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Current Perspectives on the Biological Effects of Exosomes in Ophthalmic Diseases

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Abstract: *Exosomes represent a class of nanoscale particles with a diameter of 50–100 nm, which are secreted by a multitude of cell types, and contain a plethora of biomolecules such as proteins, lipids, RNA, and DNA. These cysts can transmit information between cells and participate in a myriad of vital biological processes, including immune regulation, tissue repair, and angiogenesis. This review begins with an introduction to the fundamental aspects of exosomes, focusing on the biosynthesis process, biological function, and the techniques employed for characterization. Thereafter, the review delineates the research progress of exosomes in relation to ophthalmic diseases, with a focus on diabetic retinopathy, age-related macular degeneration, glaucoma, traumatic optic neuropathy, and corneal diseases. The current state of research, including the achievements and challenges in translating exosomes from experimental research to clinical application will also be discussed. Finally, we will conclude with an outlook on the potential of exosome therapy.*

Keywords: *Exosomes, Extracellular vesicles, Ophthalmic diseases, Diabetic retinopathy*

1. Introduction

Visual impairment, neovascular diseases, and tumors represent three significant global health concerns that have a profound impact on the quality of life of individuals worldwide[1]. It is estimated that by 2050, 834 million individuals worldwide will be affected by visual impairment, with 61 million suffering from blindness[2]. The impact of visual impairment extends beyond the individual to the socio-economic structure and public health system, as well as the country's socio-economic development and public health policies. Conventional treatments for ophthalmic diseases, employ pharmacological and surgical interventions, nevertheless, these options are associated with limited efficacy, significant adverse effects, and considerable treatment costs. It is therefore imperative to develop efficacious new therapeutic strategies to combat visual impairment, improve the quality of life for patients, and alleviate the healthcare burden. Cell-derived exosome therapies are becoming increasingly useful in the treatment of ophthalmic diseases, and they are now the subject of intense research interest. The following review will provide an overview of the existing research on exosomes, and examine the research progress of exosomes in ophthalmology. Furthermore, the review will examine the challenges of exosome-based therapeutic strategies and investigate the prospective of this developing therapeutic modality

2. Overview of exosomes

2.1. Biosynthetic processes of exosomes

It is a general biological phenomenon that all cells in an organism, regardless of their prokaryotic or eukaryotic characteristics, are capable of actively releasing extracellular vesicles (EVs) as part of their regular physiological processes. Furthermore, EVs are also released in the event of the occurrence of acquired abnormalities[3]. EVs refer to a heterogeneous mixture of membrane particles that have been distinguished into three subgroups based on their diameters and mechanism of occurrence[4]: Exosomes, initially defined as lipid bilayer particles measuring 50–100 nm in diameter, are released from cells. However, most studies employ a particle size range of 30–100 nm; subsequently, the size range has expanded to encompass particles with a diameter of 20 nm or less and particles with a diameter of up to

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150 nm. Microvesicles, which are typically larger than exosomes, with a size range of 50–1,000 nanometers. Apoptotic bodies, in contrast, are smaller, ranging in size from 50–5,000 nanometers[5].

Microvesicles and apoptotic bodies are produced by distinct processes of protrusion through the plasma membrane in living and programmed dead cells, respectively. Exosomes differ from microvesicles and apoptotic vesicles in size, content, and production mechanism [6].

The classical mechanism for exosome biogenesis[7], in which the cytoplasmic membrane bulges inward, leading to the capture of membrane molecules and the formation of intracellular early endosomes[8], is the endosomal pathway. Trans-Golgi network (TGN)-derived vesicles can fuse with early endosomes. During subsequent maturation, early endosomes fuse with late endosomes, leading to invagination of the endosomal membrane into the lumen and the formation of intraluminal vesicles (ILVs), which in turn lead to the form of multivesicular bodies (MVBs) with a characteristic multivesicular appearance[9]. However, not all MVBs can fuse with the plasma membrane, only certain MVBs can undergo this fusion, and it has been demonstrated that MVBs with a high cholesterol content are capable of fusing with the plasma membrane and releasing exosomes[10]. An alternative fate for MVBs is fusion with lysosomes, which results in degradation and recirculation of their proteinaceous, nucleic, and lipid components[11] (Figure 1). During the release of exosomes, some components of the Rab family, including Rab27a, Rab27b, Rab35, and Rab11, play a pivotal role in exosome release by directing MVB translocation to the cellular periphery and eventual fusion with the plasma membrane[12]. The key cellular mechanism for this process of endosomes formation into exosomes is the endosomal sorting complex required for transport (ESCRT) mechanism, which is composed of four protein complexes (ESCRT-0, -I, -II, and -III) as well as accessory proteins (Alix, VPS4, and VTA-1), with the ESCRT-0 sub-complex sequestering the ubiquitinated cargo, ESCRT-I/II/III complex inducing inward ILV outgrowth and division to form MVBs, and the VPS4 complex ensuring eventual membrane cleavage and/or ESCRT recycling[11], [13].

