

Mesenchymal stem cell-derived extracellular vesicles as a new therapeutic strategy for ocular diseases

Bo Yu, Xiao-Rong Li, Xiao-Min Zhang

ORCID number: Bo Yu (0000-0003-1754-5798); Xiao-Rong Li (0000-0001-6855-7671); Xiao-Min Zhang (0000-0003-4898-4152).

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Bo Yu, Xiao-Rong Li, Xiao-Min Zhang, Tianjin International Joint Research and Development Center of Ophthalmology and Vision Science, Tianjin Key Laboratory of Retinal Functions and Diseases, Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, Tianjin 300384, China

Corresponding author: Xiao-Min Zhang, MD, PhD, Chief Doctor, Professor, Tianjin International Joint Research and Development Center of Ophthalmology and Vision Science, Tianjin Key Laboratory of Retinal Functions and Diseases, Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, No. 251, Fukang Road, Tianjin 300384, China. xzhang08@tmu.edu.cn

Abstract

Mesenchymal stem cells (MSCs) have attracted considerable attention for their activity in the treatment of refractory visual disorders. Since MSCs were found to possess the beneficial effects by secreting paracrine factors rather than direct differentiation, MSC-derived extracellular vesicles (EVs) were widely studied in various disease models. MSCs generate abundant EVs, which act as important mediators by exchanging protein and genetic information between MSCs and target cells. It has been confirmed that MSC-derived EVs possess unique anti-inflammatory, anti-apoptotic, tissue repairing, neuroprotective, and immunomodulatory properties, similar to their parent cells. Upon intravitreal injection, MSC-derived EVs rapidly diffuse through the retina to alleviate retinal injury or inflammation. Due to possible risks associated with MSC transplantation, such as vitreous opacity and pathological proliferation, EVs appear to be a better choice for intravitreal injection. Small size EVs can pass through biological barriers easily and their contents can be modified genetically for optimal therapeutic effect. Hence, currently, they are also explored for the possibility of serving as drug delivery vehicles. In the current review, we describe the characteristics of MSC-derived EVs briefly, comprehensively summarize their biological functions in ocular diseases, and discuss their potential applications in clinical settings.

Key words: Mesenchymal stem cells; Extracellular vesicles; Exosomes; Ocular diseases; Drug delivery

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Core tip: The therapeutic potential of Mesenchymal stem cell (MSC)-derived extracellular vesicles (EVs) has been widely studied in various diseases. In the current

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review, we summarize all the studies about the use of MSC-derived EVs in different ocular disorders, such as corneal injury, glaucoma, uveitis and retinal diseases. We also discuss the history and properties of MSC-derived EVs, the advantages of their use in treating eye diseases and their drug delivery potential. This review also provides future directions for enhancing the therapeutic effect of MSC-derived EVs in treating ocular diseases.

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INTRODUCTION

Visual impairment and blindness are global issues, leading to a significant financial and medical burden. The number of visually impaired people in 2017 was estimated to be 285 million worldwide^[1]. The leading causes of moderate or severe vision impairment among the global population in 2015 were uncorrected refractive error, cataract, age-related macular degeneration, glaucoma, and diabetic retinopathy, which will not change until 2020. Among them, vision loss caused by refractive error and cataract is avoidable. However, vision loss caused by age-related macular degeneration, glaucoma, and diabetic retinopathy is sometimes preventable, but incurable and irreversible^[2]. The patient's quality of life is affected considerably, imposing a serious burden on their families. At present, few effective methods are available for the treatment of retinal and neural damage caused by various ocular diseases. Hence, alternative solutions, such as regenerative cell-based therapy, are being explored^[3-5].

MSCs can produce immunosuppressive, anti-inflammatory, and trophic factors, and are explored widely as therapeutic agents for regenerative cell-based therapy of ocular diseases^[6]. Although MSC transplantation has shown beneficial effects in treating many refractory diseases, ethical and safety concerns after intravenous injection on undesired differentiation and their ability to promote tumor growth are still a matter of debate, while intravitreal injection could lead to severe vision loss due to proliferative vitreoretinopathy (PVR)^[7,8]. Since the therapeutic effects of MSCs can be mediated primarily by the paracrine signaling of EVs^[9], MSC-derived EVs, either as a therapeutic agent or as a drug delivery system, are explored widely for the treatment of ocular disorders^[10]. The majority of live cells secrete EVs^[11]. However, MSC is the only human cell type with a scalable ability for mass production of EVs^[12]. In this review, we summarize recent studies on the role of MSC-derived sEVs in the treatment of eye diseases and discuss the possibility of future clinical application.

