

World Journal of *Stem Cells*

World J Stem Cells 2020 March 26; 12(3): 168-240



**OPINION REVIEW**

- 168** Mesenchymal stem cells in neurodegenerative diseases: Opinion review on ethical dilemmas
Scopetti M, Santurro A, Gatto V, La Russa R, Manetti F, D'Errico S, Frati P, Fineschi V

REVIEW

- 178** Mesenchymal stem cell-derived extracellular vesicles as a new therapeutic strategy for ocular diseases
Yu B, Li XR, Zhang XM
- 188** Gut commensal bacteria, Paneth cells and their relations to radiation enteropathy
Gao YL, Shao LH, Dong LH, Chang PY

ORIGINAL ARTICLE**Basic Study**

- 203** Efficient differentiation of vascular smooth muscle cells from Wharton's Jelly mesenchymal stromal cells using human platelet lysate: A potential cell source for small blood vessel engineering
Mallis P, Papapanagiotou A, Katsimpoulas M, Kostakis A, Siasos G, Kassi E, Stavropoulos-Giokas C, Michalopoulos E
- 222** CR6-interacting factor-1 contributes to osteoclastogenesis by inducing receptor activator of nuclear factor κ B ligand after radiation
Xiang LX, Ran Q, Chen L, Xiang Y, Li FJ, Zhang XM, Xiao YN, Zou LY, Zhong JF, Li SC, Li ZJ

ABOUT COVER

Editorial Board Member of *World Journal of Stem Cells*, Sujeong Jang, PhD, Assistant Professor, Physiology, Chonnam National University Medical School, Hwasun-gun 58128, South Korea

AIMS AND SCOPE

The primary aim of *World Journal of Stem Cells* (*WJSC*, *World J Stem Cells*) is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJSC publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryoid bodies, embryonal carcinoma stem cells, hemangioblasts, hematopoietic stem cells, lymphoid progenitor cells, myeloid progenitor cells, *etc.*

INDEXING/ABSTRACTING

The *WJSC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Biological Abstracts, and BIOSIS Previews. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for *WJSC* as 3.534 (5-year impact factor: N/A), ranking *WJSC* as 16 among 26 journals in Cell and Tissue Engineering (quartile in category Q3), and 94 among 193 journals in Cell Biology (quartile in category Q2).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL

World Journal of Stem Cells

ISSN

ISSN 1948-0210 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Tong Cao, Shengwen Calvin Li, Carlo Ventura

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-0210/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

March 26, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

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).

Author contributions: All authors equally contributed to this manuscript.

Supported by National Natural Science Foundation of China, No. 81800825, No. 81870651 and No. 81870675.

Conflict-of-interest statement: The authors have no conflicts to declare.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: December 27, 2019

Peer-review started: December 27, 2019

First decision: February 20, 2020

Revised: February 22, 2020

Accepted: March 22, 2020

Article in press: March 22, 2020

Published online: March 26, 2020

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

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

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

P-Reviewer: Khan I, Ranghino A
S-Editor: Ma YJ
L-Editor: A
E-Editor: Xing YX



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.

Citation: Yu B, Li XR, Zhang XM. Mesenchymal stem cell-derived extracellular vesicles as a new therapeutic strategy for ocular diseases. *World J Stem Cells* 2020; 12(3): 178-187

URL: <https://www.wjgnet.com/1948-0210/full/v12/i3/178.htm>

DOI: <https://dx.doi.org/10.4252/wjsc.v12.i3.178>

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/IEVs) [> 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]. Samaeikia *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.

REFERENCES

1. **Elmannai W**, Elleithy K. Sensor-Based Assistive Devices for Visually-Impaired People: Current Status, Challenges, and Future Directions. *Sensors (Basel)* 2017; **17**: 565 [PMID: 28287451 DOI: 10.3390/s17030565]
2. **Flaxman SR**, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, Das A, Jonas JB, Keeffe J, Kempen JH, Leasher J, Limburg H, Naidoo K, Pesudovs K, Silvestre A, Stevens GA, Tahhan N, Wong TY, Taylor HR; Vision Loss Expert Group of the Global Burden of Disease Study. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health* 2017; **5**: e1221-e1234 [PMID: 29032195 DOI: 10.1016/S2214-109X(17)30393-5]
3. **Bertelli PM**, Pedrini E, Guduric-Fuchs J, Peixoto E, Pathak V, Stitt AW, Medina RJ. Vascular Regeneration for Ischemic Retinopathies: Hope from Cell Therapies. *Curr Eye Res* 2020; **45**: 372-384 [PMID: 31609636 DOI: 10.1080/02713683.2019.1681004]
4. **Kuai L**, Peng J, Jiang Y, Zheng Z, Zhou X. Apolipoprotein E-Mimetic Peptide COG1410 Enhances Retinal Ganglion Cell Survival by Attenuating Inflammation and Apoptosis Following TONI. *Front Neurosci* 2019; **13**: 980 [PMID: 31607842 DOI: 10.3389/fnins.2019.00980]
5. **Kohen MC**, Tatlipinar S, Cumbul A, Uslu Ü. The effects of bevacizumab treatment in a rat model of retinal ischemia and perfusion injury. *Mol Vis* 2018; **24**: 239-250 [PMID: 29681725]
6. **Joe AW**, Gregory-Evans K. Mesenchymal stem cells and potential applications in treating ocular disease.

