhibiting abnormal angiogenesis.[82–84] Among them, Tetrahedral framework nucleic acid (tFNA) material has attracted much attention as a DNA nanomaterial. Nucleic acid tetrahedrons allow for targeted delivery of anti-angiogenic drugs, increasing drug concentration at the lesion site and reducing systemic side effects.[85] Its efficient cell penetration allows it to provide non-invasive therapy through localized application. In a study by Mao et al tFNAs loaded with doxorubicin were shown to be able to penetrate the extravasated blood-retinal barrier and to accomplish sustained administration for three days.[81] (Figure 4) This result is certainly exciting because drug delivery systems that can penetrate the blood-retinal barrier are important for minimally or noninvasive treatment of retinopathy.[86] Tetrahedral framework nucleic acid (TFNA) has great potential for application in vascular retinopathy, especially in targeted drug delivery and molecular recognition. However, its clinical application still faces several challenges. Firstly, long-term use may trigger immune reactions or degradation by in vivo enzymes. Second, existing synthesis methods are still complex and costly, which limits the feasibility of their clinical application. Further, the size and morphology of tetrahedral framework nucleic acids may affect their effective delivery deep in the

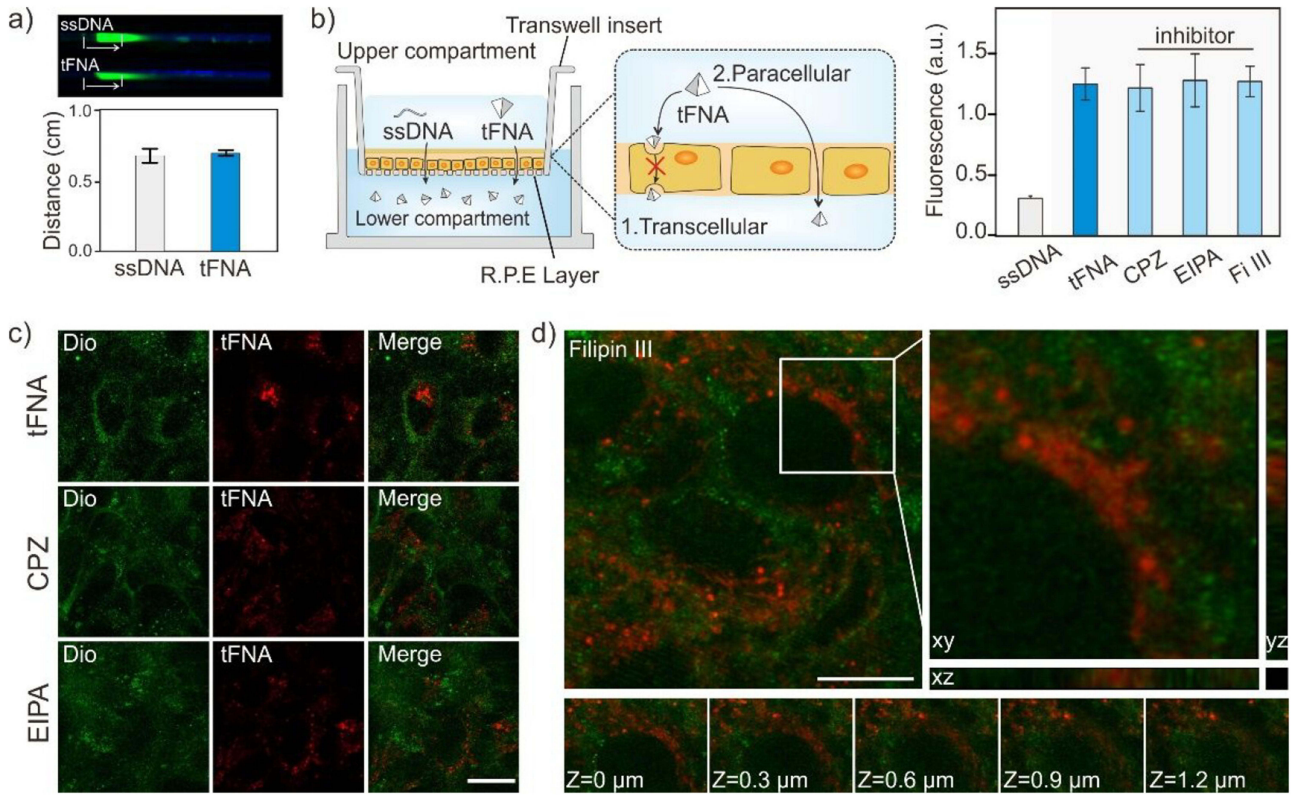

Figure 4 Assessing integrity and penetrability of tFNA in vitro. (**a**) Penetration-rate fluorescence image of tFNA and ssDNA in agarose gel. (**b**) Schematic illustration of the in vitro RPE model using a transwell system to evaluate the penetrability of ssDNA and tFNA, and histogram results of the fluorescence in the lower chamber after tFNA penetrating the RPE model. (**c**) Confocal images of an internalized Cy5- tFNA particle (red), colocalized with DiO-labeled lipid (green), with CPZ and EIPA, respectively. Scale bar: 25 μm. (**d**) Reconstructed 3D images of a DiO-stained cell incubated with Cy5- tFNA and Filipin III for 6 h. Scale bar: 25 μm. Reprinted with permission from Wang R, Liu Y, Xiao W, et al. Framework Nucleic Acids as Blood-Retinal-Barrier-Penetrable Nanocarrier for Periocular Administration. *ACS Appl Mater Interfaces*. 2023;15 (1):541–551. Copyright © 2022 American Chemical Society.[81]

