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REVIEW

Mesenchymal Stem Cell-Derived Exosomes for Ocular Diseases: Therapeutic Mechanisms and Clinical Perspectives

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Abstract: Ocular diseases represent a major and increasing public health concern. Although current treatment options are available, the management of complex cases, such as corneal diseases, diabetic retinopathy, glaucoma, age-related macular degeneration, and uveitis, remains inadequate. Recent studies have demonstrated that mesenchymal stem cell-derived exosomes (MSC-Exos), obtained from bone marrow, adipose tissue, and umbilical cord, have emerged as a promising cell-free therapeutic platform for various ocular diseases. These nanovesicles can be delivered via systems such as topical eye drops and intravitreal injection, targeting ocular tissues to exert anti-inflammatory, anti-apoptotic, and tissue-repairing effects. This review systematically synthesizes recent advances and the molecular mechanisms underlying the use of MSC-Exos in treating ocular diseases. Moreover, it provides an in-depth discussion of the challenges in the clinical application of MSC-Exos in ophthalmology, including standardized production, dosage optimization, delivery system improvement, and targeting enhancement, and proposes engineered targeting strategies based on surface modification and carrier optimization. Overall, this work establishes a rigorous framework for advancing MSC-Exos from experimental models to clinical implementation, offering novel therapeutic strategies through these innovative biopharmaceuticals for previously untreatable ocular conditions.

Keywords: mesenchymal stem cells, targeted therapy, exosomes, ocular diseases, therapeutic mechanisms

Introduction

Ocular diseases are a major and growing global health concern, and the primary causes of vision impairment worldwide are uncorrected refractive error, cataracts, age-related macular degeneration, glaucoma, and diabetic retinopathy.[1] It is estimated that by 2020, out of the global population of 7.79 billion, approximately 43.3 million people were blind, and an additional 295 million people suffered from moderate to severe visual impairment, resulting in a visual impairment prevalence rate of 4.34%.[2] Ocular diseases significantly disrupt daily life, often presenting with subtle early symptoms that can go unnoticed. Additionally, the intricate anatomical structure of the eye and the presence of physiological barriers pose significant challenges to the early diagnosis and treatment of ocular diseases.[3] Traditional small-molecule drugs and steroids often face fundamental challenges, including low bioavailability and off-target effects, in treating ocular diseases. Furthermore, due to the eye's physiological barriers (eg, the cornea and blood-retinal barrier), these agents struggle to reach the lesion site and maintain effective therapeutic concentrations, often necessitating frequent administration. This increases the risk of systemic side effects, such as elevated intraocular pressure and cataract formation associated with long-term steroid use.[4,5] In contrast, while most of the therapeutic proteins and peptides exhibit superior targeting specificity, they are plagued by inherent limitations, including poor stability, high susceptibility to degradation, and short half-life.[6] Given the significant shortcomings and limitations of current prevention and

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treatment methods, which fail to effectively prevent or halt the progression of ocular surface and retinal diseases, exploring more effective alternative therapeutic approaches becomes crucial.[7,8]

Mesenchymal stem cells (MSCs) are multipotent stem cells that can differentiate into multilineage cells, such as osteoblasts, chondrocytes, and adipocytes,[9] which are extensively distributed in various tissues and organs of the human body, including bone marrow, adipose tissue, umbilical cord, and dental pulp.[10] In recent years, MSCs have been widely used in stem cell therapies for the treatment of various diseases, for instance, retinal diseases, due to their remarkable immunosuppressive capabilities and differentiation potential.[11–13] However, MSCs also have their shortcomings, such as poor quality control, tumorigenicity, lack of standardized management, and heterogeneity, which limit their clinical development.[14,15] To circumvent these challenges, an increasing number of studies are focusing on a new aspect of MSCs: their exosomes, which are nanosized extracellular vesicles (EVs) with a diameter ranging from 30 to 150 nm that are secreted by almost all cells and are believed to play a more critical role in intercellular communication.[16,17] Notably, although challenges related to scalable production, storage stability, and batch-to-batch standardization still need to be addressed in clinical applications, MSC-Exos possess significant advantages compared to emerging alternative therapies (such as viral vectors for gene therapy or synthetic nanoparticles): they exhibit innate biocompatibility, demonstrate low immunogenicity, possess natural tissue-homing capabilities, and circumvent the mutagenic risks associated with gene therapies.[18,19] As an innovative treatment modality, MSC-Exos demonstrate the potential to integrate multiple advantages. Firstly, as natural nanocarriers, their excellent biocompatibility and low immunogenicity enable them to effectively cross physiological barriers and deliver protective bioactive cargo (eg, nucleic acids, proteins) to otherwise hard-to-reach areas within the eye.[20] Secondly, unlike synthetic nanoparticles, MSC-Exos inherently carry therapeutic functions from their parent cells, including anti-inflammatory, anti-fibrotic, and neuroprotective activities, thereby unifying the "drug" and the "delivery system".[21] Beyond their role as innate biological vehicles, they can be strategically engineered into precision therapeutic platforms. Their membranes can be functionally modified with targeting ligands (eg, peptides), and their lumens can be loaded with exogenous therapeutic agents (eg, small-molecule drugs, nucleic acids), thereby enhancing their specificity and efficacy in treating ocular diseases.[17,22,23] This engineering flexibility provides MSC-Exos with a distinct advantage over traditional small-molecule drugs and steroids, enabling a targeted, multi-mechanistic therapeutic approach for complex pathologies.

In addition, engineered MSC-Exos can also enhance their targeting ability and become a precise drug delivery system, especially in the treatment of inflammatory and autoimmune diseases.[24–26] Studies have shown that subconjunctival injection of human umbilical cord MSC-Exos (hucMSC-Exos) can improve the proliferation and migration of corneal epithelial cells, thereby promoting corneal wound healing and regeneration.[27,28] In addition, adipose mesenchymal stem cell-derived exosomes (ADSC-Exos) can regulate microglia-mediated neuroinflammation to alleviate retinal ganglion cells (RGCs) damage caused by high intraocular pressure, thereby assisting in the treatment of glaucoma.[29] These results indicate that MSC-Exos therapeutic strategies have shown multifaceted potential in the treatment of ocular diseases and bring new hope for many intractable ophthalmic diseases.

In this review, to comprehensively cover MSC-Exos research in ocular diseases, we searched PubMed, Google Scholar, Scopus, and Web of Science. Keywords like "mesenchymal stem cell exosomes", "retinal diseases", "corneal wound healing", "glaucoma", and "age-related macular degeneration" were used. We focused on English-language studies published from 2019 to the present, encompassing research articles and reviews regarding MSC-Exos in the aspects of ocular diseases. We then concentrated on discussing the therapeutic potential and mechanism of MSC-Exos in ocular diseases such as retinal diseases, corneal diseases, uveitis, and glaucoma (Figure 1). Furthermore, the limitations and challenges hindering clinical translation of MSC-Exos, along with strategies to overcome them, are discussed. The purpose of this review is to facilitate the clinical translation of MSC-Exos, spur in-depth research in related fields, and accelerate the development and application of new therapies.

Ocular Diseases

Eyes, as vital sensory organs, are fundamental for vision and play a pivotal role in human perception, which are composed of critical structures, including the cornea, iris, and lens, which work together to facilitate light perception, shape recognition, and color differentiation.[30] However, ocular diseases often pose a significant threat to this organ.[31]

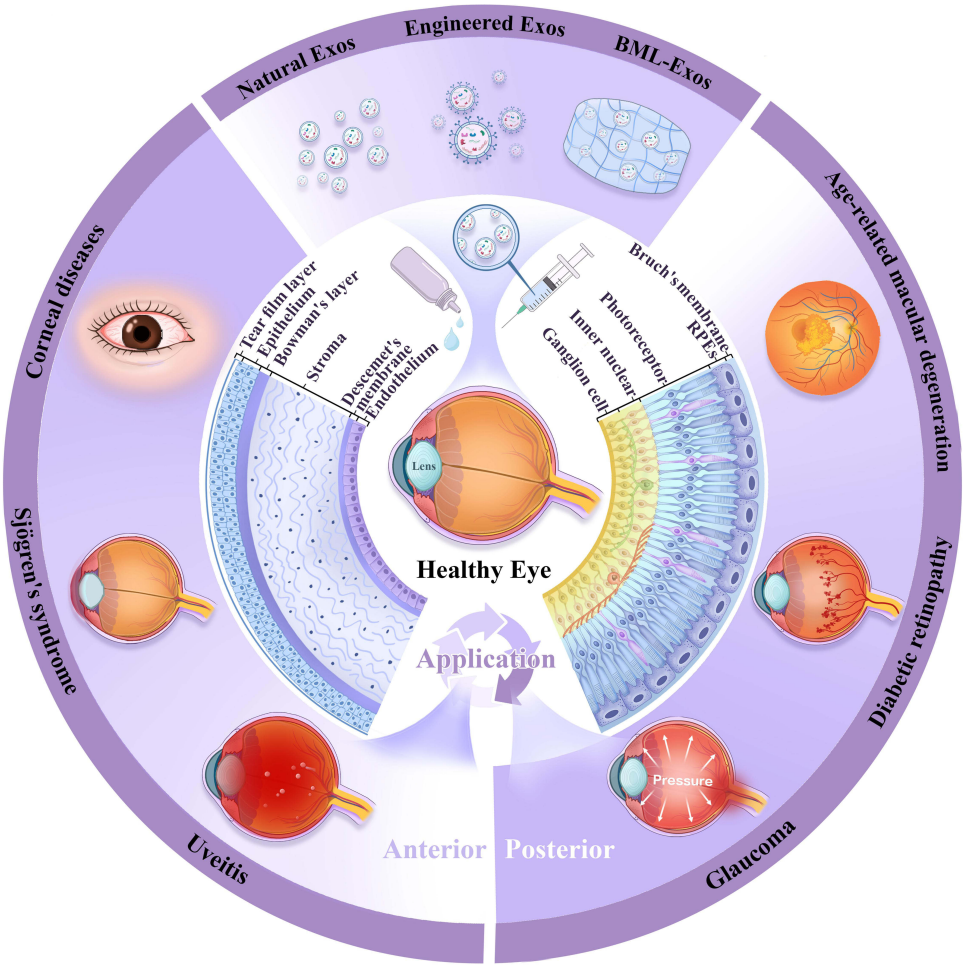

Figure 1 Schematic illustration of mesenchymal stem cell-derived exosomes (MSC-Exos) in ocular disease therapy.
Notes: MSC-Exos-based delivery systems, categorized into natural exosomes, engineered exosomes, and biomaterial-loaded exosomes (BML-Exos), enable targeted therapeutic interventions for ocular pathologies. MSC-Exos-based therapies are applied via diverse delivery routes (eg, topical, intravitreal) to manage anterior segment disorders (eg, corneal injury, uveitis) and posterior segment pathologies (eg, glaucoma, diabetic retinopathy, age-related macular degeneration). The illustration further highlights the anatomical complexity of ocular tissues, particularly the cornea and retina, to contextualize disease-specific therapeutic targeting. RPEs, retinal pigment epithelium cells.

The symptoms of ocular diseases are diverse and multifaceted. Visually, patients may experience blurred, decreased, or distorted vision, as well as night blindness, which are closely linked to lesions in various parts of the eye.[32] For instance, opacity and ulceration in the cornea can disrupt the normal refraction and entry of light, leading to vision problems, while retinal disorders result in distorted or diminished vision.[33,34] Eye discomfort may manifest as pain, swelling, photophobia, tearing, and itching, often accompanied by abnormal visual phenomena, such as floaters and flashes of light.[35] Structurally, glaucoma can lead to optic nerve atrophy and visual field defects, while uveitis is associated with characteristic changes, including iris congestion, adhesions, and vitreous opacities.[36,37]

Ocular diseases encompass a broad spectrum, ranging from corneal and conjunctival disorders in the anterior segment of the eye, to retinal and optic nerve diseases in the posterior segment, with each category further subdivided into numerous specific conditions.[38] These complexities require clinicians to possess extensive expertise and substantial clinical experience, making accurate diagnosis and differentiation of ocular diseases particularly challenging. Many ocular diseases progress insidiously during the early stages with subtle or undetectable symptoms. For example, age-related macular degeneration and retinitis pigmentosa develop gradually over a prolonged course, resulting in significant and lasting damage to vision and eye health.[39,40] In contrast, acute infectious keratitis presents with rapid onset and pronounced symptoms.[41] Additionally, the eye's structure is highly sensitive to genetic variations and vulnerable to adverse environmental factors. The intricate interplay of internal and external influences critically determines the health

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and functionality of the visual system.[42,43] A variety of pathologic conditions, including corneal diseases, glaucoma, diabetic retinopathy, age-related macular degeneration, and uveitis, frequently result in visual impairment. These disorders are further complicated by systemic factors, such as diabetes or autoimmune diseases, which exacerbate progression and complicate treatment.[44,45] Structural or functional damage often accumulates over time, culminating in chronic damage that is frequently irreversible, even with advanced therapeutic interventions.[46] Thus, timely diagnosis and treatment are imperative to safeguarding eye health and preserving vision.

