Eye and Brain

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Exosome-Based Approaches in Regenerative Medicine and Targeted Therapy for Eye Malignancies: A Comprehensive Review

Mohammad Mehdi Falahi Tabar[1], Arian Yavari[1], Masood Bagheri[2], Parnian Yavari[1,3], Kamran Mansouri[4], Gelavizh Rostaminasab[2,*], Shima Rahmati[5,*]

[1]Student Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran; [2]Clinical Research Development Center, Imam Khomeini and Mohammad Kermanshahi and Farabi Hospitals, Kermanshah University of Medical Sciences, Kermanshah, Iran; [3]Immunology Department, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran; [4]Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran; [5]Cancer Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

*These authors contributed equally to this work

Correspondence: Shima Rahmati, Cancer Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran, Tel +989133854865, Email shimarahmati1987@gmail.com; Gelavizh Rostaminasab, Clinical Research Development Center, Imam Khomeini and Mohammad Kermanshahi and Farabi Hospitals, Kermanshah University of Medical Sciences, Kermanshah, Iran, Tel +989188583059, Email rostamishiva.1365@gmail.com

Abstract: Diagnosing and treating ocular malignancies—such as uveal melanoma, retinoblastoma, intraocular lymphoma, and conjunctival tumors—can be very difficult given their rarity, complicated pathophysiology, and a high potential for complications that threaten vision or life. Traditional treatments such as chemotherapy, radiation, and surgery result in limited clinical value because of systemic toxicity, versatile drug resistance, and insufficient local control. Exosomes (EXOs)—naturally occurring nanoscale vesicles held in biocompatible structures—represent a uniquely advantageous platform for targeting and delivering miRNAs, proteins and/or gene editing molecules across ocular barriers to create corrective, sustained, and targeted diagnostics, drug delivery, and immune modulation. Mesenchymal stem cell-derived exosomes (MSC-EXOs) also possess regenerative potential in both animal and human models of retinal and ocular injury, engaging biological pathways involved in modulating inflammation and neuroprotection such as HMGB1 and PI3K/AKT pathways. While the use of EXOs presents a promising option for ocular treatment application, several factors complicate actual clinical translation, including standardization of isolation, scalable manufacture, and regulatory issues. In general, EXO-based nanomedicine may be a promising new direction for precision therapy and regenerative ophthalmology with the increasing introduction of synthetic and bioengineered EXOs introducing precursor paving new avenues for clinically scalable and biologically customizable EXO therapeutics.