- Curr Eye Res* 2010; **35**: 941-952 [PMID: 20958182 DOI: 10.3109/02713683.2010.516466]
- 7 **Volarevic V**, Markovic BS, Gazdic M, Volarevic A, Jovicic N, Arsenijevic N, Armstrong L, Djonov V, Lako M, Stojkovic M. Ethical and Safety Issues of Stem Cell-Based Therapy. *Int J Med Sci* 2018; **15**: 36-45 [PMID: 29333086 DOI: 10.7150/ijms.21666]
 - 8 **Kuriyan AE**, Albini TA, Townsend JH, Rodriguez M, Pandya HK, Leonard RE 2nd, Parrott MB, Rosenfeld PJ, Flynn HW Jr, Goldberg JL. Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD. *N Engl J Med* 2017; **376**: 1047-1053 [PMID: 28296617 DOI: 10.1056/NEJMoa1609583]
 - 9 **Lai RC**, Arslan F, Lee MM, Sze NS, Choo A, Chen TS, Salto-Tellez M, Timmers L, Lee CN, El Oakley RM, Pasterkamp G, de Kleijn DP, Lim SK. Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury. *Stem Cell Res* 2010; **4**: 214-222 [PMID: 20138817 DOI: 10.1016/j.scr.2009.12.003]
 - 10 **Harrell CR**, Simovic Markovic B, Fellabaum C, Arsenijevic A, Djonov V, Arsenijevic N, Volarevic V. Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes in the Treatment of Eye Diseases. *Adv Exp Med Biol* 2018; **1089**: 47-57 [PMID: 29774506 DOI: 10.1007/5584_2018_219]
 - 11 **Simpson RJ**, Lim JW, Moritz RL, Mathivanan S. Exosomes: proteomic insights and diagnostic potential. *Expert Rev Proteomics* 2009; **6**: 267-283 [PMID: 19489699 DOI: 10.1586/epr.09.17]
 - 12 **Yeo RW**, Lai RC, Zhang B, Tan SS, Yin Y, Teh BJ, Lim SK. Mesenchymal stem cell: an efficient mass producer of exosomes for drug delivery. *Adv Drug Deliv Rev* 2013; **65**: 336-341 [PMID: 22780955 DOI: 10.1016/j.addr.2012.07.001]
 - 13 **Théry C**, Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, Antoniou A, Arab T, Archer F, Atkin-Smith GK, Ayre DC, Bach JM, Bachurski D, Baharvand H, Balaj L, Baldacchino S, Bauer NN, Baxter AA, Bewawy M, Beckham C, Bedina Zavec A, Benmoussa A, Berardi AC, Bergese P, Bielska E, Blenkiron C, Bobis-Wozowicz S, Boilard E, Boireau W, Bongiovanni A, Borràs FE, Bosch S, Boulanger CM, Breakefield X, Breglio AM, Brennan MÁ, Brigstock DR, Brisson A, Broekman ML, Bromberg JF, Bryl-Górecka P, Buch S, Buck AH, Burger D, Busatto S, Buschmann D, Bussolati B, Buzás EI, Byrd JB, Camussi G, Carter DR, Caruso S, Chamley LW, Chang YT, Chen C, Chen S, Cheng L, Chin AR, Clayton A, Clerici SP, Cocks A, Cocucci E, Coffey RJ, Cordeiro-da-Silva A, Couch Y, Coumans FA, Coyle B, Crescitelli R, Criado MF, D'Souza-Schorey C, Das S, Datta Chaudhuri A, de Candia P, De Santana EF, De Wever O, Del Portillo HA, Demaret T, Deville S, Devitt A, Dhondt B, Di Vizio D, Dieterich LC, Dolo V, Dominguez Rubio AP, Dominici M, Dourado MR, Driedonks TA, Duarte FV, Duncan HM, Eichenberger RM, Ekström K, El Andaloussi S, Elie-Caille C, Erdbrügger U, Falcón-Pérez JM, Fatima F, Fish JE, Flores-Bellver M, Förstner A, Frelet-Barrand A, Fricke F, Fuhrmann G, Gabrielsson S, Gámez-Valero A, Gardiner C, Gärtner K, Gaudin R, Gho YS, Giebel B, Gilbert C, Gimona M, Giusti I, Goberdhan DC, Görgens A, Gorski SM, Greening DW, Gross JC, Gualerzi A, Gupta GN, Gustafson D, Handberg A, Haraszti RA, Harrison P, Hegyesi H, Hendrix A, Hill AF, Hochberg FH, Hoffmann KF, Holder B, Holthofer H, Hosseinkhani B, Hu G, Huang Y, Huber V, Hunt S, Ibrahim AG, Ikezu T, Inal JM, Isin M, Ivanova A, Jackson HK, Jacobsen S, Jay SM, Jayachandran M, Jenster G, Jiang L, Johnson SM, Jones JC, Jong A, Jovanovic-Talisman T, Jung S, Kalluri R, Kano SI, Kaur S, Kawamura Y, Keller ET, Khamari D, Khomyakova E, Khvorov A, Kierulff P, Kim KP, Kislinger T, Klingeborn M, Klinken DJ 2nd, Kornek M, Kosanović MM, Kovács ÁF, Krämer-Albers EM, Krasemann