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Potential in exosome-based targeted nano-drugs and delivery vehicles for posterior ocular disease treatment: from barriers to therapeutic application

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Abstract
Posterior ocular disease, a disease that accounts for 55% of all ocular diseases, can contribute to permanent vision loss if left without treatment. Due to the special structure of the eye, various obstacles make it difficult for drugs to reach lesions in the posterior ocular segment. Therefore, the development of highly permeable targeted drugs and delivery systems is particularly important. Exosomes are a class of extracellular vesicles at 30–150 nm, which are secreted by various cells, tissues, and body fluids. They carry various signaling molecules, thus endowing them with certain physiological functions. In this review, we describe the ocular barriers and the biogenesis, isolation, and engineering of exosomes, as exosomes not only have pharmacological effects but also are good nanocarriers with targeted properties. Moreover, their biocompatibility and immunogenicity are better than synthetic nanocarriers. Most importantly, they may have the ability to pass through the blood–eye barrier. Thus, they may be developed as both targeted nano-drugs and nano-delivery vehicles for the treatment of posterior ocular diseases. We focus on the current status and potential application of exosomes as targeted nano-drugs and nano-delivery vehicles in posterior ocular diseases.

Keywords Exosome · Posterior ocular disease · Targeted nano-drugs · Targeted nano-delivery vehicles

Introduction

The eye is one of the most precious organs of the human body, and it is a unique sensory organ in both anatomy and physiology [1]. The eye is usually divided into the anterior and posterior segments by lens interface. The anterior segment contains the cornea, conjunctiva, pupil, aqueous humor, iris, ciliary body, and lens, taking up about one-third of the eye. And the posterior segment comprises about two-thirds of the eye, including the sclera, choroid, retina, Bruch membrane, vitreous, and optic nerve [2, 3]. At least 2.2 billion people worldwide are visually impaired or blind, according to the World Health Organization. Of all ophthalmic diseases, 55% are posterior ocular diseases, which can lead to permanent vision loss if left without treatment. Posterior eye diseases mainly include age-related macular degeneration (AMD), diabetic retinopathy (DR), uveitis, diabetic macular edema (DME), cytomegalovirus retinitis (CMV), and retinitis pigmentosa (RP) [4–7]. Among them, AMD and DR are considered to be the leading causes of irreversible visual impairment. At present, the conventional treatment of the posterior ocular diseases are vitreous injection and implants [8]. Vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab and ranibizumab are commonly used for the treatment of AMD by vitreous injection. The frequent vitreous injection can cause some risks such as endophthalmitis and retinal detachment, leading to poor patient compliance [9]. Implants overcome many disadvantages of intravitreal injection. However, the risk of surgical procedures and drug deposition may lead to adverse effects [10]. Topical administration can avoid the risk of

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vitreous injections and implants, which is the simplest and most commonly used method.

Due to the special structure of the eye, there are various barriers for the local drug delivery. Various physiological structures and tear turnover result in low drug bioavailability, poor tissue permeability, systemic side effects, and other problems. Traditional delivery systems, such as suspensions, eye drops, and ointments, are rarely regarded as very effective dosage forms for the treatment of posterior ocular diseases [11]. The development of nanotechnology makes it possible to overcome these obstacles. Due to their nanoscale size, nano-delivery systems facilitate drugs through tightly connected cells, thereby enhancing drug permeability and increasing drug bioavailability [12]. Nanomedicines can have the ability to target lesion sites through certain modification materials, which increase drug concentration in the local area [13]. In recent years, many promising nano-preparations have been developed and investigated for drug delivery to the ocular posterior segment, such as liposomes, lipid nanoparticles, polymer nanoparticles, nanoemulsions, nanomicelles, and dendrimers [4, 14]. Various synthetic nanocarriers have been extensively researched and have shown potential therapeutic effects. However, these synthetic nanomaterials can induce unanticipated immune responses and interaction with protein, which may lead to toxicity and therapeutic failure [15–18].

Exosomes, the endogenous nanocarriers, avoid the problems mentioned above. They have the potential to interoperate with receptor cells, specifically, and penetrate tissues while protecting internal cargo from disintegration [19–21]. Recent studies have established that exosomes are able to carry small molecules such as drugs and biomolecules within cells [22]. Compared to synthetic nanocarriers, exosomes isolated from the patient's cells have higher biocompatibility, lower toxicity, and lower immunogenicity [23, 24]. More importantly, exosomes can cross the blood–brain barrier (BBB) [25]. Blood–eye barrier and the BBB have a similar neuroepithelial origin, microstructure, and vascular system and function [26]. The BBB and blood–eye barriers are formed by polarized endothelial cells and epithelial cells and have similar transport proteins [27, 28]. The evidence reveals its potential to penetrate the blood–eye barrier. Exosomes are vesicles of 30–150 nm [29]. A particle size of 20–200 nm is deemed to be the appropriate particle size to pass through the ocular barrier: less than 20 nm is easily cleared by the blood and lymphatic circulation, and more than 200 nm will decrease the permeability [14, 30]. It is obvious that exosomes are within this particle size range. In addition, exosomes carry certain molecules during their synthesis, making them therapeutic.

This review describes the current challenges in delivering drugs to the back of the eye based on the physiological barriers of the eye and summarizes the biogenesis, isolation, and engineering of exosomes. In addition, the review is to discuss the potential opportunities of exosomes including their therapeutic effects and as delivery vehicles in the treatment of posterior eye diseases.