MSC-Exos

Characteristics and Functions of MSC-Exos

According to the size and cell origin, EVs can be divided into three main categories, namely exosomes (30–150nm in diameter), microvesicles (100–1000nm), and apoptotic bodies (>1000nm).[47] Exosomes originate from the endocytic pathway, forming early endosomes in the cell membrane, further evolving into late endosomes, and finally transforming into multivesicular bodies (MVB). MVB contain internal vesicles (future exosomes). Ultimately, MVB can fuse with lysosomes or autophagosomes and then be degraded, or fuse with the cell membrane and release exosomes to the cellular outside through exocytosis (Figure 2A).[48–50] Exosomes can be released from various types of cells, including but not limited to macrophages, dendritic cells, lymphocytes, and even tumor cells, among others.[51] Among these cell types, MSCs are notable for their ability to secrete a higher quantity of exosomes compared to many others.[17] MSC-Exos have common surface markers like CD81, CD9, and CD63, which are also found in exosomes from other sources (Figure 2B). Moreover, they specifically express the surface markers of MSCs such as CD90, CD44, and CD73, convenient for confirming the identity of MSC-Exos and distinguishing them from other types of exosomes.[52,53] As a signaling molecule, MSC-Exos not only exert the same effects as parent cells, but also have a more stable membrane structure than MSCs, providing broader prospects for disease treatment.

MSC-Exos have a wide range of biological functions, and gaining insight into these functions is essential for understanding their role in health and disease. 1) Signal transduction: As a medium for intercellular communication, MSC-Exos can transport their cargo to receptor cells in a variety of ways, such as directly binding to cell surface receptors, fusing with the plasma membrane, or internalizing, thereby interacting with the receptor cells and regulating various physiological and pathological processes (Figure 2C).[54,55] 2) Inflammation regulation: On the one hand, MSC-Exos may carry and transmit inflammatory mediators, such as cytokines and miRNAs, and then promote the activation of inflammasomes and the aggravation of inflammatory responses. On the other hand, they can reduce the production of inflammatory factors by transmitting specific miRNAs, such as miR-181c, which can reduce TLR4 expression and NF-κB activation.[56] 3) Immunomodulation: MSCs affect the polarization state of immune cells through MSC-Exos. For example, MSC-Exos can promote the generation of anti-inflammatory M2 macrophages or regulate the immune response by affecting the differentiation and function of T cells.[57] 4) Repair and regeneration: MSC-Exos exhibit protective and therapeutic properties in wound healing and tissue regeneration by promoting the repair of damaged tissues, highlighting their significant potential in regenerative medicine.[58–60] 5) Disease diagnosis: Proteins, nucleic acids and other molecules contained in MSC-Exos can be used as biomarkers for early disease diagnosis and monitoring.[61,62] The functional molecules found in exosomes differ depending on the cells from which they are secreted and are affected by the surrounding cellular environment. This diversity in molecular composition enables MSC-Exos to perform various biological functions.[63]

Preparation and Modification of MSC-Exos

To develop a rapid, simple isolation method with high purity and high recovery is crucial for advancing MSC-Exos research and their large-scale application in medical practice.[64] Currently, commonly used exosome extraction and isolation methods primarily include ultracentrifugation, size exclusion chromatography, ultrafiltration, polymer precipitation, and immunoaffinity. Ultracentrifugation is widely used, but time-consuming, labor-intensive, and may produce impurities (Figure 3a).[65,66] Size exclusion chromatography is another promising method for MSC-Exos separation.[67,68] The separation principle is that a solution containing exosomes passes through a stationary phase composed of a porous

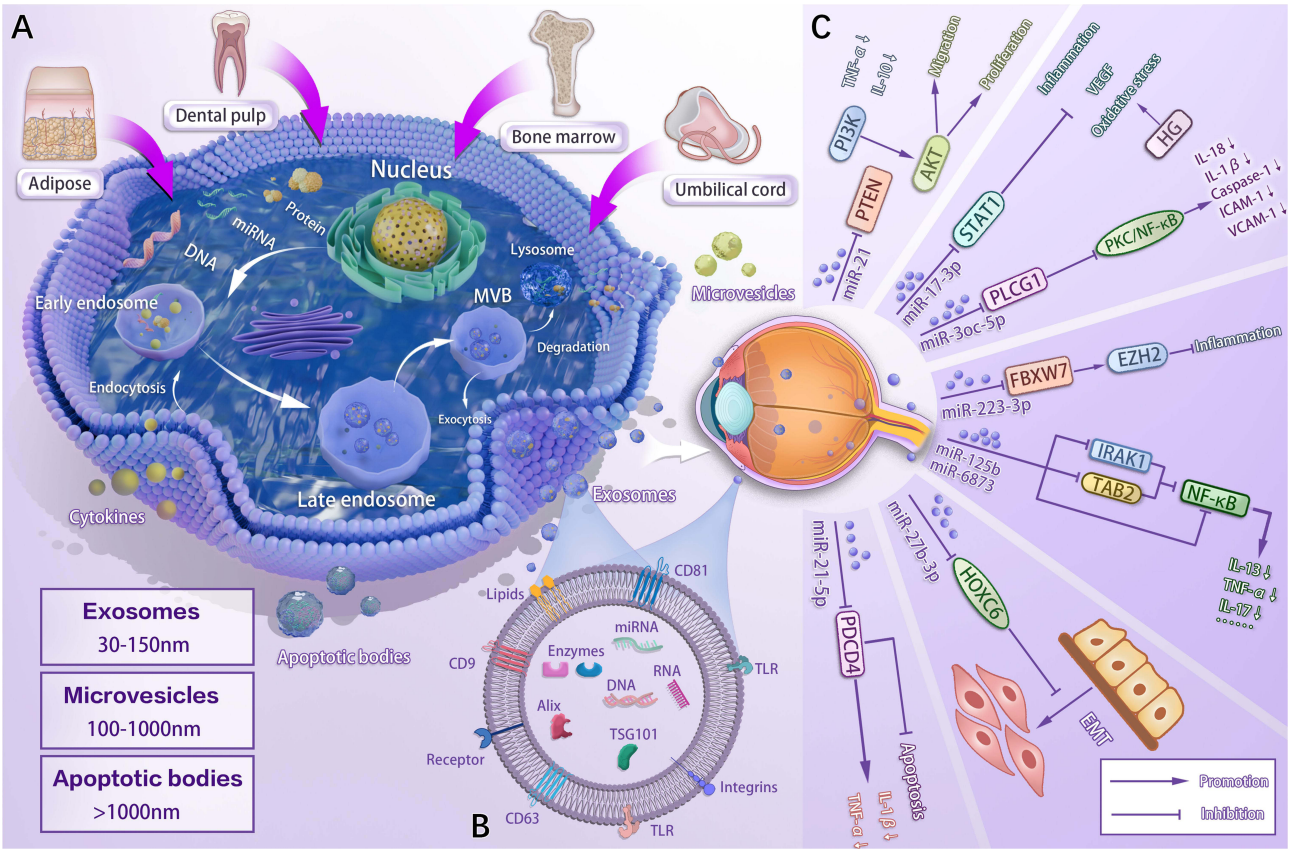

Figure 2 Biogenesis, contents, and mechanisms of action of mesenchymal stem cell-derived exosomes (MSC-Exos) in ocular diseases.

Notes: (**A**) MSC-Exos originate from the endocytic pathway, form early endosomes within the cell membrane, further evolve into late endosomes, and finally transform into multivesicular bodies (MVB). MVB can fuse with lysosomes for degradation, or fuse with the cell membrane and release exosomes to the outside of the cell through exocytosis. (**B**) MSC-Exos are rich in a variety of typical contents, including CD9, CD63, CD81 and other iconic membrane proteins, which belong to the tetraspanins family; Alix, TSG101 and other exosome-related proteins, which participate in the formation and secretion regulation of multivesicular bodies; mRNA, DNA, RNA, which can mediate the transmission of genetic information between cells; functional proteins include Integrins that can regulate target cell adhesion, and TLR (Toll-like receptors) that participate in immune regulation. (**C**) These molecules together give exosomes functional characteristics such as regulating intercellular communication, tissue repair and immune regulation.

Abbreviations: IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; PTEN, phosphatase and tensin homolog; STAT1, signal transducer and activator of transcription 1; PKC, protein kinase C; NF-κB, nuclear factor kappa B; HG, high glucose; VEGF, vascular endothelial growth factor; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; PLCG1, phospholipase Cγ1; FBXW7, F-box and WD repeat domain-containing protein 7; EZH2, enhancer of zeste homolog 2; IRAK1, interleukin-1 receptor-associated kinase 1; TAB2, TGF-Beta activated kinase 1 (MAP3K7) binding protein 2; PDCD4, programmed cell death 4; HOXC6, homeobox protein Hox-C6; EMT, epithelial-mesenchymal transition.

polymer. Particle molecules then pass through in order of size (large particles are eluted first, and small particles are eluted later), thus achieving material separation (Figure 3b).[69] Similar to the principle of size exclusion chromatography, ultrafiltration is a method for screening exosomes by using filter membranes with different pore sizes or molecular weight cut-offs (Figure 3c).[70] Currently, commercial exosome isolation kits based on polymer precipitation are commercially available (Figure 3d).[71,72] The immunoaffinity technique involves the isolation of exosomes through the tagging of exosome membrane proteins, enabling them to bind specifically to specific antibodies (Figure 3e).[73] Despite the array of techniques accessible for MSC-Exos isolation, none have proven entirely efficacious to date. Each method is accompanied by its own distinct constraints.[74,75] In recent years, the integration of multiple separation and purification techniques has emerged as a dependable approach for the effective isolation of exosomes.[76–78] For example, methods combining tangential flow filtration and size exclusion chromatography can improve the efficiency of separation and the purity of MSC-Exos.[79] In addition, the development of microfluidic technology based on physical and biological properties provides new possibilities for MSC-Exos isolation.[80] This technology utilizes the characteristics of microscale fluids to capture and analyze exosomes, featuring high-throughput, low sample consumption, and high purity.[81,82]

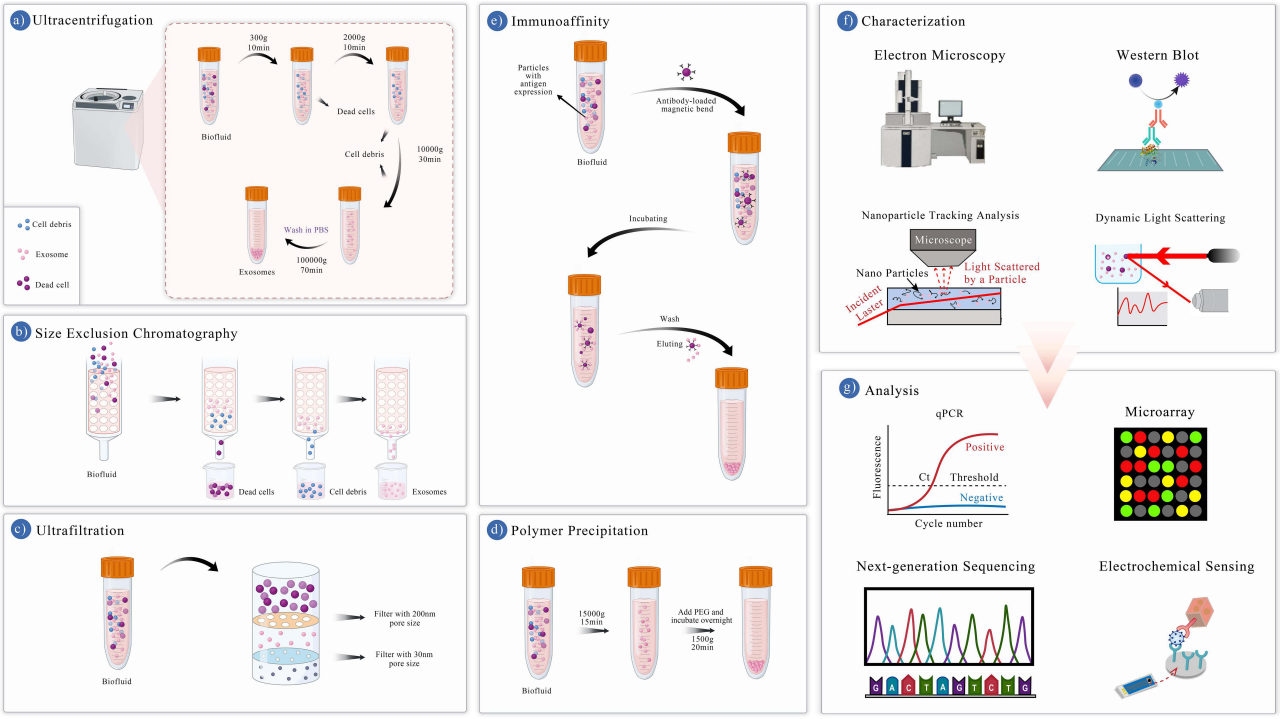

Figure 3 Schematic diagram of the isolation, characterization, and analysis of functional properties of mesenchymal stem cell-derived exosomes (MSC-Exos).
Notes: (**a**) Ultracentrifugation is to centrifuge the biological fluid at different speeds and times in sequence, remove dead cells and cell debris in turn, and finally separate the exosomes by centrifugation at a high speed of 100000g for 70 minutes. (**b**) Size exclusion chromatography is to let the biological fluid pass through the chromatographic column, separate according to molecular size, and then the exosomes with small particles will flow out. (**c**) Ultrafiltration is to let the biological fluid pass through filter membranes of different pore sizes in sequence, first remove dead cells and debris, and then retain exosomes. (**d**) Polymer precipitation is to add polyethylene glycol (PEG) to the biological fluid and incubate overnight to form a hydrophobic microenvironment around it, thereby causing exosome precipitation, and then further purifying the exosomes. (**e**) Immunoaffinity is to mix the biological fluid with magnetic beads carrying antibodies to capture particles containing specific antigens, wash impurities and elute exosomes. (**f**) Common characterization methods for exosomes include electron microscopy, Western blot (WB), nanoparticle tracking analysis (NTA), and dynamic light scattering (DLS). (**g**) Common analytical methods for exosomes include quantitative real-time polymerase chain reaction (qPCR), microarrays, next-generation gene sequencing, and electrochemical sensing technology.