Keywords: exosome, regenerative medicine, eye malignancies, ocular diseases

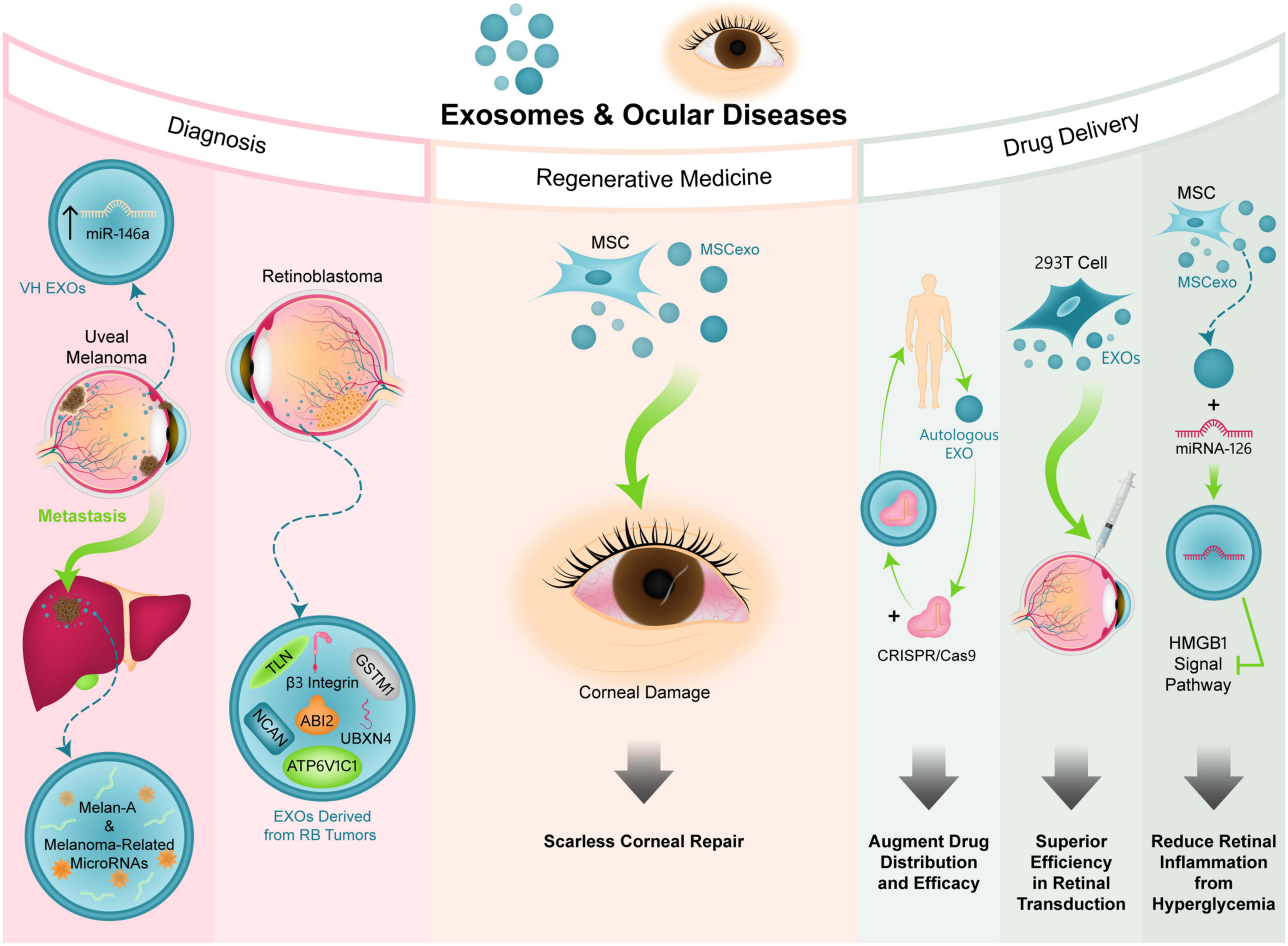
Introduction

Types of Eye Cancer (Primary or Secondary)

Primary eye cancers like uveal melanoma (UM) and retinoblastoma are infrequent occurrences. UM typically affects the choroid, especially in people with light pigmentation, like those with European background. Retinoblastoma primarily affects the retina in children and happens more frequently across the world. Secondary (metastatic) ocular tumors arise in the context of patients suffering from systemic cancers. The uvea, particularly the post-equatorial choroid, is the most common site of metastasis in the eye.[1] Primary tumors that produce metastasis in the eye most commonly include breast (37%), lung (27%), kidney (4%), gastrointestinal tract (4%), cutaneous melanoma (2%), lung carcinoid (2%), prostate (2%), thyroid (1%), pancreas (1%), and other cancers (3%). Ocular malignancies, both primary and secondary, will represent the

https://doi.org/10.2147/EB.S563110
Received: 25 August 2025
Accepted: 27 January 2026
Published: 19 February 2026

Graphical Abstract



majority of clinically relevant cases, but present challenges in terms of diagnosing and managing them correctly due to their infrequency, complexity in pathophysiology, and potential complications that threaten vision or life.[2]

Uveal Melanoma (UM)