fundus, especially in the retinal and choroidal regions. Therefore, despite the great potential of tetrahedral framework nucleic acids, a series of technical challenges, such as their stability, delivery efficiency, and production cost, need to be solved in order for them to be used in the clinical treatment of vascular retinopathy.

Liposomes

Classical liposomes consist of one or more phospholipid bilayers encapsulating an aqueous core. Due to their biocompatibility, ability to encapsulate hydrophilic and hydrophobic drugs, and potential for targeted delivery, they have received much attention in drug delivery systems.[87] Liposomes consist of naturally occurring phospholipids that are biocompatible and biodegradable, reducing the risk of toxicity.[88] Its unique structure allows for encapsulation of hydrophilic drugs within an aqueous core and hydrophobic drugs within a lipid bilayer, enabling simultaneous delivery of multiple drugs with different solubility characteristics. By adjusting the composition and fluidity of lipid membranes, liposomes allow for controlled and sustained drug release, helping to maintain therapeutic drug levels for extended periods of time and reducing the frequency of administration.[89] In addition, liposomes can be modified with targeted ligands for specific delivery to target tissues or cells, minimizing off-target effects and increasing drug concentrations at disease sites.[90,91] Encapsulation within liposomes protects the drug from degradation by enzymes and other biological processes, improving stability and bioavailability.

Although the use of liposomes in many diseases has been extensively studied, unfortunately there is still a lack of direct studies to demonstrate the therapeutic effects in vascular retinopathy. However, the therapeutic effects of liposomes in other diseases of ophthalmology are exciting. For example, Wang et al developed a liposome that inhibits corneal neovascularization by selectively inhibiting iron prolapse, and this study demonstrated the significant efficacy of liposomes in treating corneal neovascularization.[92] This provides a solid theoretical basis for liposome therapy for vascular retinopathy, but more research is still needed.

https://doi.org/10.2147/OPTH.S503273

Solid Lipid Nanoparticles (SLN)