MSC-Exos are progressively undergoing modifications to enhance their functionality, stability, and targeting capabilities owing to their natural biocompatibility.[83] A diverse array of methodologies, encompassing biological, chemical, and physical approaches, is utilized in the generation of modified exosomes.[84] Biological modification of MSC-Exos usually involves genetic engineering of parent cells to direct the fusion of the gene sequence of a protein or peptide with the gene sequence of a selected exosomal membrane protein. Yang et al introduced cancer cell-specific peptides CDX (FKESWREARGTRIERG) and CREKA (Cys-Arg-Glu-Lys-Ala) into the N-terminus of CD47 (a transmembrane protein abundant in exosomes) and transfected parental cells with plasmids encoding peptide-CD47 fusions, and the surface-modified exosomes showed significant targeting ability in brain tumors in vivo.[85] Modification of exosome surface with targeting peptides through covalent and noncovalent modification to improve the specificity of exosomes for their targets is another effective chemical strategy for engineering MSC-Exos.[86,87] Xing et al proposed a strategy to add nitrogen groups to MSC-Exos via metabolic glycoengineering and then used click chemistry to anchor these exosomes to dibenzocyclooctyne (DBCO)-modified collagen hydrogels, thus slowing down the in vivo clearance of MSC-Exos. After subcutaneous implantation, the release of MSC-Exos contents from this composite system promoted angiogenesis.[88] By modifying MSC-Exos using physical factors such as ultrasound, electrical stimulation, magnetic field, light radiation, and temperature, engineered exosomes can achieve more precise targeting capabilities.[89,90] In addition, in order to efficiently load therapeutic molecules to enhance the therapeutic potential of MSC-Exos, a variety of techniques have been developed, including ultrasonic treatment, electroporation, mechanical extrusion, freeze-thaw cycles, cell membrane permeabilization, and hypotonic pressure dialysis.[91–93] Yerneni et al incorporated albumin and curcumin into exosomes sequentially using sonication.[94] This process produced MSC-Exos as carriers with remarkable

stability and anti-inflammatory properties. Therefore, the modification of MSC-Exos has become a key area of biomedical research. With the continuous advancement and optimization of drug loading strategies and modification technologies, the clinical application prospects of MSC-Exos will become broader.

Rigorous characterization of isolated MSC-Exos is crucial for verifying their quality and authenticity. This process typically requires a combination of techniques to analyze their physical properties and biological composition (Figure 3f and g). Electron microscopy, such as transmission electron microscopy (TEM) or scanning electron microscopy (SEM), is regarded as the gold standard for directly observing the cup-shaped morphology and integrity of vesicles.[95] It provides direct evidence of the presence, size, and morphology of exosomes. Nanoparticle tracking analysis (NTA) and dynamic light scattering (DLS) are commonly used techniques for determining particle size distribution and concentration.[96] NTA allows for tracking the Brownian motion of individual nanoparticles in liquid suspension and measures exosome movement by monitoring each particle through image analysis.[97,98] This motion can then be correlated with particle size. In contrast, DLS is a technique used to determine the average hydrodynamic diameter of isolated particles with a relatively uniform size distribution.[98] It calculates the average particle size in a sample by analyzing light scattering patterns. Additionally, Western blot (WB) remains a core method for detecting specific exosomal marker proteins (eg, CD9, CD63, CD81, TSG101, Alix).[99]

Furthermore, a comprehensive analysis of the molecular cargo of MSC-Exos is essential. Several molecular methods are available for exosome analysis. Microarray technology enables high-throughput screening of nucleic acid expression profiles within exosomes, facilitating the rapid identification of differentially expressed genes or miRNAs.[100] However, microarrays are limited to detecting sequences homologous to those on the array.[99] Quantitative real-time polymerase chain reaction (qPCR) is the gold standard for validating the expression levels of specific nucleic acids, offering high sensitivity and specificity, though its throughput is limited.[99] Next-generation sequencing is a hypothesis-free approach that does not rely on prior sequence information. It offers the capability to detect novel genes with good sensitivity to quantify rare variants and transcripts.[97] Recently, electrochemical sensing has emerged as a promising technology. It utilizes specific recognition elements (eg, antibodies, aptamers) to generate detectable electrical signals, enabling ultrasensitive and rapid quantification of exosomal surface markers or cargo.[101] Although further optimization of specificity and standardization are still needed, this approach holds great potential for point-of-care diagnostics. In summary, these complementary techniques allow for rigorous characterization of exosomes in terms of their physical properties, molecular composition, and functional features.

Applications of MSC-Exos in Ocular Diseases

Corneal Diseases

The cornea, one of the most important components, is the outermost transparent refractive medium of the eye, serving not only to focus light but also to shield the internal ocular structures from potential environmental hazards.[102] From a structural perspective, the human cornea consists of five distinct layers, which include the epithelium, Bowman's layer (anterior elastic layer), stroma (also known as the substantia propria), Descemet's membrane (posterior elastic layer), and endothelium. The epithelium, stroma, and endothelium are regarded as the most pivotal ones among the corneal structure, because their respective functional roles are fundamental to maintaining the cornea's normal physiological functions and its ability to repair when damaged.[103] The etiology of corneal diseases is multifaceted, encompassing external environmental oxidative stress, injury-induced stimuli, microbial infections, autoimmune conditions, inflammation due to medical interventions, neovascularization, scarring, and ulceration, which seriously impair patients' life quality and psychosocial well-being.[104–106] The recovery from corneal conditions involves multiple mechanisms including the survival, proliferation, and migration of corneal epithelial cells.[107] Additionally, neuroinflammation within the corneal microenvironment and the remodeling of the extracellular matrix (ECM) are essential aspects of the healing process.[108,109] The management of corneal injuries currently incorporates a spectrum of therapeutic strategies, ranging from topical applications (comprising antibiotics, artificial tear substitutes, immunomodulatory agents, and anti-inflammatory drops) to surgical procedures (including laser treatments and corneal transplant surgeries).[110,111] Due to the invasiveness of surgical procedures and the constraints associated with donor corneal availability, MSC-Exos therapy

is garnering significant research interest for the treatment of corneal diseases, attributed to its low immunogenicity and high biocompatibility.[112,113]

Studies have shown that MSC-Exos exhibit excellent therapeutic effects when applied to animal models of corneal burns. The study found that in both in vitro and in vivo experiments, ADSC-Exos can promote the proliferation and migration of corneal endothelial cells (CECs), inhibit cell senescence and endothelial-mesenchymal transition, improve mitochondrial function and regulate related signaling pathways, thereby repairing and regenerating corneal damage.[114] Further investigations have clarified the mechanisms behind the therapeutic effects of exosome-based therapies. Specifically, miR-21 delivered by MSC-Exos promotes CECs proliferation and migration to accelerate corneal wound healing by specifically targeting the 3' untranslated region of PTEN, thereby suppressing PTEN expression, activating the PTEN/PI3K/Akt signaling pathway, and ultimately facilitating the repair of corneal injuries.[27] Moreover, MSC-Exos seem to reduce inflammation and apoptosis after corneal injury, demonstrated by an increase in the expression of the anti-inflammatory factor IL-10 and a decrease in the RNA levels of pro-inflammatory cytokines, including IL-13, IL-5, and TNF-α, along with the pro-apoptotic protein Caspase-8.[115] Beyond their anti-inflammatory actions, MSC-Exos also promote the restoration and viability of injured neurons.[116] In addition, corneal stromal MSC-Exos (CSSC-MSC-Exos) were found to decrease the expression of Acta2, a fibrotic gene. These exosomes also inhibited neutrophil infiltration, minimized scarring, and helped restore the normal morphology of the cornea by transferring microRNAs to keratocytes.[117] Likewise, MSC-Exos exerted a favorable effect on corneal epithelial wound healing by reducing the levels of angiogenesis-related matrix metalloproteinases (MMP-2 and MMP-9) and downregulating pro-angiogenic factor (VEGF).[115,118] Furthermore, miR-21-5p, delivered by MSC-Exos, effectively inhibited scar formation by targeting the programmed cell death protein 4 (PDCD4) gene. This action reduced the expression of genes related to fibrosis and collagen, thereby promoting the preservation of corneal transparency and maintaining retinal structural integrity.[119] Taken together, MSC-Exos exhibit significant effects in the treatment of corneal diseases, effectively improving the healing process after corneal injury by regulating immune responses and promoting corneal epithelial cell proliferation and migration.

Various engineering methods have been used to enhance the ability of MSC-Exos to deliver drugs or bioactive molecules to corneal lesions, bringing new hope for corneal damage repair. Electroporation technology was used to load miRNA 24–3p into ADSC-Exos (Exos-miRNA 24–3p), which was then incorporated into a thermosensitive hyaluronic acid hydrogel-controlled release system. In a corneal alkali burn model, this system effectively regulated the release of Exos-miRNA 24–3p, thereby accelerating corneal epithelial defect healing, reducing stromal fibrosis and macrophage activation, and significantly promoting the regeneration of damaged corneal tissue.[22] A thermosensitive chitosan-based hydrogel (CHI) was developed and enriched with induced pluripotent stem cell-derived MSC-Exos (iPSC-MSC-Exos) containing miR-432-5p which can target translocation-associated membrane protein 2 (TRAM2), thereby prevent ECM deposition and enhancing regeneration of the corneal epithelium and stroma (Figure 4A–E).[113] Similarly, by employing a peptide linker cleavable by matrix metalloproteinases (MMPs), anti-tumor necrosis factor-α antibody (aT) was precisely anchored onto ADSC-Exos to create a surface-modified exosome complex (aT-Exos). Compared to aT alone, natural exosomes, or their simple mixture, aT-Exo displayed superior performance in reducing inflammation and promoting corneal repair in a corneal injury model. Notably, the elevated expression of MMPs in the corneal injury microenvironment facilitated the release of aT from the exosome surface, significantly increasing its local concentration at the injury site. This precise targeted delivery not only enhanced the anti-inflammatory effects but also markedly promoted corneal tissue repair and regeneration.[120] Taken together, current evidence demonstrates that MSC-Exos offer unique advantages in the treatment of corneal diseases. Engineering technologies enable precise loading and targeted delivery of bioactive molecules, coupled with controlled release systems to precisely regulate the release and extend the duration of therapeutic efficacy. However, there remains a limited body of literature on combined therapeutic strategies in Exos-based corneal wound healing treatments. Therefore, future research should focus on developing and integrating these strategies, including the rational selection of specific targeting ligands and optimization of controlled release systems, to better enhance the therapeutic potential of MSC-Exos.