EVs were used to be referred to as exosomes or microvesicles (MVs) in many studies. In 2018, the International Society for Extracellular Vesicles published minimal information for studies of EVs (MISEV2018), in which the authors were urged to use operational terms for EV subtypes based on their size ("small EVs" (sEVs) [< 100 nm or < 200 nm] and "medium/large EVs" (m/lEVs) [> 200 nm]), density (low, middle, high, with each range defined) or biochemical composition (CD63⁺/CD81⁺ EVs, annexin A5-stained EVs, *etc.*) in place of terms such as exosomes and MVs^[13]. All studies that described the effect of MSC-EVs on ocular disorders were using the term of exosomes. Based on the size of the EVs mentioned in these studies, we used sEVs instead of exosomes in this review.

Characteristics of MSC-derived sEVs

MSCs are a population of non-hematopoietic stem cells with self-renewal ability. In addition to fetal tissues, MSCs can also be isolated from adipose tissue, umbilical cord blood, peripheral blood, skeletal muscle, liver, gingival and dental tissue, skin, breast milk, cartilage, and corneal limbal stroma of the eye^[14]. MSCs have the potential to differentiate into mesenchymal or non-mesenchymal cell lineages, such as osteoblasts, chondrocytes, and adipocytes^[15]. MSCs possess the ability to migrate to the injury sites to promote wound healing and tissue regeneration and inhibit the immune response by modulating the proliferation and function of innate and acquired immune cells. The beneficial effect of MSCs can be attributed to sEVs, soluble factor secretion, and membrane protein CD73^[16-18].

MSC-derived sEVs have a narrow diameter of < 200 nm and were supposed to be mostly exosomes in earlier studies with a major peak particle size of 65-75 nm^[19]. The exosomes are composed of lipid bilayer membrane and cargo of proteins, nucleic acids (mRNA, miRNAs, DNA, and long noncoding RNAs), and raft-associated lipids^[20]. Their biogenesis has two steps; the first step is the inward budding of late endosomes, and the second step involves the production of multivesicular body and extracellular release^[21]. After being secreted into the extracellular space, the exosomes enter various biological fluids and can travel to remote organs while protecting the inside cargo from decomposing. Due to their small size, they can easily traverse through different biological barriers, and communicate with recipient cells by releasing and transporting cargos.

The contents released from sEVs, mostly being exosomes, derived from MSCs originating from different tissues are not identical and influence their potential bioactivity. For example, CD9, CD81, CD44, and CD90 are expressed commonly on the membrane of all MSC-derived sEVs. However, bone marrow MSC-derived sEVs express CD71 and CD166, human umbilical cord MSC-derived sEVs express CK8 and HLA-II, while HLA-I and HLA-ABC are present on the membrane of adipose tissue MSC-derived sEVs^[22]. Hence, they exhibit differential effects on the same disease or cell model. For example, MSC-derived sEVs from the bone marrow and umbilical cord decreased cell proliferation and suppressed tumor growth, whereas adipose tissue MSC-derived sEVs enhanced tumor cell proliferation^[23]. The sEVs content also varies based on the microenvironment to which MSCs are exposed to^[24]. Over 4000 gene products, miRNAs, and nearly 2000 proteins have been detected and identified in the MSC-derived sEV cargo^[25,26].

The role of MSC-derived sEVs was explored initially in a mouse model of myocardial ischemia/reperfusion injury^[27]. In kidney injury models, MSC-derived sEVs showed improvement in renal function through the transport of miRNA^[28]. In animal neurodegeneration disease models, MSC-derived sEVs promoted neurogenesis and angiogenesis, reduced neuroinflammation, and facilitated functional recovery (increasing memory improvement and spatial learning)^[29]. MSC-derived sEVs were also effective in treating brain injury through suppression of early inflammatory responses or shift of microglial M1/M2 polarization^[30,31]. In liver fibrosis models, MSC-derived sEVs protected hepatocytes by inhibiting epithelial-to-mesenchymal transition^[32]. MSC-derived sEVs also showed beneficial effects in the treatment of many other disease models, such as graft-versus-host disease^[33], type 2 diabetes mellitus^[34], tumors^[35], and cutaneous wounds^[36].