S, Krause M, Kurochkin IV, Kusuma GD, Kuypers S, Laitinen S, Langevin SM, Languino LR, Lannigan J, Lässer C, Laurent LC, Lavieu G, Lázaro-Ibáñez E, Le Lay S, Lee MS, Lee YXF, Lemos DS, Lenassi M, Leszczynska A, Li IT, Liao K, Libregts SF, Ligeti E, Lim R, Lim SK, Linē A, Linnemannstons K, Llorente A, Lombard CA, Lorenowicz MJ, Lőrincz ÁM, Lötvall J, Lovett J, Lowry MC, Loyer X, Lu Q, Lukomska B, Lunavat TR, Maas SL, Malhi H, Marcilla A, Mariani J, Mariscal J, Martins-Uzunova ES, Martin-Jaular L, Martinez MC, Martins VR, Mathieu M, Mathivanan S, Maugeri M, McGinnis LK, McVey MJ, Meckes DG Jr, Meehan KL, Mertens I, Minciacci VR, Möller A, Möller Jørgensen M, Morales-Kastresana A, Morhayim J, Mullier F, Muraca M, Musante L, Mussack V, Muth DC, Myburgh KH, Najrana T, Nawaz M, Nazarenko I, Nejsup M, Neri C, Neri T, Nieuwland R, Nimrichter L, Nolan JP, Nolte-t Hoen EN, Noren Hooten N, O'Driscoll L, O'Grady T, O'Loughlin A, Ochiya T, Olivier M, Ortiz A, Ortiz LA, Osteikoetxea X, Østergaard O, Ostrowski M, Park J, Pegtel DM, Peinado H, Perut F, Pfaffl MW, Phinney DG, Pieters BC, Pink RC, Pisetsky DS, Pogge von Strandmann E, Polakovicova I, Poon IK, Powell BH, Prada I, Pulliam L, Quesenberry P, Radeghieri A, Raffai RL, Raimondo S, Rak J, Ramirez MI, Raposo G, Rayyan MS, Regev-Rudski N, Rinklefs FL, Robbins PD, Roberts DD, Rodrigues SC, Rohde E, Rome S, Rouschop KM, Rughetti A, Russell AE, Saá P, Sahoo S, Salas-Huenuleo E, Sánchez C, Saugstad JA, Saul MJ, Schiffelers RM, Schneider R, Schøyen TH, Scott A, Shahaj E, Sharma S, Shatnyeva O, Shekari F, Shelke GV, Shetty AK, Shiba K, Siljander PR, Silva AM, Skowronek A, Snyder OL 2nd, Soares RP, Sódar BW, Soekmadji C, Sotillo J, Stahl PD, Stoorvogel W, Stott SL, Strasser EF, Swift S, Tahara H, Tewari M, Timms K, Tiwari S, Tixeira R, Tkach M, Toh WS, Tomasini R, Torrecillas AC, Tosar JP, Toxavidis V, Urbanelli L, Vader P, van Balkom BW, van der Grein SG, Van Deun J, van Herwijnen MJ, Van Keuren-Jensen K, van Niel G, van Royen ME, van Wijnen AJ, Vasconcelos MH, Vechetti JJ Jr, Veit TD, Vella LJ, Velot É, Verweij FJ, Vestad B, Viñas JL, Visnovitz T, Vukman KV, Wahlgren J, Watson DC, Wauben MH, Weaver A, Webber JP, Weber V, Wehman AM, Weiss DJ, Welsh JA, Wendt S, Wheelock AM, Wiener Z, Witte L, Wolfram J, Xagorari A, Xander P, Xu J, Yan X, Yáñez-Mó M, Yin H, Yuana Y, Zappulli V, Zarubova J, Žekas V, Zhang JY, Zhao Z, Zheng L, Zheutlin AR, Zickler AM, Zimmermann P, Zivkovic AM, Zocco D, Zuba-Surma EK. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles* 2018; **7**: 1535750 [PMID: 30637094 DOI: 10.1080/20013078.2018.1535750]
 - 14 **Veréb Z**, Pólska S, Albert R, Olstad OK, Boratkó A, Csontos C, Moe MC, Facskó A, Petrovski G. Role of Human Corneal Stroma-Derived Mesenchymal-Like Stem Cells in Corneal Immunity and Wound Healing. *Sci Rep* 2016; **6**: 26227 [PMID: 27195722 DOI: 10.1038/srep26227]
 - 15 **Deskins DL**, Bastakoty D, Saraswati S, Shinar A, Holt GE, Young PP. Human mesenchymal stromal cells: identifying assays to predict potency for therapeutic selection. *Stem Cells Transl Med* 2013; **2**: 151-158 [PMID: 23362238 DOI: 10.5966/sctm.2012-0099]
 - 16 **Wong SP**, Rowley JE, Redpath AN, Tilman JD, Fellous TG, Johnson JR. Pericytes, mesenchymal stem cells and their contributions to tissue repair. *Pharmacol Ther* 2015; **151**: 107-120 [PMID: 25827580 DOI: 10.1016/j.pharmthera.2015.03.006]
 - 17 **Ayala-Cuellar AP**, Kang JH, Jeung EB, Choi KC. Roles of Mesenchymal Stem Cells in Tissue Regeneration and Immunomodulation. *Biomol Ther (Seoul)* 2019; **27**: 25-33 [PMID: 29902862 DOI: 10.4062/biomolther.2017.260]