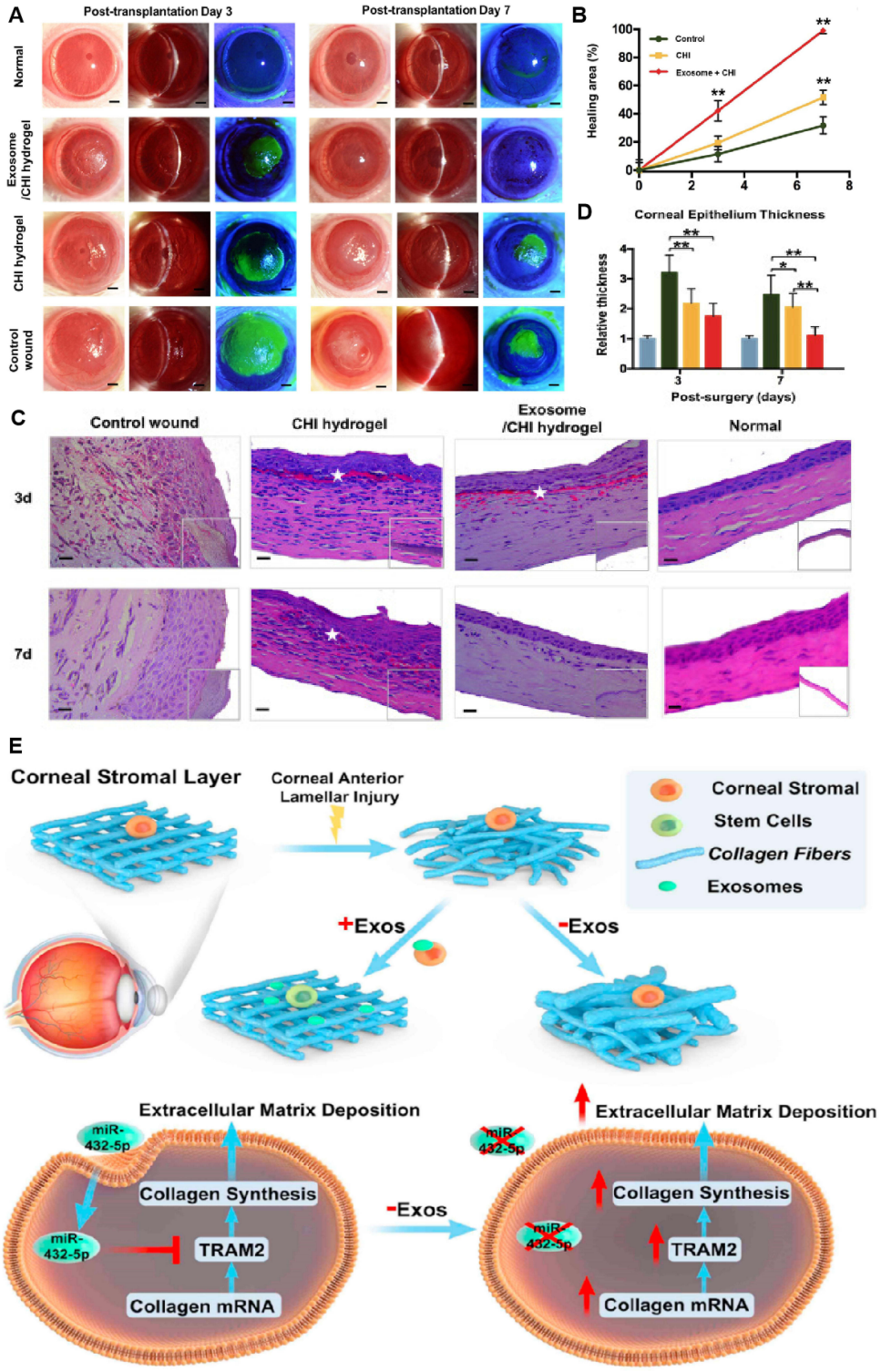

Figure 4 Application of iPSC-MSC-Exos hydrogels for corneal regeneration.

Notes: (**A**) Comparison of healing effects among the control group, CHI hydrogel group, and iPSC-MSC-Exos/CHI hydrogel group on day 3 and day 7 after corneal anterior lamellar injury. (**B**) Comparison of corneal epithelial healing rate after transplantation. Corneal wound area stained using a fluorescent dye and quantified under cobalt blue light. **P < 0.01 vs the control wound group. (**C**) The remaining CHI hydrogel (white asterisks) was shown in the newly synthesized corneal stroma, and the H&E staining in the iPSC-MSC-Exos/CHI hydrogel group exhibited more regular organization. (**D**) The epithelium regenerated to almost its normal thickness in the iPSC-MSC-Exos/CHI hydrogel treatment. *P < 0.05. **P < 0.01. (**E**) The interaction between corneal stromal stem cells and iPSC-MSC-Exos during the ECM remodeling after corneal anterior lamellar injury. Reproduced with permission from Tang Q, Lu B, He J et al. Exosomes-loaded thermosensitive hydrogels for corneal epithelium and stroma regeneration. Biomaterials. 2022;280:121320. *Copyright © 2022 Elsevier.*[113]

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Diabetic Retinopathy

Diabetic retinopathy (DR), a common microvascular complication of diabetes and the leading cause of blindness in adults, can be divided into two main stages based on the pathogenesis: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).[121,122] NPDR is often considered an early form of DR, characterized by the increase of vascular permeability and blockage, leading to retinal microaneurysms, cotton-wool spots, hemorrhages, and exudates. This stage progresses slowly, and patients may not notice the gradual worsening of the disease. PDR is a late stage of DR, characterized by the appearance of new but fragile blood vessels that are prone to rupture and cause bleeding.[123] Current treatments include laser photocoagulation, surgical ablation of neovascularization, and injection of anti-angiogenic drugs. However, the efficacy of these methods is limited, and there is a potential risk of disease recurrence and serious adverse reactions.[124,125]

Multiple preclinical investigations have examined the potential of MSC-Exos as a treatment for DR and its related complications.[126] Intravitreal administration of MSC-Exos suppressed neuroinflammation and apoptosis in a rat retinal ischemia model.[127] Inflammation is a core pathological process in the development of ocular diseases, particularly in conditions such as DR, AMD, and glaucoma.[128,129] MSC-Exos have been shown to possess potent anti-inflammatory properties and reduce ocular inflammation through multiple pathways. Firstly, MSC-Exos are rich in anti-inflammatory cytokines (eg, TNF-α, IL-6, and IL-1β), which can dampen the activation of pro-inflammatory pathways.[130] By delivering these molecules directly to target cells in the inflamed ocular tissue, MSC-Exos can promote the resolution of inflammation.[131] Additionally, MSC-Exos are equipped with a variety of microRNAs that can target and regulate the expression of genes involved in inflammation. For instance, microRNA-17-3p from hucMSC-Exos was found to specifically target signal transducer and activator of transcription 1 (STAT1), effectively mitigating inflammation and oxidative stress in DR mouse models.[132] By suppressing STAT1 activity, exosomal miR-17-3p alleviated oxidative damage, regulated blood glucose levels, decreased the levels of inflammatory mediators and VEGF, and protected retinal cells from apoptosis in DR mice (Figure 5A–K).

Subsequent studies have shown that in a streptozotocin (STZ)-induced diabetic retinopathy rat model, injection of MSC-Exos can inhibit retinal cell apoptosis and oxidative stress, protect retinal pigment epithelial cells (RPEs) from apoptosis and oxidative damage caused by high glucose (HG) conditions, and thus alleviate the development of diabetic retinopathy.[133] Mathew et al conducted a study evaluating the effects of MSC-Exos in a rat retinal ischemia model and found that retinal function was restored and neuroinflammation and apoptosis were reduced within 24 h after injection compared to injured but untreated controls.[127] In addition, after treatment with MSC-Exos, a significant improvement in apoptosis was observed in all layers of the retina, especially in the ganglion cell layer, where ischemia-induced apoptosis was significantly reduced. Moreover, MSC-Exos treatment also reduced the activation level of microglia and the expression of pro-inflammatory cytokines TNF-α and IL-6. Recent research has also unveiled the potential therapeutic role of hucMSC-Exos in the treatment of DR.[134] In a rat model of diabetes induced by STZ, the administration of hucMSC-Exos significantly suppressed the activation of the NLRP3 inflammasome, thereby alleviating retinal inflammation.[135] Histological examinations demonstrated that hucMSC-Exos improved the morphological structure of the retina, and concurrently, the functionality of the blood-retinal barrier (BRB) was enhanced, contributing to the mitigation of DR progression. Comparable findings were noted in the STZ-induced diabetic rat model, where BM-MSC-Exos mitigated retinal damage by suppressing the Wnt/β-catenin signaling pathway, leading to reduced oxidative stress and inflammation, effectively inhibiting pathological angiogenesis and attenuating vascular hyperpermeability.[136]

The study revealed that engineered MSC-Exos specifically targeted the HIF-1α/EZH2/PGC-1α signaling pathway by delivering miR-5068 and miR-10228, exhibiting excellent efficacy in improving retinal function.[137] Similarly, hucMSC-Exos delivered miR-30c-5p to target cell phospholipase Cγ1 (PLCG1), downregulated its expression in the DR model, blocked the PKC/NF-κB pathway, reduced the release of inflammatory factors (IL-1β, IL-18, Caspase-1), decreased the levels of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), and alleviated inflammation.[138] HucMSCs-Exos are also thought to improve diabetic retinal damage by delaying inflammatory response and angiogenesis in DR by targeting miR-18b of the MAP3K1/NF-κB axis.[139] MSC-Exos containing high levels of miR-133b-3p negatively regulate the expression of the fibrillin-1 gene (FBN1) for the treatment of DR.[140] BM-MSC-Exos

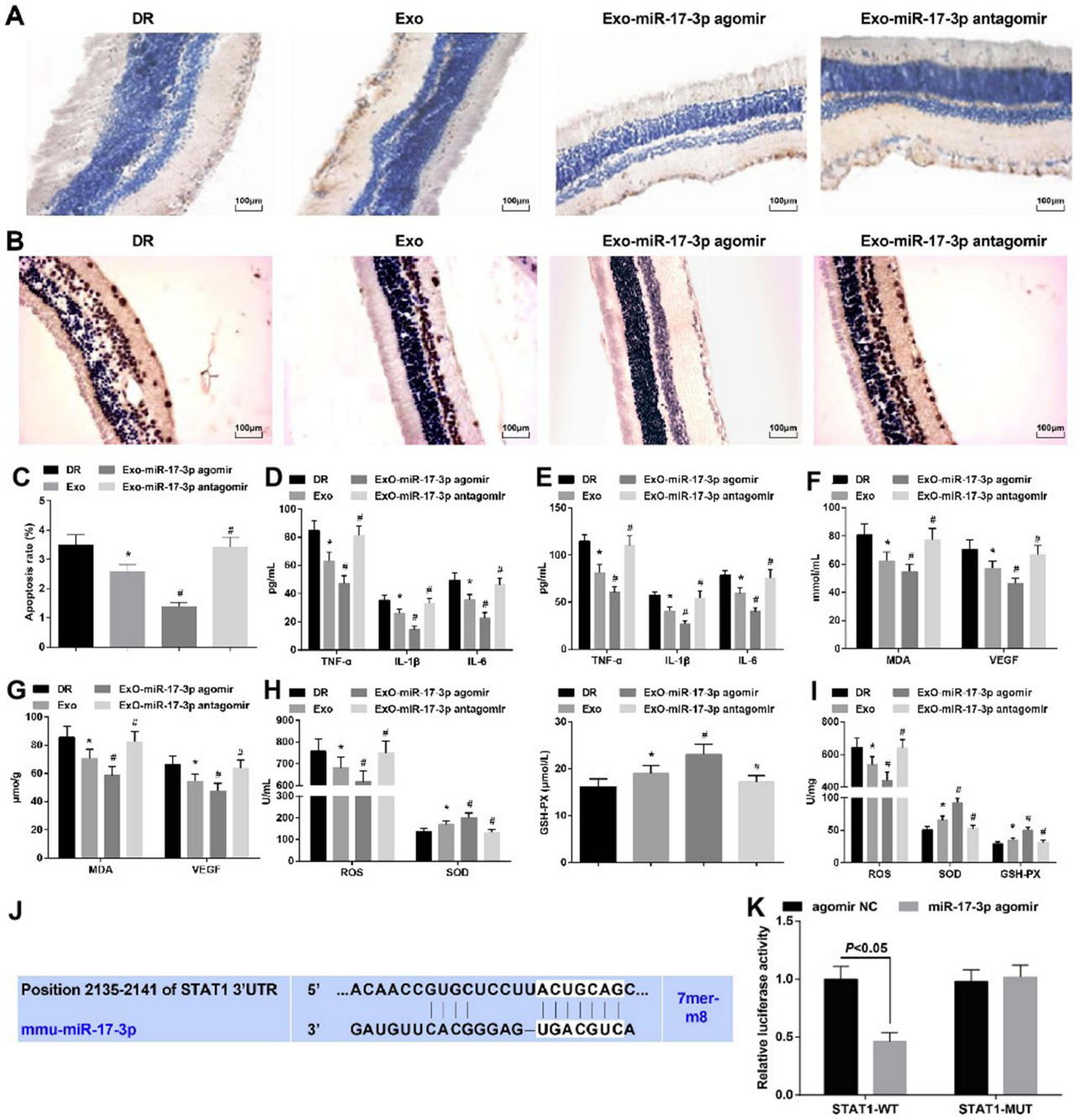

Figure 5 Therapeutic potential of hucMSC-Exos overexpressing miR-17-3p (Exo-miR-17-3p agomir) in diabetic retinopathy.