APPLICATION OF MSC-DERIVED SEVS IN OCULAR DISEASES

Corneal diseases

The corneal epithelium covers the outermost part of the cornea, and its integrity forms the foundation of normal corneal function. Trauma, infection, and physical abrasion can cause persistent epithelial defects, a leading cause of vision loss in different ocular surface diseases. While corneal disease treatment and protection have achieved significant progress, wound healing after severe corneal disease or injury remains challenging^[37]. In recent years, MSCs were shown to aid corneal surface healing^[38]. Samaeekia *et al*^[39] evaluated the effect of MSC-derived sEVs on corneal wound healing and showed that human corneal MSC-derived sEVs significantly increased the proliferation of human corneal epithelial cells *in vitro*, and accelerated corneal wound closure in a murine epithelial mechanical injury model (Table 1).

Corneal stroma accounts for 90% of the corneal thickness and is important for the maintenance of corneal transparency. Severe corneal diseases affect the corneal stroma, causing a corneal scar and a significant decline in vision^[40]. Currently, the conventional treatment modality is keratoplasty, and the disadvantages, especially immunological rejection, are challenging to avoid or overcome. MSC-based therapy is a promising method in prompting corneal stroma healing, which has been tested in several studies^[41,42]. Recent reports showed that MSCs exert their therapeutic effect by secreting sEVs^[43]. Shen *et al*^[44] reported that the co-culture of corneal stromal cells (CSCs) with MSCs resulted in enhanced viability and proliferative ability along with increased plasticity. Treatment of CSCs with MSC-derived sEVs caused changes in the matrix metalloproteinases and collagen levels of CSCs and promoted extracellular matrix (ECM) synthesis and CSC proliferation. The protective effect might be exerted through promoting CSC transformation into fibroblasts or myofibroblasts. The ECM-promoting activity of MSC-derived sEVs was reported to be similar to that of MSCs, thus highlighting the potential clinical use of MSC-derived sEVs for the treatment of

Table 1 Effects of mesenchymal stem cell derived extracellular vesicles in ocular disorders

Ref.	Origin	Delivery way	Biological function
Yu <i>et al</i> ^[74] , 2016	Human umbilical cord derived MSCs	Intravitreal injection	Ameliorate retinal laser injury
Mead <i>et al</i> ^[64] , 2017	Human bone marrow derived MSCs	Intravitreal injection	Promote RGC survival in optic nerve crush model
Kuroda <i>et al</i> ^[58] , 2017	Human bone marrow derived MSCs	Intravenous injection	Prevent EAU development
Moisseiev <i>et al</i> ^[77] , 2017	Human bone marrow derived MSCs	Intravitreal injection	Decrease the severity of retinal ischemia
Bai <i>et al</i> ^[57] , 2017	Human umbilical cord derived MSCs	Periocular injection	Inhibit inflammatory cell migration in EAU
Shen <i>et al</i> ^[44] , 2018	Rabbit adipose derived MSCs	In vitro	Contribute to the growth and plasticity of corneal stromal cells
Samaeekia <i>et al</i> ^[39] , 2018	Human corneal MSCs	Topical application	Accelerate corneal epithelial wound healing
Mead <i>et al</i> ^[67] , 2018	Human bone marrow derived MSCs	Intravitreal injection	Promote neuroprotection in glaucoma model
Safwat <i>et al</i> ^[72] , 2018	Rabbit adipose derived MSCs	Intravenous, intraocular or subconjunctival injection	Attenuate retina degeneration in diabetic retinopathy
Zhang <i>et al</i> ^[71] , 2018	Human umbilical cord derived MSCs	Intravitreal injection	Ameliorate hyperglycemia-induced retinal inflammation
Mathew <i>et al</i> ^[76] , 2019	Human bone marrow derived MSCs	Intravitreal injection	Protect retinal cells from cell death in retinal ischemia

MSCs: Mesenchymal stem cells; EVs: Extracellular vesicles.

corneal stromal damage^[44].

Corneal endothelium, regulating stromal hydration level and maintaining corneal deturgescence, covers the posterior corneal surface^[45]. The loss of endothelial cells will lead to stromal edema and severe vision loss^[46]. Recently, MSCs as a potential therapeutic cell source for corneal endothelial diseases were also reported^[47,48]. However, MSCs exerted the therapeutic effects on endothelial cell defect mainly through direct differentiation, and no application of MSC-derived EVs has been reported so far.

Our previous study demonstrated that MSC administration was effective in prolonging corneal allograft survival and exerted therapeutic effect against corneal allograft rejection^[49,50]. Recently, we found MSC-derived sEVs acted similarly as MSCs in corneal allograft rejection (unpublished data).