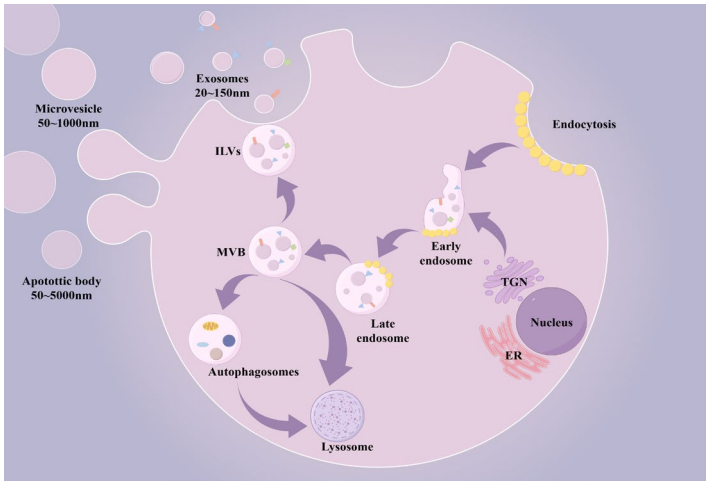

Figure 1: Biogenesis and secretion of exosomes, microvesicles, and apoptotic bodies. The classical formation mechanism for exosome biogenesis is the endosomal pathway.

2.2. Biological properties of exosomes

Exosomes can carry a wide range of biologically active molecules, including proteins, RNAs, and DNAs, and deliver them to the recipient cell by fusion or endocytosis with the target cell, thereby affecting cellular function and behavior (Figure 2). Exosomes may function through some of the following mechanisms in the treatment of a diverse range of diseases.

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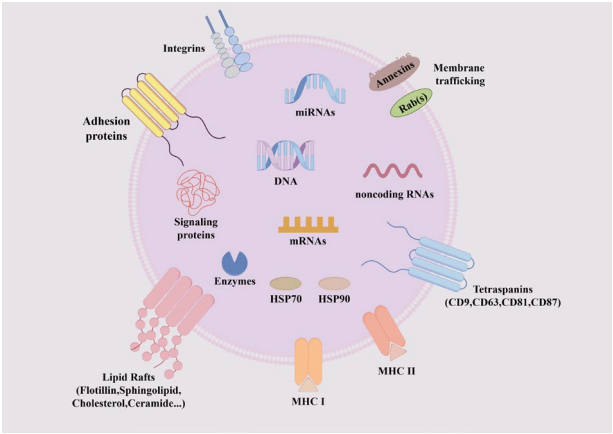

Figure 2: Structure and composition of exosomes. Exosomes contain various DNAs, RNAs, proteins, lipids, and metabolites. By Figdraw.

2.2.1. Mediation of cell-cell communication

Cell-cell communication is a fundamental process for all multicellular organisms. As originally conceived, exosomes were thought to assist cells eliminate unwanted metabolic waste by functioning as a cellular waste disposal system. The available evidence is increasingly suggestive of a role for these vesicles as intercellular communicators. Exosomes perform intercellular signaling functions via a variety of mechanisms[14]. One such way is by directly contacting and activating target cells via surface ligands. For instance, exosomes derived from dendritic cells (DCs) have been demonstrated to directly activate natural killer (NK) cells via ligands of tumor necrosis factor (TNF) superfamily located on the plasma membrane[15]. Additionally, exosomes can transfer surface receptors or cytoplasmic proteins to target cells. For example, to enhance drug resistance and reduce apoptosis in sensitive cancer cells, exosomes can transfer annexin A6 (ANXA6) from drug-resistant cancer cells to sensitive cancer cells[16]. Thirdly, exosomes of diverse cellular provenance can facilitate the transfer of RNAs (predominantly mRNAs and miRNAs) at the intercellular level. For instance, exosomes can shuttle RNA between human mast cells and $CD34^{+}$hematopoietic progenitors[17]. To summarize, exosomes have undergone an evolutionary transformation from a relatively simple cellular waste disposal mechanism into a central component of an intricate network of cell-cell communication, thereby playing a pivotal role in maintaining cellular homeostasis and coordinating cellular processes.

2.2.2. Immunomodulation

The immunoreactivity of exosomes affects several immunoregulatory mechanisms, including the regulation of antigen presentation, immunosuppression, immune activation, and immunosurveillance[18]. B lymphocyte-derived exosomes can utilize major histocompatibility complex (MHC) I and II proteins on their surface to achieve antigen presentation[19]. Exosomes can exert immunosuppressive effects through multiple mechanisms: The Fas ligand and TAIL on their surface promote apoptosis of DCs [20], and pro-apoptotic factor exosomes contain, such as galectin-1 induces $CD8^{+}$ lymphocyte suppression[21]. Furthermore, exosomes are able to directly inhibit the killing function of NK cells in a manner independent of T cells[22]. Meanwhile, exosomal miRNAs also contribute to tumorigenesis by inducing tumor-associated macrophages (TAMs) to switch to the M2 phenotype[23]. Vice versa, exosomes are also involved in immune activation through different mechanisms: TNF-α in mature DC-derived exosomes stimulates the proliferation and activation of NK cells [24], and exosomes in bronchoalveolar lavage fluid (BALF) from tuberculosis patients are capable of activating monocyte[25]. The rapid recognition and response of the body's immune system to invading microorganisms depends predominantly on the recognition of pathogen-associated molecular patterns (PAMP), and it was shown that exosomes released from pathogen-infected macrophages(Mφs) contain PAMP that provide immune surveillance of intracellular pathogens, which in turn activates the immune responses[26]. Another study indicated that pre-metastatic tumor exocyst exosomes, by triggering immune surveillance, initiate a broad patrolling monocyte (PMo)-dependent innate immune response that contributes to cancer cell clearance in the premetastatic microenvironment[27]. These observations highlight the versatility of exosomes in immunoregulatory mechanisms that not only influence disease pathogenesis but also represent potential avenues for the development of innovative immunotherapy strategies.