UM is the most prevalent primary intraocular cancer in adults. Europe and the US have a yearly incidence of ~6 per million people. UM similar to cutaneous melanoma, is associated with various genetic mutations. UMs are caused by GNAQ or GNA11 mutations, unlike cutaneous melanomas, which have BRAF or NRAS mutations. Risk factors include BAP1-tumor predisposition syndrome, fair complexion, light eyes, congenital ocular melanocytosis, and ocular melanocytoma.[3] In a study conducted by Lorigan et al, research was performed on 110 patients with uveal melanoma who exhibited metastatic developments. Research indicates that hepatic metastasis occurred in 92% of patients, followed by pulmonary metastasis at 31%, bone metastasis at 23%, skin and subcutaneous metastasis at 17%, lymph node metastasis at 14%, brain metastasis at 4%, adrenal gland metastasis at 3%, stomach metastasis at 2%, and spleen metastasis at 2%.[4] As many as 50% of patients with initial UM will eventually have distant metastases. Metastatic dissemination transpires via the bloodstream, with the liver often being involved. The collaborative ocular melanoma study (COMS) determined cumulative metastatic rates of 25% at 5 years and 34% at 10 years. Patients are at risk of developing metastases for up to 20 years following the initial diagnosis.[5]

Intraocular Lymphoma

The overall incidence of intraocular lymphoma is predicted to constitute 1.86% of ocular malignant neoplasms.[6] Lymphoma represents an uncommon type of intraocular malignancy, likely constituting approximately 0.01% of ophthalmic diseases.[7,8] The majority of patients are over the age of 50. The majority of intraocular lymphoma is classified as primary vitreoretinal lymphoma (PVRL), which affects the retinal pigment epithelium and vitreous, in contrast to secondary lymphomas like metastatic systemic lymphoma that involve the uvea.[9] PVRL is an uncommon high-grade extranodal non-Hodgkin lymphoma that impacts the vitreous, retina, or, in rare instances, the optic nerve, without the involvement of brain parenchyma.[10] PVRL occurs within the intraocular compartment, without any brain involvement, representing a rare subgroup of primary central nervous system lymphoma (PCNSL).[11] PVRL is significantly linked to PCNSL, as the majority of cases that present with ocular involvement are likely to progress to CNS lymphoma.[9] When PCNSL first affects the retina, it is referred to as primary intraocular lymphoma.[12] The majority of PVRL cases represent a high-grade form of diffuse large B-cell lymphoma (DLBCL). Similar to PCNSL, PVRL can be classified as belonging to the activated-B cell type of lymphoma, more specifically within the subgroup of ABC DLBCL. It is characterized by frequent mutations in CD79 and MYD88L265P, and it tends to have a less favorable outcome compared to other ABC subgroups. Uncommon instances of unclassifiable B-cell lymphoma, follicular lymphoma, and T-cell lymphoma are observed. The pathophysiology of PVRL is yet to be fully understood. The origin of lymphoma cells remains unidentified; however, like to PCNSL, it is probable that the transformation of tumor cells occurs outside the CNS before their migration to the eye and subsequent proliferation.[13] Another unique form of intraocular lymphoma is primary choroidal lymphoma.[14] Ocular irradiation has the danger of causing cataracts, radiation retinopathy, and optic neuropathy, however it is the recommended ocular treatment in many centers. Intravitreal chemotherapy with methotrexate 400 μg in 0.1 mL in an intense induction-consolidation-maintenance regimen of 25 injections delivered over 1 year is used to avoid radiation effects, however it carries hazards of keratopathy, maculopathy, and drug resistance. There have been no claims that radiation is more effective than intraocular chemotherapy. Fewer intravitreal injections and more widely spaced injections have been advised to improve the acceptability of intraocular chemotherapy.[9]

Conjunctival Tumors

Among the most common adnexal and ocular tumors are conjunctival tumors. This group includes benign lesions like nevus or papilloma and malignant ones like epidermoid carcinoma or melanoma, the latter of which can cause blindness or even death to the sufferer.[15] Conjunctival tumors comprise a wide array of diagnosis. The three most significant malignant tumors are ocular surface squamous neoplasia (OSSN) at 14%, melanoma at 12%, and lymphoma at 7%.[16]