Obstruction of drug administration in posterior ocular disease

Local administration mainly delivers drugs to the posterior ocular tissue through the following three pathways: (i) corneal pathway: The drugs pass through the cornea, into the aqueous humor, lens/iris, vitreous, and eventually into the retina; (ii) conjunctiva-sclera pathway: the drugs pass through the conjunctiva, sclera and then enter the choroid and retina; (iii) other pathways: The drugs penetrate to the systemic cycle by nasolacrimal drainage/corneal capillaries and then reach the retina through the blood–retinal barrier (BRB) [31, 32]. However, various physiological barriers of the eye can lead to low drug bioavailability and difficulty in reaching the lesion site. We briefly discuss the challenges of drug delivery to fundus lesion sites (Fig. 1).

Tear film barrier

The tear film is the outermost membrane of the eye, which is the first barrier. The tear film with a thickness of 3 μm consists of three layers: the outermost layer is a lipid membrane, the middle layer is composed of water and protein, and the mucin layer is at the base [33]. Therefore, the hydrophilic/lipophilic nature of the drugs affects their ability to penetrate the tear film barrier. Meanwhile, mucins are electronegative, so the electrical charges between the drug molecules and carriers determine how the drugs interact with the eye surface [34]. Tear film turnover (1–2 $\mu L \cdot min^{-1}$) reduces drug retention time on the corneal surface, which is the main factor limiting the local retention time [35]. Human tear volume is about 7 μL, and the volume of eye drops can reach 50 μL. Although the capsule tail can temporarily stay at 30 μL, most of the drugs through nasolacrimal drainage enter directly into the systemic circulation, resulting in low drug bioavailability [36]. Therefore, the physicochemical properties of drug molecules and their carriers, as well as their interactions with the tear, determine whether the drugs can cross the tear membrane barrier and enter the subsequent tissues.

Cornea barrier

The cornea is the second major barrier for drug penetration, which is a transparent avascular connective tissue, consisting

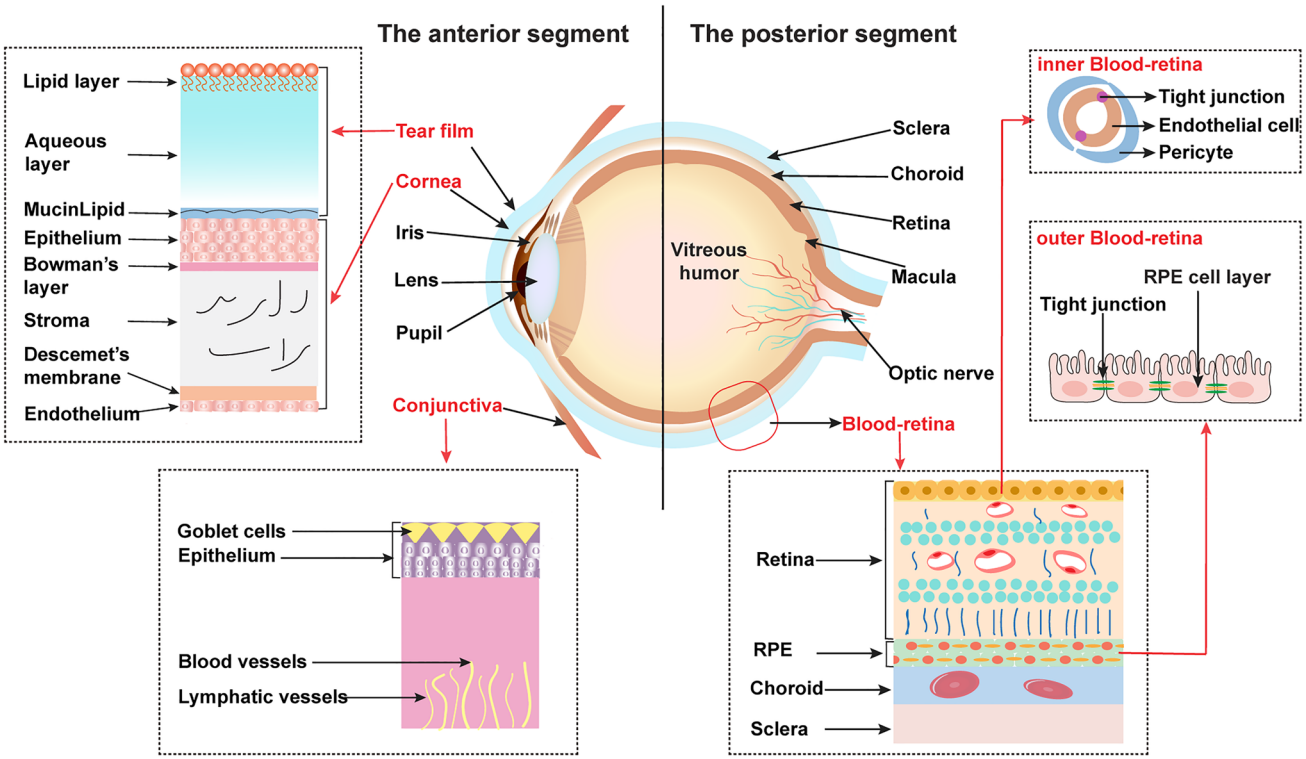

Fig. 1 A graphical depiction of the vital ocular barriers that provide the challenge of drug delivery to posterior eye segment

of 5 layers, respectively, epithelium, stroma, endothelium, Bowman membrane, and Descemet membrane [37]. The surface of the cornea is lined with closely connected hydrophobic epithelial cells, which prevents hydrophilic substances such as tears and macromolecular substances from entering the intercellular space [38]. The stroma accounts for approximately 90% of the corneal thickness and is made up of collagen fibrils and glycosaminoglycans. The highly hydrated structure of the stroma is a rate-limiting barrier to the penetration of lipophilic drug molecules [39]. Thus, the drugs entry into the corneal barrier depends on their hydrophilicity/hydrophobicity and molecular weight. In addition, the drug delivery systems with both hydrophobic and hydrophilic structures are more likely to enter the eye through the corneal pathway.