Notes: (**A**) HE staining showed that Exo-miR-17-3p alleviated the pathological changes of retinal tissues. (**B**) TUNEL staining revealed that Exo or Exo-miR-17-3p agomir inhibited retinal cell apoptosis. (**C**) Apoptosis rate of retinal cells in mice treated with exosomes. (**D**) Contents of TNF-α, IL-1β and IL-6 in serum of mice treated with exosomes. (**E**) Contents of TNF-α, IL-1β and IL-6 in retinal tissues of mice treated with exosomes. (**F**) Contents of MDA and VEGF in serum of mice treated with exosomes. (**G**) Contents of MDA and VEGF in retinal tissues of mice treated with exosomes. (**H**) Contents of ROS, SOD and GSH-Px in serum of mice treated with exosomes. (**I**) Contents of ROS, SOD and GSH-Px in retinal tissues of mice treated with exosomes. (**J**) The bioinformatics website predicted the presence of binding sites between miR-17-3p and STAT1. (**K**) Detection of the targeting relationship between miR-17-3p and STAT1 by dual luciferase reporter gene assay. *P < 0.05 vs the DR group. #P < 0.05 vs the Exo group. Reproduced with permission from Li W, Jin L yu, Cui Y bo, Xie N. Human umbilical cord mesenchymal stem cells-derived exosomal microRNA-17-3p ameliorates inflammatory reaction and antioxidant injury of mice with diabetic retinopathy via targeting STAT1. International Immunopharmacology. 2021;90:107010. *Copyright © 2021 Elsevier.*[132]

enriched in miR-486-3p also suppressed oxidative stress, inflammation, and apoptosis and promoted the proliferation of Müller cells under HG conditions.[141] In addition, the researchers found that loading bevacizumab (an anti-VEGF drug widely used in the treatment of DR) into BM-MSC-Exos successfully achieved a sustained neuroprotective effect on retinal cells. Specifically, this combined application mode significantly prolonged the duration of the therapeutic effect,

from only one month when used alone to two months, and remarkably reduced the frequency of intravitreal injections required for DR treatment.[142] Nevertheless, neither the sole use of bevacizumab alone nor its combination with BM-MSC -Exos effectively alleviated retinal inflammation. In a word, in animal models of DR, MSC-Exos including natural Exos and engineered Exos, exert anti-apoptosis and neuroprotective effects, which help maintain the structure and function of the retina. This, in turn, paves the way for the future clinical application of exosomes. Nonetheless, when it comes to the treatment of DR with MSC-Exos, in-depth and detailed research is still lacking in three key aspects: determining the appropriate dosage, selecting the optimal injection time, and optimizing the injection method. Conducting further research is of utmost significance as it enables us to comprehensively explore and precisely understand the applicability of MSC-Exos in the clinical treatment of DR.

Uveitis

Uveitis, a broad term referring to inflammation of the iris, ciliary body, vitreous body, retina and/or choroid, is a leading cause of visual impairment globally, which can be classified into five categories based on its cause: 1) pure ophthalmological entities, 2) infectious disease, 3) inflammatory disease, 4) masquerade syndrome, and 5) drug-related uveitis.[143] Corticosteroids, including dexamethasone and triamcinolone acetonide, are commonly used in systemic or topical treatments and are effective in controlling early-stage inflammation, while combination immunosuppressants (eg, methotrexate, cyclosporine) are employed as follow-up adjunctive therapies to address long-term chronic inflammation.[144–147] Although effective, long-term administration of topical or intraocular corticosteroids can lead to glaucoma or cataract formation, as well as other complications, such as vitreous hemorrhage, elevated intraocular pressure (IOP), and retinal toxicity.[144,145] Consequently, the search for effective treatments has emerged as a key area of research in uveitis.

Extensive experimental evidence indicates that MSC-Exos have a beneficial effect on inflammatory eye diseases such as experimental autoimmune uveitis (EAU).[148,149] EAU is frequently employed as a model for autoimmune ocular inflammation in humans, which is orchestrated by T-lymphocytes. Using the established EAU mouse model, MSC-Exos were administered systemically or locally for treatment and their therapeutic efficacy was evaluated. Using the adoptive transfer model of EAU, the researchers demonstrated that MSC-Exos can inhibit the infiltration of retinal antigen-reactive T cells into the eye.[8] Specifically, after the injection of MSC-Exos into mice that received the adoptive transfer of inter-photoreceptor retinal binding protein (IRBP)-reactive T cells, MSC-Exos significantly reduced the expression of IFN-γ, IL-17f, and TNF-α in the eyes of recipient mice, while effectively inhibiting the inflammatory response and preventing the development of EAU. To further enhance the therapeutic effects, Li and his team extracted MSC-Exos overexpressing IL-10, a key anti-inflammatory cytokine responsible for the immunosuppressive properties of MSCs.[150] Their findings revealed that IL-10-enriched MSC-Exos were more efficient than normal MSC-Exos in inhibiting the proliferation and differentiation of T-helper cells (Th1 and Th17). Subsequent studies showed that a delivery system, prepared by exogenously loading IL-10 into MSC-Exos, exhibited similar therapeutic effects and higher drug loading efficiency.[151] In addition, lentiviral transduction of MSC-Exos with high expression of CD73 significantly inhibited inflammation and tissue damage in EAU mice.[152] In vitro experiments further showed that MSC-Exos-CD73 enhanced their immunosuppressive effect in EAU. Further investigation by Li et al explored the therapeutic effects of rapamycin-loaded MSC-Exos (Rapa-MSC-Exos) on EAU.[153] Traditionally, rapamycin is administered to patients with uveitis via intravitreal injection, which can lead to serious complications such as intraocular hemorrhage and retinal detachment due to the high frequency of injections. By using drug-loaded exosomes that can be delivered to the retina via subconjunctival injection, the risk of complications associated with intravitreal administration is significantly reduced. Furthermore, Rapa-MSC-Exos showed efficacy in reducing inflammatory cell infiltration and alleviating retinal damage in an experimental autoimmune uveitis model, highlighting their promising potential in the treatment of uveitis. Crucially, Rapa-MSC-Exos enhanced the delivery of Rapamycin to the eye within 24 h after a subconjunctival injection. The modifications and localized drug delivery strategies enhance the therapeutic efficacy and reduce the risks associated with traditional treatment methods, thus highlighting the promising role of MSC-Exos in optimizing pharmaceutical delivery and effectiveness for ocular treatments.

Glaucoma

Glaucoma is a chronic progressive optic neuropathy characterized by the gradual loss of RGCs, which ultimately results in irreversible vision loss.[154] It is the leading cause of permanent blindness worldwide and is projected to affect around 112 million people by 2040, placing a significant financial burden on both individuals and healthcare systems.[155] Reducing IOP with eye drops or surgical procedures can effectively treat glaucoma, but these approaches only slow the progression of the disease and help maintain some degree of vision.[156] Additionally, while glaucoma medications are primarily delivered through topical application, this method faces several challenges such as poor patient adherence, difficulty in administering the drops, toxicity to the ocular surface, and fluctuating efficacy over time.[157] Certain medications, such as corticosteroids, anticholinergics, and topiramate, have been reported to increase the risk of angle-closure glaucoma.[158] Additionally, glaucoma surgery often relies on traditional filtering procedures, such as trabeculectomy, which can be associated with complications, and more complex glaucoma cases require the use of intubation or anti-fibrotic drugs to improve surgical success rates.[159]

Given the above-mentioned shortcomings of local and surgical treatments for glaucoma, MSC-Exos, with long-term stability in the ocular microenvironment, have become the most widely used new therapeutic agent in glaucoma cell therapy.[160,161] Intravitreal injection of MSC-Exos promoted sustained neuroprotection and regeneration of RGCs after optic nerve injury in a rat model of optic nerve crush.[162] Retinal ischemia-reperfusion injury (IRI) is one of the main pathogenic mechanisms of glaucoma. Yu et al showed that intravitreal injection of gingival MSC-Exos (GMSC-Exos) could significantly reduce the thickness of the inner retinal plexiform layer (IPL) induced by IRI.[163] Mechanistically, the GMSC-Exos target and inhibit PDCD4, and this inhibition effectively mitigates the activation of caspase-8/3 and the release of inflammatory factors, consequently safeguarding the survival of RGCs and improving retinal function. In sum, this study presents a novel neuroprotective approach for the treatment of IRI. In addition, Seong et al extracted exosomes rich in growth factors (GF) and neurotrophic factors (NF) from human amniotic stromal stem cells (AMMSCs) and amniotic epithelial stem cells (AMESCs) and explored the effects of these exosomes in a rat model of acute glaucoma induced by high IOP. The results showed that intravitreal injection of the exosomes significantly restored IOP, promoted RPEs proliferation, protected RGCs and reversed the contraction of the retinal layer.[164] Similar effects were also observed in chronic glaucoma rats by transplanting cultured conjunctival fibroblasts (CFs) into the anterior chamber of the rat eye to simulate glaucoma-induced optic nerve damage. HucMSC-Exos were able to significantly reduce retinal damage, increase the number of retinal ganglion cells, and inhibit the activation of caspase-3 protein associated with apoptosis.[165] Besides, intravitreal injection of hucMSC-Exos had no significant effect on IOP, indicating that it is safe in controlling IOP. MSC-Exos facilitate the transfer of neuroprotective factors to RGCs, offering potential support for preserving optic nerve function in patients with glaucoma.[165–167] Nevertheless, the relatively short-lived nature of exosome-mediated effects persists as a significant concern. This might be ascribed to the clearance of MSC-Exos and the degradation of their cargo. In the context of glaucoma patients, this issue is particularly pronounced. Glaucoma, being a chronic and progressive condition, necessitates long-term treatment strategies for patients to regulate intraocular pressure and safeguard their retinas. In animal models, any therapeutic impact of MSC-Exos must be enduring. Specifically, the duration of the neuroprotective effects exerted on damaged neuronal tissues requires more in-depth scrutiny. It was reported that MSC-Exos had limited neuroprotective effects against optic nerve injury and had no significant effect on axonal regeneration 21 days after treatment,[168] suggesting that improvements may be needed to engineer them for sustained and long-term effects. Another crucial consideration of MSC-Exos-based therapies lies in the limited knowledge regarding the precise pharmacokinetics and therapeutic efficacy of MSC-Exos post-intravitreal injection, especially when considering the eyes of larger animals such as non-human primates. Therefore, based on the current evidence, the appropriate time interval between injections for patients remains unknown.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a degenerative disease caused by the focal accumulation of drusen, lipid-rich membrane fragments, and is one of the leading causes of blindness and visual impairment worldwide.[169] AMD primarily affects those aged 55 and older, compromising the sharp central vision needed for crucial activities such as

reading, driving, and facial recognition. In clinical classification, AMD is mainly divided into two types: dry AMD, also known as geographic atrophy (GA), and wet AMD, also known as choroidal neovascularization (CNV).[170] Although anti-VEGF therapy is widely used, not every patient experiences optimal results, and some may face serious complications, including endophthalmitis and retinal detachment, which can threaten vision. Additionally, the need for frequent intravitreal injections can create challenges for patient adherence to the treatment regimen.[171,172] MSC-Exos offer a dual advantage for AMD therapy: their biocompatibility and barrier-penetrating capacity enable sustained drug delivery to target tissues (eg, choroidal neovascularization), reducing reliance on invasive intravitreal injections while enhancing therapeutic precision.[65,173] A key factor in the pathogenesis of AMD is dysfunction of the RPE, whose structural and metabolic failures accelerate the accumulation of macular sclerosis and photoreceptor degeneration.[174,175]

RPEs interact with photoreceptors at the apical side and contact Bruch's membrane and choroidal capillaries at the basal side. With aging and accumulation of environmental stress, RPEs may malfunction or even die, leading to impaired retinal function.[176,177] Therefore, maintaining the function and structural integrity of RPEs is crucial for treating AMD. In order to solve the above problems, researchers are actively exploring the therapeutic potential of MSCs and MSC-Exos.[11] Specifically, MSCs can protect RPEs from sodium iodate-induced death by inhibiting the NF-kB pathway that activates the NLRP3 inflammasome, a mechanism that helps maintain mitochondrial integrity. Moreover, MSC-Exos protect RPEs from apoptosis, which is crucial in AMD development (Figure 6A–G).[178] They regulate the expression of apoptosis-related proteins Bax and Bcl-2, increasing the Bcl-2/Bax ratio in vitro and in vivo. Since Bcl-2 inhibits apoptosis and Bax promotes it, this ratio increase reduces RPEs apoptosis induced by oxidative stress and other factors, maintaining the RPEs integrity and function to aid in AMD treatment.