SLN are a widely studied nanocarrier system consisting of solid lipids that can be tolerated by the body for drug delivery and protection of bioactive substances. Unlike the closed vesicular structure of liposomes, SLN does not have a cavity but a multilayered core structure. Such nanoparticles with both a gel core and a lipid shell have been widely demonstrated to have excellent loading capabilities for hydrophilic small molecule drugs. SLN is suitable for ocular drug delivery due to its simple preparation method, good biocompatibility and degradability, and the ease with which it can cross biological barriers.[93,94] Meanwhile, the solid structure of SLN ensures the stability of the drug and has a long retention time, which helps to prolong the action of the drug at the local level.[95] By adjusting its particle size, surface properties and encapsulation of the drug, SLN can achieve slow release and targeted release of the drug, thus increasing the concentration of the drug at the lesion site without affecting the eyesight.[96] Therefore, SLNs are often used to load drugs that have gastrointestinal toxicity or are capable of causing systemic reactions in order to mitigate side effects and prolong drug retention time.[97] For example, Ramadan et al successfully developed vildagliptin-loaded SLNs, which achieved enhanced drug retention time and stability while improving respiratory infection and diarrhea responses to oral vildagliptin, and optimized the drug loading rate and release rate of the SLNs by double-emulsion/melt dispersion technology. Load and release rates of SLN were optimized by double-emulsion /melt dispersion technology.[98] Delivery of hydrophilic small molecule drugs to the retina using SLN has gained widespread attention[99,100]. For example, in one study, researchers encapsulated sunitinib as a solid up to nanoparticles via vitreous injection to treat vascular retinal disease with good results and demonstrated no toxicity.[101] In addition to this, SLN has good stability and long retention time, which helps to improve drug bioavailability and therapeutic efficacy. Therefore, the use of SLN to piggyback miRNAs or siRNAs, etc. for the purpose of gene silencing also has a wide range of application prospects.[102] SLN nanoparticles loaded with siRNA/miRNA have been well studied and developed in tumor therapy. For example, a study by Liu et al indicated that cationic solid lipid nanoparticles (SLN) delivering microRNA-200c (miR-200c) in combination with paclitaxel-loaded nanostructured lipid carriers (NLC/PTX) inhibited tumor cell resistance while significantly enhancing the cytotoxicity of paclitaxel against breast cancer stem cells.[103] Because RNA activity in the body is difficult to maintain in order to reach target tissues, the traditional method is to use viral vectors to infect cells for the purpose of delivering genetic material. However, due to the cost and technical difficulties, it is difficult to be widely used, so the use of SLN to carry nucleic acids has become a new alternative.[104] Research on the delivery of nucleic acid drugs such as siRNAs and plasmids to the retina using SLNs has been progressing at a rapid pace.[105,106]

Although SLN drug-carrying systems have many advantages, they also have some major disadvantages. First, the drug loading capacity is limited, especially for hydrophobic drugs.[107] Secondly, it is less stable and susceptible to oxidation, dissociation and aggregation in vivo and ex vivo, and this structural instability affects drug release and therapeutic efficacy.[108] In addition, in terms of distribution in the body, SLN may be unevenly distributed, resulting in excessive drug concentrations in some tissues or organs and inadequate concentrations in other sites.[109] But even so, SLN still has the potential to treat vascular retinopathy from its good biocompatibility and specific drug delivery ability.

Metal Nanoparticles

Gold Nanoparticles (AuNPs)

Gold nanoparticles are of interest as drug carriers in the treatment of vascular retinopathy.[24,110,111] These nanoparticles have unique physical, chemical and optical properties that make them potential drug delivery systems. AuNPs can achieve targeted drug delivery through surface modification, increase the local concentration of drugs at the lesion site, and reduce systemic side effects. In addition, gold nanoparticles can be utilized for optical imaging and photothermal therapy in diagnostic and therapeutic procedures by utilizing their properties such as Surface-Enhanced Raman Scattering (SERS).[112–115] By modulating the shape, size and surface properties of nanoparticles, slow and controlled release of drugs can be achieved, thereby improving therapeutic efficacy and reducing drug side effects.

Excitingly, gold nanoparticles have been reported to inhibit VEGF-induced retinal neovascularization with favorable results.[22] In addition to this, Penn developed gold nanoparticles targeting Vascular cell adhesion molecule 1 antisense hairpin DNA functionalization, enabling the monitoring and prediction of retinal microvascular endothelial cell toxicity.[116] (Figure 5) This demonstrates the great potential of gold nanoparticles in the treatment of vascular retinopathy,