Autoimmune uveitis

Autoimmune uveitis is a type of autoimmune disease involving the uveal tract and retina. It is one of leading global causes of visual disability due to severe clinical complications, including cataract, glaucoma, and retinal damage^[51]. Systemic or local administration of corticosteroids combined with immunosuppressive drugs is the traditional treatment protocol for autoimmune uveitis. However, severe adverse effects limit their long-term use in the clinic^[52]. The experimental autoimmune uveitis (EAU) model is used widely to understand the mechanism and new treatment options for non-infectious uveitis^[53]. Our previous study showed MSCs strikingly ameliorate EAU both in mice and rats^[54-56]. Recently, we proved that periocular injection of sEVs derived from umbilical cord MSCs reduced EAU severity by reducing leukocyte infiltration in the eyes of EAU rats. The *in vitro* migration of inflammatory cells such as neutrophils, NK cells, and CD4⁺ T cells was inhibited by MSC-derived sEVs, indicating that the sEVs exert their therapeutic effect at least partially by the inhibition of leukocyte migration. The study showed the possible clinical utility of MSC-derived sEVs for the treatment of autoimmune uveitis^[57]. The other study also demonstrated that MSC-derived sEVs could prevent EAU development and suppress Th1 and Th17 development in mice^[58].

Glaucoma

Glaucoma is a group of optic neuropathies characterized by the degeneration of retinal ganglion cells (RGCs) and the axons. Degeneration of RGCs results in altered optic disc appearance and visual field loss^[59]. Among vision disorders, glaucoma is second to cataract and also a leading global cause of irreversible vision loss. It was estimated that in 2020 the number of people with open-angle glaucoma and angle-closure glaucoma would be nearly 79.6 million^[60]. Currently, ocular hypotensive

drops, laser treatment, and surgery are used to lower intraocular pressure; however, they are insufficient to rescue damaged RGCs^[61]. Therefore, utilizing the neuroprotective effects of MSCs, they were shown to be effective in promoting RGCs survival in different animal models^[62-64]. The MSC-derived sEVs were also tested in glaucoma models recently to avoid the potential side-effects of MSC administration. In the rodent optic-nerve crush model, the thickness of the retinal nerve fiber layer (RNFL) decreased significantly. Mead *et al.*^[65] showed that intravitreal injection of MSC-derived sEVs preserved RNFL thickness as measured by OCT and positive scotopic threshold response (pSTR) measured by ERG. Greater than 50% of RGC function in MSC-derived sEVs treated retina was preserved, which indicated that sEVs could protect RGC from death along with retaining their function. The Ago2 knockdown reduced microRNA quantity within the sEVs and decreased sEVs neuroprotective and neuritogenesis abilities, thus indicating the dependence of the therapeutic effect on microRNA rather than protein. DBA/2J mouse is a rodent genetic model of glaucoma. In another study, MSC-derived sEVs were injected intravitreally into DBA/2J mice once a month, from 3 mo to 1 year of age. In the treated group, the number of RGCs was higher at 12-mo and had reduced axonal damage. Concerning the RGC function, pSTR amplitudes were measured by ERG, and the pSTR amplitudes in the treated group were higher at 6-mo, but not at 9- or 12-mo, which indicated that MSC-derived sEVs might prevent RGC functional decline at an early stage, but not at late stage^[66,67].

Retinal diseases

Idiopathic macular hole: An idiopathic macular hole is a common fundus disease, which causes severe vision impairment or blindness. The primary treatment is pars plana vitrectomy, and the visual recovery depends on the closure state of the hole and the function of residue photoreceptor cells in the macular area. Current treatment to achieve an ideal prognosis is challenging, especially for large or refractory holes. We previously reported a pilot clinical study, in which seven patients underwent vitrectomy combined with intravitreal injection of MSCs or MSC-derived sEVs. Among the seven patients, six achieved closure of macular holes, and five patients achieved a satisfactory improvement of visual acuity. In one patient, an epiretinal fibrotic membrane formed after MSC injection and a second surgery was performed to remove the membrane, and sEVs therapy was shown to be safer and easier to perform than MSC therapy^[68].