2.2.3. Biomarkers

Exosomes released from cells into the circulation and body fluids exhibit disparate protein and RNA

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profiles in healthy subjects and patients with diverse diseases, offering novel insights into disease diagnosis[5]. In a mouse model of alcoholic hepatitis, the expression levels of exosomal miRNAs were significantly elevated in the serum compared to normal controls. Of particular interest were the up-regulated miRNA-192, miRNA-122, and miRNA-30a, which exhibited promising diagnostic value for alcoholic liver injury[28]. Additional research has identified a particular abundance of miR-21 and miR-1246 within human breast cancer exosomes, accompanied by markedly elevated levels in the plasma of breast cancer patients. These findings suggest the potential for tumor-derived exosomal miRNAs to gain entry into the bloodstream, where they could serve as biomarkers for breast cancer[29]. Furthermore, urinary exosomal miR-146a levels are inversely correlated with albuminuria, which implies that it may be an emerging diagnostic indicator for albuminuria in essential hypertension[30]. Similarly, exosomal miRNA expression patterns differed between diabetic patients and healthy populations. Notably, miR-150-5p, miR-21-3p, and miR-30b-5p exhibited altered expression levels, which have been linked to the diagnosis of diabetic retinopathy (DR)[31]. These findings underscore the significance of investigating the role of exosomes in various diseases and their potential utility as biomarkers, offering promising insights for advancing disease diagnosis and treatment strategies.

2.2.4. Restoration and Regeneration

Exosomes have demonstrated considerable therapeutic potential in facilitating tissue repair and regeneration[32]. The restoration of blood flow following a myocardial infarction (MI) is dependent upon the formation of new vessels, which is crucial for the recovery of ischemic myocardial tissue and remodeling. The evidence suggests that the DC-derived exosome miR-494-3p stimulates myocardial angiogenesis in the aftermath of MI, thereby aiding in cardiac repair[33]. The exosomes derived from mesenchymal stem cells (MSCs) also show remarkable efficacy in osteochondral repair, facilitating rapid proliferation and infiltration of chondrocytes by coordinating multiple cell types and activating multiple signaling pathways, leading to efficient osteochondral repair[34].

Similarly, exosomes have been demonstrated to facilitate regeneration in the treatment of ocular diseases. In a rat optic nerve entrapment model, bone marrow mesenchymal stem cell-derived exosomes (BMSC-Exos) exerted a dual effect: they promoted the survival and axon regeneration of retinal ganglion cells (RGCs) and partially prevented RGCs axon loss and dysfunction. These findings indicate that BMSC-Exos possess substantial optic neuroprotective and pro-neurogenic properties[35]. In a model of ethanol-induced oxidative stress in retinal pigment epithelial (RPE) cells, exosomes released in large quantities from RPE contained mRNA encoding vascular endothelial growth factor receptors (VEGFR-1 and VEGFR-2), which promoted neovascularization[36]. Moreover, in corneal epithelial trauma experiments, corneal MSC-Exos can be taken up by corneal epithelial cells, which in turn enhances migration and proliferation, as well as accelerated wound healing[37]. In essence, exosomes, as a novel therapeutic modality, have potential applications in promoting tissue repair and regeneration across a diverse range of fields.

2.2.5. Drug delivery vehicles

Exosomes are known to facilitate intercellular communication. They are capable of carrying a variety of biological molecules, including proteins, mRNAs, miRNAs, and lipids, from donor cells to target cells[38], which makes exosomes represent a novel promising new generation of drug delivery system. In comparison to traditional nanocarriers, exosomes possess a series of unique therapeutic properties, including circulatory stability, low immunogenicity, low toxicity, biocompatibility, effective bio-barrier penetration, biocompatibility, and circulatory stability[39]. (1)Low immunogenicity and low toxicity: Studies have revealed that the composition of splenic immune cells was unaltered even after three consecutive weeks of injecting HEK293T cell-derived exosomes into mice. Additionally, no abnormalities were observed in organs such as the thymus, heart, and liver, and there were no symptoms[40]. The low immunogenicity and low toxicity of exosomes make them an ideal vehicle for targeted drug delivery in cancer therapy. For instance, the intravenous administration of exosomes loaded with the chemotherapeutic drug doxorubicin (DOX) into tumor tissues has demonstrated the potential for limited efficacy in significantly restricting tumor growth without notable toxicity[41].(2) Effective bio-barrier penetration through biological barriers: In an experiment, adeno-associated virus (AAV2) and exosome-associated adeno-associated virus (exo-AAV2) both containing the encoded green fluorescent protein (GFP) were administered intravitreally in mice. Compared to AAV2, exo-AAV2 exhibited superior depth and more robust expression in the retina than AAV2[42]. Similarly, exo-AAV2 showed enhanced traversal across the vitreous-retina barrier and augmented the transduction efficiency of retinal cleavage protein 1 (RS1) within the mouse retina, when compared to conventional AAV2[43]. (3) Biocompatibility: Exosomes are distinct from liposomes synthesized in vitro and conventional nanocarriers due to their derivation from the human body, a factor that theoretically enhances their

