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MESENCHYMAL STEM CELL-DERIVED EXTRACELLULAR VESICLES: A PROMISING THERAPEUTIC APPROACH FOR AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

Age-related macular degeneration (AMD) is a progressive retinal disorder that leads to vision loss, mainly because the retinal pigment epithelium (RPE) and photoreceptors break down. AMD pathophysiology involves complex mechanisms, such as oxidative stress, severe inflammation, and cellular degeneration, leading to drusen and lipofuscin formation. And current treatments, such as retinal laser therapy, photodynamic therapy, and even anti-vascular endothelial growth factor, showed high limitations, especially for dry AMD. So, this review revealed the systematic potential effect of mesenchymal stem cell-derived exosomes (MSC-Exos) as a novel treatment for AMD. MSC-Exos influence gene expression, remodel the extracellular matrix, and deliver growth factors. These characteristics offer a more effective treatment for AMD.

Keywords: Age-related-macular-degeneration, Exosomes, retinal-degeneration, immunomodulation

INTRODUCTION

The Retina: Structure and Function

Our review starts with the retina, the diencephalon of the central nervous system (CNS), because of its neural structure of interconnected layers of distinct cell types. The retina carries all the characteristic properties of CNS in irreversible healing, and it is involved in our disease topic, aged macular degeneration (AMD). The phototransduction process involves all retinal layers, which play a significant role in light detection and signal transduction. Photoreceptors, the primary cellular component in this process, depend on the retinal pigmentary epithelium (RPE) for essential functions such as nutrient transport, waste removal, and maintaining the blood-retinal barrier intact. Factors like oxidative stress, light damage, vascular abnormalities, and ageing disrupt cellular interactions, leading to vision impairment and progressive retinal degenerative disorders such as AMD (Holan *et al.,* 2021).

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Age-Related Macular Degeneration: An Overview

Retinal diseases like AMD, retinitis pigmentosa (RP), diabetic retinopathy (DP), and other retinal disorders share damage to the photoreceptors, and a lowering in retinal pigment epithelium (RPE) function leads to vision loss that affects daily life (Holan *et al.,* 2021). AMD is most common in adults over 45, making it a problem for the ageing population (Mead and Tomarev, 2020; Chow and Mead, 2023).

Epidemiology and Global Impact of AMD

AMD is a growing public health concern, as it counts statistically around 8.7% of adults over 45. AMD, as a visual problem, was ranked the third most serious problem by the World Health Organisation (WHO), and the numbers are expected to be around 288 million by 2024 (Wong *et al.,* 2014; Lorach *et al.,* 2015; Tian *et al.,* 2023). *Around 4-6% of the population in Jeddah, Saudi Arabia, Egypt, and Korea suffers from* AMD. These statistics show AMD is widespread (Abusharkh *et al.,* 2023). Additionally, non-human primates and albino rabbits resemble human primates by having a retina with a macula full of cone cells. This finding makes animals advantageous in studying AMD disease and other ophthalmic conditions (Peiffer *et al.,* 1994; Zeng *et al.,* 2021).

II. Pathophysiology of AMD

Oxidative Stress, Drusen, and Lipofuscin Formation

Oxidative stress plays a significant role in AMD because the retina uses a lot of oxygen, leading to the production of reactive oxygen species (ROS). These harmful molecules cause protein misfolding, lipid, and nucleic acids (Tang *et al.,* 2023). The common signs of AMD are drusen, yellow deposits made up of amyloid proteins, lipids, and different immune complexes under the retina that cannot be drained by damaged ROS in a process called drusogenesis. When these drusen are more than 125 μm, as seen on optical coherence tomography (OCT), the risk of progressing to severe AMD increases. These changes highlight how deeply oxidative stress is in contact with the progression of AMD (Fletcher *et al.,* 2014; Feng *et al.,* 2023).

Inflammation in AMD Progression

Inflammation in the body's natural defense system fights harmful pathogens and repairs damaged tissues by Pattern Recognition Receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which can spot signals from pathogens and set off a cascade including activation of NF-kB, which turns on pro-inflammatory genes. These genes produce cytokines and chemokines (Suh *et al.,* 2021). Uncontrolled inflammation causes disease development and can be systemic or local to specific areas, such as neuroinflammation, in forms that are either acute or chronic. Acute inflammation turns into chronic if it doesn't resolve. Studies on Alzheimer's disease showed that inflammation played an active role in worsening the condition, as abnormal proteins clump together and accumulate in the brain. That's why we should control inflammatory conditions in the progress of disease (Zhang *et al.,* 2023).