- 18 **Chen X**, Shao H, Zhi Y, Xiao Q, Su C, Dong L, Liu X, Li X, Zhang X. CD73 Pathway Contributes to the Immunosuppressive Ability of Mesenchymal Stem Cells in Intraocular Autoimmune Responses. *Stem Cells Dev* 2016; **25**: 337-346 [PMID: [26650818](#)]
- 19 **Nakamura Y**, Miyaki S, Ishitobi H, Matsuyama S, Nakasa T, Kamei N, Akimoto T, Higashi Y, Ochi M. Mesenchymal-stem-cell-derived exosomes accelerate skeletal muscle regeneration. *FEBS Lett* 2015; **589**: 1257-1265 [PMID: [25862500](#) DOI: [10.1016/j.febslet.2015.03.031](#)]
- 20 **Chaput N**, Théry C. Exosomes: immune properties and potential clinical implementations. *Semin Immunopathol* 2011; **33**: 419-440 [PMID: [21174094](#) DOI: [10.1007/s00281-010-0233-9](#)]
- 21 **Galland S**, Stamenkovic I. Mesenchymal stromal cells in cancer: a review of their immunomodulatory functions and dual effects on tumor progression. *J Pathol* 2019 [PMID: [31608444](#) DOI: [10.1002/path.5357](#)]
- 22 **Mushahary D**, Spittler A, Kasper C, Weber V, Charwat V. Isolation, cultivation, and characterization of human mesenchymal stem cells. *Cytometry A* 2018; **93**: 19-31 [PMID: [29072818](#) DOI: [10.1002/cyto.a.23242](#)]
- 23 **Del Fattore A**, Luciano R, Saracino R, Battafarano G, Rizzo C, Pascucci L, Alessandri G, Pessina A, Perrotta A, Fierabracci A, Muraca M. Differential effects of extracellular vesicles secreted by mesenchymal stem cells from different sources on glioblastoma cells. *Expert Opin Biol Ther* 2015; **15**: 495-504 [PMID: [25539575](#) DOI: [10.1517/14712598.2015.997706](#)]
- 24 **Lo Sicco C**, Reverberi D, Balbi C, Ulivi V, Principi E, Pascucci L, Becherini P, Bosco MC, Varesio L, Franzin C, Pozzobon M, Cancedda R, Tasso R. Mesenchymal Stem Cell-Derived Extracellular Vesicles as Mediators of Anti-Inflammatory Effects: Endorsement of Macrophage Polarization. *Stem Cells Transl Med* 2017; **6**: 1018-1028 [PMID: [28186708](#) DOI: [10.1002/scrm.16-0363](#)]
- 25 **Anderson JD**, Johansson HJ, Graham CS, Vesterlund M, Pham MT, Bramlett CS, Montgomery EN, Mellema MS, Bardini RL, Contreras Z, Hoon M, Bauer G, Fink KD, Fury B, Hendrix KJ, Chedin F, El-Andaloussi S, Hwang B, Mulligan MS, Lehtiö J, Nolte JA. Comprehensive Proteomic Analysis of Mesenchymal Stem Cell Exosomes Reveals Modulation of Angiogenesis via Nuclear Factor-KappaB Signaling. *Stem Cells* 2016; **34**: 601-613 [PMID: [26782178](#) DOI: [10.1002/stem.2298](#)]
- 26 **Chen TS**, Lai RC, Lee MM, Choo AB, Lee CN, Lim SK. Mesenchymal stem cell secretes microparticles enriched in pre-microRNAs. *Nucleic Acids Res* 2010; **38**: 215-224 [PMID: [19850715](#) DOI: [10.1093/nar/gkp857](#)]
- 27 **Lai RC**, Tan SS, Teh BJ, Sze SK, Arslan F, de Kleijn DP, Choo A, Lim SK. Proteolytic Potential of the MSC Exosome Proteome: Implications for an Exosome-Mediated Delivery of Therapeutic Proteasome. *Int J Proteomics* 2012; **2012**: 971907 [PMID: [22852084](#) DOI: [10.1155/2012/971907](#)]
- 28 **Shojaati G**, Khandaker I, Funderburgh ML, Mann MM, Basu R, Stolz DB, Geary ML, Dos Santos A, Deng SX, Funderburgh JL. Mesenchymal Stem Cells Reduce Corneal Fibrosis and Inflammation via Extracellular Vesicle-Mediated Delivery of miRNA. *Stem Cells Transl Med* 2019; **8**: 1192-1201 [PMID: [31290598](#) DOI: [10.1002/scrm.18-0297](#)]
- 29 **Ding M**, Shen Y, Wang P, Xie Z, Xu S, Zhu Z, Wang Y, Lyu Y, Wang D, Xu L, Bi J, Yang H. Exosomes Isolated From Human Umbilical Cord Mesenchymal Stem Cells Alleviate Neuroinflammation and Reduce Amyloid-Beta Deposition by Modulating Microglial Activation in Alzheimer's Disease. *Neurochem Res* 2018; **43**: 2165-2177 [PMID: [30259257](#) DOI: [10.1007/s11064-018-2641-5](#)]