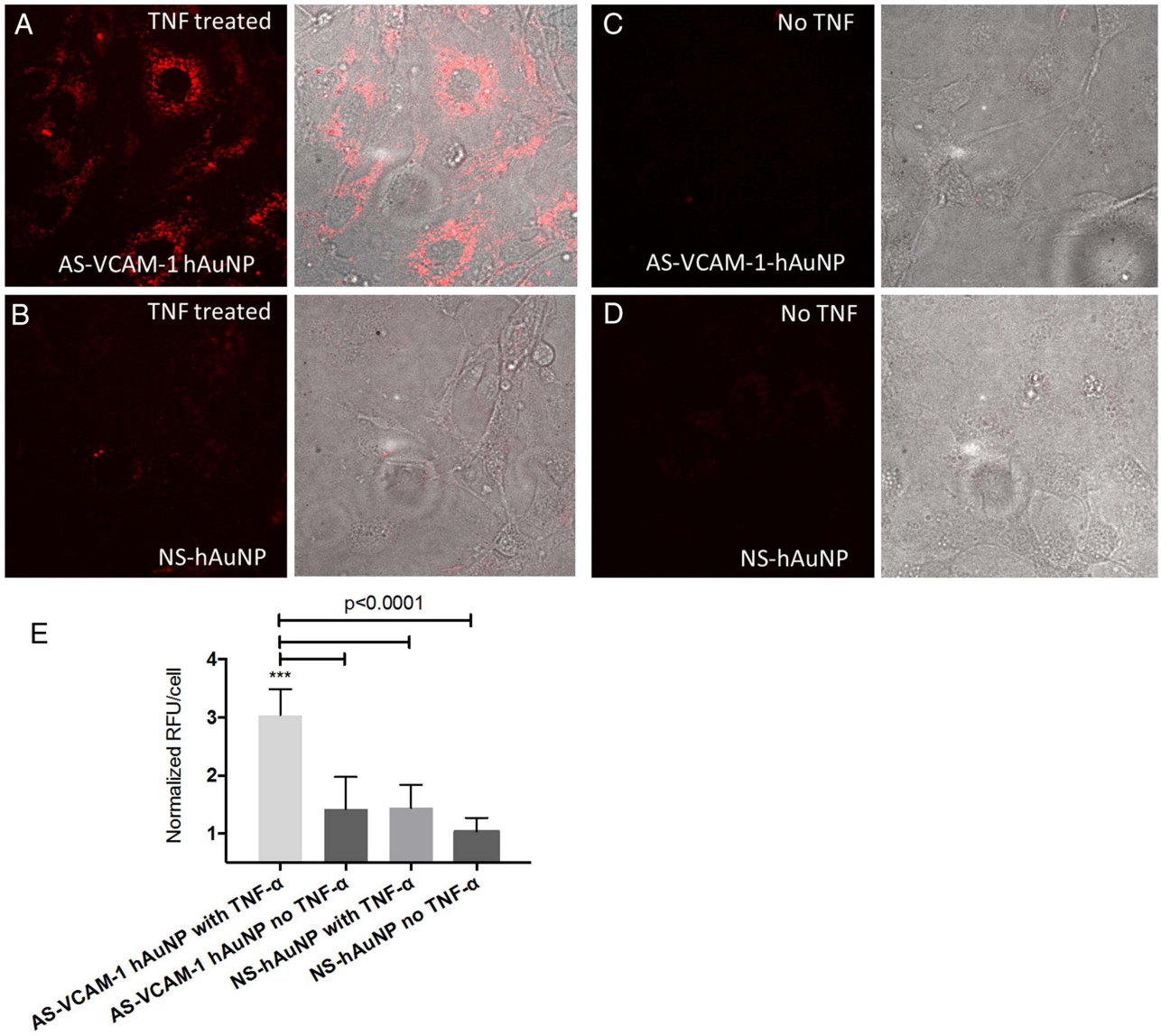

Figure 5 Confocal imaging of live MRMECs treated with AS-VCAM-1 hAuNP and NS hAuNP. Cells were cultured on microscope slides and treated with TNF-α or vehicle plus AS-VCAM-1 hAuNP or NS hAuNP in complete growth medium. After a 6-h incubation, these media were aspirated and fresh medium was added to each culture. The cells were imaged using confocal microscopy. (**A**) Strong fluorescence emission was only detected in TNF-α-activated MRMEC treated with AS-VCAM-1 hAuNP. (**B–D**) Only minimal fluorescence was detected in the other cultures. (**E**) Fluorescence intensity is expressed in relative fluorescence units (RFU) per cell over different treatment groups as measured using ImageJ software. *** represent p-value <0.001. Reprinted from *Nanomed Nanotechnol Biol Med*. Volume 14, Uddin MDI, Jayagopal A, Wong A, McCollum GW, Wright DW, Penn JS. Real-time imaging of VCAM-1 mRNA in TNF-α activated retinal microvascular endothelial cells using antisense hairpin-DNA functionalized gold nanoparticles. 63–71. Copyright ©2024, Elsevier B.V.[116]