Stages and Types of AMD

AMD progresses through three stages. In the early stage, a medium-sized drusen grows under the retina, near the RPE layer. In the intermediate stage, these drusen grow larger. In the late stage, abnormal blood vessels start to grow under the retina, called choroidal neovascularization (CNV), causing damage to the RPE-Bruchs complex and photoreceptor death. Clinically, AMD is in two forms. The dry (atrophic) causes a slow but steady breakdown of RPE, especially in the macula. The wet (neovascular) is more aggressive and occurs when those abnormal vessels grow and leak fluid and blood

(Lorach et al., 2015; Tsai *et al.,* 2022; Feng *et al.,* 2023; Chow & Mead, 2023; Wu *et al.,* 2023; Śpiewak *et al.,* 2024).

III. Current Treatment Approaches for AMD

This review provides the treatments used for AMD and highlights their benefits and limitations. The focus then shifts to the role of exosome-based therapy and those derived from mesenchymal stem cells (MSCs). We expect that exosomes may offer better outcomes for AMD. As we will mention later, some cases of macular disorder are healed by MSC-Exos later, because they not only support structural recovery of the retina, but also restore its function. Their regenerative and protective effects make them a strong candidate for future therapeutic strategies.

Retinal Laser Therapy and Photodynamic Therapy

Retinal laser therapy uses light for coagulation of abnormal tissue and slows disease progression but does not cure vision loss associated with AMD. Additionally, conventional laser therapy shows adverse effects such as subretinal fibrosis, decreased peripheral and night vision, and reduced macular sensitivity if the laser beam is directed near the macula, the pathognomonic part in AMD disease, and may involve thermal damage and irritation (Li and Paulus, 2018).

Photodynamic therapy (PDT) uses photosynthesizing agents to neutralize reactive oxygen species (ROS). When these agents are exposed to light with specific wavelengths, they absorb energy and enter an excited state, and interact with surrounding molecules like singlet oxygen, which counteract ROS damage, lowering ROS levels, and protecting retinal cells. These advantages make the agents valuable in treating neurodegenerative conditions. PDT gained popularity in the 90s with verteporfin. However, its high cost limits accessibility and hinders widespread use (Di Nicola and Williams, 2021).

Anti-VEGF Treatments

Anti-vascular endothelial growth factor therapy (anti-VEGF) drugs are the current standard treatment for wet AMD. These drugs aim to inhibit abnormal blood vessel growth by blocking choroidal neovascular-isation (CNV) and reducing vessel leakage. However, this approach is far from ideal. The treatment requires frequent, repeated injections, and outcomes are not satisfactory in many cases, as in dry AMD. (Gu *et al.,* 2023; Chow and Mead, 2023). Experimental approaches that use anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), block prostaglandin synthesis and show a limitation in therapeutic success in neurodegeneration like AMD, as it is not limited to treating inflammation only (Suh *et al.,* 2021).

Limitations of Current Therapies

Although researchers have made progress in understanding AMD, treatment options remain limited for retinal degenerative disorders, which points to the need for new regenerative therapy for those neuro-irreversible diseases (Li and Paulus, 2018; Lorach *et al.,* 2015; Thomas *et al.,* 2021).

IV. Recent therapeutic alternatives under investigation

Biosimilar treatment

Biosimilars are biological medicines that closely resemble approved reference treatments, providing a more affordable option for patients. Although biological therapies have significantly advanced the treatment of retinal diseases, their high cost and treatment duration often limit patient access (Hariprasad *et al.,* 2022). The bevacizumab is also prescribed for a different purpose, as in eye treatment, than the use announced by the FDA-approved, off-label usage. This condition limits the success of biosimilars (Sharma *et al.,* 2021). Additionally, many clinicians remain

hesitant due to ongoing concerns and uncertainty about biosimilars (Scavone *et al.,* 2017). Compared to original biologic drugs, biosimilars will likely require more time to have a more stable presence in the market. To build greater trust among physicians and improve patient acceptance, further evidence supporting the safety and effectiveness of biosimilars is needed, along with many options for biosimilars and continued reductions in cost (Kaida-Yip *et al.,* 2018).