- 30 **Ni H**, Yang S, Siaw-Debrah F, Hu J, Wu K, He Z, Yang J, Pan S, Lin X, Ye H, Xu Z, Wang F, Jin K, Zhuge Q, Huang L. Exosomes Derived From Bone Mesenchymal Stem Cells Ameliorate Early Inflammatory Responses Following Traumatic Brain Injury. *Front Neurosci* 2019; **13**: 14 [PMID: [30733666](#) DOI: [10.3389/fnins.2019.00014](#)]
- 31 **Li Y**, Yang YY, Ren JL, Xu F, Chen FM, Li A. Exosomes secreted by stem cells from human exfoliated deciduous teeth contribute to functional recovery after traumatic brain injury by shifting microglia M1/M2 polarization in rats. *Stem Cell Res Ther* 2017; **8**: 198 [PMID: [28962585](#) DOI: [10.1186/s13287-017-0648-5](#)]
- 32 **Li T**, Yan Y, Wang B, Qian H, Zhang X, Shen L, Wang M, Zhou Y, Zhu W, Li W, Xu W. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. *Stem Cells Dev* 2013; **22**: 845-854 [PMID: [23002959](#) DOI: [10.1089/scd.2012.0395](#)]
- 33 **Fujii S**, Miura Y, Fujishiro A, Shindo T, Shimazu Y, Hirai H, Tahara H, Takaori-Kondo A, Ichinohe T, Maekawa T. Graft-Versus-Host Disease Amelioration by Human Bone Marrow Mesenchymal Stromal/Stem Cell-Derived Extracellular Vesicles Is Associated with Peripheral Preservation of Naive T Cell Populations. *Stem Cells* 2018; **36**: 434-445 [PMID: [29239062](#) DOI: [10.1002/stem.2759](#)]
- 34 **Sun Y**, Shi H, Yin S, Ji C, Zhang X, Zhang B, Wu P, Shi Y, Mao F, Yan Y, Xu W, Qian H. Human Mesenchymal Stem Cell Derived Exosomes Alleviate Type 2 Diabetes Mellitus by Reversing Peripheral Insulin Resistance and Relieving β -Cell Destruction. *ACS Nano* 2018; **12**: 7613-7628 [PMID: [30052036](#) DOI: [10.1021/acsnano.7b07643](#)]
- 35 **Che Y**, Shi X, Shi Y, Jiang X, Ai Q, Shi Y, Gong F, Jiang W. Exosomes Derived from miR-143-Overexpressing MSCs Inhibit Cell Migration and Invasion in Human Prostate Cancer by Downregulating TFF3. *Mol Ther Nucleic Acids* 2019; **18**: 232-244 [PMID: [31563120](#) DOI: [10.1016/j.omtn.2019.08.010](#)]
- 36 **Ma T**, Fu B, Yang X, Xiao Y, Pan M. Adipose mesenchymal stem cell-derived exosomes promote cell proliferation, migration, and inhibit cell apoptosis via Wnt/ β -catenin signaling in cutaneous wound healing. *J Cell Biochem* 2019; **120**: 10847-10854 [PMID: [30681184](#) DOI: [10.1002/jcb.28376](#)]
- 37 **Li F**, Zhao SZ. Mesenchymal stem cells: Potential role in corneal wound repair and transplantation. *World J Stem Cells* 2014; **6**: 296-304 [PMID: [25126379](#) DOI: [10.4252/wjsc.v6.i3.296](#)]
- 38 **Holan V**, Javorkova E. Mesenchymal stem cells, nanofiber scaffolds and ocular surface reconstruction. *Stem Cell Rev Rep* 2013; **9**: 609-619 [PMID: [23733704](#) DOI: [10.1007/s12015-013-9449-0](#)]
- 39 **Samaeekia R**, Rabiee B, Putra I, Shen X, Park YJ, Hematti P, Eslani M, Djalilian AR. Effect of Human Corneal Mesenchymal Stromal Cell-derived Exosomes on Corneal Epithelial Wound Healing. *Invest Ophthalmol Vis Sci* 2018; **59**: 5194-5200 [PMID: [30372747](#) DOI: [10.1167/iovs.18-24803](#)]
- 40 **Määttä M**, Väisänen T, Väisänen MR, Pihlajaniemi T, Tervo T. Altered expression of type XIII collagen in keratoconus and scarred human cornea: Increased expression in scarred cornea is associated with myofibroblast transformation. *Cornea* 2006; **25**: 448-453 [PMID: [16670484](#) DOI: [10.1097/01.icc.0000183537.45393.1f](#)]
- 41 **Arnalich-Montiel F**, Pastor S, Blazquez-Martinez A, Fernandez-Delgado J, Nistal M, Alio JL, De Miguel MP. Adipose-derived stem cells are a source for cell therapy of the corneal stroma. *Stem Cells* 2008; **26**: 570-579 [PMID: [18065394](#) DOI: [10.1634/stemcells.2007-0653](#)]
- 42 **Ma XY**, Bao HJ, Cui L, Zou J. The graft of autologous adipose-derived stem cells in the corneal stromal after mechanic damage. *PLoS One* 2013; **8**: e76103 [PMID: [24098428](#) DOI: [10.1371/journal.pone.0076103](#)]