Conjunctiva barrier

The conjunctiva is a thin and translucent vasiform mucus membrane that surrounds the cornea. The conjunctiva is divided into the epithelium, the basement membrane, and the lamina propria [40]. The epithelium consists of goblet cells and lamellar cells that are closely connected. It operates as a barrier for the transport of hydrophilic substances by the side of the cell. One of its main functions is to help maintain the tear film [41]. Lamina propria is a loose layer of fibrous vascular connective tissue [42]. The conjunctiva surface is larger than the cornea, its permeability is 2–30 times higher than the cornea, and its absorbable diameter is less than 300 nm [43]. Therefore, the conjunctiva absorbs more drugs than the cornea. However, the conjunctiva still absorbs very few drugs. The conjunctiva contains abundant lymphoid tissue, which is involved in the immune defense system of the ocular surface and resists the entry of drugs [40].

Len barrier

The lens is a double convex and transparent tissue, held suspended by the suspensory ligaments between the iris and vitreous chamber [44]. It is the only refractive substrate of the eyeball with accommodative capacity [45]. Hence, it is a major instrument for vision formation.

Sclera barrier

The sclera, which is composed of non-keratinized laminated squamous epithelium and goblet cells, is covered by conjunctiva. Microscopically, the sclera is made up of dense fibers of different diameters that are interlaced with each other.

Collagen fibers and proteoglycans in the interfibrous matrix of the sclera allow hydrophilic substances to diffuse through the scleral tissue [46]. The sclera is highly permeable, and its penetration primarily depends on the molecular radius of the drugs rather than the lipophilicity of the drugs. Moreover, the permeability of the sclera does not significantly decrease with age [43]. The sclera has a large surface area. Few proteolytic enzymes or protein-binding sites can degrade or isolate drugs, which facilitates drug transport [47].

Choroid barrier

The choroid is a flexible layer of blood vessels adjacent to the sclera. Its main function is to provide nutrition to the retina [48]. Moreover, choroidal clearance is based on the high plasma flow and the porous leaky structures of choroidal capillaries that prevents the transport of macromolecular drugs [49, 50].

Blood–eye barrier

The blood–eye barrier consists of a blood–aqueous barrier (BAB) located in the anterior uveal membrane and a BRB located in the retro-ocular region. It has three key functions: maintaining tissue and fluid components, producing aqueous humor, and preventing pathogens from entering the eye [7]. BAB and BRB, due to their tight connections between cells, not only limit the invasion of pathogens to protect the retina but also limit the circulation of drugs from the body to the eye and from the eye to the body [51].

The BAB is composed of the compact capillary endothelium of the iris and ciliary epithelium [52]. Tight junctions act as gatekeepers for paracellular transport, restricting the selective diffusion of ions and small solutes through the spaces between adjacent cells [53]. Drug transporters in the iris and ciliary body not only reduce the penetration of drugs into the aqueous humor but participate in the elimination of aqueous humor drugs, thereby reducing the bioavailability of drugs [54].

The BRB is made up of two successive monolayer cells with unique spatial orientation and construction. The retinal pigment epithelium cells (RPEC) are the main constituent of the outer BRB (oBRB), and the retinal microvascular endothelial cells (RMEC) are the core component of the inner BRB (iBRB) [55]. They have tight intercellular connections and thus form a powerful barrier for drug penetration [56]. However, the retina has selective permeability [57]. The tight connections of cells in iBRB limit the penetration of hydrophilic drugs into the retina, whereas hydrophobic drugs penetrate more freely. And the permeability of the drugs through the oBRB decreases as the molecular radius increases [58, 59]. In general, lipophilic drugs and lower molecular weight drugs have higher permeability in BRB.

To sum up, the corneal route is the primary route of local drug delivery to the eye. The conjunctiva-sclera local administration route is short [7], so it is considered to be the main route of local administration. In addition, due to the presence of the blood–eye barrier, drugs are limited to reaching the retinal region on account of nasolacrimal drainage and capillary penetration. In order to achieve therapeutic intraocular concentrations, high doses of drugs are required. As a result, drugs are distributed and accumulated in the tissues of the body, causing side effects. Although it is difficult to treat ocular diseases with topical eye drops, it is still the safest, most convenient, and highly compliant way. Therefore, ocular preparation technology with strong permeability, good retention, and even targeted release is urgently needed.

Exosome-a lipid bilayer nanostructure

Exosomes are extracellular vesicles (EVs) of 30–150 nm and have a lipid bilayer structure, which contains many important bioactive molecules such as proteins, enzymes, and nucleic acids (mRNA, miRNA, DNA) in the interior and surface [29, 60, 61]. Some specific physiological functions such as therapeutic effects and targeting properties are given by these active molecules. Their nano-lipid bilayer structure allows them to cross ocular barriers. Therefore, exosomes have the potential as drugs and carriers in posterior ocular diseases [62]. Recently, researchers are not only limited to studying natural exosomes as drugs and carriers. In order to give exosomes more functions, engineered exosomes have aroused the great interest of researchers.

