# Mesenchymal Stem Cell-Derived Exosomes in Anterior Segment Diseases

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Exosomes, which are derived from MSCs, are nanoparticle vesicles that possess therapeutic properties such as anti-inflammatory, anti-apoptotic, tissue-repairing, neuroprotective, and immunomodulatory functions, much like their parent cells. By using MSC-derived exosomes as a drug-delivery system, their potential advantages can be fully exploited. Due to their ability to penetrate the blood-brain barrier, it is inferred that they may also better penetrate biological barriers such as the blood-retinal barrier. Additionally, their cargo is protected from degradation, resulting in increased bioavailability in ocular tissues. Research suggests that utilizing MSC-derived exosomes as a treatment option could offer several benefits over traditional MSC-based therapies in the field of regenerative medicine. Exosome-based therapy provides an alternative approach that avoids potential risks associated with MSC-centered therapies, such as allogeneic immunological rejection, unwanted differentiation, and obstruction of small vessels caused by intravenous MSC injection. By circumventing these risks, treatment outcomes can be optimized.

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## 1. MSC-Derived Exosomes for Corneal Regeneration

Corneal regeneration is a complex process that involves inflammation, cellular proliferation, and extracellular matrix (ECM) remodeling. When the cornea is damaged, cytokines and mediators are released, attracting immune cells to the area and stimulating surviving keratocytes to proliferate and differentiate into fibroblasts. These fibroblasts migrate to the injured region and secrete ECM and enzymes involved in ECM remodeling, such as matrix metalloproteinases (MMPs) and collagenase. Additionally, they can transform into myofibroblasts, which help with wound closure and contraction [1]. However, prolonged or excessive activation of myofibroblasts can lead to inappropriate deposition of collagen fibers, scar tissue formation, and corneal opacification, resulting in the loss of transparency [2].. Excessive inflammation and pathological angiogenesis may also contribute to corneal scarring and opacity [3]. To successfully regenerate the cornea, therapeutic interventions must promote healing while controlling inflammation, neovascularization, and the collagen-rich ECM to preserve corneal transparency.

Exosomes have gained interest in treating corneal pathologies due to their ability to promote tissue repair and suppress inflammation. MSC-derived exosomes have been found to promote corneal epithelial cell proliferation and migration in vitro, accelerating reepithelialization, which has been successfully translated to in vivo animal studies. The presence of miR-21 within MSC-derived exosomes has been suggested to contribute to their corneal wound healing effects, with MSC-exosomes reducing inflammation, apoptosis, and angiogenesis following corneal damage. Additionally, MSC-exosomes have been shown to promote the growth of corneal stromal stem cells and inhibit their apoptosis, suggesting their potential use in ECM remodeling to reduce corneal opacity.

Autophagy is a cellular process that plays a role in maintaining corneal homeostasis [4][5]. Combining MSC-exosomes with an autophagy activator (AA), Rapamycin, has been shown to have positive effects on corneal regeneration. In a study by Ma et al. (2022), the combination of MSC-exosomes and AA was found to have superior effects on corneal epithelial cell proliferation, migration, and apoptosis compared to exosomes or AA alone. The combined treatment also resulted in reduced haze grade and downregulation of proinflammatory genes TNF-α, IL-1β, IL-6, and CXCL-2 [6]. Autophagy activators have the potential to be a useful supplement to exosome-based therapies for corneal pathologies.

Animal experiments have investigated bioengineered hydrogels as scaffolds for corneal repair, modified for sustained release of MSC-exosomes. Implantation of thermosensitive chitosan-based hydrogels (CHI) with sustained-release iPSC-MSC-exos in a rat corneal anterior lamellar injury model showed higher corneal transparency and downregulation of collagen expression. miR-432-5p, found to downregulate collagen biosynthesis in CSSCs, was identified in iPSC-MSC-exos. A thermosensitive hydrogel with DEGMA was developed for controlled release of exosomes rich in miRNA-24-3p from adipocyte-derived MSCs. Its application in rabbits improved corneal epithelial defect healing, reduced corneal stromal fibrosis, and decreased macrophage activation, promoting corneal epithelial cell migration and corneal repair. Combining biosynthetic hydrogels with MSC-exosome delivery shows promise as an alternative to conventional penetrating keratoplasty, which is associated with various complications [7][8][9].