Gene therapy

Genome techniques like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), described as molecular scissors, provide specific changes to DNA. CRISPR enables targeted cuts at specific locations in the genome. This technology generates hope for treating inherited eye conditions, such as retinal degenerative diseases. Despite this advantage, CRISPR has several limitations, as the target DNA sequence must be adjacent to a specific shift motif known as the protospacer adjacent motif (PAM), which restricts the editing range, and sometimes CRISPR may introduce unintended edits at similar-looking sequences elsewhere in the genome. This unfavorable phenomenon is called off-target effects (Chan *et al.,* 2017).

Complement inhibitors

The complement system is significant, as people who carry two copies of a specific genetic variant in the complement factor H (CFH) gene, known as the Y402H variant, have around a 5.5-fold increased risk of developing AMD. Pegcetacoplan (SYFOVRE), the first FDA-approved treatment for geographic atrophy in AMD, works by terminating the complement cascade. It's contraindicated in patients with intraocular bleeding, floaters, and blurry vision, and may cause more severe effects like optic nerve damage or retinal vasculitis. Additionally, it elevates the risk of wet AMD development, especially at higher doses (Ong *et al.,* 2024).

V. Extracellular Vesicles (EVs)

Types and Characteristics of EVs

Any cells in our body release various extracellular vesicles (EVs). Those EVs were first identified in 1967 by Peter Wolf and mentioned as "platelet dust" because he observed small structures released from platelets during blood clotting using electron microscopy (Joo *et al.,* 2020). EVs represent a wide category of lipid bilayer-encased structures released into the extracellular environment. EVs are divided into three main subtypes based on biogenesis, size, and functional characteristics: exosomes (around 30–150 nm in diameter), microvesicles (100–1000 nm), and apoptotic bodies (100–5000 nm). So, exosomes possess a nanoscale size, which allows them to diffuse passively through tissues (Manzoor *et al.,* 2023). Exosomes are secreted by various cell types, like immune cells, cancer cells, endothelial cells, and mesenchymal stem cells, and are present in many biological fluids, such as tears, aqueous humour, and vitreous humour. This presence enables us to use exosomes in eye problem conditions as a diagnosis and treatment (Liu *et al.,* 2020; Joo *et al.,* 2020).

Exosome Biogenesis and Release Mechanisms

Exosomes originate from intraluminal vesicles (ILVs). These ILVs form inside larger compartments known as multi-vesicular bodies (MVBs). When multi-vesicular bodies (MVBs) fuse with the plasma membrane, they release intraluminal vesicles (ILVs) as exosomes, which are part of the endosomal pathway. These exosomes carry bioactive molecules like proteins, lipids, and nucleic acids. These bioactive molecules enable exosomes to communicate between cells and influence physiological and pathological processes (Liu *et al.,* 2020; Manukonda *et al.,* 2022). Because these molecules, when released to the recipient cells, can alter gene expression, promote tissue repair, and even differentiate into

cells, as in the case of RPE-damaged cells, recipient cells absorb exosomes by endocytosis, receptor-ligand interactions, or the fusion of exosomes with the cell membrane (Cui *et al.,* 2021). The exosome formation relies on the Endosomal Sorting Complex Required for Transport (ESCRT) system. ESCRT requires helper proteins to form ILVs. The process starts with identifying specific proteins, folding the endosomal membrane inward, and separating ILVs from the membrane. There is an alternative pathway when the ESCRT system is inhibited, involving different proteins and lipids, the syndecan-syntenin-ALIX, and the ceramide-based pathway. The protein composition of exosomes differs according to changed pathways (Xunian and Kalluri, 2020; Joo *et al.,* 2020).