Exosome biogenesis

Exosomes are a sort of EVs, the phenomenon of sheep reticulocytes secreting nanovesicles during maturation was detected as early as the 1980s after these vesicles became known as exosomes [63, 64]. Exosome biogenesis is a successive cytological process depending on endosomes (Fig. 2). Firstly, cytoplasmic membrane endocytosis can form early endosomes. As early endosomes mature, RNA, DNA, and proteins are encapsulated in the cytoplasm to form late endosomes [65]. Then late endosomes form multivesicular bodies (MVBs), which include intraluminal vesicles (ILVs) that are created by budding inward through the membrane of late endosomes [66, 67]. The optimal mechanism for MVBs and ILVs formation is driven by the endoplasmic sorting complex required for transport (ESCRT) [68]. Subsequently, MVBs with the highest cholesterol content merge with the cytoplasmic membrane to expel ILVs out of the cell to form exosomes, which are consistent with the cholesterol-rich exosomes [69]. Another avenue for MVBs is to fuse

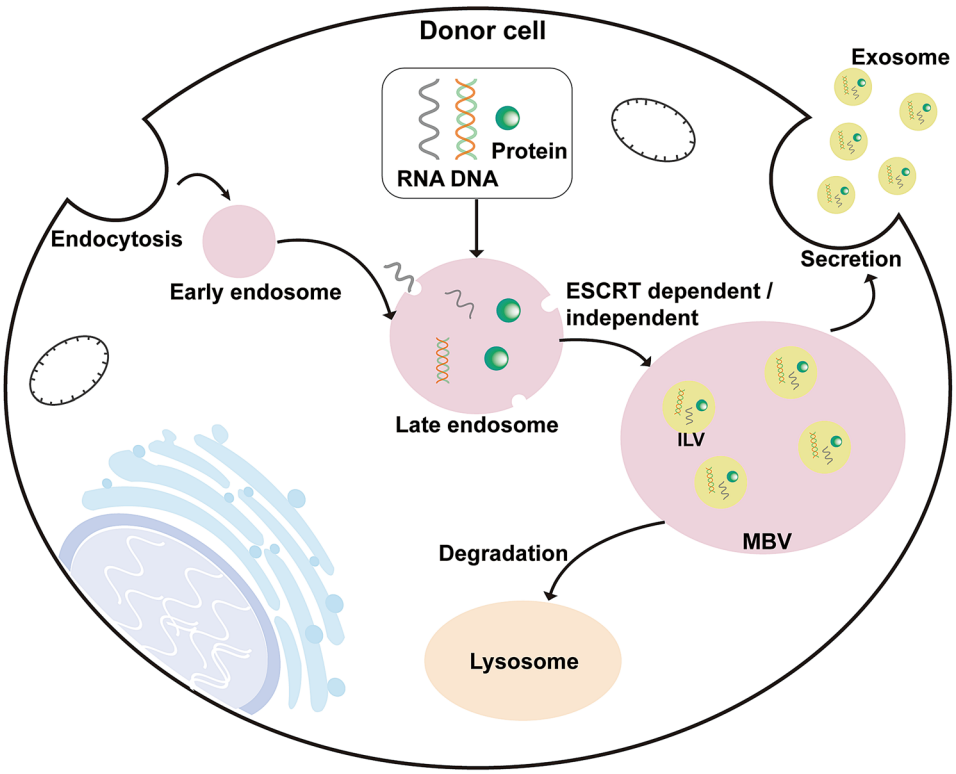

Fig. 2 Biogenesis and secretion of exosomes. Exosome formation originates from early endosomes formed by endocytosis in the cytoplasmic membrane. The membranes of late endosomes buss inward to form ILVs and convert them into MVBs. After MVBs merge with the cytoplasmic membrane to expel ILVs out of the cell to form exosomes

with lysosomes and are later degraded, which is the main fate of MVBs [70, 71].

Natural exosomes

Exosomes are secreted by a variety of cells, including epithelial cells, mesenchymal stem cells, dendritic cells, neurons, reticulocytes, cancer cells, B and T cells, and astrocytes, under normal or pathological conditions [72–76]. They are widely present in plasma [77], urine [78], milk [79], saliva [80], nasal secretion [81], amniotic fluid [82], and cerebrospinal fluid [83]. Exosomes are promising natural therapeutic agents, due to the variety of biomolecules in the synthesis process.

A variety of methods have been used to isolate exosomes. The most common method of isolation is ultracentrifugation, which is based on the difference in density and size between exosomes and impurities [84]. The methods of representative ultracentrifugation for exosomes are differential ultracentrifugation and density gradient ultracentrifugation [85]. Ultracentrifugation is able to collect a large number of exosomes [86]. Polymer-based precipitation separation is also commonly used to isolate exosomes [87]. The highly hydrophilic polymers associated with water molecules around exosomes to form a hydrophobic microenvironment, which causes the exosomes to precipitate. Both ultrafiltration and size exclusion chromatography are dependent on the size difference between exosomes and other components in the sample [88]. In addition to the strategy of isolating exosomes based on their sizes, densities, and other physical properties. There are other methods for isolating exosomes, such as immunoaffinity capture through interaction between antibodies and some specific proteins, lipids, and polysaccharides on the surface of exosomes [89]. Each method has its advantages and disadvantages (Table 1). The combined application of multiple methods has been widely studied and applied to adapt to mass production. Moreover, there are no established standards for the isolation and purification of exosomes, which is also an important research direction for researchers in the future.

Engineered exosomes

Due to the limited tissue and cell-specific targeted properties, there are many challenges when considering natural exosomes as therapeutic drugs and delivery carriers, so it is necessary to modify exosomes according to physiological requirements. At this time, engineered exosomes emerged to meet specific therapeutic purposes. Engineered exosomes adopt two modification strategies, namely cargo engineering and surface engineering (Fig. 3).

Cargo engineering

Cargo engineering refers to the loading of therapeutic drugs into exosomes, including pre-loading and post-loading.