- 10.1371/journal.pone.0076103]
- 43 **Yoshida S**, Yoshimoto H, Hirano A, Akita S. Wound Healing and Angiogenesis through Combined Use of a Vascularized Tissue Flap and Adipose-Derived Stem Cells in a Rat Hindlimb Irradiated Ischemia Model. *Plast Reconstr Surg* 2016; **137**: 1486-1497 [PMID: 27119923 DOI: 10.1097/PRS.0000000000002062]
 - 44 **Shen T**, Zheng QQ, Shen J, Li QS, Song XH, Luo HB, Hong CY, Yao K. Effects of Adipose-derived Mesenchymal Stem Cell Exosomes on Corneal Stromal Fibroblast Viability and Extracellular Matrix Synthesis. *Chin Med J (Engl)* 2018; **131**: 704-712 [PMID: 29521294 DOI: 10.4103/0366-6999.226889]
 - 45 **Bonanno JA**. Molecular mechanisms underlying the corneal endothelial pump. *Exp Eye Res* 2012; **95**: 2-7 [PMID: 21693119 DOI: 10.1016/j.exer.2011.06.004]
 - 46 **Kocaba V**, Damour O, Auxenfans C, Burillon C. [Corneal endothelial cell therapy, a review]. *J Fr Ophthalmol* 2018; **41**: 462-469 [PMID: 29773311 DOI: 10.1016/j.jfo.2018.01.002]
 - 47 **Yamashita K**, Inagaki E, Hatou S, Higa K, Ogawa A, Miyashita H, Tsubota K, Shimmura S. Corneal Endothelial Regeneration Using Mesenchymal Stem Cells Derived from Human Umbilical Cord. *Stem Cells Dev* 2018; **27**: 1097-1108 [PMID: 29929442 DOI: 10.1089/scd.2017.0297]
 - 48 **Gutermuth A**, Maassen J, Harnisch E, Kühlen D, Sauer-Budge A, Skazik-Voogt C, Engelmann K. Descemet's Membrane Biomimetic Microtopography Differentiates Human Mesenchymal Stem Cells Into Corneal Endothelial-Like Cells. *Cornea* 2019; **38**: 110-119 [PMID: 30308581 DOI: 10.1097/ICO.0000000000001765]
 - 49 **Jia Z**, Jiao C, Zhao S, Li X, Ren X, Zhang L, Han ZC, Zhang X. Immunomodulatory effects of mesenchymal stem cells in a rat corneal allograft rejection model. *Exp Eye Res* 2012; **102**: 44-49 [PMID: 22800963 DOI: 10.1016/j.exer.2012.06.008]
 - 50 **Jia Z**, Li F, Zeng X, Lv Y, Zhao S. The effects of local administration of mesenchymal stem cells on rat corneal allograft rejection. *BMC Ophthalmol* 2018; **18**: 139 [PMID: 29884142 DOI: 10.1186/s12886-018-0802-6]
 - 51 **Tsirouki T**, Dastiridou A, Symeonidis C, Tounakaki O, Brazitikou I, Kalogeropoulos C, Androudi S. A Focus on the Epidemiology of Uveitis. *Ocul Immunol Inflamm* 2018; **26**: 2-16 [PMID: 27467180 DOI: 10.1080/09273948.2016.1196713]
 - 52 **Egwuagu CE**, Sun L, Kim SH, Dambuza IM. Ocular Inflammatory Diseases: Molecular Pathogenesis and Immunotherapy. *Curr Mol Med* 2015; **15**: 517-528 [PMID: 26238372 DOI: 10.2174/1566524015666150731095426]
 - 53 **Bansal S**, Barathi VA, Iwata D, Agrawal R. Experimental autoimmune uveitis and other animal models of uveitis: An update. *Indian J Ophthalmol* 2015; **63**: 211-218 [PMID: 25971165 DOI: 10.4103/0301-4738.156914]
 - 54 **Zhang X**, Ren X, Li G, Jiao C, Zhang L, Zhao S, Wang J, Han ZC, Li X. Mesenchymal stem cells ameliorate experimental autoimmune uveoretinitis by comprehensive modulation of systemic autoimmunity. *Invest Ophthalmol Vis Sci* 2011; **52**: 3143-3152 [PMID: 21296818 DOI: 10.1167/iovs.10-6334]
 - 55 **Zhao PT**, Zhang LJ, Shao H, Bai LL, Yu B, Su C, Dong LJ, Liu X, Li XR, Zhang XM. Therapeutic effects of mesenchymal stem cells administered at later phase of recurrent experimental autoimmune uveitis. *Int J Ophthalmol* 2016; **9**: 1381-1389 [PMID: 27803852 DOI: 10.18240/ijo.2016.10.03]
