• Review Article •

Progress in exosomes and their potential use in ocular diseases

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Abstract

● Exosomes contain a variety of biological active substances such as proteins, miRNAs, lncRNAs and lipids, and exosomes from different cells play different biological functions. Exosomes, as a carrier, are involved in many pathological processes such as nerve injury and repair, vascular regeneration, immune response, and fibrosis formation. It plays an important role in the treatment of eye diseases such as glaucoma, diabetic retinopathy, and keratitis. This paper reviews the research progress of exosomes in various diseases *in vivo*, which provides a new way for the treatment of eye diseases.

● **KEYWORDS:** exosomes; ocular diseases; progress; treatment

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INTRODUCTION

Glaucoma, corneal disease, and retinal disorders are the three major types of ocular blinding diseases. Since the pathogenesis of these eye diseases are not completely clear at present, the treatment methods for these diseases have not been perfected, so the clinical treatment effect of the current methods for these eye diseases is currently not satisfactory. Exosomes are extracellular small vesicles that are formed by the regulation of endocytosis, fusion, and efflux. The effects of exosomes depend on the cell origin and are therefore different. At present, more and more studies have been carried out on the role and mechanism of exosomes in the occurrence and development of ocular related diseases.

Basic Characteristics of Exosomes Exosomes were first discovered in the supernatant of sheep red blood cells cultured *in vitro*, described as vesicle like bodies with a diameter of about 30-150 nm. At present, most scholars believe that the process of exosomes endogenesis and secretion is the lysosomal microparticles in the cell membrane sink into endosomes, and then form multivesicular bodies. The outer membrane of the multivesicles merges with the cell membrane and is secreted to form exosomes[1-2]. By the electron microscope, the exosomes structure can be seen as a double-layered capsule lipid structure, which is actively secreted by cells. The exosomes are rich in tetratransmembrane protein family (CD63, CD81, and CD9), heat shock protein families, and some specific proteins involved in exosomes transport.

Function of Exosomes Exosomes are widely found in all biological fluids, including blood, milk, urine, saliva, tears, sweat, and cell culture supernatants. Exosomes with different cell origins have different functions. The ways in which exosomes function include: 1) Cell-cell communication. For example, as a carrier to present antigen, which is the main way for exosomes to function; 2) Garbage transfer station. Exosomes can exclude excess or harmful molecules from cells or tissues. As in an inflammatory environment, cells kill monocytes by releasing exosomes to alleviate the inflammatory response; 3) Ideal biomarker. Lipid bimolecular layer of exosomes plays a good protective role for DNA, RNA, and proteins in cell bodies. The exosomes come from a wide range of sources (plasma, urine, milk, aqueous humor, and cerebrospinal fluid, *etc*.), and the collection method is relatively noninvasive; 4) The immune system *in vivo* is regulated by stress-sensitive proteins and miRNAs. Exosomes have a variety of biologically active substances such as proteins, miRNAs, lncRNAs, lipids and antigen presenting molecules[3]. Through these bioactive substances, the exosomes vesicles specifically bind to target cells and exerts different biological functions, such as repairing damaged nerves, promoting fibrosis, participating in immune responses, increasing

angiogenesis, *etc*. Studies have shown that exosomes play a very important role in the treatment of glaucoma, diabetic retinopathy, keratitis, macular degeneration, and other eye diseases.

Exosomes can promote the repair of injured nerves Some bioactive substances in exosomes play the role of repairing nerves by affecting the related signal pathways and the expression of some proteins. Spinal marrow injury is the most serious complication of spinal column injury, characterized by irreversible damage to nerves and impaired function. The traditional treatment of spinal marrow injury (including surgery, drugs, hyperbaric oxygen chamber, *etc*.) cannot repair the damaged nerve, but research has proved that stem cell-derived exosomes can do this. Ren *et al*[4] found that after the exosomes derived from adipose stem cells (ADSCs) were modified by miR-133b, they may promote the functional recovery of injured nerves by affecting the protein signal transduction pathways related to neurofilament (NF), glial fibrillary acidic protein (GFAP), growth associated protein 43 (GAP43) and myelin basic protein (MBP); Similarly, Yuan *et al*[5] found that the exosomes of mesenchymal stem cell (MSC) modified by miR-126 can protect neurons of rats with spinal cord injury, stimulate axon regeneration, and promote the recovery of motor function of hind limbs. Yu *et al*[6] used lasers to cause retinal damage in animals, and then injected mesenchymal stem cell-derived exosomes (MSC-exo) into the vitreous cavity. The results showed that exosomes could reduce the infiltration of immune cells such as CD68, inhibit the apoptosis of retinal ganglion cell (RGC) and reduce the damage of retina by down regulating the expression of monocyte chemotactic protein (MCP)-1. Intravenous injection of MSC-exo can improve nerve injury, neurite remodeling and neovascularization after ischemic brain injury[7]. At present, there is no effective treatment for the irreversible loss of vision caused by optic neuropathy, glaucoma and other reasons. Perhaps exosomes therapy can effectively solve this problem.