Table 1 The different isolation methods and their advantages/disadvantages

C	Principle	Advantages	Disadvantages	References
Ultracentrifugation	The difference in density and size	Mature technology, large production, cheap	The long time for preparation, lower purity, damage of exosomes by high-speed centrifugation	[85]
Polymer-based precipitation	The influence of highly hydrophilic polymers on the solubility of exosomes	Simple, fast and convenient, without the requirement of special equipment	Cost of a large number of initial samples	[148]
Ultrafiltration	The difference in molecular weight and size	Simple, fast and without the requirement of special equipment	Low recovery rate	[89]
Size exclusion chromatography	The difference in size	The preservation of the integrity and biological activity of the exosome	The long time for preparation	[84]
Immunoaffinity capture	The interactions between proteins on the surface of exosomes and antibodies	Specificity and simple technological process	Expensive antibodies and low efficiency	[84]

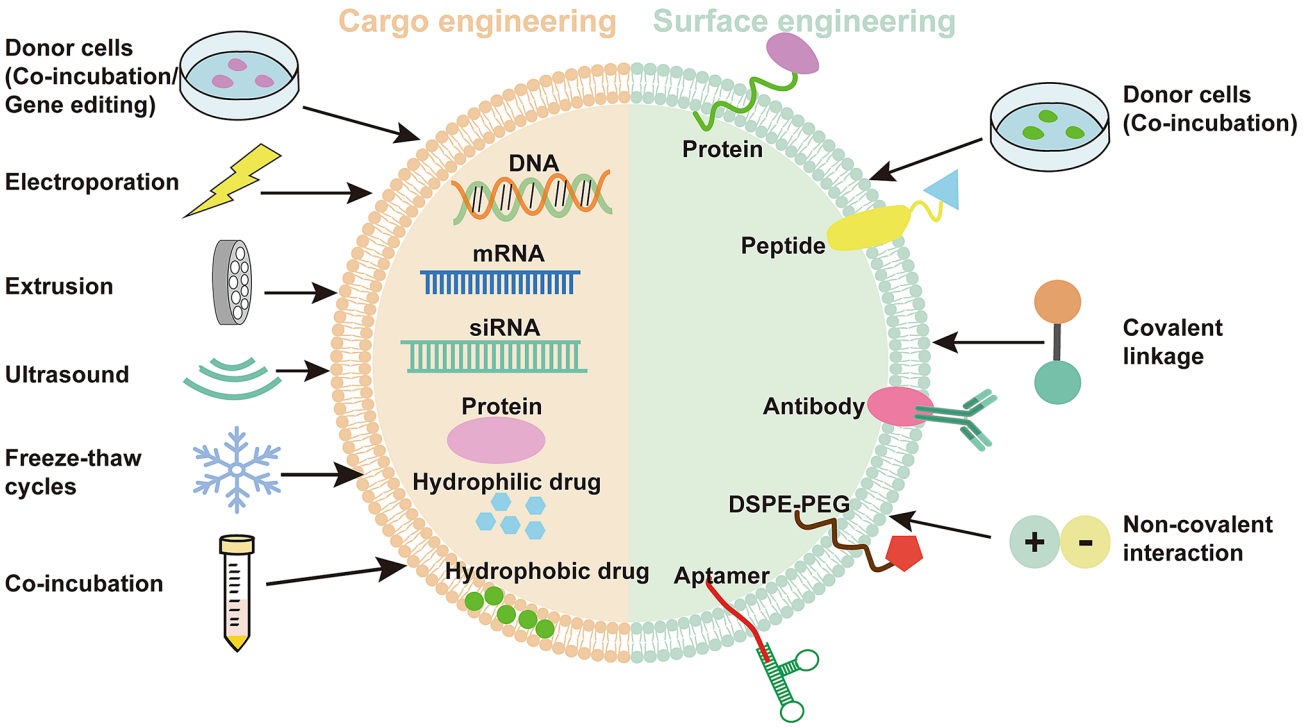

Fig. 3 Engineering exosomes via cargo engineering and surface engineering. Cargo engineering encapsulates proteins, DNA, RNA and other therapeutic drugs into exosomes via different methods. Suface engineering modifies different targeting molecules to give exosomes stronger targeting properties by genetic engineering and chemical modification

Pre-loading is the loading of drugs before exosome separation, and post-loading is the loading of drugs after separation [90].

Pre-loading uses therapeutic drugs to treat donor cells so that the cells secrete drug-laden exosomes. It is mainly through the co-incubation with the donor cells to secrete the corresponding exosomes. This approach aims to cause the donor cells to accumulate therapeutic compounds and secrete exosomes that contain the therapeutic compounds. Due to its non-targeting property, the yield of this method is low [91]. Another approach is gene editing, which uses genes to modify parental cells so they overexpress therapeutic RNA, proteins and peptides, and then load them into exosomes [92].

Post-loading is the loading of therapeutic molecules such as DNA, RNA, proteins, and small molecules directly into exosomes. For the post-loading of exosomes, passive and active-loading techniques are usually used. Passive-loading involves the co-incubation of drugs and exosomes, with the drugs diffusing into the exosomes along a concentration gradient. This passive-loading strategy is based on the concentration gradient and the hydrophobicity of the cargos, as hydrophobic drugs may interact with the lipid bilayer membrane of the vesicles. This method usually has a low loading capacity [93]. Active-loading allows the drugs to diffuse into the exosomes by temporarily disrupting the exosomal membrane through external forces. Active-loading mainly includes ultrasound, extrusion, electroporation, freeze–thaw cycles, and permeabilization [94]. Compared to passive-loading, active-loading capacity can be increased by a multiple of approximately 11 [95].