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biocompatibility. The composition of exosomes includes a multitude of lipids, such as sphingolipids, sphingomyelin (SM), cholesterol (CHOL), and phosphatidylserine (PS), among others, which are vital in defining the structure of exosome membranes[44]. Given that the exosome membrane structure is analogous to that of the cell membrane–namely, comprising an aqueous core and a lipid bilayer–exosomes are capable of carrying drugs in both the aqueous and lipid phases, facilitating the delivery of hydrophilic and hydrophobic drugs to target cells with greater efficiency than traditional nanocarriers[45].(4) Cycling stability: Zeta potential (ZP) is a commonly used measure of exosome surface potential and an indicator of surface charge[46]. Exosomes exhibit a near-neutral, slightly negative zeta potential that renders well well-suited for longer-term cycling circulation in vivo[47]. Furthermore, exosomes are coated with complement proteins or other proteins that prevent them from being recognized and engulfed by immune phagocytosis, resulting in a longer half-life and greater stability of exocytosis in the bloodstream[48]. For example, exosomes loaded with curcumin enhanced the stability and bioavailability of curcumin[49].

Overall, exosomes have immense potential for use as drug delivery vehicles, representing a novel avenue for advancing drug development and therapy.

The efficacy of exosomes as delivery vehicles for therapeutic agents hinges primarily on their capacity to effectively encapsulate the desired cargos. Exosomes can be engineered to carry a diverse range of biomolecules, including nucleic acids, lipids, proteins, and small molecule drugs[50]. At present, two principal techniques are utilized for the incorporation of drugs into exosomes, namely passive and active loading. Passive loading is a relatively straightforward method that encompasses either drug incubation with exosomes or drug incubation with exosome donor cells. In the case of exosome incubation, the drug diffuses naturally into the exosome based on per concentration gradient. By contrast, in the context of donor cells, the cells are initially subjected to treatment with the pharmaceutical agent, which is then secreted in the form of exosome-loaded drug exosomes[51]. The efficiency is contingent upon the concentration and hydrophobicity of drugs. Higher concentrations of hydrophobic drugs achieve higher loading efficiencies[52]. This method offers several advantages, including simplicity of operation, preservation of exosome integrity, and maintenance of exosome activity[53]. Nevertheless, this approach exhibits reduced loading efficiency and necessitates a larger drug amount. Active loading, in comparison, enhances the loading efficacy of drugs through more robust techniques, including the utilization of physical methods such as sonication, electroporation, extrusion, and freeze-thawing to facilitate the penetration of drug molecules into exosomes.

Recent findings indicate that certain advanced drug loading techniques excel in improving loading efficiency. Especially microfluidic technology offers new opportunities for efficient load of therapeutic agents into exosomes[54]. The Exosome Nanopore Apparatus (ENP), as a novel nanofluidic device, employs nanoscale channels that are compatible with exosome dimensions for the targeted delivery of therapeutic agents. The exosome's structural and functional integrity is preserved through a process of mechanical compression and fluid shear, which facilitates the permeabilization of the exosome membrane and enables the loading of drugs from the surrounding solution into the exosome[55].

All in all, the characteristics of the drug, the stability of the exosome, and the ultimate therapeutic effect must be considered when selecting an appropriate loading method (Figure 3). As exosome delivery research continues, more innovative and efficient drug loading techniques may be developed in the future.

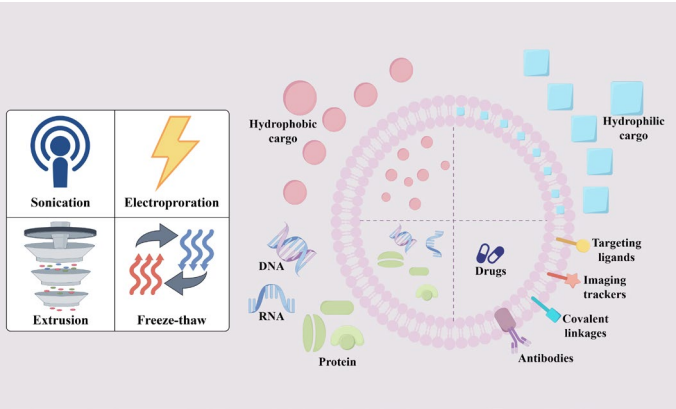

Figure 3: The most common exosome active cargo loading techniques currently employed (left) and different types of cargoes loaded with exosome (right).

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2.2.6. Characterization of exosomes