Exosomes can inhibit fibrosis The formation of fibrosis is mainly due to the increase of a large number of fibroblasts and abnormal proliferation of extracellular matrix, resulting in organ dysfunction caused by excessive fibrosis of organs. As a cell signaling substance, exosomes contain a variety of biologically active substances, which can induce fibrosis of organs by binding to specific target cells under certain conditions. Examples of this are cardiomyocyte fibrosis, liver fibrosis and renal fibrosis, *etc*. In the study by Yang *et al*[8], the mechanism of cardiomyocyte-derived exosomes regulating fibroblast production was emphasized. miRNA-208a isolated from cardiomyocyte-derived exosomes promotes cardiac fibroblast proliferation and myofibroblast differentiation *in vitro*, while Dyrk2 acts as a target gene binding site for miR-208a in cardiac myofibroblastic differentiation where it plays an important role. Overproduction of angiotensin II is a key factor in inducing myocardial fibrosis and even heart failure. Wang *et al*[9] showed that increased angiotensin II in myocardial fibrosis models led to down-regulation of miR-425 and miR-744 in cardiomyocyte-derived exosomes. By using luciferase assay and immunoblotting, transforming growth factor-β1 (TGF-β1) was identified as a direct target for miR-425 and miR-744, which induced an increase in collagen I. However, in the CCL4-induced rat liver fibrosis model, transplantation of spinal mesenchymal stem cell-derived exosomes (HBMSCs-Exo) can slow the progression of liver fibrosis in rats and reduce inflammation. The mechanism of action is to promote the expression of WISP1 and CyclinD1 through Wnt/β - Catenin (PPARγ, Wnt3a, Wnt10b, β-Catenin, WISP1, CyclinD1) pathway, so as to inhibit the activation of hepatic stellate cells, reduce the expression of type I collagen, and reduce liver fibrosis[10]. Xiao *et al*[11] found that rat bone marrow mesenchymal stem cells exosomes (BMSCs-exo) can transfer miR-340 to endometrial stromal cells (ESC). miRNA-340 can inhibit the increase of collagen 1α1 and α-SMA protein caused by TGF-β1, reduce endometrial damage and collagen accumulation, and prevent endometrial fibrosis. The healing process of wounds (cornea, conjunctiva, *etc*.) needs to undergo epithelial cell proliferation and migration, myofibroblast formation, inflammatory response, and collagen deposition. Shojaati *et al*[12] removed the corneal epithelium of mice. After the treatment of MSCs from corneal structural stem cells exosomes (CSSC-Exo), the expression of wound fibrosis genes COL3A1 and ACTA2 decreased, neutrophil infiltration decreased, and corneal scarring reduce. Scarring of cornea can lead to the decrease of vision. At present, corneal transplantation is the first choice for patients with large area scarring of cornea, so the lack of fresh corneal donors becomes the biggest obstacle. Exosomes come from a wide range of sources, which can effectively solve the shortage of corneal donors and eliminate the rejection caused by corneal transplantation.

Exosomes can modulate immune function Khare *et al*[13] confirmed that spinal cord MSC-derived exosomes can inhibit the proliferation of monocytes, T cells and B cells, especially B lymphocytes. Further, measured by ELISA, the production of IgM was significantly inhibited, but the production of IgG and IgA did not change significantly. At the present, MSC transplantation has been used to treat a variety of immune-related diseases, such as type I diabetes, graft-versus-host disease, bronchopulmonary dysplasia, multiple sclerosis, Crohn's disease, *etc*[14]. Compared with stem cells, exosomes derived from stem cells have stronger immunoregulatory function. Type 1 diabetes (T1DM), also known as insulin-

dependent diabetes, is an autoimmune disease. According to a study by Nojehdehi *et al*[15], explanted adipose mesenchymal stem cells exosomes (AMSC-Exo) from rats in a ureazide-induced model of T1DM were compared to control group. Rat blood glucose levels remained stable. In the study, they found that levels of TGF-β, IL-4, and IL-10 were significantly increased in AMSC-Exo treated rats, while IL-17 and interferon-γ levels were decreased. The conclusion of the Nojehdehi *et al*[15] experiment is that AMSC-Exo plays a role in stabilizing T1DM blood glucose levels by increasing the regulatory T cell types and their products. Autoimmune uveitis is one of the main causes of vision decline in young women. Generally, long-term hormone or immunosuppressive agents are used for treatment. These drugs have large systemic side effects, and even aggravate the development of glaucoma and cataract. Therefore, new treatment methods are needed to treat ocular autoimmune diseases. Bai *et al*[16] treated mice with autoimmune uveitis by injection of MSC-exo. The results of histopathological analysis showed that the number of Gr-1$^+$ granulocytes, CD4$^+$ T cells, CD68$^+$ macrophages and CD161$^+$ natural killer (NK) cells in the retina decreased significantly. MSC-exo can inhibit the occurrence of intraocular inflammation by inhibiting the effects of CCL2 and CCL21 chemokines.