opening new avenues for innovative retinopathy therapeutic strategies by utilizing their metallic properties to enable disease-associated small-molecule monitoring, in addition to their use as traditional drug carriers.[117,118]

Silver Nanoparticles (AgNPs)

Silver nanoparticles show potential advantages as drug carriers in the treatment of vascular retinopathy. Its antimicrobial and antioxidant properties are effective in preventing and managing infectious complications and reducing retinal damage from oxidative stress.[119,120] In addition, silver nanoparticles have optical properties that can be used in optical imaging and photothermal therapy to improve therapeutic efficacy.[121] Through surface modification, silver nanoparticles can achieve targeted delivery and controlled release of drugs, thus increasing the local concentration of drugs at the lesion

https://doi.org/10.2147/OPTH.S503273

site and reducing systemic side effects. Silver nanoparticles have good biocompatibility and stability, which helps to improve the bioavailability and therapeutic effect of drugs.

Due to the unique biological properties of silver nanoparticles, in addition to piggybacking on the drug it has good anti-inflammatory and anti-infective properties in its own right.[122,123] As early as 2010, Sheikpranbabu et al showed that silver nanoparticles had a significant inhibitory effect on advanced glycation end-products (AGEs)-mediated vascular retinopathy.[124] These recent findings provide solid support for the use of silver nanoparticles in vascular retinopathy.

Magnetic Nanoparticles

Magnetic metal nanoparticles offer unique advantages as drug carriers in the treatment of vascular retinopathy. These nanoparticles combine the magnetic and nanoscale effects of metals with good biocompatibility and stability.[125] By precisely controlling the morphology, size and surface properties of nanoparticles, slow and controlled release of drugs can be achieved, thereby improving therapeutic efficacy and reducing drug toxicity.[126,127] Using an external magnetic field, magnetic metal nanoparticles enable targeted drug delivery, increasing the local concentration of the drug in the lesion area while reducing the adverse effects on the surrounding tissues.

It is worth mentioning that magnetic metal nanoparticles can also be applied to magnetic resonance imaging (MRI) for precise localization and monitoring of lesions. In a study conducted by Rotenstrich et al, fluorescent iron oxide (IO) nanoparticles (NPs) were administered via suprachoroidal injection into a rat model of retinal degeneration and subsequently evaluated by magnetic resonance imaging (MRI), enabling the assessment of nanoparticle stability and localized enrichment within the target tissue.[128] MRI can track nanoparticles injected into the back of the eye, demonstrating the potential use of MRI for translational studies in animals and future clinical studies. There are also retrospective studies pointing out that these functionalized magnetic NPs have significant therapeutic effects on vascular retinopathy and could be used in future translational and clinical studies to prolong the release of drug delivery in the fundus.[129]

Inorganic Non-Metallic Nanocarriers

Inorganic non-metallic nanomaterials have shown significant value as drug carriers in the field of medicine. These materials include carbon nanomaterials and silicates with excellent biocompatibility and chemical stability.[130,131] Their surfaces are easily modified for targeted delivery and controlled release of drugs. Due to their large specific surface area and porous structure, these materials can efficiently carry and release drugs. In addition, some of the inorganic non-metallic nanomaterials have excellent optical, magnetic or acoustic properties, which can be applied to bio-imaging and therapeutic monitoring. However, there are few reports on inorganic nonmetallic nanocarriers for the treatment of vascular retinopathy, so in the following we have reviewed the inorganic nonmetallic nanocarriers that have the most potential for application in vascular retinopathy.