Surface engineering

Apart from achieving specific efficacy by loading drugs, exosomes can also be engineered. Although exosomes are natural carriers, surface modifications still be easily performed. The modified strategies can be divided into two types, genetic engineering and chemical modification [93]. Genetic engineering makes proteins or peptides fuse with membrane proteins on the surface of the exosomes by co-incubation. Genetic engineering has its intrinsic drawbacks, such as the complexity of the operation and the limited range of proteins that can be applied [96]. Chemical modification refers to modifying a diversity of chemical ligands or functional molecules onto the surface of exosomes by covalent linkages or non-covalent interactions [96, 97]. In addition, other methods such as electrostatic interactions, ligand-receptor interactions, and aptamer-based surface modification were performed by anchoring CP05 peptides that have been used for surface modification of exosomes [98]. All of the methods mentioned above are used to empower exosomes with targeting functions by modifying specific molecules onto the surface of the exosomes.

As mentioned above, exosome is an endogenous substance with targetability and adequate security. Exosomes are endowed with some therapeutic effects because they carry signaling molecules during synthesis. And exosomes are good drug carriers due to their lipid bilayer structure and their ability to cross multiple physical barriers. Hence, exosomes are promising drug carriers for delivering various drugs to the posterior segment of the eye through the ocular barriers [39]. Meanwhile, exosomes themselves are easy to be modified to achieve stronger targeting.

Application of exosomes in posterior ocular disease

Many studies have demonstrated that exosomes play significant roles in the treatment of many diseases, including cancer [99], cardiovascular diseases [100, 101], neurodegenerative diseases [102], and tissue injury [103, 104]. And some studies based on exosomes to treat diseases are already in clinical trials, for example, cancer and COVID-19 pneumonia [105]. In a prospective clinical trial of dry eye disease, miR-204-containing exosomes as eye drops notably alleviate GVHD-associated dry eye disease by suppressing inflammation and improving epithelial recovery. This study suggests that exosomes as eye drops are feasible and efficacious in treating GVHD-associated dry eye disease [106]. The eye, due to its unique sensitivity and multiple barriers to postocular administration, requires a highly specific, penetrative, and non-toxic therapeutic strategy. Exosomes are a potential "cell-free" therapy that is suitable for the treatment of posterior ocular diseases due to their ability to cross barriers, migrate to the targets, and their safety is also confirmed [107]. Meanwhile, exosomes are ideal vehicles because of their higher biocompatibility and lower immunogenicity. In addition, the exosome membrane prevents the degradation of their molecular contents before arriving at the target cells [62]. In this section, we will discuss application of exosome in posterior ocular disease, including them as therapeutic agents and carriers.

Exosomes as targeted drugs to treat posterior ocular disease

Due to the variety of biological information they carry, the function of exosomes is mainly determined by the substances they carry [108]. Exosomes provide a novel perspective and potential therapeutic approach for treating posterior ocular diseases.

Exosomes for the treatment of AMD

AMD is a progressive degenerative disease of the macula, the region of the retina in charge of vision and color. It is divided into dry AMD and wet AMD, and wet AMD is the leaking AMD, which is characterized by abnormal growth of new blood vessels invading the retinal pigment epithelium (RPE) from the choroidal layer [109, 110]. In recent years, the use of exosomes to treat AMD has received more and more attention from researchers.

Hajrasouliha et al. [111] injected of RAC-Exos by extro-ocular and exosomes started to appear in the neural retina at 15 min, gradually increased after 30 min, and then became more diffuse throughout the neural retina. This injection

method alleviates the side effects of intravitreal injection, such as intraocular inflammation, and the exosomes still reach the target tissue. Because exosomes have the ability to migrate to target tissues and target cells. RAC-Exos mainly targets macrophages and vascular endothelial cells, and inhibits angiogenesis by reducing the release of inflammatory and angiogenic factors [112, 113]. RAC-Exos contained known anti-angiogenic proteins, such as endothelial inhibitors and PEDF, which may be operative in the inhibition of laser-induced choroidal neovascularization (CNV) in mice. RPE-Exos do not have this ability. But subretinal injection of RPE-Exos can diminish the apoptosis of photoreceptors and inhibit the expression level of inflammatory cytokines, which can also achieve the effect of retinal protection [114]. Microglia-derived exosomes can also inhibit the expression of angiogenic factors such as VEGF and reduce retinal angiogenesis, thereby reducing visual damage [115]. During subretinal fibrosis secondary to neovascular AMD, RPE cells lose their characteristic epithelial morphology and function and then transform into myofibroblasts, which is known as epithelial-mesenchymal transformation (EMT). Another study demonstrated that the intravitreal injection of human umbilical cord MSC-derived exosomes (HUCMSC-Exos) effectively ameliorated laser-induced CNV and subretinal fibrosis via the suppression of EMT process [116]. In addition, it has been reported that intravitreal injection of MSC-derived exosomes (MSC-Exos) can ameliorate retinal laser damage by reducing damage and inhibiting apoptosis and inflammatory responses [117].

In summary, exosomes play a therapeutic role at various stages of AMD through anti-inflammatory, anti-angiogenesis, anti-apoptosis, and inhibition of fibrosis. Many studies have shown that exosomes play a similar role in the treatment of diseases such as cancer and stroke and it is proven to have good therapeutic responses [118, 119]. The effectiveness of exosomes in the treatment of AMD is supported by these evidences.

Exosomes for the treatment of DR

DR is a usual complication of diabetes mellitus and a primary reason for blindness and visual impairment in mid-aged and elderly people, affecting their quality of life severely [120]. It is characterized by progressive changes in the retinal microvasculature, leading to increased vascular permeability, pathological intraocular hyperplasia, inflammation, angiogenesis, and retinal ischemia. Consistent with AMD, anti-inflammation and anti-angiogenesis are also ways to treat DR. At the same time, DR can cause retinal neuropathy. Photoreceptor cells are a class of cells in the neural retina that play an important role in the retina [121, 122]. Recently, the research on exosomes in the treatment of DR gradually has been increasing.