Exosomes can affect angiogenesis A large number of studies in recent years have shown that exosomes can significantly promote angiogenesis. Mathiyalagan *et al*[17-18] and Sahoo *et al*[19] reported that CD34$^+$ stem cell-derived exosomes can significantly induce angiogenesis. By injecting CD34$^+$ stem cell-derived exosomes into limb ischemia mice, the level of miRNA-126-3p in the ischemic limb was increased, so as to inhibit the expression of SPRED1 and promote angiogenesis. At the same time, miRNA-126-3p can modulate the gene expression involved in angiogenesis, such as vascular endothelial growth factor (VEGF), ANG1, ANG2, MMP9, TSP1 *etc*. The study found that exosomes extracted from pericardial effusion in patients with heart failure can significantly induce therapeutic angiogenesis[20-21]. Similarly, in animal models of bone defects, endothelial progenitor-derived exosomes accelerate bone regeneration during distraction osteogenesis by stimulating angiogenesis, whereas endothelial progenitor exosomes rely primarily on miRNA-126[22].

Although most studies have shown that MSCs are expressed as pro-angiogenic, some studies have shown that tumor-derived MSC-derived exosomes can inhibit angiogenesis by reducing the level of VEGF[23], but the specific mechanism is not yet clear. Whether the final MSCs can promote angiogenesis varies with the microenvironment of the tumor, and the mechanism of action is different, and the results are different.

The proliferative stage of diabetic retinopathy is mainly due to retinal ischemia, which leads to a large number of vulnerable neovascularization growth, resulting in a series of serious clinical symptoms (such as fundus hemorrhage). Surgery and drug treatment cannot fundamentally solve the growth of new blood vessels in the fundus. At present, it is believed that exosomes can be used not only as a biomarker, but also as an effective therapeutic target for neovascularization[24].

Exosomes and Eye Diseases

Exosomes and autoimmune diseases of the eye The eyeball acts as a visual function organ with immune gratification characteristics, and its immune regulation process is extremely complicated[25]. This immune privilege feature removes both local pathogenic microorganisms and protects the eye tissue from immune attack and ultimately affects vision. Once the immune system of the eye is destroyed, various autoimmune diseases occur. For example, keratopathy, uveitis, Graves' ophthalmopathy, sympathetic ophthalmia, dry syndrome, optic neuritis, *etc*[26]. Liao *et al*[27] obtained exosomes by ultracentrifugation of rabbit aqueous humor, and Western blot revealed that the exosomes contain a large number of immunosuppressive molecules like TGF-β, thereby inhibiting T lymphocyte proliferation. This indicates that aqueous humor exosomes can effectively increase ocular immune tolerance to prevent ocular autoimmune diseases and reduce rejection after corneal transplantation.

Exosomes and large area corneal damage As a kind of nano vesicle, exosomes can transfer protein and RNA to receptor cells. Studies have confirmed that human corneal mesenchymal cell-derived exosomes can accelerate wound healing of corneal epithelial cells[28], providing a new approach for the treatment of large corneal lesions. Han *et al*[29] found that mouse corneal epithelial-derived exosomes induce corneal myofibroblastic transformation by binding to the corneal cell matrix. The presence of exosomal vesicles was detected between the epithelial cells and the stroma after observation of the damaged corneal epithelium in the rat by electron microscopy. However, in the uninjured rat corneal epithelium, the presence of exosomal vesicles was not found in the same area. By fluorescent staining, it was demonstrated that mouse corneal epithelial-derived exosomes cause mouse corneal fibroblast proliferation by inducing α-SMA recombination.