Exosomes can be characterized by their size, protein, and lipid content. Several techniques have been developed to characterize exosomes, including Fluorescence activated Cell Sorting (FACS), Western blotting (WB), nanoparticle tracking analysis (NTA), dynamic light scattering (DLS), mass spectrometry (MS), and various microscopy techniques. These techniques provide key tools for a comprehensive investigation of exosome structure and function[56]. The official document published by the International Society for Extracellular Vesicles (ISEV) provides indicative recommendations for the characterization of exosomes: Primarily, individual exosomes should be characterized by at least two different techniques, whereby exosome size obtained by NTA or DLS should be compared with image structures provided by transmission electron microscopy (TEM) or atomic force microscopy (AFM) to image structures to differentiate exosomes from non-vesicular extracellular particles (NVEP). Second, the characterization of exosomes entails the identification of specific surface marker proteins, while the absence or underrepresentation of other proteins is excluded[57]. The specific surface-marketed proteins are divided into two categories: extracellular proteins that are transmembrane or lipid-bound, which typically include the four transmembrane proteins (CD81, CD63, CD87, and CD9), and cytoplasmic proteins, the main ones of which include actin, microtubulin, GAPDH, ALIX, and TSG101[58]. Both categories are commonly implicated in membrane fusion, signal, and exosome biogenesis[59]. The most frequently used negative marker proteins are apolipoprotein A1/2 (APOA1/2), apolipoprotein B (APOB), and albumin (ALB)[60]. In addition to these specific markers, characterization of exosomes often detects other proteins such as flotillin, various Rab proteins, antigen-presenting proteins (MHCI and MHCII), and heat shock proteins (Hsp70 and Hsp90)[61]. While the proteins that characterize exosomes are extensively studied, the lipid composition is not as detailed. The comprehensive lipidomic profile of exosomes is typically ascertained through MS. Discrepancies in the lipidome between exosomes and their parental cells can be attributed to the incorporation of lipids originating from the Golgi apparatus in the former [62]. It has been shown that cholesterol (CHOL), SM, glycosphingolipids, and PS are 2–3 times more abundant in exosomes than in cells[63], which increases the stiffness of exosome membrane. The stiffness is essential for their stability and circulation in biological fluids, which helps exosomes prevent degradation[64].

3. Therapeutic role of exosomes in ophthalmic diseases

3.1. Diabetic retinopathy (DR)

DR is a common microvascular complication of diabetes mellitus (DM) and one of the leading causes of vision loss in adults, one-third of whom have DR. It is a complex retinal vascular disease of the retina characterized by increased vascular permeability, retinal ischemia, and edema, and neovascularization[65]. DR is generally classified into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Early features of NPDR include increased vascular permeability, capillary obstruction, microaneurysms, punctate hemorrhages, hard exudation, and wadding soft exudation[66]. PDR is a much more advanced stage of DR characterized by neovascularization, vitreous hemorrhage, and traction retinal detachment due to severe hypoxia [67]. Diabetic macular edema (DME) can occur at any stage of DR and is the leading cause of vision loss [68]. At present, the main therapeutic strategy for DR is to manage microvascular complications. Intravitreal injection of anti-vascular endothelial growth factor (VEGF) therapy has been widely used for the treatment of DME and to inhibit retinal neovascularization, which improves visual function and reduces neovascularization to some extent. However, the use of anti-VEGF drugs is hampered by frequent injections, potential therapeutic resistance, patient compliance, and financial burden[69]. Additionally, within 1-6 weeks of anti-VEGF therapy, patients may develop anti-VEGF syndrome with sudden loss of vision[70]. Prior to the advent of anti-VEGF therapy, laser photocoagulation was the standard of care for DME and PDR, by damaging the poorly perfused areas of retina, reducing oxygen demand and hypoxia, and decreasing VEGF production, thereby increasing the oxygen supply to the remaining retina[71], preventing neovascularization and promoting its atrophy, but this approach may also lead to choroidal effusion, exudative retinal detachment, macular edema, visual field defects, and night vision loss, among other complication[72]. Treatment options for PDR also include intravitreal injections of CS, which bypass blood-ocular barrier, exert anti-inflammatory, and inhibitory effects on vascular proliferation and vascular permeability, but also increase risk of cataract formation, elevated IOP, and retinal detachment [73]. In light of these considerations, the development of new therapeutic strategies to enhance the efficacy of DR treatment, including those based on exosomes, has become a particularly pressing priority.

ISSN 2706-6819 Vol.8, Issue 1: 35-50, DOI: 10.25236/IJFM.2026.080105

The results of several studies indicate that MSC-Exos have the potential to serve as effective therapeutic agents for the treatment of DR. In a high-glucose-induced DR rat model, the intravitreal injection of MSC-Exos overexpressing miR-126 effectively inhibited the high-mobility group box 1 (HMGB1) signaling pathway, thereby reducing retinal inflammation [74]. Other studies likewise indicate that BMSC-Exos containing miR-133b-3p suppressed angiogenesis and oxidative stress in DR mice by downregulating FBN1[75]. Similarly, the inhibition of integrin subunit α1 (ITGA1) and phospholipase Cγ1 (PLCG1) by MSC-Exos containing miR-222[76] and miR-30c-5p[77], respectively, has been demonstrated to retarded inflammatory responses and angiogenesis in DR. In addition to MSC-Exos, exosomes derived from alternative sources may be employed in DR therapy. The retinal microvasculature is composed of two primary cellular components: pericytes and endothelial cells. The formation, maturation, and stabilization of microvessels necessitate the interaction of these two cell types, and pathological fibrosis in PDR is associated with endothelial-mesenchymal transition (EndMT)[78]. The findings of a recent study indicate that retinal pigment epithelium-derived exosomes (ARPE-Exos) containing miR-202-5 inhibit EndMT through the TGF/Smad pathway, thereby offering a new avenue for the treatment of PDR[79].