Carbon Nanomaterials

Carbon Nanotubes (CNTs)

Carbon Nanotubes (CNTs) have a wide range of applications in various diseases, and are expected to be used clinically as drug carriers and contrast agents, and also show potential applications in the treatment of vascular retinopathy. Chen et al showed that Multiwalled carbon nanotubes (MWCNTs) were able to inhibit angiogenesis by disrupting the formation of human umbilical vein endothelial cells (HUVECs) and their cell migration ability.[132] In addition, a novel Carbon Nanotube Polymer Scaffolds have also been developed by combining carbon nanotubes (CNTs) and poly(lactic-co-glycolic acid) (PLGA), which can be loaded by human- induced pluripotent stem cells for the purpose of retinal ganglion cell regeneration.[133] This indicates the safety and versatility of CNTs in the fundus microenvironment, which provides new ideas for their use in vascular retinopathy.

Graphene

Graphene, as a novel two-dimensional nanomaterial, exhibits a wide range of applications in the medical field, especially in the treatment of vascular retinopathy, which has potential applications. Graphene has many excellent properties, including high specific surface area, excellent electrical and thermal conductivity, excellent mechanical properties, and

good biocompatibility, which provide a good basis for its applications in drug delivery, bioimaging, tissue engineering, and biosensing.[134,135]

In the treatment of vascular retinopathy, graphene can be used as a drug carrier to achieve slow and controlled release of drugs by adsorption or embedding of drugs, to increase the local concentration of drugs in the lesion site and to reduce systemic toxicity and side effects. In addition, graphene can also realize targeted delivery of drugs through surface modification to improve the therapeutic effect. Some researchers have used Graphene Oxide (GO) as a drug carrier and immobilized anti-vascular endothelial growth factor (VEGF) siRNA on the surface of graphene to construct a tumor-targeted drug delivery system.[136] This study found that GO-VEGF-siRNA complexes could effectively inhibit abnormal angiogenesis in tumors, thus achieving tumor suppression. In addition, the GO-anti-VEGF complex showed good biocompatibility and low toxicity in vivo, providing a good theoretical basis for its application in vascular retinopathy. Graphene, as a novel nanomaterial, although shows potential application in the treatment of vascular retinopathy, however, due to its still controversial aspects such as safety and toxicity in living organisms, further in-depth research and evaluation of its feasibility and safety in clinical applications are needed.[135]

Porous Silicon Nanoparticles

Porous Silicon Nanoparticles (pSiNPs), as a new type of nanomaterials, show a wide range of applications in the field of medicine, especially in the treatment of vascular retinopathy with potential applications. Porous silicon nanoparticles have the following characteristics: high specific surface area, good biocompatibility, degradability and unique optical properties, which provide a good basis for their applications in drug delivery, bio-imaging and therapy monitoring.[137] The application of porous silicon nanoparticles (pSiNPs) in the treatment of vascular retinopathy has gained significant attention and research. For example, Sailor et al successfully synthesized porous silicon nanoparticles (F-pSiNPs) containing rabbit VEGF-siRNA and injected them into the vitreous humor, and showed that the nanoparticles had significant and non-toxic therapeutic effects on retinal vascular diseases.[138,139] This nanoparticle, which can effectively inhibit retinal neovascularization leakage, also has biodegradability and good biocompatibility, which helps to reduce the potential side effects of long-term use, further validating its promising prospects in clinical applications.[139]

Prospects and Challenges

Controlled Release of Drugs

Nanoparticle drug carrier systems have potential in the treatment of vascular retinopathy, especially in drug controlled release. Nanoparticles can prolong the residence time of drugs in ocular tissues, improve drug bioavailability, and reduce the distribution of drugs in non-targeted tissues, thereby reducing drug side effects.[140–142] However, nanoparticles are complicated to prepare, may cause immune responses, and may lead to cytotoxicity with long-term accumulation.[143] Therefore, future research needs to address these challenges to advance the use of nanoparticle drug carrier systems in the treatment of vascular retinopathy. The development of advanced nanoparticle drug delivery systems capable of controlled and sustained drug release is another area for future research. By incorporating stimulus-responsive materials into the nanoparticles, drug release can be triggered by external stimuli such as pH, temperature or light.[144,145] This approach allows for precise control of drug release kinetics, ensuring optimal efficacy over a longer period of time.