 - 56 **Zhang L**, Zheng H, Shao H, Nian H, Zhang Y, Bai L, Su C, Liu X, Dong L, Li X, Zhang X. Long-term therapeutic effects of mesenchymal stem cells compared to dexamethasone on recurrent experimental autoimmune uveitis of rats. *Invest Ophthalmol Vis Sci* 2014; **55**: 5561-5571 [PMID: 25125599 DOI: 10.1167/iovs.14-14788]
 - 57 **Bai L**, Shao H, Wang H, Zhang Z, Su C, Dong L, Yu B, Chen X, Li X, Zhang X. Effects of Mesenchymal Stem Cell-Derived Exosomes on Experimental Autoimmune Uveitis. *Sci Rep* 2017; **7**: 4323 [PMID: 28659587 DOI: 10.1038/s41598-017-04559-y]
 - 58 **Shigemoto-Kuroda T**, Oh JY, Kim DK, Jeong HJ, Park SY, Lee HJ, Park JW, Kim TW, An SY, Prockop DJ, Lee RH. MSC-derived Extracellular Vesicles Attenuate Immune Responses in Two Autoimmune Murine Models: Type 1 Diabetes and Uveoretinitis. *Stem Cell Reports* 2017; **8**: 1214-1225 [PMID: 28494937 DOI: 10.1016/j.stemcr.2017.04.008]
 - 59 **Jonas JB**, Aung T, Bourne RR, Bron AM, Ritch R, Panda-Jonas S. Glaucoma. *Lancet* 2017; **390**: 2183-2193 [PMID: 28577860 DOI: 10.1016/S0140-6736(17)31469-1]
 - 60 **Quigley HA**, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 2006; **90**: 262-267 [PMID: 16488940 DOI: 10.1136/bjo.2005.081224]
 - 61 **Weinreb RN**, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA* 2014; **311**: 1901-1911 [PMID: 24825645 DOI: 10.1001/jama.2014.3192]
 - 62 **Su W**, Li Z, Jia Y, Zhu Y, Cai W, Wan P, Zhang Y, Zheng SG, Zhuo Y. microRNA-21a-5p/PDCD4 axis regulates mesenchymal stem cell-induced neuroprotection in acute glaucoma. *J Mol Cell Biol* 2017; **9**: 289-301 [PMID: 28655163 DOI: 10.1093/jmcb/mjx022]
 - 63 **Johnson TV**, Bull ND, Hunt DP, Marina N, Tomarev SI, Martin KR. Neuroprotective effects of intravitreal mesenchymal stem cell transplantation in experimental glaucoma. *Invest Ophthalmol Vis Sci* 2010; **51**: 2051-2059 [PMID: 19933193 DOI: 10.1167/iovs.09-4509]
 - 64 **Mead B**, Hill LJ, Blanch RJ, Ward K, Logan A, Berry M, Leadbeater W, Scheven BA. Mesenchymal stromal cell-mediated neuroprotection and functional preservation of retinal ganglion cells in a rodent model of glaucoma. *Cytotherapy* 2016; **18**: 487-496 [PMID: 26897559 DOI: 10.1016/j.jcyt.2015.12.002]
 - 65 **Mead B**, Tomarev S. Bone Marrow-Derived Mesenchymal Stem Cells-Derived Exosomes Promote Survival of Retinal Ganglion Cells Through miRNA-Dependent Mechanisms. *Stem Cells Transl Med* 2017; **6**: 1273-1285 [PMID: 28198592 DOI: 10.1002/scrm.16-0428]
 - 66 **Libby RT**, Anderson MG, Pang IH, Robinson ZH, Savinova OV, Cosma IM, Snow A, Wilson LA, Smith RS, Clark AF, John SW. Inherited glaucoma in DBA/2J mice: pertinent disease features for studying the neurodegeneration. *Vis Neurosci* 2005; **22**: 637-648 [PMID: 16332275 DOI: 10.1017/S0952523805225130]
 - 67 **Mead B**, Ahmed Z, Tomarev S. Mesenchymal Stem Cell-Derived Small Extracellular Vesicles Promote Neuroprotection in a Genetic DBA/2J Mouse Model of Glaucoma. *Invest Ophthalmol Vis Sci* 2018; **59**: 5473-5480 [PMID: 30452601 DOI: 10.1167/iovs.18-25310]
 - 68 **Zhang X**, Liu J, Yu B, Ma F, Ren X, Li X. Effects of mesenchymal stem cells and their exosomes on the healing of large and refractory macular holes. *Graefes Arch Clin Exp Ophthalmol* 2018; **256**: 2041-2052 [PMID: 30167916 DOI: 10.1007/s00417-018-4097-3]
 - 69 **Nentwich MM**, Ulbig MW. Diabetic retinopathy - ocular complications of diabetes mellitus. *World J Diabetes* 2015; **6**: 489-499 [PMID: 25897358 DOI: 10.4239/wjd.v6.i3.489]