## 2. MSC-Derived Exosomes for Dry Eye Disease (DED)

Dry Eye Disease (DED) is a complex condition caused by a variety of factors and characterized by reduced tear quality or production, leading to ocular surface inflammation and damage. Symptoms include discomfort, visual disturbances, and tear film instability. Treatments for DED range from artificial tears and ointments to topical corticosteroids, immunosuppressants, and autologous tear therapy depending on disease severity [9].

Current treatments for Dry Eye Disease (DED) have limitations, such as declining patient compliance with artificial tears, side effects of long-term topical steroid use, and the cost and multiple visits required for autologous tear therapy. In addition, DED can reduce the effectiveness of topical medications by affecting ocular drug delivery. However, MSC-derived exosomes offer hope as a promising therapeutic option for DED, addressing the root causes of the condition effectively [10].

## 2.1. GVHD-Associated DED

MSC-exosomes have shown immunomodulatory effects in mice with chronic graft-versus-host disease (cGVHD) by suppressing Th17 expression and inducing Treg expression, and recent studies have shown promising results for the future of cGVHD-associated DED management. Topical application of MSC-exosomes in mice with DED resulted in increased tear secretion, longer tear break-up time, preserved goblet cells, fewer corneal defects, and improved epithelial structure. Inflammation was reduced, as observed by downregulation in proinflammatory genes such as IL-6, IL-1β, IL-17α, and Cd86, decreased levels of dendritic cells with suppression of MHC II expression, and suppression of NLRP3 inflammasome activation. The most abundant miRNA in MSC-exosomes, miR-204, was found to be important in ocular development and responsible for the suppression of the IL-6/IL-6R/Stat3 pathway, and its knockdown induced the reversal of the M1 to M2 macrophage transformation and abolition of therapeutic effects. Additionally, the addition of ascorbic acid to MSC-exosomes has been shown to enhance their therapeutic effects in DED by improving reactive oxygen species scavenging [11][12][13][14][15][16][17].

A recent clinical trial (NCT04213248) evaluated the efficacy of MSC-derived exosomes in treating GVHD-associated DED refractory to conventional treatments. Fourteen patients received exosomes as eye drops, administered four times a day for two weeks. The results showed a significant reduction in corneal damage and improvement in epithelial recovery, along with relief from symptoms such as burning, stinging, redness, and crusting. No effects on intraocular pressure or complications related to the treatment were observed. The findings suggest that short-term use of MSC-exosomes may be a safe and effective treatment for severe GVHD-associated DED [18].

A phase 1/2 clinical trial (NCT04213248) is investigating the use of umbilical MSC-derived exosomes for treating dry eye symptoms from cGVHD. The study will enroll 27 subjects who will receive artificial tears for two weeks to establish a baseline, followed by the exosome intervention dosed at 10 µg/drop, administered four times a day for 14 days. The study will measure the progression of dry eye at a 12-week follow-up post-treatment. Currently, the study is recruiting participants and is expected to be completed by May 2023 [19].

## 2.2. Sjogren's Syndrome Dry Eye (SSDE)

Studies have investigated the role and mechanisms of MSC-derived exosomes in the management of SSDE. MSC-exosomes have been found to have a significant enrichment of miR-21, which could play a crucial role in exosome-related immune regulation [20]. In CD4+ T cells, MSC-derived exosomes restore the balance in miRNA-125b-5p and miRNA-155-5p expression, with miRNA-125b inhibiting PRDM1 translation and miRNA-155 being linked with cytokine production and CD8+ T cell proliferation [21][22][23]. Furthermore, MSC-derived exosomes have been shown to reduce signs of SSDE and promote the repair, regeneration, and function of salivary and lacrimal glands in mice [20]. Treatment with exosomes derived from olfactory ecto-MSC, which secrete IL-6, has also led to increased saliva flow rate and reduced tissue damage in mice eyes [24]. This is likely due to IL-6's ability to increase the immunosuppressive capacity of myeloid-derived suppressor cells by activating the STAT3 pathway [24].

# 3. MSC-Derived Exosomes for Corneal Clouding in Mucopolysaccharidosis

Mucopolysaccharidosis IVA patients exhibit corneal clouding due to the accumulation of GAGs, keratan sulfate, and chondroitin-6-sulfate in lysosomes, leading to visual impairment. MSC transplantation has been shown to reduce corneal haze and GAGs accumulation in mucopolysaccharidosis VII animal models. Recently, human umbilical MSC-derived EVs were studied for their potential to treat MPS IVA by transferring GALNS to deficient cells. UMSC-EVs were shown to secrete active GALNS that could be taken up by deficient cells in vitro. However, the low quantity of GALNS present in the EV isolates necessitated the transformation of a UMSC line to express the enzyme, and the transfection technique still requires optimization for consistency and stability. These findings hold promise for developing new therapeutic approaches for treating MPS in avascular tissues like the cornea [25][26][27].