VI. Mesenchymal Stem Cell-Derived Extracellular Vesicles (MSC-EVs)

Advantages of MSC-EVs over Traditional Cell Therapies

Whole-cell therapies, such as mesenchymal stem cells (MSCs), are complex and require strict storage conditions. This complexity can trigger immune responses (Lukomska *et al.,* 2019;Sanabria-de la Torre *et al.,* 2021; Zhou *et al.,* 2021). While platelet-rich plasma (PRP) can be effective, it depends on the individual's health condition and valuable rich plasma factors (Ra Hara and Basu, 2014). In contrast, exosomes are simpler structures with minimal surface proteins, causing less trigger any immune response and several benefits in storage and transport because they do not require nutrients or oxygen. And tolerate freezing and thawing better. These characteristics direct attention toward MSC-derived exosomes (MSC-Exos) over traditional whole-cell therapies and PRP, especially in AMD disease (Ma *et al.,* 2020; Muthu *et al.,* 2021; Tang *et al.,* 2023).

Immunomodulatory Potential of MSC-EVs

MSC-Exos can lower inflammatory molecules like TNF-α, IL-6, and IL-1β. Shift macrophages from a damaging pro-inflammatory (M1) to a healing anti-inflammatory (M2) state. This strong immunomodulatory potential supports microglia to promote tissue repair and protect RPE cells from severe inflammatory damage (Arabpour *et al.,* 2021; Che *et al.,* 2024; Chan *et al.,* 2019). Additionally, MSC-Exos regulate gene expression post-transcriptionally through microRNA profiles and contribute to extracellular matrix (ECM) remodelling by modulating matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), helping prevent fibrosis by modulating fibroblast activity and delivering growth factors (TGF-β, CTGF). These combined properties position MSC-EVs as promising therapeutic agents for AMD, offering immune modulation, anti-apoptotic effects, and Extra-Cellular Matrix (ECM) remodelling (Wu and Ahmad, 2023).

MSC-Exos in Neuroinflammation and Retinal Degeneration

Exosomes in neurodegenerative diseases can repair damaged nerve cells. In spinal cord injury, a study revealed that MSC-Exos helps nerve healing by regulating signalling pathways and protein expression by reducing harmful NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome activation in microglial cells, a key player in nervous system inflammation (Che *et al.,* 2024). In the context of brain injuries, MSC-Exos showed effective results in the Alzheimer's model by promoting anti-inflammatory macrophages and balancing cytokines (Manukonda *et al.,* 2022; Suh *et al.,* 2021). In ophthalmology, retinal diseases are challenging due to retina's limited ability to regenerate. Studies using MSC-Exos showed the protection of retinal ganglion cells and boosted neuroprotection, like in optic nerve crush injuries (Mead and Tomarev, 2017).

VII. Molecular Mechanisms of MSC-EVs in AMD

Modulation of Oxidative Stress Responses

MSC-Exos carry superoxide dismutase (SOD) and catalase enzymes. SOD drains excess harmful ROS and delivers microRNAs and protective proteins that turn on antioxidant systems, making cells more resistant to stress by restoring balance and boosting natural defenses in the cells. This anti-oxidation property helps damaged tissue recover, like neurodegenerative and retinal disorders (Che *et al.,* 2024).

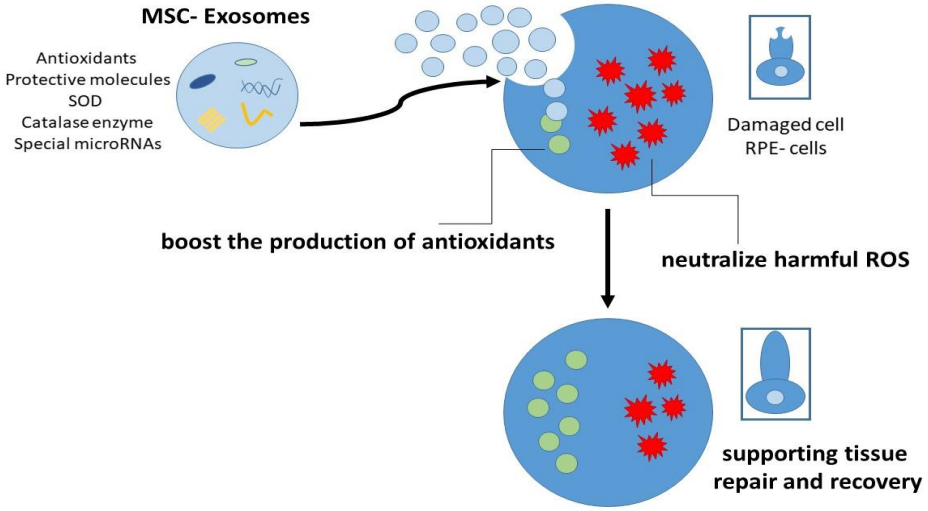

Figure 1: MSC-derived exosomes reduce oxidative stress and support repair in damaged RPE cells.