Combination Therapy

Nanoparticle drug delivery systems show remarkable potential in combination therapy for vascular retinopathy, achieving significant therapeutic efficacy through synergistic multidrug action, precise targeted delivery and controlled release.[146] For example, nanoparticles can be loaded with both anti-angiogenic and anti-inflammatory drugs for targeted delivery to retinal lesions, increasing local drug concentrations, reducing systemic side effects, and prolonging drug duration of action, decreasing dosing frequency, and enhancing patient compliance. However, its clinical application faces many challenges, including how to optimize the delivery efficiency of nanoparticles, improve biocompatibility, address the potential toxicity problems accumulated over time, as well as reduce the manufacturing cost and achieve large-scale production.[147] Therefore, further in-depth research and optimization of nanoparticle design and performance, as well as

systematic long-term safety assessment, are needed to promote their clinical translation in the treatment of vascular retinopathy.

Non-Invasive Drug Delivery

Nanoparticle drug delivery systems show significant promise for non-invasive drug delivery in vascular retinopathy. Administering drugs through non-invasive means such as eye drops or ophthalmic gels not only improves patient compliance and reduces discomfort during treatment, but also effectively penetrates the cornea and sclera to deliver drugs precisely to the retinal lesion site, improving drug bioavailability and therapeutic efficacy.[148–150] Nanoparticles enable controlled release of drugs, prolonging the retention time of drugs in ocular tissues and reducing the frequency of administration, thus providing a more sustained therapeutic effect. In addition, by modifying specific ligands on the surface, nanoparticles can achieve targeted delivery, allowing the drug to focus on the diseased area, reducing the impact on healthy tissues and reducing systemic side effects.[151]

However, the clinical application of nanoparticles in non-invasive drug delivery still faces many challenges. First, non-invasive drug delivery is less efficient, and nanoparticles may be limited by barriers in penetrating the cornea and sclera, making it difficult to adequately reach the site of retinal pathology.[152,153] Further optimization of the physical and chemical properties of nanoparticles, such as particle size, surface charge, and hydrophilicity, is needed to improve their ability to penetrate the barrier. Secondly, the stability of nanoparticles in the ocular environment need to be further validated. Nanoparticles may cause localized irritation or adverse reactions, and materials with excellent biocompatibility need to be designed to ensure their safe use in the eye.[154] How to efficiently load drugs in nanoparticles and achieve precise release control still requires in-depth research. The control of drug loading, release rate and release time is crucial for therapeutic efficacy, and the development of nanoparticle designs that enable precise controlled release is needed. Finally, the long-term safety of nanoparticles for ocular use is unclear, and systematic long-term toxicity studies and clinical trials are needed.[155] Long-term accumulation of nanoparticles may trigger potential toxic reactions, and their long-term safety needs to be comprehensively evaluated to ensure their safe application in chronic therapy.

Conclusion

Nanotechnology holds great promise for revolutionizing ophthalmic drug delivery by providing targeted and sustained release therapeutic agents for a variety of ophthalmic diseases. The use of nanomaterials and nanoparticle drug delivery systems has great potential to improve the efficacy of ophthalmic treatments and reduce side effects.

Future developments in nanotechnology will focus on enhancing targeted drug delivery to specific ocular tissues such as the retina, choroid and cornea. By designing surface-modified nanoparticles that recognize and bind to specific receptors or biomarkers on target cells, it will be possible to achieve higher drug concentrations at the desired site of action while minimizing systemic exposure and toxicity. However, the clinical application of nanoparticles in vascular retinopathy still faces challenges in biocompatibility, targeted delivery, and long-term safety, while high R&D costs and production processes limit their widespread dissemination. In order to realize its clinical application, in addition to breakthroughs in efficacy and safety, the challenges of cost control and economic efficiency need to be addressed to ensure its sustainability in medical practice.

Data Sharing Statement

There are no data and no material associated with this manuscript.

Ethics Approval and Consent to Participate

There is no human subject, and this is a review, so there is no need for ethical approval and consent.

Consent for Publication

There are no data in this manuscript, so this is not relevant.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution 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.

Funding

This review was supported by Zhejiang Provincial public welfare fund research project experimental animal project (LGD20H120001) and Jinhua municipal science and technology plan project social development key project (2023-3-114).

Disclosure

The authors declare no competing interest in this work.

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