# 4. MSC-Derived Exosomes for Glaucoma

Glaucoma is a leading cause of irreversible blindness worldwide, characterized by progressive vision loss and optic nerve damage. While current treatments focus on managing intraocular pressure (IOP), they do not address permanent retinal ganglion cell damage or vision loss in advanced or normotensive cases. To address these issues, ongoing research is investigating neuroprotective strategies for glaucoma. MSC-derived exosomes have emerged as a promising approach to promote neuroprotection and deliver neuroprotective molecules to the posterior segment of the eye [28].

## 4.1. MSC-Derived Exosomes for Glaucomatous Optic Neuropathy

MSC-derived exosomes have been shown to have neuroprotective effects on retinal ganglionic cells (RGCs), as observed in glaucomatous and ONC animal models where treated RGCs had increased survival compared to non-treated RGCs [29][30][31][32][33]. These effects have been attributed to mechanisms such as the suppression of cis p-tau accumulation, miRNA modulation, and secretion of neurotrophic factors (NTFs) [29][31][34]. Additionally, human placental MSC-EVs have been shown to attenuate hypoxic injury and repair mitochondrial function in R28 retinal progenitor cells in vitro, and in vivo they promote the expression of antioxidants Prdx2 and Prdx 5 [35]. Mead et al. (2020) proposed TNF-α priming of MSCs to enhance the neuroprotective effects of the derived exosomes, which yielded significant improvement in neuroprotection and quantities of exosomal NTFs such as PEDF, VEGF-A, and PDGF-AA [34]. However, the therapeutic benefits of MSC-exosomes have been shown to halt 6 months after treatment and completely disappear between 9 and 12 months [29], indicating that intravitreal injections would need to be administered every few months to maintain the therapeutic window. This may increase the risk of adverse effects and complications.

In a glaucomatous rat model, bone marrow MSC-exosomes' neuroprotective effects were partially abolished when transfected with an Argonaute-2 (Ago2) inhibitor, which depletes miRNA content, indicating that MSC-exosomes' beneficial effects are miRNA-dependent [33]. Among the proposed miRNA candidates are miR-21, miR-146a, and

miR-17-92, present within bone marrow MSC-exosomes [31][36][37]. MiR-17-92 downregulates phosphatase and tensin homolog (PTEN) expression, which suppresses RGC axonal growth and survival. MiR-146a targets the epidermal growth factor receptor, whose inhibition promotes RGC regeneration [38][39][40]. MiR-21 regulates PTEN expression and the EGFR pathway and affects astrocyte activation [30][41][42]. However, the therapeutic role of miR-21 remains unclear, and further studies are needed to determine its importance in RGC regeneration [41]. Bone marrow MSC-exosomes promote neurogenesis with moderate RGC axonal regeneration significant at short distances from the site of the lesion (<1 mm), whereas umbilical MSC-exosomes have no axogenic effect, indicating that the miRNA compositions of MSC-exosomes vary, affecting their therapeutic effects [30].

### 4.2. MSC-Derived Exosomes for Intraocular Pressure (IOP) Lowering Effect

An alternative therapeutic target for MSC-exosomes in glaucoma has been suggested, through potential alleviation of trabecular meshwork dysfunction induced by oxidative stress, preventing the increase in intraocular pressure (IOP) [43][44][45]. Exosomes derived from human bone marrow MSCs have been shown to decrease the production of intracellular reactive oxygen species (iROS) and downregulate proinflammatory factors IL-1α, IL-1β, IL-6, and IL-8 in human trabecular meshwork cells (hTMCs) under oxidative stress [45]. This was accompanied by upregulation of matrix metalloproteinases MMP-2 and MMP-3, which have the potential to regulate ECM remodeling in a way that increases aqueous outflow capacity [46]. Moreover, specific miRNAs have been linked to the mechanism of action. Downregulation of miR-126-5p in the treated group may imply a reduced risk of glaucoma, as it has been previously identified as upregulated in the tears of patients with open-angle glaucoma [[47]. In addition, miR-3529-3p was upregulated in the treated group, while its target gene, CXCL5, was downregulated. The inflammatory chemokine CXCL5 has been shown to be significantly elevated in the aqueous humor of patients with glaucoma [48].

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