Diabetic retinopathy: Diabetic retinopathy (DR) is currently the leading cause of vision loss and blindness in working-age people. Patients are usually asymptomatic until severe vision decline occurs in the late disease phase^[69]. Blindness due to DR is preventable but irreversible and poses a substantial economic burden on the family and society. It is estimated that the blindness caused by DR will reach 3.2 million in 2020^[2]. Laser therapy, anti-vascular epithelial growth factor (VEGF) agents, and vitrectomy were usually used to treat diabetic retinopathy. However, not all patients respond well to current therapies^[70]. A study conducted by Zhang *et al.*^[71] showed that intravitreal injection of MSC-derived sEVs into the vitreous of streptozotocin (STZ) induced diabetic rats, effectively reduced the expression of inflammatory markers and adhesion molecules. MSC-derived sEVs reversed the increased expression of HMGB1 and its downstream target proteins in retinas of diabetic rats. Consistent with the *in vivo* results, the MSC-derived sEVs suppressed the inflammatory response in high glucose-stimulated human retinal epithelial cells and highlighted the critical role of microRNA126 in inflammatory regulation. The sEVs derived from microRNA126-transfected MSCs inhibited HMGB1 signaling pathway more effectively to reduce inflammation in diabetic retinopathy^[71]. In another study, MSC-derived sEVs were injected by different routes (intravenous, subconjunctival, and intraocular) into rabbits with STZ-induced diabetes, and the results showed that both subconjunctival and intraocular injection of MSC-derived sEVs could protect retinal tissue structure from damage, while intravenous injection failed to ameliorate DR progression. The authors also showed an association of decreased microRNA222 expression in retinal tissues with extensive hemorrhage and severe retinal injury. MSC-derived sEVs mediated transfer of microRNA222 resulted in increased microRNA222 expression level and enhanced regenerative retinal changes^[72].

Retinal injury: Retinal damage caused by ischemia, infection, or physical injury leads to photoreceptor cell degeneration or death, as well as severe vision loss. No effective neuroprotective drugs are available in the clinic to restore the damaged cells. Our research group showed that intravenous MSC transplantation was effective in alleviating photoreceptor damage^[73], and further studies demonstrated that intravitreal injection of MSC-derived sEVs resulted in reduced photoreceptor

apoptosis and protection of visual function, a protective effect comparable to that of MSCs. *In vitro* experiments showed that MSC-derived sEVs could reduce heat injury-induced retinal cell loss by downregulating MCP-1^[74]. We also demonstrated recently that subretinal injection of MSC-derived sEVs exhibited therapeutic effect in rat retinal detachment model by inhibiting inflammatory cytokine secretion, reducing apoptosis, and activating autophagy^[75]. In a rodent ischemia-reperfusion model, intravitreal injection of MSC-derived sEVs increased retinal functional recovery after ischemic injury. After intravitreal injection, a large number of sEVs were observed in ischemic retina and were concentrated in RGCs and microglial cells. The injected sEVs could be detected in the vitreous humor up to four weeks after administration^[76]. In another study of a murine oxygen-induced retinopathy model, Moisseiev *et al*^[77] showed that intravitreal injection of MSC-derived sEVs decreased the severity of retinal ischemia. *In vitro* experiments showed that pretreatment of R28 cells with sEVs could protect cells against oxygen and glucose deprivation conditions.

MSC-DERIVED SEVS AS DRUG DELIVERY SYSTEM IN OPHTHALMOLOGY

With lipid bilayer membrane to protect their cargo from degradation, sEVs can travel a long distance and even traverse through biological barriers to the target cells to transfer biological message. Therefore, they are natural carriers for the transport of proteins, lipids, or RNAs to recipient cells with high biocompatibility^[20], and are utilized in basic research for drug or other bioactive substance delivery^[78]. MSCs are a rich source of sEVs, and MSC-derived sEVs, which have many beneficial effects for many diseases, are ideal for drug delivery and were used in studies of many diseases^[12,79-81].

The nanometer size of MSC-derived sEVs facilitates their transport after intravitreal injection across the retina and choroid. Our data showed that after both periocular and intravenous injection, sEVs reach the retina rapidly (unpublished data). In contrast to the MSCs, the MSC-derived sEVs, do not cause vitreous opacity, immunologic rejection, or proliferative vitreous retinopathy^[68,76]. Therefore, they could be an alternative drug delivery option for ocular disease treatment. The therapeutic substances could be loaded into sEVs by two methods: One by loading high doses of the selective therapeutic drug into MSCs and collecting the secreted sEVs, and the other is to load sEVs directly through co-culture or electroporation. Owing to the advantages of EV-based therapy, the use of MSC-derived sEVs as nanocarriers loaded with proteins, miRNAs, or other drugs hold promise for the treatment of refractory ocular disorders.

CONCLUSION

Recently, several studies showed the critical role of MSC-derived sEVs in treating ophthalmic diseases. They are also ideal nanocarriers to deliver drugs because of their high biocompatibility, bi-lipid membrane structure, and small size. With increasing evidence of their therapeutic efficacy, it is promising to transform MSC-derived sEV based therapy into clinic for treating ocular diseases in the future.

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