As DR progresses to the PDR stage, neovascularization results in the occurrence of hemorrhage, leakage, and hyperplasia of the surrounding fibrous tissues, which collectively give rise to the formation of a fibrovascular membrane that leads to vitreous hemorrhage and detachment of the pulling retina[80]. Retinal Müller cells (MCs) play a pivotal role in retinal fibrosis, assuming the role of fibroblasts in the retina[81], and their secretion of connective tissue growth factor (CTGF), which is highly expressed in PDR retinas[82], is instrumental in promoting this fibrotic process. Platelet plasma-derived exosomes (PRP-Exos) isolated from the plasma of DM rats enhanced the fibrotic activity of MCs and upregulated CTGF expression via the PI3K/Akt pathway. It is thought that inhibiting this signaling pathway may prove beneficial in preventing the development of retinal fibrosis in PDR [83].

3.2. Age-related macular degeneration (AMD)

AMD is a degenerative eye disease that affects the macular region of the retina. It is prevalent among elderly population of Western countries, typically developing after the age of 50, with prevalence increasing with age [84]. The generally accepted pathogenesis of AMD is an ever-increasing demand on the ARPE for the degradation and removal of metabolic waste products throughout lifespan. With aging, ARPE is unable to meet this demand[85], leading to the deposition of retinal pigment and the formation of drusen, which is the typical clinical manifestation of AMD[86]. AMD is classified into early, intermediate, and advanced stages. Early AMD, which usually does not affect visual function, is characterized by medium-sized vitreous drusen (63 μm -125 μm). Intermediate AMD is characterized by the presence of large vitreous drusen (>125 μm) and/or ARPE abnormalities[87]. Two clinical forms of advanced AMD exist: (1) Atrophic (dry) AMD: presents as a non-exudative lesion, mainly characterized by focal atrophy of the ARPE and loss of macular receptors. (2) Neovascular (wet) AMD: presents as an exudative lesion, mainly characterized by the formation of choroidal neovascularization (CNV)[88]. At present, research into the treatment of dry AMD is in its infancy, and no significant progress has been made[89]. Treatment of wet AMD primarily aimed at CNV[90], and anti-VEGF therapy is the gold standard of care for patients with wet AMD[91], but this approach with unsatisfactory results due to the traumatic effects of repeated intraocular injections and long-term side effects (especially retinal atrophy)[92]. Consequently, the development of more personalized therapeutic and diagnostic strategies is of paramount importance. Exosomes are currently the subject of active investigation as a potential candidate for therapeutic intervention and as a means of providing an alternative to cellular therapies.

Upregulation of VEGF, a cytokine that plays a key role in angiogenesis and vascular permeability, drives this pathologic vascular growth in CNV [93]. Some evidence suggests that exosomal miR-410 is associated with the VEGF signaling pathway[94], and in the mouse model of oxygen-induced retinopathy (OIR), exosomal miR-410 effectively inhibits the expression of VEGF and prevents retinal neovascularization (RNV)[95]. Retinal astrocyte-derived exosomes were shown to inhibit VEGF-induced CNV by suppressing retinal microvascular endothelial cells migration in the laser-induced retinal injury rat model, an in vivo model of CNV in wet AMD [96]. Mφs are important cell populations in the vascular microenvironment, they can be polarized into a classically activated (M1) phenotype, which is pro-angiogenic, and an alternatively activated (M2) phenotype, which is anti-angiogenic, depending on the microenvironment. M2 contributes to a variety of pathological angiogenesis processes, including CNV and RNV [97]. MSC-Exos was shown to modulate Mφs polarization, reduce VEGF secretion, control aberrant neovascularization, and attenuate the pathogenesis of AMD[98].

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3.3. Glaucoma and Traumatic Optic Neuropathy (TON)

Glaucoma is a chronic optic neuropathy characterized by a progressive loss of RGCs in the optic nerve, leading to progressive, irreversible vision loss. The disease is typically accompanied by an elevation in intraocular pressure (IOP), which can lead to the death of RGCs if left untreated[99]. Glaucoma can be divided into two principal categories, primary and secondary, as well as two types, open-angle glaucoma (OAG) and closed-angle glaucoma (ACG)[100]. IOP is regulated by the dynamics between AH secreted by the non-pigmented ciliary epithelium (NPCE) and its drainage through two independent pathways—the trabecular meshwork (TM) and uveoscleral outflow pathway—determines the IOP[101]. Elevated IOP is considered to be the primary cause of glaucoma, thus, current strategies for glaucoma aim to reduce IOP, which can be achieved through pharmacological, laser therapy, or surgical intervention. The majority of therapeutic medications are formulated as eye drops, comprising prostaglandin analogs, which facilitate AH outflow, and beta-blockers, which reduce AH production. However, the use of eye drops is contingent upon the patient's adherence to a daily regimen over an extended period, affording only temporary respite from elevated IOP, furthermore, they do not forestall the onset of glaucoma. Long-term use may be accompanied by undesirable effects, including conjunctivitis, dry eye, and itching [102]. Laser therapy can moderately reduce IOP, however, to which IOP is reduced may prove challenging to control, with the potential for complications to arise, including insufficient or excessive IOP reduction, inflammation, pupillary aberrations, and glare[103]. The success of surgical intervention for glaucoma is contingent upon the occurrence of complications pertaining to wound healing. In certain cases, patients may necessitate prolonged pharmacological intervention beyond the immediate postoperative period [104] It is noteworthy that despite the effective control of IOP, some glaucoma patients continue to experience persistent RGCs loss and progressive optic nerve damage [105]. The utilization of exosomes as a therapeutic modality has recently emerged as a promising approach, with the potential to attenuate IOP and mitigate RGCs loss.