Regulation of Apoptosis and Cell Survival

Apoptosis is known as programmed cell death, which occurs when excess ROS builds up in the cell, causing oxidative damage. These ROS damage mitochondrial function and activate intrinsic apoptotic pathways, causing mitochondrial outer membrane permeabilization. This phenomenon is caused by the Bcl2-family protein that releases cytochrome-c into the cytoplasm. This release activates cascade-9 & -3. The FoxO3 protein pushes cells toward death when excessive stress is received. MSC-Exos protects the cell from apoptosis by delivering molecules like heat shock proteins, growth factors, and microRNAs that support cell survival and reduce damage (Wen *et al.,* 2020).

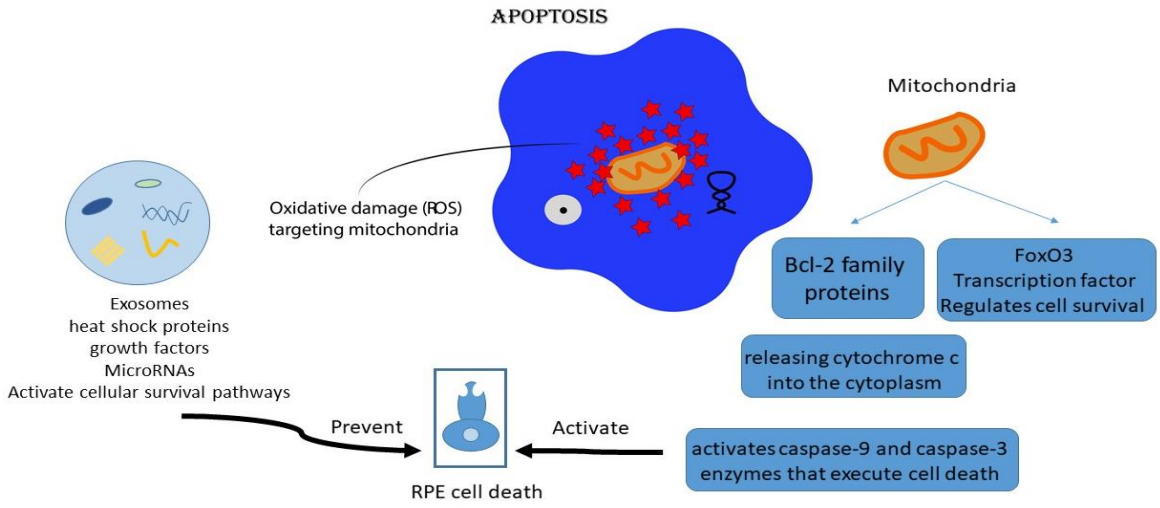

Figure 2: Exosome-mediated protection of RPE cells against oxidative stress-induced apoptosis by modulating mitochondrial pathways and promoting cell survival.

The PI3K/Akt/FoxO3 Signalling Axis in AMD Therapy

The PI3K/Akt pathway with FoxO3 regulation helps restore equilibrium between oxidant/antioxidant states, called redox balance. This process starts when Akt phosphorylates FoxO3, so phosphorylated FoxO3 is prevented from entering the nucleus and blocking those death signal genes, such as *Bim*. This balance is really important in conditions like neurodegenerative diseases, by protecting RPE cells from death and reducing retinal damage by oxidative stress. Researchers show that MSC-Exos activate the PI3K/AKT/FoxO3 pathway (Peng *et al.,* 2024).