Retinoblastoma (RB)

RB constitutes 3% of all pediatric cancers and is the predominant intraocular malignancy in children. The global incidence is reported to be between 1 in 15,000 and 23,000 live births. The tumor manifests bilaterally in 30–40% of instances. Among newly diagnosed retinoblastoma cases, only 6% are familial, while 94% are sporadic.[17] The predominant clinical manifestation is leukocoria (50%), succeeded by strabismus (20%). Additional manifestations encompass diminished vision, painful erythematous eye, hyphema, or proptosis.[18]

Challenges in Diagnosis and Treatment of Eye Cancer

Ocular cancers are unique among eye diseases, endangering vision and life. Typically, the diagnosis is made through a detailed clinical history and specialized eye examination. Diagnosing eye cancer depends largely on imaging methods like high-frequency ultrasound, fluorescein angiography, optical coherence tomography for both anterior and posterior segments, computed tomography (CT), and magnetic resonance imaging (MRI).[17]

Treatment decisions depend on the tumor's location, size, local extension, growth patterns, and secondary complications once the diagnosis is established.[17] Chemotherapy, a significant contributor to enhanced survival rates, has transformed the treatment of retinoblastoma during the past several decades. Treatment protocols encompass the

intravenous delivery of chemotherapeutic drugs, direct tumor targeting through administration via the ocular artery, and, most recently, intravitreal injection of melphalan to address vitreous seeds.[19]

Chemotherapies, which are common treatments, often target and disrupt DNA, leading to mutations or genomic instability, a significant characteristic of both cancer and aging. Many chemotherapy drugs can damage DNA and interfere with how it works in different ways, and each one behaves differently in the body and has different effects.[20]

Intra-arterial chemotherapy (IAC), for retinoblastoma was originally devised by Kaneko and associates as a vision-sparing treatment in Japan, where enucleation is culturally unacceptable.[21,22] IAC is controversial. Since the medications are solely given to the eye, the procedure should reduce systemic chemotherapy problems. However, neutropenia in some situations suggests that the medications have systemic effects. Intra-arterial chemotherapy can often cure retinoblastomas. However, the method has limits and does not always work. IAC treats only the eye, which is both good and bad. It targets one organ, but its apparent inability to control systemic metastases is a drawback. IAC may allow metastasis to develop more than intravenous systemic chemotherapy. At least one in five retinoblastoma-enucleated eyes have high-risk traits that require adjuvant systemic intravenous chemotherapy.[23]

Diagnosis also has its challenges. A significant clinical problem for ophthalmologists is distinguishing between a benign nevus and a melanoma that requires prompt treatment for improved prognosis. Dr. Carol Shields and her team looked at 1329 cases from the oncology service at Wills Eye Hospital and identified certain signs that suggest a pigmented spot is likely to grow and is probably a melanoma that needs treatment.[24,25]

The Role of EXOs in Modern Medicine

Exosomes (EXOs) are nanosized, membrane-bound extracellular vesicles (EVs) with an endosomal origin. They are formed within multivesicular bodies and released upon fusion with the plasma membrane, representing a well-defined subclass of EVs involved in intercellular communication and molecular transport. These vesicles carry a variety of biological cargo that performs a wide range of physiological functions and can also be used to diagnose various diseases. EXOs are regarded as potentially useful tools for the delivery of therapeutic drugs due to their inherent characteristics, which include stability, biocompatibility, and the ability to remain undetected.[26] This property enables EXOs to play a role in the treatment of a variety of diseases, including cancer. Moreover, EXOs demonstrate resistance to challenging environmental conditions, including low blood pH, positioning them as promising biocarriers for pharmaceuticals, nucleic acids, and imaging agents in cancer treatment. The potential of exosomes as delivery systems for anticancer medicines, especially those with low solubility and restricted off-target delivery, is of considerable interest.[27]