The TM, a porous structure situated in the anterior chamber of the eye, is composed of endothelial cells and extracellular matrix (ECM). It serves as a crucial regulator of AH and IOP. The remodeling of ECM is vital for maintaining a healthy IOP[106]. Active Wnt signaling plays a role in TM-mediated ECM expression and TM cell sclerosis. Aberrant Wnt signaling may lead to increased resistance to AH outflow, and elevated IOP[107]. NPCE-derived exosomes regulate the Wnt signaling pathway of the TM by transferring proteins and RNAs to influence ECM remodeling [108]. In two disparate models of transient glaucoma, induced with microbeads and laser photocoagulation in the anterior chamber, respectively, BMSC-Exos promoted neuroprotection and functional preservation of the RGCs, while simultaneously preventing progressive thinning of the retinal nerve fiber layer (RNFL) [109]. In the same year, results from the same authors demonstrated that BMSC-Exos exhibited a protective effect on RGCs and their axons in a long-term glaucoma model with high IOP, which they attributed to the miRNAs delivered to RGCs by BMSC-Exos[110].

Both TON and glaucoma can lead to irreversible visual impairment and loss of RGCs, sharing similar characteristics with respect to their underlying mechanisms. In a rodent model of optic nerve crush (ONC), intravitreal injection of MSC-Exos significantly ameliorated RGCs injury and promoted RGCs survival, as demonstrated by reference[111]. Additionally, human umbilical Wharton jelly-derived MSCs (hWJ-MSCs) demonstrated efficacy in protecting RGCs and promoting axonal regeneration to central targets, along with partial restoration of synaptic function in an ONC rat model[112]. Nevertheless, hWJ-MSC-Exos have primarily investigated their potential in treating glaucoma and TON through the enhancement of RGC survival and the promotion of glial cell activation, rather than in axonal regeneration like hWJ-MSCs per se[113].

3.4. Corneal diseases

The transparent, avascular cornea is located in the anterior sixth of the eye. Its dual function is to serve as the protective covering of internal structures while also providing approximately two-thirds of the dioptre[114]. The human cornea consists of five layers in order from anterior to posterior as follows: epithelium, stroma, endothelium, Bowman’s layer, and Descemet’s membrane. Each of the synergistic functions of these layers is critical for maintaining the physiological properties of the cornea and ensuring optimal visual vision[115]. Corneal diseases may have a number of etiological factors, including trauma, chemical burns, infection, or other underlying diseases[116]. They cause scarring, opacity, cloudiness, edema, and fibrosis of the cornea[117] that interfere with the normal structural and physiological functions of the cornea resulting in vision loss. Healing of corneal injury is a complex, multistep process that involves the death of keratinocytes beneath the corneal epithelium at the wound site, proliferation

ISSN 2706-6819 Vol.8, Issue 1: 35-50, DOI: 10.25236/IJFM.2026.080105

and migration of adjacent keratinocytes, differentiation of keratinocytes into myofibroblasts, proinflammatory chemokines-induced infiltration of inflammatory cells entry into the injured area[118], remodeling of ECM [119], and excess myofibroblasts leading to corneal fibrosis[120]. Therapeutic options for corneal disease include topical CS, nonsteroidal anti-inflammatory drugs (NSAIDs), immunomodulators, and antibiotics to modulate the inflammation, promote wound healing, and minimize scarring[121], but these therapies are not free of toxic side effects. Significant side effects of CS may accelerate the development of posterior subcapsular cataracts and elevated IOP[122]. NSAIDs have been linked to corneal ulceration and melting, with a high likelihood of corneal erosion and melting when NSAIDs with CS[123]. Common side effects of immunomodulators include ocular surface irritation, conjunctival congestion, and blurred vision[122]. Overuse of antibiotics can result in resistance and has a poor ability to penetrate the corneal stroma[121] and prove ineffective for deep corneal wounds. Corneal transplantation is a treatment for severe corneal disease, replacing scarred and fibrotic tissue, restoring clarity, and improve visual acuity. However, immune-mediated allograft rejection is a significant cause of corneal graft failure[124]. As discussed in the preceding section, in response to the associated physiological and pathological responses, a growing body of evidence supports that exosomes play a reparative and regenerative role in the corneal wound healing process.

The majority of corneal diseases affect the corneal stroma, which constitutes 90% of corneal thickness and plays a pivotal role in maintaining corneal transparency and resilience. It has been demonstrated that adipose mesenchymal stem cell-derived exosomes (ADSC-Exos) play an integral role in the treatment of corneal diseases by promoting proliferation and plasticity of corneal stromal cells through inhibition of matrix metalloproteinases(MMPs) and stimulation of collagen expression, as well as significantly increasing ECM synthesis[125]. The occurrence of corneal neovascularization following corneal injury is a common phenomenon, leading to persistent inflammation, consequently resulting in a reduction in corneal transparency through the promotion of a fibrotic response [126]. In the context of an excimer laser-induced corneal injury model in rats, MSC-Exos application topically reduced corneal inflammation, promoted corneal epithelial wound repair, diminished the formation of corneal clouds, and inhibited corneal neovascularization[127]. Despite the cornea's immune privilege, allogeneic rejection remains a significant challenge to successful corneal transplantation, with recipient T cell recognition of donor MHC antigen pathway driving the rejection[128]. In light of the immunomodulatory properties of MSC-Exos, subconjunctival injection of MSC-Exos attenuated inflammation, inhibited infiltration of $CD4^+$ T cells and $CD25^+$ T cells into the grafts, impeded the Th1 signaling pathway, thus promoted immune tolerance. To a certain extent, it suppressed corneal allograft rejection and prolonged corneal graft survival[129], [130]. It is anticipated that exosomes will prove to be an efficacious means of regulating the immune systems of organ transplant recipients.