- 70 **Pezzullo L**, Streatfeild J, Simkiss P, Shickle D. The economic impact of sight loss and blindness in the UK adult population. *BMC Health Serv Res* 2018; **18**: 63 [PMID: [29382329](#) DOI: [10.1186/s12913-018-2836-0](#)]
- 71 **Zhang W**, Wang Y, Kong Y. Exosomes Derived From Mesenchymal Stem Cells Modulate miR-126 to Ameliorate Hyperglycemia-Induced Retinal Inflammation Via Targeting HMGB1. *Invest Ophthalmol Vis Sci* 2019; **60**: 294-303 [PMID: [30657854](#) DOI: [10.1167/iovs.18-25617](#)]
- 72 **Safwat A**, Sabry D, Ragiae A, Amer E, Mahmoud RH, Shamardan RM. Adipose mesenchymal stem cells-derived exosomes attenuate retina degeneration of streptozotocin-induced diabetes in rabbits. *J Circ Biomark* 2018; **7**: 1849454418807827 [PMID: [30397416](#) DOI: [10.1177/1849454418807827](#)]
- 73 **Jiang Y**, Zhang Y, Zhang L, Wang M, Zhang X, Li X. Therapeutic effect of bone marrow mesenchymal stem cells on laser-induced retinal injury in mice. *Int J Mol Sci* 2014; **15**: 9372-9385 [PMID: [24871366](#) DOI: [10.3390/ijms15069372](#)]
- 74 **Yu B**, Shao H, Su C, Jiang Y, Chen X, Bai L, Zhang Y, Li Q, Zhang X, Li X. Exosomes derived from MSCs ameliorate retinal laser injury partially by inhibition of MCP-1. *Sci Rep* 2016; **6**: 34562 [PMID: [27686625](#) DOI: [10.1038/srep34562](#)]
- 75 **Ma M**, Li B, Zhang M, Zhou L, Yang F, Ma F, Shao H, Li Q, Li X, Zhang X. Therapeutic effects of mesenchymal stem cell-derived exosomes on retinal detachment. *Exp Eye Res* 2020; **191**: 107899 [PMID: [31866431](#) DOI: [10.1016/j.exer.2019.107899](#)]
- 76 **Mathew B**, Ravindran S, Liu X, Torres L, Chennakesavalu M, Huang CC, Feng L, Zelka R, Lopez J, Sharma M, Roth S. Mesenchymal stem cell-derived extracellular vesicles and retinal ischemia-reperfusion. *Biomaterials* 2019; **197**: 146-160 [PMID: [30654160](#) DOI: [10.1016/j.biomaterials.2019.01.016](#)]
- 77 **Moisseiev E**, Anderson JD, Oltjen S, Goswami M, Zawadzki RJ, Nolte JA, Park SS. Protective Effect of Intravitreal Administration of Exosomes Derived from Mesenchymal Stem Cells on Retinal Ischemia. *Curr Eye Res* 2017; **42**: 1358-1367 [PMID: [28636406](#) DOI: [10.1080/02713683.2017.1319491](#)]
- 78 **Antimisiaris SG**, Mourtas S, Marazioti A. Exosomes and Exosome-Inspired Vesicles for Targeted Drug Delivery. *Pharmaceutics* 2018; **10** [PMID: [30404188](#) DOI: [10.3390/pharmaceutics10040218](#)]
- 79 **Pascucci L**, Coccè V, Bonomi A, Ami D, Ceccarelli P, Ciusani E, Viganò L, Locatelli A, Sisto F, Doglia SM, Parati E, Bernardo ME, Muraca M, Alessandri G, Bondiolotti G, Pessina A. Paclitaxel is incorporated by mesenchymal stromal cells and released in exosomes that inhibit in vitro tumor growth: a new approach for drug delivery. *J Control Release* 2014; **192**: 262-270 [PMID: [25084218](#) DOI: [10.1016/j.jconrel.2014.07.042](#)]
- 80 **Zhang L**, Song Y, Chen L, Li D, Feng H, Lu Z, Fan T, Chen Z, Livingston MJ, Geng Q. MiR-20a-containing exosomes from umbilical cord mesenchymal stem cells alleviates liver ischemia/reperfusion injury. *J Cell Physiol* 2020; **235**: 3698-3710 [PMID: [31566731](#) DOI: [10.1002/jcp.29264](#)]
- 81 **Chen S**, Tang Y, Liu Y, Zhang P, Lv L, Zhang X, Jia L, Zhou Y. Exosomes derived from miR-375-overexpressing human adipose mesenchymal stem cells promote bone regeneration. *Cell Prolif* 2019; **52**: e12669 [PMID: [31380594](#) DOI: [10.1111/cpr.12669](#)]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