In addition, subretinal fibrosis is a late feature of wet AMD, and treatment at this stage is particularly critical. Studies have shown that in laser-induced CNV and subretinal fibrosis models, hucMSC-Exos administered intravitreally can effectively alleviate the symptoms of subretinal fibrosis.[179] Moreover, hucMSC-Exos can not only effectively inhibit the migration of RPEs through the cargo miR-27b-3p, but also reverse the epithelial-mesenchymal transition (EMT) process induced by transforming growth factor-β2 (TGF-β2) by downregulating the expression of homeobox protein Hox-C6 (HOXC6). These discoveries highlight the pivotal role of MSC-Exos in the treatment of AMD, as they possess the unique dual capability to simultaneously inhibit neovascularization and mitigate RPE dysfunction, thereby playing an indispensable role in restoring the retina to its normal physiological state. In recent years, MSC-Exos from diverse sources have emerged as a promising therapeutic modality for AMD.[180] These exosomes have demonstrated not only beneficial effects in anti-inflammatory, anti-angiogenic, and antioxidant therapies but also significant potential as drug carriers for retinal drug delivery, thereby facilitating the development of a novel and highly promising treatment strategy for AMD. However, several critical aspects of this approach remain inadequately understood. Due to the complex and highly specialized architecture of the retina, the mechanisms underlying the ability of MSC-Exos to traverse the BRB and their specific penetration capabilities remain unclear. Furthermore, following intravitreal injection, the distribution patterns and elimination kinetics of MSC-Exos within the ocular environment have yet to be fully characterized. Therefore, it is crucial that future research endeavors address these unresolved questions. Only through such investigations can the practical application of MSC-Exos in the treatment of AMD be effectively optimized and translated into clinical practice.

Other Ocular Diseases

Retinitis pigmentosa (RP) is an inherited retinal disease characterized by genetic mutations or abnormalities in the photoreceptors and retinal pigment epithelium, leading to degeneration of photoreceptors (rods and cones) and ultimately progressive vision loss.[181,182] RP is more common in young patients.[183] The initial clinical feature of most RP patients is the loss of rod photoreceptors, followed by the degeneration and death of cone photoreceptors. This progressive degeneration of the cones leads to the subsequent atrophy of RPEs, causing a gradual decline in visual field function and, ultimately, blindness.[184] Interestingly, recent studies have revealed the remarkable role of MSC-Exos in neuroprotection, especially showing great promise in preventing photoreceptor damage.[185] By using intravitreal MSCs transplantation (MSCT) into a mouse model of N-methyl-N-nitrosourea (MNU)-induced photoreceptor loss, the generated MSC-Exos effectively counteracted photoreceptor cell apoptosis and alleviated retinal morphology and functional degradation.

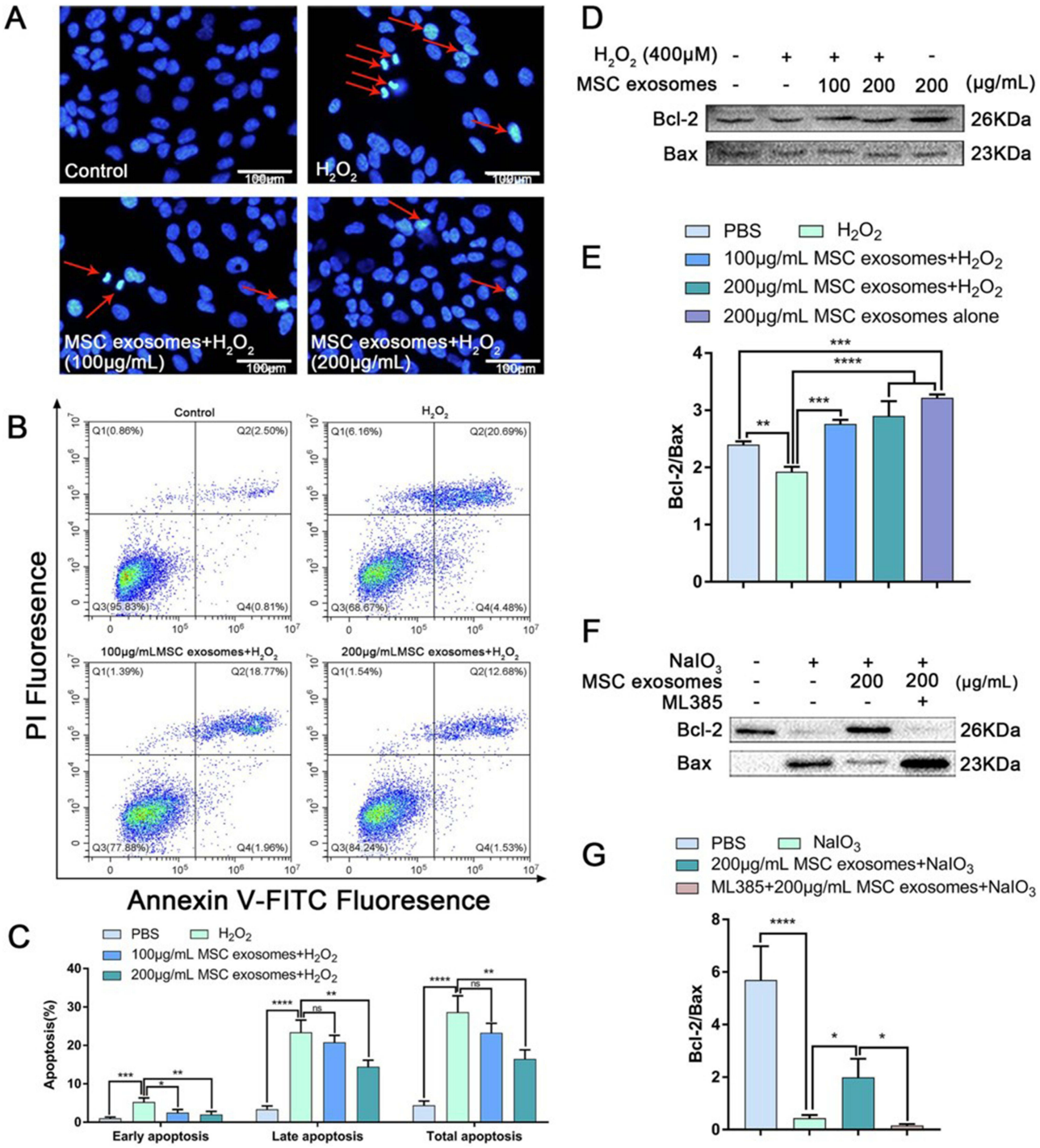

Figure 6 MSC-Exos protect RPEs from apoptosis in vitro and in vivo.

Notes: (**A**) Morphological changes in the nuclei of RPEs were analyzed with DAPI staining and the red arrows indicated damaged cells. (**B**) The percentages of early and late apoptotic retinal pigment epithelial cells (RPEs) after treatment with MSC-exosomes were measured by flow cytometry based on Annexin V and PI binding. (**C**) Histogram of the percentage of early apoptotic, late apoptotic and total apoptotic cells. (**D**) The expression of in vitro apoptosis-related proteins were determined by Western blotting. (**E**) Quantification of in vitro apoptosis-related proteins. (**F**) The expression of in vivo apoptosis-related proteins were determined by Western blotting. (**G**) Quantification of in vivo apoptosis-related proteins. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. ns, not significant. Reproduced with permission from Tang Y, Kang Y, Zhang X, Cheng C. Mesenchymal stem cell exosomes as nanotherapeutics for dry age-related macular degeneration. Journal of Controlled Release. 2023;357:356–370. *Copyright © 2023 Elsevier.*[178]

Further experiments showed that the MSC-Exos cargo miR-21 effectively maintained the viability of photoreceptors in MNU-driven retinal injury by targeting PDCD4, and this effect could be maintained for up to 1–2 months. Another study has identified that the intravitreal administration of MSC-Exos into the rd10 mouse model of RP can significantly enhance the survival of photoreceptors, preserve their structural integrity, and ameliorate visual function in the mice, underscoring the potential of MSC-Exos as a therapeutic option for RP.[186] In addition, exosomes derived from tonsil-derived MSC (T-MSC-Exos) also showed excellent effects in preventing and treating RPEs death. Transcriptome sequencing results revealed that T-MSC-Exos can regulate intracellular oxidative stress responses and effectively protect RPEs from oxidative damage.[187] These findings highlight the potential of MSC-Exos to enhance RPEs replacement therapies in treating patients with RP. However, as these preclinical findings are primarily derived from animal models, additional clinical trials are necessary to confirm whether similar outcomes can be achieved in human subjects.

Sjögren's syndrome dry eye (SSDE), an autoimmune disease characterized by focal inflammation of exocrine glands, commonly causes dry and tired eyes and is a leading cause of severe dry eye disease (DED).[188] Effectively suppressing ocular inflammatory responses is pivotal for treating SSDE and DED.[189,190] Although eye drops or eye ointments containing components like anti-inflammatory drugs and immunosuppressants have been utilized for the management of dry eye disease, their therapeutic efficacy is substantially hindered by the tear film and corneal barrier.[191,192] In fact, less than 5% of the drugs can be absorbed by the ocular tissues, and the proportion of drugs reaching the lacrimal gland is even lower, which severely undermines the treatment effect. The role and mechanisms of MSC-Exos in the management of SSDE have been the subject of various studies.[193] Intravenous infusion of Olfactory ecto-MSC-Exos (OE-MSC-Exos) has been found to upregulate arginase expression in SSDE mice, while increasing the levels of ROS and NO, thereby significantly improving the restrictive effect of myeloid suppressor cells (MDSCs).[194] Mechanistically, IL-6 secreted by OE-MSC-Exos increased the immunosuppressive capacity of MDSCs by activating the JAK2/STAT3 pathway. In addition, multiple miRNAs (such as miR-125b and miR-6873) were significantly enriched in MSC-Exos, which are associated with immunosuppression.[195] MiRNAs contained in MSC-Exos can restore the homeostasis of the ocular surface by inhibiting the activation of the IRAK1/TAB2/NF-κB pathway through multi-targeting, regulating the inflammatory cytokines (IL-10, IL-13, IL-17 and TNF-α) of tears and ocular surface. Another study explored the therapeutic effect of miR-223-3p of MSC-Exos in a dry eye model, showing that miR-223-3p of MSC-Exos directly targeted Fbxw7 expression in mouse corneal epithelial cells (MCEC) to inhibit the degradation of EZH2, thereby inhibiting the inflammatory response in the dry eye model.[196] Furthermore, MSC-Exos alleviated the symptoms of SSDE and promoted the repair, regeneration, and functional recovery of salivary and lacrimal glands in mice.[193,197] In conclusion, MSC-Exos exhibit substantial potential in mitigating inflammation across various subtypes of DED and promoting corneal healing in the context of ocular surface disorders.[198] However, the precise molecular mechanisms underlying the therapeutic effects of MSC-Exos remain poorly understood. Building on the current findings, further research is warranted to elucidate the detailed mechanisms by which MSC-Exos exert their beneficial effects in the treatment of DED.

The mechanisms and applications of MSC-Exos therapy in recent years are summarized in Table 1.

Clinical Trials

Although substantial research has been conducted in laboratory and animal studies, the clinical application of MSCs and their exosomes remains limited. While numerous clinical trials have been conducted, only five studies involving MSC-Exos for ocular disease treatment have been reported on clinicaltrials.gov (Table 2). Notably, among these registered trials, only one (NCT06242379) is currently listed as "Recruiting", which is insufficient to assess the safety and efficacy of MSC-Exos-based therapies. This highlights the need for further research to validate their efficacy in clinical settings.