4. Advances in exosomes in clinical trials

Exosomes, as a novel cell-free therapeutic vehicle, have shown great potential and promise in the treatment of multiple areas, including ophthalmic diseases. Ongoing clinical trials: are investigating exosomes derived from plants and human biological specimens[131]. Table 1 briefly summarizes exosomes that have been incorporated into clinical trials and for which complete clinical studies are available (Table 1).

Table1. Summary of the use of exosomes in clinical trials (source: clinical trials.com)

Indications	Year/Phase/Patients	Exosome source	Administration	Results/status
Dry eye post-refractive surgery and associated with blepharospasm (NCT05738629)	Feb.2023, Phase1/2, n=12	PSC-MSCs	Eye drops, 0.125 ml/single eye/1 time, QID for 12 weeks	Not yet recruiting
Dry eye in patients with cGVHD (NCT04213248)	Dec.2019, Phase1/2, n=27	UMSCs	Eye drops, 10ug/drop, QID for 14 days	Unknown status
Retinitis pigmentosa(NCT05413148)	Aug.2022, Phase2/3, n=135	WJ-MSCs	Single subtenon's injection for single eye	Recruiting

Abbreviations: UMSCs: Umbilical cord mesenchymal stem cells, PSC-MSCs: Pluripotent stem cell-derived mesenchymal stem cells, WJ-MSCs: Wharton jelly derived mesenchymal stem cells, QID:

ISSN 2706-6819 Vol.8, Issue 1: 35-50, DOI: 10.25236/IJFM.2026.080105

quarter in die, cGVHD: Chronic graft-versus-host disease.

Although some exosomes were used in clinical trials and complete clinical trial reports are available, scientific research on exosomes is primarily concentrated in the academic realm, and the number of exosomes that can fulfill research requirements is limited. Consequently, there are still problems and challenges in the realization of large-scale production of exosomes to support preclinical and clinical trials[132]. Consequently, there are still problems and challenges in the realization of large-scale production of exosomes to support preclinical and clinical trials[132]. In order to effectively convert exosomes into clinical-grade therapeutics, it is important to be in compliance with Good Manufacturing Practice (GMP) workflows. Within GMP standards, there are several key points to focus on: (1)High volume production: The production of exosomes is typically low volume, which is a limitation to their use in clinical therapeutics. (2) High quality and consistency: The physicochemical properties of exosomes and their purity are contingent upon the separation technique; thus, it is imperative to guarantee that the collected exosomes are of superior quality and consistency. (3) Storage conditions: The implementation of standardized storage conditions is necessary to ensure the stability and optimal activity of exosomes. (4) Therapeutic potential: Enhancing the therapeutic effect of exosomes can be achieved by an increase in the expression or concentration of therapeutic-acting biomolecules. (4) Precise delivery: The key to achieving therapeutic effects is to ensure that exosomes can be precisely delivered to specific tissues or cells. Since exosome biological effects depend on target cell uptake, controlling exosome secretion in organisms is crucial for clinical application[133].

Although some clinical studies have shown positive results, several aspects still need improvement and optimization to bring GMP-compliant exosome therapies to into clinical application stage.

5. Conclusions and future perspectives

Exosomes are rapidly emerging as a highly anticipated research hotspot in the field of ophthalmology, where they are valuable in the diagnosis, treatment, and prevention of ocular diseases, mainly due to they carry bioactive molecules, such as proteins, RNAs, and DNAs, which enables them to perform a variety of biological functions, including facilitating intercellular communication, immune regulation, biomarkers, restoration and regeneration, and as drug delivery vehicles. In studying ocular diseases, exosomes have therapeutic potential in various aspects such as anti-inflammation, anti-apoptosis, neovascularization inhibition, repair and regeneration, neuroprotection, and immunomodulation. However, there are still some challenges to realize the translation from bench to bedside: (1)Isolation and purification: Currently, traditional techniques are not efficient to isolate and purify exosomes, and it is difficult to obtain high-quality and high-purity products. (2) Large-scale production: Large-scale production of GMP-compliant exosomes on a large scale is a prerequisite for clinical trials, and but an effective solution has yet emerged. (3) Heterogeneity: Due to the heterogeneity of exosomes, their molecular mechanisms and signaling pathways in the treatment of ophthalmic diseases still inadequately studied. These issues still require further research and investigation.

To summarize, Exosome therapy is a novel cell-free therapeutic approach to diagnose, therapeutically treat and prevent ophthalmologic disease. It is necessary for multidisciplinary researchers to work together to address the above challenge. There is every reason to believe that exosomes will be a revolution in the treatment of ophthalmic diseases game-changer for ophthalmic disease treatment and a better future for patients.

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