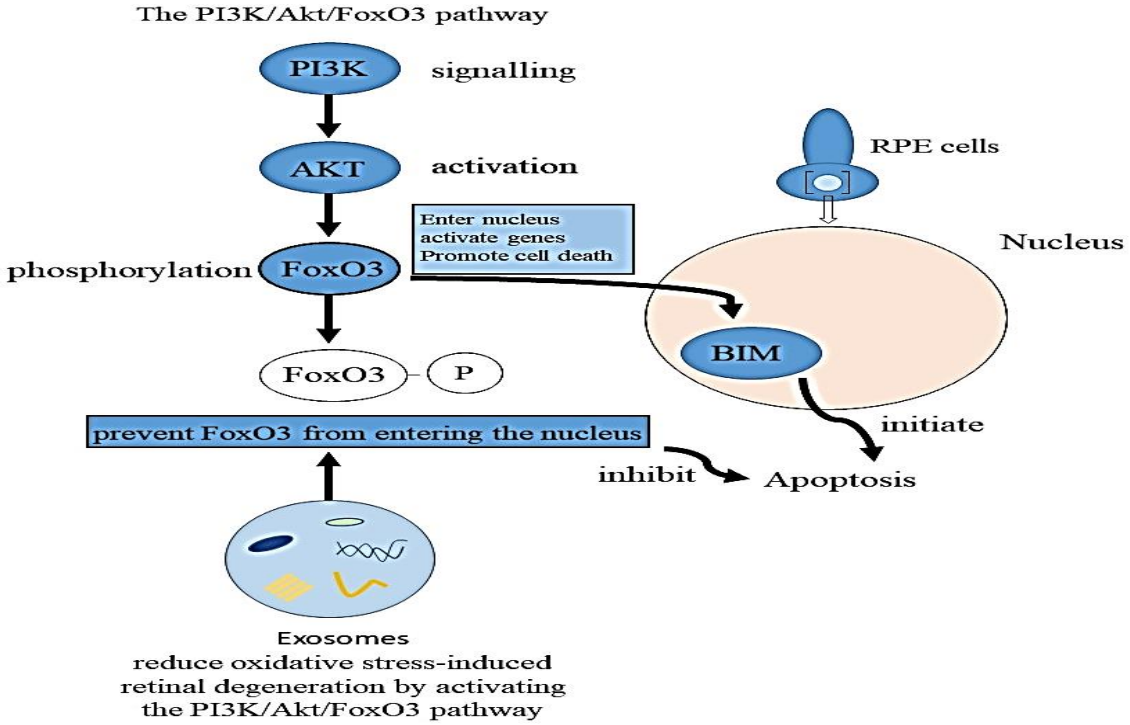

Figure 3: MSC-derived exosomes activate the PI3K/Akt/FoxO3 signaling pathway, promoting redox balance and protecting RPE cells from oxidative stress-induced apoptosis in AMD.

VIII. Future Perspectives and Challenges:

The translational hurdles facing MSC-EV therapy isolation technique

Common ways for successful exosome isolation are ultracentrifugation (UC) and ultrafiltration (UF). UC as differential-UC (DUC) works by spinning samples at very high speeds, sometimes up to 1000000 g, to get pure exosomes, even though unwanted particles may pull. It's time-consuming. Researchers use density gradient ultracentrifugation (DGUC), which involves adding layers of dense solutions such as sucrose or iodixanol to achieve purer exosomes, however, this method is slow and difficult to scale up. Rate zonal and isopycnic-UC are even more accurate. Their side effects include being too complex and slow for routine or clinical use. UF, the second exosome isolation technique, uses filters with tiny pores to catch exosomes based on size. It's much faster and doesn't need expensive machines. These properties make UF a good fit for large batches or clinical work exosome isolation. We have to adjust the pressure from filtration, as it's the only issue that could damage the exosomes. A variation called sequential efficiency is easy to automate, quick, efficient, and adaptable to large volumes, so the method you choose depends on whether you need high purity or

a high number of exosomes (Nikfarjam *et al.,* 2020).

Storage time and temperature

Researchers examined the effect of different storage times and temperatures on the freeze-dried MSC-Exos in Wharton's jelly medium, like -80°C, -20°C, 4°C, and room temperature (RT), by checking the samples after 3 months up to 30 months; the storage at -80°C was protecting their molecules even for 30 months. But at 4°C and RT, many molecules and factors, like brain-derived neurotrophic factor (BDNF), beta nerve growth factor (beta-NGF), and soluble vascular cell adhesion molecule-1 (sVCAM-1), declined, and the detection of some molecules was lost at -20°C. Trehalose, a sugar used to protect molecules, can help a little at -4°C and RT, but couldn't match the preservation at -80°C. These results showed that -80°C was fit for keeping MSC-Exos in long-term use (Rogulska *et al.,* 2024).