Here, we summarize the possible reasons for the limited number of clinical trials involving MSC-Exos in ocular diseases: MSC-Exos exhibit marked functional and compositional variability depending on their parental cell origin.[199] For example, hucMSC-Exos are rich in immune-related proteins and miRNAs such as miR-125b-5p, which may be more beneficial for the treatment of immune-related diseases like acute kidney injury.[200] Additionally, MSC-Exos derived from dental pulp contain more proteins related to the nervous system.[199] Fetal-derived MSC-Exos exhibit superior osteogenic differentiation capacity compared to adult sources, indicating advantages for developmental tissue repair.[201] Therefore, this heterogeneity necessitates rigorous characterization of exosomal cargo and therapeutic mechanisms to optimize donor cell

Table 1 Summary of the Mechanisms and Applications of MSC-Exos Therapy

Application	Disease Model	Exos Source	Effector Molecules	Mechanism	Refs.
Corneal repair and regeneration	Corneal freezing burn model	ADSC-Exos	miRNA: miR-23a-3p, etc.	ADSC-Exos improved mitochondrial function and inhibited autophagy to delay cellular aging, promote wound healing, and enhance endothelial cell regeneration.	Ryu et al, 2023[114]
Promotion of corneal wound healing	Corneal mechanical wound model	hucMSC-Exos	miR-21	MSC-Exos promoted corneal epithelial cell proliferation and migration by targeting the PTEN/PI3K/Akt pathway.	Liu et al, 2022[27]
Reduction of corneal injury inflammation and apoptosis	Corneal alkali injury model	hPMSC-Exos	Protein: caspase-8, etc.	MSC-Exos inhibited angiogenesis, reduced pro-inflammatory factors (eg, IL-13, IL-5, and TNF-α), and accelerated corneal wound healing in mice.	Tao et al, 2019[115]
Promotion of corneal injury healing	Corneal alkali injury model	BM-MSC-Exos	/	MSC-Exos inhibited TNF-α-induced inflammatory responses in human CECs, promoting neuronal repair and survival while maintaining corneal homeostasis.	Saccu et al, 2022[116]
Reduction of corneal fibrosis and inflammation	Corneal injury model	CSSC-MSC-Exos	miRNA	CSSC-MSC-Exos reduced the expression of Col3a1 and Acta2, suppressed neutrophil infiltration, minimized scar formation, and restored corneal transparency.	Shojaati et al, 2019[117]
Corneal repair and regeneration	Corneal alkali burn model	BM-MSC-Exos	miR-21-5p	MSC-Exos delivered miR-21-5p, which inhibited scar formation by targeting PDCD4 and downregulating fibrosis-related collagen genes.	Wang et al, 2024[119]
Immunomodulation	Corneal alkali burn model	ADSC-Exos	miR-24-3p	ADSC-Exos accelerated corneal epithelial defect healing, reduced stromal fibrosis, and suppressed macrophage activation through miR-24-3p delivery.	Sun et al, 2023[22]
Corneal repair and regeneration	Corneal injury model	iPSC-MSC-Exos	miR-432-5p	IPSC-MSC-Exos prevented ECM deposition and promoted regeneration of corneal epithelium and stroma by targeting TRAM2.	Tang et al, 2022[113]
Inflammation regulation and promotion of corneal repair	Corneal injury model	ADSC-Exos	aT	ADSC-Exos released aT in the MMP-enriched corneal injury microenvironment, reducing local inflammation and enhancing tissue repair.	Yu et al, 2024[120]
Inhibition of neuroinflammation and cell apoptosis	DR model	hucMSC-Exos	miR-17-3p	MSC-Exos delivered miR-17-3p, which specifically targeted STAT1, reduced oxidative damage, regulated blood glucose, decreased inflammatory mediators and VEGF levels, and protected retinal cells from apoptosis.	Li et al, 2021[132]
Inhibition of cell apoptosis and oxidative stress	DR model	hucMSC-Exos	NEDD4	MSC-Exos inhibited retinal cell apoptosis and oxidative stress by protecting RPEs from HG-induced damage.	Sun et al, 2022[133]
Restoration of retinal function	Retinal ischemia model	BM-MSC-Exos	/	MSC-Exos reduced neuroinflammation and apoptosis, suppressed microglial activation, and decreased pro-inflammatory cytokines (TNF-α and IL-6), thereby restoring retinal function.	Mathew et al, 2019[127]
Relief from retinal inflammation	DR model	hucMSC-Exos	miR-22-3p	MSC-Exos delivered miR-22-3p, which significantly inhibited NLRP3 inflammasome activation, alleviated retinal inflammation, and improved retinal structure.	Chen et al, 2024[134]
Relief from retinal damage	DR model	BM-MSC-Exos	miR-129-5p	MSC-Exos alleviated retinal damage by inhibiting the Wnt/β-catenin pathway, reducing oxidative stress, inflammation, angiogenesis, and vascular leakage.	Ebrahim et al, 2022[136]
Improvement of retinal function	DR model	hucMSC-Exos	miR-5068, miR-10228	MSC-Exos improved retinal function by specifically targeting the HIF-1α/EZH2/PGC-1α signaling pathway.	Sun et al, 2024[137]

(*Continued*)

Table 1 (Continued).

Application	Disease Model	Exos Source	Effector Molecules	Mechanism	Refs.
Relief from inflammation	DR model	hucMSC-Exos	miR-30c-5p	MSC-Exos downregulated PLCG1 expression to block PKC/NF-κB pathway and inhibited inflammatory expression and ICAM-1 and VCAM-1 levels	He et al, 2022[138]
Immunomodulation	DR model	hucMSC-Exos	miR-18b	MSC-Exos delayed inflammation and angiogenesis by targeting the MAP3K1/NF-κB axis through miR-18b.	Xu et al, 2021[139]
Neuroprotection	DR model	BM-MSC-Exos	miR-133b-3p	MSC-Exos negatively regulated FBN1 expression via miR-133b-3p, inhibiting angiogenesis and oxidative stress.	Liang et al, 2022[140]
Anti-inflammatory effects and promotion of cell regeneration	DR model	BM-MSC-Exos	miR-486-3p	MSC-Exos suppressed oxidative stress, inflammation, and apoptosis, while promoting cell proliferation through miR-486-3p.	Li et al, 2021[141]
Neuroprotection	DR model	BM-MSC-Exos	bevacizumab	MSC-Exos loaded with bevacizumab achieved sustained neuroprotection and prolonged therapeutic effects in retinal cells.	Reddy et al, 2023[142]
Improvement of EAU and protection of retinal function	EAU model	BM-MSC-Exos	/	MSC-Exos inhibited retinal antigen-reactive T cell infiltration and reduced pro-inflammatory cytokine expression.	Kaur et al, 2024[8]
Immunomodulation	EAU model	hucMSC-Exos	IL-10	MSC-Exos suppressed the proliferation and differentiation of Th1 and Th17 cells by delivering IL-10.	Li et al, 2022; Li et al, 2024[150,151]
Inhibition of inflammation and tissue damage, enhancement of immunosuppression	EAU model	hucMSC-Exos	CD73	MSC-Exos overexpressing CD73 inhibited inflammation and tissue damage while enhancing immunosuppressive activity.	Duan et al, 2024[152]
Immunomodulation, promotion of healing in damaged cells	EAU model	hucMSC-Exos	Rapamycin	MSC-Exos loaded with rapamycin reduced inflammatory cell infiltration, alleviated retinal damage, and enhanced drug delivery efficiency in the eye.	Li et al, 2022[153]
Neuroprotection	Chronic glaucoma model	hucMSC-Exos	/	MSC-Exos promoted sustained neuroprotection and regeneration of RGCs after optic nerve injury.	Wang et al, 2021[12]
Signal transduction and inflammation regulation	IRI model	GMSC-Exos	miR-21-5p	MSC - Exos downregulated PDCD4 via the MEG3/miR-21-5p axis, thereby inhibiting the activation of caspase-8/3 and the upregulation of IL-1β and TNF-α in retinal IRI.	Yu et al, 2022[163]
Neuroprotection and regeneration	Acute glaucoma model	AMMSC-Exos	GF, NF	MSC-Exos restored IOP, promoted RPE proliferation, protected RGCs, and reversed retinal layer contraction.	Seong et al, 2023[164]
Neuroprotection and regeneration	Chronic glaucoma model	Rat ucMSC-Exos	/	MSC-Exos reduced retinal damage, increased retinal ganglion cell counts, and inhibited caspase-3 activation.	Yu et al, 2023[165]
Anti-fibrosis and tissue regeneration	CNV model and subretinal fibrosis model	hucMSC-Exos	miR-27b-3p	MSC-Exos alleviated subretinal fibrosis by inhibiting RPE migration, downregulating HOXC6, and reversing TGF-β2-induced EMT.	Li et al, 2021[179]
Neuroprotection and regeneration	MNU-induced photoreceptor loss mouse model	BM-MSC-Exos	miR-21	MSC-Exos maintained photoreceptor viability in MNU-induced retinal injury by targeting PDCD4.	Deng et al, 2021[185]

Neuroprotection and regeneration	rd10 mouse model	hucMSC-Exos	miR-146a	MSC-Exos improved photoreceptor survival, preserved retinal structural integrity, and enhanced visual function in rd10 mice.	Zhang et al, 2022[186]
Promotion of cell proliferation and anti-oxidation	RP model	T-MSC-Exos	/	MSC-Exos protected RPEs from oxidative damage by regulating intracellular oxidative stress responses.	Choi et al, 2023[187]
Improvement of myeloid suppressor cell restriction and regulation of ocular surface homeostasis	SSDE model	OE-MSC-Exos	IL-6	MSC-Exos enhanced the immunosuppressive capacity of myeloid-derived suppressor cells (MDSCs) by activating the JAK2/STAT3 pathway through IL-6, thereby improving ocular surface homeostasis.	Rui et al, 2021[194]
Immunomodulation	DED model	hucMSC-Exos	miR-125b, miR-6873, etc.	MSC-Exos alleviated DED by inhibiting the IRAK1/TAB 2/NF-κB pathway, increasing goblet cell density, and regulating inflammatory cytokines in tears and ocular surface.	Wang et al, 2023[195]
Inflammation regulation	DED model	mADSC-Exos	miR-223-3p	MiR-223-3p of MSC-Exos directly targets Fbxw7 expression in MCECs to inhibit degradation of EZH2 and thereby suppress inflammation	Wang et al, 2024[196]

Abbreviations: ADSC-Exos, adipose mesenchymal stem cell-derived exosomes; hucMSC-Exos, human umbilical cord mesenchymal stem cell-derived exosomes; hPMSC-Exos, human placental mesenchymal stem cell-derived exosomes; BM-MSC-Exos, bone marrow mesenchymal stem cell-derived exosomes; CSSC-MSC-Exos, corneal stromal MSC-Exos; iPSC-MSC-Exos, induced pluripotent stem cell-derived MSC-Exos; DR, diabetic retinopathy; RPEs, retinal pigment epithelium cells; HG, high glucose; EAU, experimental autoimmune uveitis; GMSC-Exos, gingival MSC-Exos; AMMSC-Exos, human amniotic MSC-Exos; CNV, choroidal neovascularization; CECs, Corneal endothelial cells; Col3a1, Collagen type III alpha 1 chain; MNU, N-methyl-N-nitrosourea; RP, retinitis pigmentosa; T-MSC-Exos, tonsil-derived MSC-Exos; SS, Sjögren's syndrome; OE-MSC-Exos, Olfactory ecto-MSC-Exos; DED, dry eye disease; MCECs, Mouse corneal endothelial cells; PTEN, phosphatase and tensin homolog; ECM, Extracellular matrix; VEGF, vascular endothelial growth factor; NLRP3, NOD-like receptor family pyrin domain containing 3; HIF-1α, hypoxia-inducible factor-1 alpha; EZH2, enhancer of zeste homolog 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PLCG1, phospholipase Cγ1; FBN1, Fibrillin 1 gene; IOP, Intraocular pressure; HOXC6, homeobox protein Hox-C6; EMT, Epithelial-mesenchymal transition; MDSCs, myeloid suppressor cells.