The study demonstrated that vitreous injection of MSC-derived exosomes (MSC-Exos) reduced IL-B, IL-18, and caspase-1 levels after hyperglycemic stimulation. Further studies showed that miR-126 in MCS-Exos down-regulated the expression of high mobility group box 1 (HMGB1) protein and its downstream inflammatory factors [123]. Thereinto, HMGB1 is a danger-associated protein pattern receptor which can sense high glucose as a stressor and HMGB1is a key player in retinal inflammation in DR [124]. Since retinal ischemia was a common underlying mechanism in DR. Vitreous administration of MCS-Exos can reduce the severity of retinal ischemia and neovascularization, and immunogenicity is not detected when exosomes are administered to mice with normal immune function [125]. The other study revealed that injection of 293 T cell-derived exosomes (293 T-Exos) into the vitreous fluid of ischemic eyes reduced the apoptosis of retinal cells and 293 T-Exos mainly ingested by retinal neurons and ganglion cells [126]. Therefore, 293 T-Exos have the potential to treat retinal diseases. Dongyan Pan et al. also found that exosomes may exert neuroprotective effects by promoting the survival of retinal ganglion cells (RGCs) and activation of glial cells through the administration of HUCMSC-Exos in a mouse optic nerve crush model [127].

Exosomes may improve the occurrence and development of DR through anti-inflammatory, improvement of retinal ischemia and neovascularization, and protection of optic nerve. Meanwhile, exosomes did not show immunogenicity, which is a very appealing novel non-cellular therapeutic approach that warrants further exploration in ophthalmology.

Exosomes for the treatment of autoimmune uveitis

Autoimmune uveitis is a disease characterized by intraocular inflammation, which can lead to visual impairment and even blindness if not diagnosed and treated appropriately [128]. Conventional treatment is the local or systemic use of corticosteroids and immunosuppressive agents, which are highly efficacious, but can be associated with serious systemic side effects [129]. New therapeutic approaches for attenuation of autoimmune uveitis are urgently needed.

Lingling Bai et al. [130] proved that MSC-Exos efficiently alleviated experimental autoimmune uveitis (EAU), established murine model of autoimmune uveitis, indicating their potential therapeutic use in the treatment of this disease. Both clinical and histological analysis revealed that periocular injection of MSC-Exos significantly improved EAU, and protected retinal function in experimental rats. Subsequently, the proportion of Gr-1^+, $CD161^+$, $CD68^+$, and $CD4^+$ cells in the inflamed retina decreased. CCL2 and CCL21 chemokines are involved in chemotaxis of inflammatory cells in the injured eyes. But MSC-Exos suppressed effects of CCL2 and CCL21 chemokines. Mice treated with

exosomes that contain IL-35 (i35-Exos) by retro-orbital injection showed only mild EAU compared to control mice (PBS). The results of optical coherence tomography (OCT) analysis revealed substantial accumulation of inflammatory cells in vitreous and optic nerve head of control untreated eyes compared to mice treated with i35-Exos. Meanwhile, reduction of Th17 cells in eyes of mice treated with i35-Exos but not to control mouse eyes. Th17 cells are closely related to the production of EAU [131]. In another study, circulating exosomes were isolated from the blood of rats with EAU (EAU-Exos) induced by immunization with IRBP R16 peptide. However, EAU-Exos selectively suppressed the immune response of R16-specific T cells in vitro. Afterward, naive Lewis rats were pre-inoculated with EAU-Exos and these rats were induced to recur EAU, the results showed that EAU-Exos could reduce the frequency and severity of EAU recurrence. Therefore, the use of autologous circulating exosomes as a vaccine has the potential to inhibit the recurrence of autoimmune uveitis [132]. Results obtained above strongly suggest that exosomes efficiently suppress inflammatory response in inflamed retina, should be further explored as novel therapeutic agents for the treatment of human autoimmune uveitis.

To sum up, exosomes have shown outstanding therapeutic effects as a cell-free therapy in ophthalmology and their safety and targeting ability have been affirmed. In addition to the above major retinal pathologies, exosomes have also demonstrated positive therapeutic effects in foundational studies of other retinal diseases such as DME [133]. Due to the sensitive physiology of the eye, the development of topical formulations that can be administered as eye drops without the risk of injection needs to be further explored.

Exosomes as targeted delivery vehicles to treat posterior ocular disease

There are different nanocarriers with both natural and synthetic origins that have been developed for the treatment of a wide variety of diseases. These nanocarriers present different matrix compositions, highlighting liposomes, nanoparticles, nanomicelles, or dendrimers [134]. As mentioned above, exosomes have a lipid bilayer nanostructure secreted by various cells [22, 29]. Compared with synthetic nanocarriers, exosomes have lower immunogenicity and higher biocompatibility. Exosomes represent a promising nanomedicine strategy mainly due to their ability penetrate the most difficult barriers to penetrate, including the BBB [25]. Moreover, exosomes are easily modified to achieve the desired function. They have intrinsic targeting and promising physiological features to be used as a nanocarrier for delivering therapeutic molecules to the posterior segment of the eye [135]. The therapeutic molecules including various types of nucleic acids, proteins, and small-molecule drugs can be loaded into the exosomes as cargo to treat posterior ocular diseases.