Integrating Regenerative Medicine and Nanotechnology in Ocular Oncology

Nanomedicine refers to the utilization of nanotechnology in the medical field, and it holds the potential for a substantial influence on cancer treatment. Nanomedicine is a comprehensive word that includes several forms of medication delivery technologies within the nanoscale range.[28]

To achieve medical benefit, nanomedicine employs engineered nanodevices and nanostructures to monitor, control, build, repair, defend, and improve human biological systems at the molecular level, massively in parallel at the single cell level. The first nanomedicine applications are likely to be in biopharmaceuticals, implantable materials (tissue regeneration scaffolds, bioresorbable materials), implantable devices, and diagnostic tools. Artificial vision, microsensors and feedback devices, ultrahigh-resolution in vivo imaging, and regenerative medicine will all benefit from nanotechnology. Nanoparticles containing gene transcription factors and other modifying chemicals are used in "regenerative nanomedicine", a new field of nanomedicine, to modify cells in vivo.[29] Almost every type of cell in both prokaryotic and eukaryotic organisms continuously releases extracellular vesicles (EVs), which are a wide variety of nanoscale structures, into the extracellular space. EVs are made up of different components that are meant to be delivered to nearby or distant target cells. They have an internal aqueous core that is protected by a lipid bilayer membrane. The late endosomal trafficking machinery produces EXOs, which are EVs with a diameter of 30 to 150 nm and a density of 1.13 to 1.19 g/mL in sucrose. They are produced intracellularly in organelles called multivesicular bodies (MVBs), which fuse with the plasma membrane to release them into the extracellular environment.[30]

EXOs: Key Players in Cellular Communication and Therapy

Biogenesis and Characteristics of EXOs

Cells release a spectrum of extracellular vesicles (EVs) that differ in size and intracellular origin. This diversity—together with non-vesicular extracellular nanoparticles—complicates efforts to define the composition and function of individual secreted components. Pinpointing which RNA, DNA, and proteins reside in specific extracellular compartments, and clarifying how they are exported, is essential for robust biomarker discovery and for designing future pharmacological interventions. Exosomes (EXOs) are small EVs (sEVs), typically ~30–150 nm, that arise from the endosomal system and are produced by most cell types. Diverse RNA species—mRNA, microRNA (miRNA), and other non-coding RNAs—along with DNA and lipids, are actively and selectively packaged into intraluminal vesicles (ILVs) within multivesicular endosomes (MVEs), which serve as precursors to EXOs.[31] ILVs are generated through the action of the ESCRT machinery together with accessory proteins such as ALG2-interacting protein X (ALIX) and tumor susceptibility gene 101 (TSG101). These molecules gather ubiquitylated proteins at the multivesicular body (MVB) membrane and support the inward budding process.[32] Upon formation, the MVBs may either fuse with lysosomes for degradation or with the plasma membrane to facilitate the release of EXOs into the extracellular space.[33] see Figure 1 for a schematic overview of EXO biogenesis).

Multiple biological signals influence these decisions. The coordination of EXOs release through MVB fusion with the plasma membrane facilitates the release of EXOs from cells, enabling potential targeting of adjacent cells or entry into the bloodstream.[34] Several factors regulate the release of EXOs, including cellular insults such as hypoxia and