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Table 2 Summary of Clinical Trials of MSC-Exos for the Treatment of Ocular Diseases (from ClinicalTrials.gov)

Research Title	Condition/Disease	Intervention/ treatment	Phase	Latest Update	Status	Trial Identifier
Safety and Efficacy of Pluripotent Stem Cell-derived Mesenchymal Stem Cell Exosome (PSC-MSC-Exo) Eye Drops Treatment for Dry Eye Diseases Post Refractive Surgery and Associated With Blepharospasm	DED	PSC-MSC-Exos	I/II	February 22, 2023	Unknown	NCT05738629
Effect of UMSCs Derived Exosomes on Dry Eye in Patients With cGVHD	cGVHD-related dry eye syndrome	UMSC-Exos	I/II	February 11, 2022	Unknown	NCT04213248
The Effect of Stem Cells and Stem Cell Exosomes on Visual Functions in Patients With Retinitis Pigmentosa	RP	MSC-Exos	II/III	September 7, 2022	Unknown	NCT05413148
Safety and Efficacy of Stem Cell Small Extracellular Vesicles in Patients With Retinitis Pigmentosa	RP	BM-MSC-Exos	I/II	May 29, 2024	Recruiting	NCT06242379
MSC-Exos Promote Healing of MHs (MSCs)	MHs	MSC-Exos	I	April 6, 2021	Unknown	NCT03437759

Abbreviations: DED, Dry eye diseases; cGVHD, chronic Graft-Versus-Host Disease; RP, Retinitis pigmentosa; MHs, Macular holes; PSC-MSC-Exo, Pluripotent stem cell-derived mesenchymal stem cell exosome; UMSC-Exos, Umbilical mesenchymal stem cell-derived exosomes; MSC-Exos, Mesenchymal stem cell-derived exosomes; BM-MSC-Exos, bone marrow mesenchymal stem cell-derived exosomes.

selection for specific ocular pathologies. Secondly, MSC-Exos obtained by different methods may have differences in purity, size, and content, which can lead to inconsistent experimental results and make it difficult to compare data from different studies.[202] Undoubtedly, uniform quality control standards, with specific surface markers or RNA content as prime examples, stand as the next formidable hurdle in the way of designing and conducting relevant clinical studies.[202] Laboratory-level production is difficult to meet clinical needs, and a large-scale production process that meets Good Manufacturing Practice (GMP) standards needs to be developed.[203] In addition, it is reported that only approximately 100 μg of MSC-Exos can be obtained from 500 mL of MSCs conditioned media using commercial separation kits.[204] However, numerous published studies have used more than 100 μg of MSC-Exos in in vitro and in vivo models of ocular diseases.[115,132,152] This highlights the significant challenges in producing sufficient quantities of MSC-Exos to meet the dosing requirements for future clinical trials, necessitating substantial financial and time investments. Finally, storing MSC-Exos can be challenging, with common methods including short-term storage at 4°C or room temperature, and long-term storage at −20°C or −80°C.[205,206] However, MSC-Exos may become unstable during long-term storage, and repeated freeze-thaw cycles at −80°C can lead to structural damage or reduced activity.[207] To address this, suitable storage conditions need to be identified, such as the use of cryoprotectants or determining the optimal storage temperature.[207,208] Additionally, the high cost of cold-chain transportation and temperature fluctuations during transport can further compromise the quality of MSC-Exos, presenting a challenge for multicenter clinical trials conducted globally.[209]

Limitations, Perspectives and Challenges

Although robust animal studies have demonstrated that MSC-Exos, whether administered topically or systemically, can reach therapeutic tissue targets (eg, the eye), their clinical applicability remains relatively marginalized. A comprehensive understanding of MSC-Exos remains lacking, compounded by a myriad of challenges and limitations. There is a lot of exciting potential for MSC-Exos therapy, but translating this potential into a true treatment will depend on continued progress in several key areas. As previously noted, the foremost obstacle lies in addressing the heterogeneity of MSC-Exos composition, which is influenced by both the donor source and the method of isolation. While MSC-Exos can be extracted from various tissues, their therapeutic suitability is contingent upon factors such as their biochemical composition and functional properties. MSC-Exos obtained through differing isolation and enrichment techniques may exhibit variable compositions and functionalities, depending on the tissue of origin. For instance, ADSC-Exos contain neutral lysins at levels four times greater than those found in BM-MSC-Exos. Conversely, BM-MSC-Exos demonstrate markedly higher expression of proteins implicated in the Notch signaling pathway, rendering them more suitable for applications in bone and cartilage regeneration, as well as angiogenesis.[210] Accordingly, selecting the appropriate MSC-Exos tissue source based on specific therapeutic objectives is essential to achieving optimal treatment outcomes. Variations in isolation methods further exacerbate inter-batch discrepancies: under identical MSC culture conditions, PEG precipitation yields six to seven times more particles and protein compared to ultracentrifugation. Nevertheless, ultracentrifugation produces MSC-Exos with miR-146a-6p levels two to three times higher, which may significantly influence their therapeutic efficacy.[211] Ideally, the production method should maximize the therapeutic payload of the resulting MSC-Exos. Moreover, the development of stringent quality standards is imperative to reduce batch-to-batch variability and to safeguard the reproducibility, consistency, safety, and efficacy of MSC-Exos. Realizing these standards will necessitate ongoing research efforts and collaborative engagement across the field.

During the clinical translation process, the relatively short duration of action of MSC-Exos therapy poses another significant obstacle that must be addressed. Although a single administration has demonstrated efficacy in acute injury models, the chronic and progressive nature of many blinding diseases, such as diabetic retinopathy and glaucoma, often requires sustained therapeutic effects to control the condition.[212] This transient effect may arise from rapid clearance by the immune system, dilution within the vitreous cavity, or the intrinsic biological turnover mechanisms of exosomes. To overcome this limitation, future research must shift towards developing strategies that extend the duration of therapeutic action and efficacy.[213] Key directions include optimizing dosing regimens through systematic studies to determine the optimal administration frequency, concentration, and route, as well as designing advanced delivery systems that function as sustained-release reservoirs. For instance, encapsulating MSC-Exos within biocompatible hydrogels or microparticles

can significantly prolong their retention at the target site, thereby reducing the frequency of intravitreal injections or topical administrations and improving patient compliance.

Another notable limitation pertains to scalability challenges in achieving production that complies with Good Manufacturing Practice (GMP) standards. Clinical translation of MSC-Exos mandates adherence to rigorous GMP protocols, particularly with respect to standardizing large-scale production. This imposes stringent demands on equipment, personnel, and procedural integrity, significantly inflating costs and posing further obstacles to clinical implementation.[214] Conventional 2D culture methods are low-cost and straightforward to operate, remaining appropriate for fundamental research applications. However, 3D culture—particularly via bioreactor systems—surpasses 2D methods in terms of yield, efficiency, and therapeutic efficacy, rendering it more aligned with clinical application requirements. Nonetheless, it necessitates specialized equipment such as hollow fiber bioreactors, and entails a higher technical threshold and initial investment cost compared to 2D culture.[215,216] The development of scalable, cost-efficient, and GMP-compliant 3D bioreactor platforms constitutes a pivotal future direction to surmount the scalability barrier in MSC-Exos production. In addition, refining standard operating procedures for MSC-Exos isolation and storage will aid in mitigating variability and ensuring consistent, high-quality production. Breakthroughs in the above direction will also help address patient concerns regarding immunogenicity, stability, and long-term administration of MSC-Exos. Furthermore, cross-sector collaboration between academia, industry, and regulatory authorities is vital for establishing universal benchmarks governing the quality, safety, and efficacy of MSC-Exos production. It is imperative to formulate guidelines for the standardized production of MSC-Exos as therapeutic agents, thereby facilitating their transition from the laboratory to clinical application.[217]

Although lipid nanomolecular therapy and gene therapy have been explored as alternative strategies, their limited targeting accuracy within the intricate ocular microenvironment continues to constrain their utility in precision medicine. By contrast, MSC-Exos, owing to their nanoscale dimensions and inherent biocompatibility, can be engineered to achieve targeting specificity, thereby surmounting biological barriers that conventional drugs and gene therapies often fail to penetrate. Notably, MSC-Exos possess the capacity to traverse formidable biological barriers, including the blood-brain barrier and blood-ocular barrier, an attribute rarely achievable with traditional delivery vectors such as liposomes and nanoparticles. Engineering strategies aimed at enhancing the targeting capability, drug-loading efficiency, and intelligent responsiveness of MSC-Exos are pivotal to overcoming existing bottlenecks and enabling precision therapeutics. Key engineering approaches currently under investigation include: (i) CRISPR-mediated modification of parental cells to enrich therapeutic miRNAs;[218,219] (ii) Insertion of targeting ligands (peptides, antibodies, or aptamers) into the exosomal lipid bilayer or membrane-anchored proteins, enabling specific homing to diseased tissues/cells;[83,220] (iii) biomaterials-loaded MSC-Exos (eg, stimuli-responsive hydrogels) to create "smart" therapeutics capable of dynamically responding to pathological microenvironments (eg, pH, enzymatic activity, or ROS), thereby enhancing cellular uptake and controlled cargo release.[113,120] Concurrently, with a better understanding of the pathological characteristics of various ocular disease in progression stages, more precise and targeted MSC-Exos treatment plans are expected to be developed. By addressing these critical challenges and harnessing the power of engineering, MSC-Exos hold immense promise to usher in a new era of precision ophthalmology. In the future, targeted and long-lasting MSC-Exos therapies may well supplant invasive interventions, offering renewed hope for vision preservation on a global scale.

Conclusions

MSC-Exos have emerged as a transformative acellular platform for treating a spectrum of ocular diseases. This review has synthesized evidence demonstrating their efficacy in facilitating tissue repair (eg, in corneal wounds), mitigating neuroinflammation (eg, in diabetic retinopathy and glaucoma), and restoring immune homeostasis (eg, in uveitis), benefits largely attributed to their innate biocompatibility, ability to traverse biological barriers, and delivery of a multifaceted cargo of bioactive molecules. Collectively, these attributes position MSC-Exos as a paradigm shift in ocular therapeutics, with significant potential to supplant conventional invasive treatments and advance the field of precision ophthalmology. To fully realize this potential, future efforts must prioritize establishing standardized GMP production protocols, advancing the clinical translation of engineered exosomes, and optimizing dosing regimens to achieve sustained therapeutic effects. The ongoing integration of deeper pathological insights with bioengineering

innovations is therefore crucial to propel MSC-Exos from promising experimental agents to mainstream clinical solutions for global vision preservation.

Abbreviations

ADSC-Exos, Adipose mesenchymal stem cell-derived exosomes; AMD, Age-related macular degeneration; AMESCs, Human amniotic epithelial stem cells; AMMSCs, Human amniotic stromal stem cells; Acta2, Alpha-smooth muscle actin 2; aT, Anti-tumor necrosis factor-α antibody; BM-MSC-Exos, Bone marrow mesenchymal stem cell-derived exosomes; BRB, Blood-retinal barrier; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CFs, Conjunctival fibroblasts; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; CECs, Corneal endothelial cells; CHI, Chitosan-based hydrogel; CNV, Choroidal neovascularization; CSSC-MSC-Exos, Corneal stromal MSC-Exos; GA, Geographic atrophy; GMP, Good Manufacturing Practice; DBCO, Dibenzocyclooctyne; DED, Dry eye disease; DR, Diabetic retinopathy; EAU, Experimental autoimmune uveitis; ECM, Extracellular matrix; EMT, Epithelial-mesenchymal transition; EVs, Extracellular vesicles; EZH2, Enhancer of zeste homolog 2; FBN1, Fibrillin-1 gene; GF, Growth factors; GMSC-Exos, Gingival MSC-Exos; HG, High glucose; HIF-1α, Hypoxia-inducible factor-1 alpha; HOXC6, Homeobox protein Hox-C6; hPMSC-Exos, Human placental mesenchymal stem cell-derived exosomes; hucMSC-Exos, Human umbilical cord mesenchymal stem cell-derived exosomes; ICAM-1, Intercellular adhesion molecule-1; IL-10, Interleukin-10; IL-5, Interleukin-5; IL-13, Interleukin-13; IPL, Inner plexiform layer; IRBP, Inter-photoreceptor retinal binding protein; IOP, Intraocular pressure; IRI, Retinal ischemia-reperfusion injury; iPSC-MSC-Exos, Induced pluripotent stem cell-derived MSC-exosomes; MDSCs, Myeloid suppressor cells; MMPs, Matrix metalloproteinases; MAP3K1, Mitogen-activated protein kinase kinase kinase 1; MMP-2, Matrix metalloproteinase-2; MMP-9, Matrix metalloproteinase-9; MVB, Multivesicular bodies; MNU, N-methyl-N-nitrosourea; MSC-Exos, Mesenchymal stem cell-derived exosomes; MSCs, Mesenchymal stem cells; MSCT, MSCs transplantation; NF, Neurotrophic factors; NF-κB, Nuclear factor kappa B; NTA, Nanoparticle tracking analysis; NLRP3, NOD-like receptor family pyrin domain containing 3; NPDR, Non-proliferative diabetic retinopathy; NO, Nitric oxide; OE-MSC-Exos, Olfactory ecto-MSC-Exos; PDCD4, Programmed cell death 4; PDR, Proliferative diabetic retinopathy; PEG, Polyethylene glycol; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PLCG1, Phospholipase Cγ1; PTEN, Phosphatase and tensin homolog; qPCR, Quantitative real-time polymerase chain reaction; Rapa-MSC-Exos, Rapamycin-loaded MSC-Exos; ROS, Reactive oxygen species; RGCs, Retinal ganglion cells; RP, Retinitis pigmentosa; RPEs, Retinal pigment epithelium cells; SEM, Scanning electron microscopy; SSDE, Sjögren's syndrome dry eye; STAT1, Signal transducer and activator of transcription 1; STAT3, Signal transducer and activator of transcription 3; STZ, Streptozotocin; T-MSC-Exos, Tonsil-derived MSC-Exos; TGF-β, Transforming growth factor-beta; TNF-α, Tumor necrosis factor alpha; TRAM2, Translocation-associated membrane protein 2; Th1, T helper 1 cells; Th17, T helper 17 cells; TLR4, Toll-like receptor 4; TEM, Transmission electron microscopy; VCAM-1, Vascular cell adhesion molecule-1; VEGF, Vascular endothelial growth factor; Wnt/β-catenin, Wnt/β-catenin signaling pathway.

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Disclosure

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