Exosomes and retinopathy of prematurity Retinal tissue metabolism is extremely strong, and the blood supply to the inner layer is derived from the retinal blood vessels of the terminal branches, so ischemic lesions are highly prone to occur. The retinal tissue is where the visual neurons are located. Once ischemia occurs, the damage to the vision is extremely serious. Among them, retinopathy of prematurity (ROP) is an ischemic neovascularization disease mainly affecting premature infants. It is one of the main causes of

childhood blindness in the world. Microglia is one of the glia cell subtypes, which are not only inflammatory cells, but also involved in the development of normal blood vessels in the retina[30]. Studies have shown that microglia exosomes downregulate the expression of VEGF and TGF-β in hypoxia-induced photoreceptors in hypoxic-induced mouse optic neuropathy. It also reduces apoptosis and significantly inhibits neovascularization. It was showed that the level of miRNA-24-3p was extremely high in microglia exosomes, indicating that miRNA-24-3p is a key molecule that inhibits the expression of IRE1α induced by hypoxia[31]. It is predicted that microglia exosomes can promote the normal angiogenesis and visual enhancement of hypoxia-induced retinal mice, which provides a new idea for the treatment of ROP.

Exosomes and diabetic retinopathy Diabetic retinopathy is one of the most common microvascular complications of diabetes. Patients show signs of decreased vision and severe blindness. Recent studies have shown that the complement system is a major player in vascular injury and diabetic retinopathy. The complement system plays an important role in the host's defense against infectious pathogens by activating the inflammatory response. The complement system can be activated in three ways: the classical pathway, the alternative pathway, and the lectin pathway. All three complement activation pathways result in the production of C3/C5 convertase and ultimately lead to the formation of membrane attack complex (MAC)[32]. Huang *et al*[33] established a mouse model of diabetic retinopathy to demonstrate that exosomes containing IgG can cause retinal vascular damage by activating the classical complement pathway, and the number of these exosomes is significantly increased in diabetic mice. However, in diabetic mice lacking IgG exosomes, retinal vascular damage is reduced.

Exosome and age-related macular degeneration Age-related macular degeneration (AMD) refers to the degenerative lesions of the retinal tissue in the macular area over 45 years of age, and its prevalence increases with age. The cause of the disease is still unclear and may be related to heredity, chronic photodamage, nutritional disorders, poisoning, and immune diseases. AMD could cause the central vision to gradually decrease, and severe cases can cause blindness. AMD is divided into two categories: atrophic (dry) and exudative (wet). The former is characterized by atrophy of the macular area and formation of drusen. Many proteins (PDK1, ERK 1/2, AMPKα1, acetyl CoA carboxylase, *etc*.) were detected in the exosomes secreted by retinal pigment epithelium (RPE) cells by Bisutto *et al*[34]. At the same time, these proteins were also detected in the vitreous of AMD patients, suggesting an inevitable link between exosomes and AMD. An increase in related proteins such as αB crystal proteins released in RPE cells by exosomes may lead to the formation of drusen. Recent studies have shown that, exosomes secreted by RPE cells are considered to have neuroprotective effects and are closely related to the pathological processes of AMD[35].

Exosomes and glaucoma Glaucoma is a group of diseases characterized by optic atrophy, visual field defects and decreased vision. Pathological increase in intraocular pressure is the main risk factor for its onset[36]. When the intraocular aqueous drainage loss leads to an increase in pathological intraocular pressure, the increased intraocular pressure causes optic nerve damage through mechanical compression and optic nerve ischemia. The longer the duration of intraocular pressure increase, the more severe the visual impairment[37]. Most of the pathological increase in intraocular pressure is caused by the outflow of aqueous humor, such as stenosis of the anterior chamber, trabecular sclerosis, abnormal substances produced by extracellular matrix, and trabecular meshwork. Tabak *et al*[38] found that non-pigmented ciliary epithelial cells exosomes (NPCE-Exo) affect trabecular meshwork cadherin by inducing Wnt signaling in trabecular meshwork cells, reducing phosphorylated GSK3 and β-catenin expression. As an important component of the extracellular matrix, cadherin can increase the pore size of the trabecular meshwork, leading to an increase in the outflow resistance of the aqueous humor and an increase in intraocular pressure. Pan *et al*[39] studied the role of umbilical cord mesenchymal stem cell-derived exosomes (UMSCs-exo) in the rat model of optic nerve squeezing. Through exosome tracking, immunohistochemical analysis, fluorescence microscopy, *etc*. UMSCs-exo can promote the survival of RGC but does not promote axonal regeneration. Staining by GFAP antibody showed that the number of retinal glial cells treated by UMSCs-exo increased and the activity was enhanced. However, according to Mead and Tomarev[40], in the rat optic nerve crush model, BMSCs exosomes significantly promoted the survival and axonal regeneration of RGCs through miRNA dependent mechanism (especially through miRNA-17-92 and miRNA 21).

In conclusion, exosomes can be used as a therapeutic carrier to participate in multiple pathophysiological processes such as immune response, angiogenesis, and nerve repair in ocular related diseases. Research on the role of exosomes in ocular-related diseases is still in its infancy. Due to the extensive presence and accessibility of exosomes, it will become a potential way for the diagnosis and treatment of ocular diseases.

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