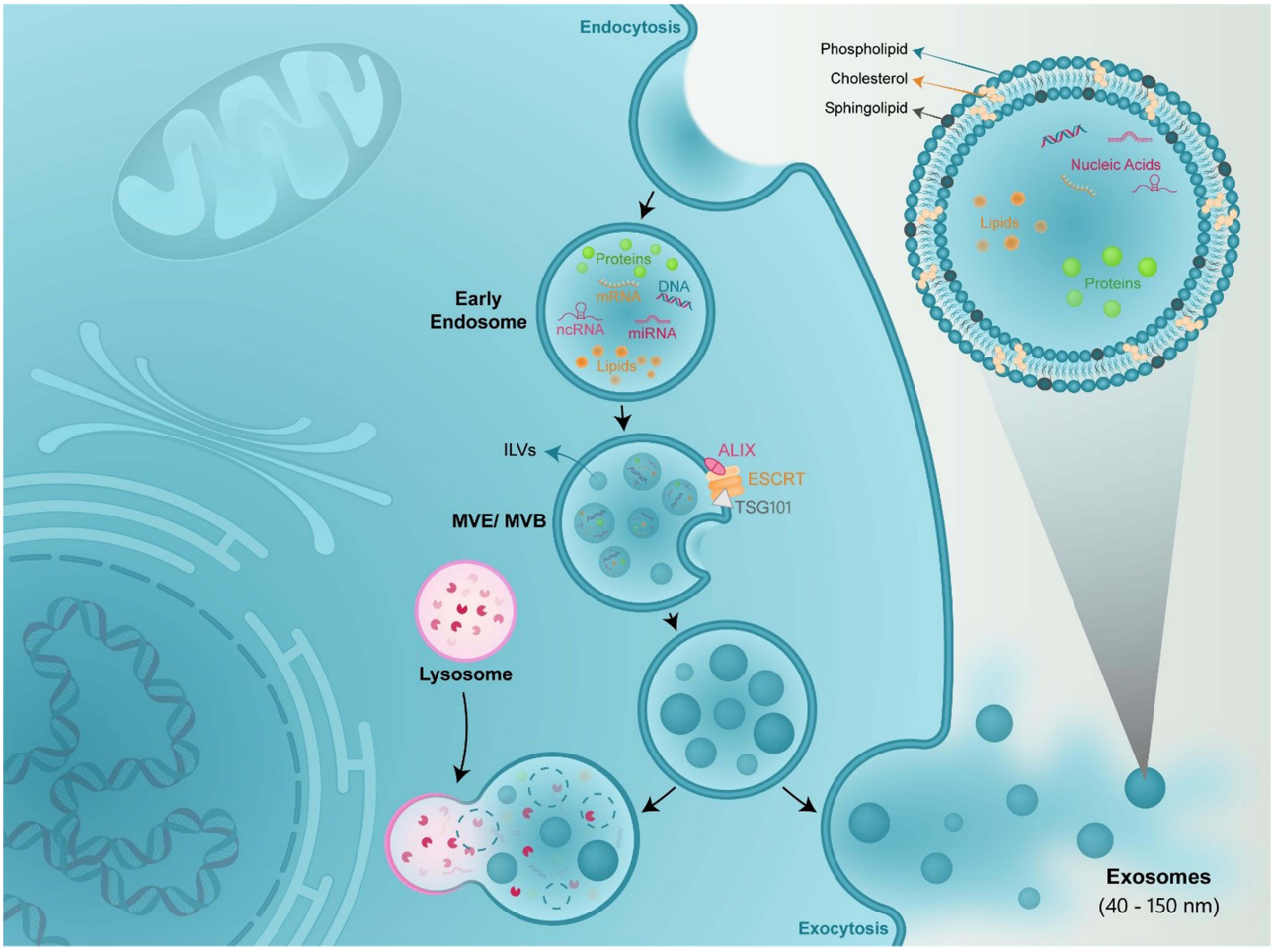


Figure 1 Biogenesis and characteristics of exosomes.

https://doi.org/10.2147/EB.S563110

inflammation, environmental changes, and various signaling pathways involving growth factors and cytokines that either inhibit or promote the release of exosomal content. EXOs accumulation may be either upregulated or downregulated about the specific signaling pathway that is activated.[35–37] Because their cargo reflects the physiological status of the parent cell, EXOs are valuable indicators for studying cellular functions and modes of communication.[36] The complex interplay between EXO formation, intracellular signaling events, and external conditions highlights the importance of tightly regulating their production to preserve homeostasis and adapt to environmental change.[38] This regulatory balance explains why EXOs are increasingly recognized as contributors to both normal physiology and a variety of disease processes.[39,40]