Delivery of nucleic acid

A variety of miRNAs have been shown to play important roles in inflammation regulation, angiogenesis, tissue repair and regeneration. Exosomes can transport miRNAs to target sites through barriers, where they are taken up by cells and subsequently regulate the receptor cells. The phototoxin N-methyl-Nnitrosourea (MNU) was used to establish a photoreceptor-specific injury model in mice. The study discovered mesenchymal stem cell transplantation (MSCT) counteracted photoreceptor apoptosis and alleviated retinal morphological and functional degeneration in a mouse model. Interestingly, effects of MSCT were inhibited after blockade of exosomal generation. Therefore, it is speculated that exosomes alleviate and inhibit the damage of photoreceptors. By studying the potential mechanisms of exosomes, the researchers identified that miR-21 critically maintained photoreceptor viability against MNU injury by targeting programmed cell death 4 (Pdcd4) and was transferred from MSC-derived exosomes in vivo for functional regulation [136]. Pakravan et al. [137] showed that miR-100 was enriched in bone marrow MSC-Exos and transferred by exosomes to inhibit angiogenesis by downregulating VEGF in breast cancer cells in vitro. Anti-VEGF therapy plays an important role in abnormal neovascularization of ocular posterior segment diseases such as AMD and DR. This study provides a direction for exosomes to transport miRNAs to targeted VEGF in the posterior segment of the eye to inhibit angiogenesis.

Therefore, it is possible to use exosomes to deliver nucleic acid to treat posterior ocular diseases, especially with their unique miRNA cargo. Many studies showed the role of miRNA in the function and survival of different retinal cells such as photoreceptors or Müller glias, and they are related to many diseases [138]. Here, exosome-delivered miRNA has been widely studied in the treatment of various diseases.

Delivery of proteins

Besides the use of nucleic acid in the treatment of posterior ocular diseases, exosomes can be used to deliver small proteins and peptides. These proteins and peptides with properties including anti-angiogenesis and anti-inflammatory can be explored. Xue Dong et al. [139] constructed an EXO-linked peptide (EXO_{KV11}) to inhibit pathological retinal angiogenesis. EXO_{KV11} and KV11 were injected by retro-orbital method. The results showed that the signal of EXO_{KV11}-injected group was stronger than that of KV11-injected group and signals were still detectable in the retina 12 h after injection,

which demonstrated that EXO_{KV11} was delivered into the eye more efficiently than KV11 and the EXO_{KV11} had high stability. In the oxygen-induced retinopathy (OIR) mouse model, EXO_{KV11} showed a stronger inhibitory effect on neovascularization and endothelial cell (EC) proliferation. In the mouse OIR model, increased VEGF secretion caused by hypoxia is the major cause of neovascularization and vascular leakage. However, EXO_{KV11} effectually suppressed VEGF-induced vascular leakage in mouse model by retro-orbital injection. In addition, bevacizumab, a very commonly used VEGF antibody against AMD, has been found to be partially taken up by RPE cells after intravitreal injection and then re-released by exosomes to produce therapeutic effects [140]. Vitreous injection is commonly used in clinical administration of bevacizumab, but there are many side effects in this way. The above studies suggest that it is feasible to use exosomes as the carrier of bevacizumab in a less invasive way such as retro-orbital injection.

It revealed that investigators could develop exosomes encapsulating some proteins such VEGF inhibitors for ocular delivery in a less invasive way to reduce the adverse effects of vitreous injections and enhance patient compliance. Meanwhile, the development of topical non-invasive formulations that can be administered as eye drops needs to be further explored. There have been studies about intranasal delivery of protein-based drugs cross the BBB by exosomes in Parkinson's, which offers strong implications for the various drugs to passage through the ocular barriers into the posterior ocular segment.

Delivery of chemical drugs

Due to the specific physiology of the eye, targeted delivery of small molecules to fundus lesion sites remains challenging. The ocular biocompatibility of systemically administered drugs is still poor, and topical drops are insufficient to achieve therapeutic concentrations of drugs in the posterior ocular lesion site [141]. Exosomes can not only encapsulate hydrophobic drugs but also hydrophilic drugs due to the fact that exosomes have a hydrophobic lipid membrane and a hydrophilic core [142, 143]. Curcumin interferes with the progression of AMD by inhibiting oxidative stress, inflammation, and angiogenesis [144]. The hydrophobicity of curcumin leads to its low bioavailability in vivo. However, encapsulation of exosomes improved the solubility and stability of curcumin, thus boosting its anti-inflammatory properties [145]. Surface-functionalized MSC-Exos with curcumin were able to distribute in ischemic brain tissue [146]. Owing to its poor pharmacokinetics, peroxidase has difficulty crossing the BBB, but its distribution in the brain has been observed by intranasal and injectable administration via exosomal delivery [147]. Since the BBB is the most difficult barrier to penetrate and the blood–eye barrier is similar to the BBB, so it is possible to deliver drugs into the blood–eye barrier via exosomes.

Exosomes have a great potential for drug delivery because of their good tissue targeting, good biocompatibility, and membrane permeability. Along this pathway, we can go further to explore its application in the novel topical drug delivery systems to delivery various drugs for the treatment of the posterior ocular diseases.

Conclusions

Diseases of the posterior segment of the eye, including AMD and DR, are major threats to vision. Although most of these diseases can be avoided, eye diseases are still a crucial study considering the proliferation of electronic products. The current review summarizes the various barriers of the eye and exosome generation, and more importantly, the potential applications of exosomes in the treatment of posterior ocular diseases. It highlights and summarizes the results of recent and past studies and acknowledges the great potential of exosomes for targeting the posterior segment of the eye, including therapeutic drugs and delivery vehicles. The increasing attention towards the exosomes is highly praiseworthy, considering their abilities contacted with specificity towards a lot of diseases that affect the human physiological system. As therapeutic molecules, exosomes can modulate posterior ocular diseases through the contents they carry. As carriers, exosomes are expected to be able to cross multiple barriers to reach the ocular lesion in a less invasive or even non-invasive way. And exosomes have good biocompatibility and immunogenicity. This potential can be seen in diseases of the posterior ocular segment, as well as in difficult diseases such as cancer and cardiovascular disease, where exosomes can play a huge role and have immeasurable promise.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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