Route of application related to AMD

Delivery of MSC-Exos in different ways, like intravenous (IV), subconjunctival (SC), and intraocular (IO) injections, revealed an increase in microRNA-222 levels in the retina (Adak *et al.,* 2021). Intravitreal injection of MSC-Exos in animal studies helped reduce retinal damage and improve visual function. This method is effective because it delivers exosomes directly where they're needed in the eye (Tang *et al.,* 2023; Wu and Ahmad, 2023).

The dose of MSC-EVS

The dose of MSC-Exos used in clinical studies isn't the same across the board. It changes depending on the route of injection and what the disease is. There is also no standard way to report the dosage. Some studies use micrograms, and others count the number of exosome particles. Because of all these different methods, it is difficult to reveal the dosage (Lotfy *et al.,* 2023). Clinical translation still faces challenges in production, dosing, and delivery (Gu *et al.,* 2023). That is why this review tried to show everything in more detail. Despite the hurdles, MSC-Exos offer a transformative approach to treating neuro-irreversible disorders.

IX. MSC-EVs Showing Therapeutic Effects

In Vitro and In Vivo Studies in AMD Models.

Although this study wasn't conducted in a retinal ischemia model, not on an AMD-specific model, it gives us valuable insight, as researchers tested MSC-Exos that were modified to overexpress miR-424, called FEE424, which showed a strong protective and anti-inflammatory effect both in vivo and in vitro (Mathew *et al.,* 2023). MSC-Exos in lab-based studies were able to protect cells from damage by reducing LDH activity. LDH is a marker of cell damage that causes lowering ROS levels by increasing SOD activity. In animal studies, MSC-Exos helped protect important parts of the retina, such as the RPE, the photoreceptor segments, and the outer nuclear layer. Protein analysis also showed an increase in the Bcl-2/Bax ratio, a sign that more cells survived after treatment with MSC-Exos (Tang *et al.,* 2023).

MSC-EVs clinical trials for retinal diseases

MCS-Exos injection into the eye during pars plana vitrectomy (PPV) has been used to treat large macular holes (MHs) in patients. This treatment has shown positive results, with around 80% of the hole closing successfully (Tian *et al.,* 2023).

CONCLUSION

AMD is still a challenge in global eye health conditions, especially the dry form, where current therapies and even the most recent therapies show high limitations. That's why our research directs the sights to MSC-Exos as a regenerative treatment for neuro-irreversible conditions like AMD. This review concisely covers the MSC-Exos mechanism of action, clinical translation hurdles, therapeutic potential, and previous clinical studies in another retinal degenerative condition. The details are comprehensive.

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الحويصلات الخارج خلوية المستخلصة من الخلايا الجذعية الميزينكيمية: نهج علاجي واعد للتنكس البقعي المرتبط بالعمر

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الضمور البقعي المرتبط بالعمر هو اضطراب تقدمي في الشبكية يؤدي إلى فقدان البصر، ويرجع ذلك أساسًا إلى انهيار الظهارة الصبغية للشبكية والمستقبلات الضوئية. تتضمن الفسيولوجيا المرضية للضمور البقعي المرتبط بالعمر آليات معقدة، مثل الإجهاد التأكسدي والالتهاب الشديد والانحلال الخلوي، مما يؤدي إلى تكوين الدروزينات والليبوفيوسين. والعلاج الحالي مثل العلاج بالليزر للشبكية، والعلاج الديناميكي الضوئي، وحتى عوامل نمو بطانة الأوعية الدموية المضادة للأوعية الدموية يظهر الكثير من القيود خاصة بالنسبة للضمور البقعي المرتبط بالعمر الجاف. لذلك كشفت هذه المراجعة بشكل منهجي عن التأثير المحتمل للإكسوسومات المشتقة من الخلايا الجذعية الوسيطة كعلاج جديد للضمور البقعي المرتبط بالعمر. تؤثر الإكسوسومات المشتقة من الخلايا الجذعية الوسيطة على التعبير الجيني، وتعيد تشكيل المصفوفة خارج الخلية وتوفر عوامل النمو. توفر هذه الخصائص علاجًا أكثر فعالية للضمور البقعي المرتبط بالعمر.