EXOs are fascinating membrane structures that encapsulate the traits of the cells from which they originate.[41] The vesicle-like structures, enveloped in a lipid composition, encompass a range of bioactive materials, including proteins, lipids, and nucleic acids.[42] The EXOs possess a lipid-rich composition, comprising phospholipids, cholesterol, and sphingolipids, which contribute to their stability, morphology, and size determination.[41–43] EXO offer a fascinating dimension as they encapsulate genetic materials, including mRNAs and microRNAs, which have the potential to alter gene expression in target cells.[44] This capability enables them to mediate crucial biological activities, including immune system responses and cellular differentiation, while also facilitating various processes.[43] Skilled in the transportation of essential components, they contribute significantly to the regular functioning of cells, as well as to the diagnostics and treatment of pathological conditions. The study of EXOs offers profound insights into the mechanisms of cellular communication and holds promise for the advancement of therapeutic strategies for various diseases.[38,45] This has the potential to broaden the horizons of EXO therapy moving forward. These and other examples illustrate the remarkable and intricate ways in which nature facilitates communication between cells.[42]

EXOs in Cancer Biology: A Double-Edged Sword

EXOs provide valuable insights into cancer biology, presenting both diagnostic and therapeutic opportunities. EXOs, through their cell-to-cell communication, play a significant role in tumor progression, metastasis, and the efficacy of therapies.[46]

EXOs have typically been characterized as cancer-promoting factors, but it's not out of the question that they may have antitumor roles and slow down disease development in some cases.[47] Numerous studies have shown a significant association between EXOs and cancer development and progression. EXOs from immune cells can inhibit tumor growth, proliferation, and metastasis. EXOs serve a dual role in cancer immunity.[48] The tumor microenvironment (TME) surrounding cancer cells consists of cancer-associated fibroblasts, blood vessels, nerve fibers, immune cells, additional stromal cells, and EVs holding diverse genetic signals. The TME is recognized for establishing a setting that inhibits the unrestricted dissemination of malignant cells since all components function in anticancerous immunosuppressive cells.[49]

The communication network between cancer and stromal cells is bidirectional, relying on the release of soluble compounds such as growth factors and EXOs.[50] It has been demonstrated that cancer EXOs affect nearby cells, which promotes tumor growth and metastasis. Through a TGFβ-dependent method, EXOs from prostate cancer cells have been shown to stimulate fibroblast differentiation into activated fibroblasts or myofibroblasts.[50] TGFβ+ EXOs highlight the distinct functions of these two forms of intercellular communication by promoting a myofibroblast phenotype that is distinct from that caused by serum TGFβ. By secreting growth hormones, chemokines, and extracellular matrix constituents, activated fibroblasts—which are commonly seen at tumor sites—are known to play a crucial role in the progression of tumors.[51] Cancer progression is a dynamic, multistep process wherein numerous extensively researched signaling events facilitate the advancement of malignancy. Tumor-derived EXOs actively influence cancer progression by initiating autocrine/paracrine oncogenesis, reprogramming stromal cells, influencing the immune system, and stimulating angiogenesis.[52] Oncosomes, a specific subtype of extracellular vesicles, were initially characterized as giant vesicles released by glioma cells.[53] These unusually large EVs, measuring 1–10 μm in diameter, are distinguished by their anomalous cargo, which includes oncogenic proteins.[54] The transfer of oncogenic chemicals via oncosomes across primary tumors induces morphological transformation and enhances anchorage-independent proliferation in recipient cancer cells.[53]

Metastasis is a complex process that includes tumor cells invading blood vessels through the basal membrane, surviving in the bloodstream, adhering to blood vessel walls, extravasating, and finally colonizing and growing in the host organ. EXOs may have an impact on the metastatic characteristics of malignant tumors since they can stimulate a variety of intratumoral biological processes.[55] Soluble or vesicle-bound bioactive molecules released by metastatic cancer cells aid in the remodeling of extracellular matrix architecture and the reprogramming of different contributing cells in distant organ sites, such as tumor-associated neutrophils (TANs), cancer-associated fibroblasts (CAF), tumor-associated macrophages (TAM), and bone marrow progenitor cells. The creation of premetastatic niches prior to cancer metastasis depends on this process.[56]

Regenerative Medicine and EXOs in Ophthalmology

Role of EXOs in Tissue Repair and Regeneration

EXOs are packed with unique elements that contribute to healing and renewal across different disease models. For instance, miRNAs can promote tissue regeneration by modulating downstream signaling cascades such as PI3K/AKT, MAPK, and STAT3, which are central to cell survival, anti-inflammation, and neuroprotection.[57,58]

Currently, EXOs have shown encouraging therapeutic effects on the repair and regeneration of soft tissues, including tendons, skeletal muscle, and peripheral nerves. These nanoparticles and their analogs can produce comparable therapeutic results to cell treatments while circumventing numerous drawbacks. The majority of experimental evidence indicates the efficacy and safety of EXO use, which is promising. EXOs facilitate soft tissue repair and regeneration in many ways.[59]

Mesenchymal stem cell (MSC) therapy has grown in the past decade. MSCs have been extensively studied for cell-based therapy in chronic ocular illnesses due to their regenerative, reparative, and immunomodulatory properties. Insufficient biocompatibility, penetration, and transport to specific ocular tissues limit MSC-based treatment.[60] The prospective advantages of utilizing MSC-derived EXOs as a drug-delivery method can be fully actualized, since they may possess enhanced capacity to traverse barriers such as the blood-retinal barrier, inferred from their demonstrated ability to pass the blood-brain barrier. Furthermore, their payload is safeguarded against degradation, leading to enhanced bioavailability in ocular tissue.[61–63]

EXO-Derived Therapies for Retinal and Corneal Damage

Injury, infection, or ischemia-induced damage to retinal cells initiates degeneration in adjacent neural cells, leading to the proliferation of morphological and functional retinal damage and irreversible visual impairment.[64]

EXOs serve as promising natural drug carriers because of their structural makeup, varied biological roles, and distinctive biological source. Evidence suggests that EXOs may serve as vehicles for both passive and active drug delivery, showcasing a variety of properties and components.[65] Also, EXOs are known to play an important role in many diseases, such as cancer,[66] cardiovascular disease,[67] and nervous system diseases.[68] The function of different cell-derived EXOs in a range of ocular disorders has been the subject of increased research in recent years. Nevertheless, little is known about how EXOs participate in ocular disorders. Research on the role of EXOs in ocular disorders has surfaced recently. Zhang et al[69] reviewed several studies on the roles of EXOs in ocular diseases, including age-related macular degeneration (AMD), diabetic retinopathy (DR), autoimmune uveitis, glaucoma, and optic nerve crush (ONC). Furthermore, their review discusses how EXOs are acquired, as well as their potential as therapeutic carriers. The study conducted by Yu et al revealed that EXOs produced from MSCs can reduce inflammation and damage to the retina in an animal model of laser-induced retinal injury.[70] Also, Mead et al[71] investigated the therapeutic potential of EVs in retinal diseases such as ONC, glaucoma, retinal ischemia, laser injury, autoimmune uveitis, and DR.

MSCs have the potential to control the inflammatory response and facilitate wound healing. EXOs have been proven to help with this repair process. They successfully limit neovascularization and increase neutrophil clearance, resulting in scarless corneal repair. EXOs in injured corneas increase the expression of antiangiogenic factors (TSP-1) and anti-inflammatory cytokines (IL-10, TGF-β1, and IL-6), while decreasing the expression of proinflammatory factors (IL-2, IFN-γ, macrophage inflammatory protein-1α, and VEGF).[72] EXOs generated from MSCs have shown tremendous

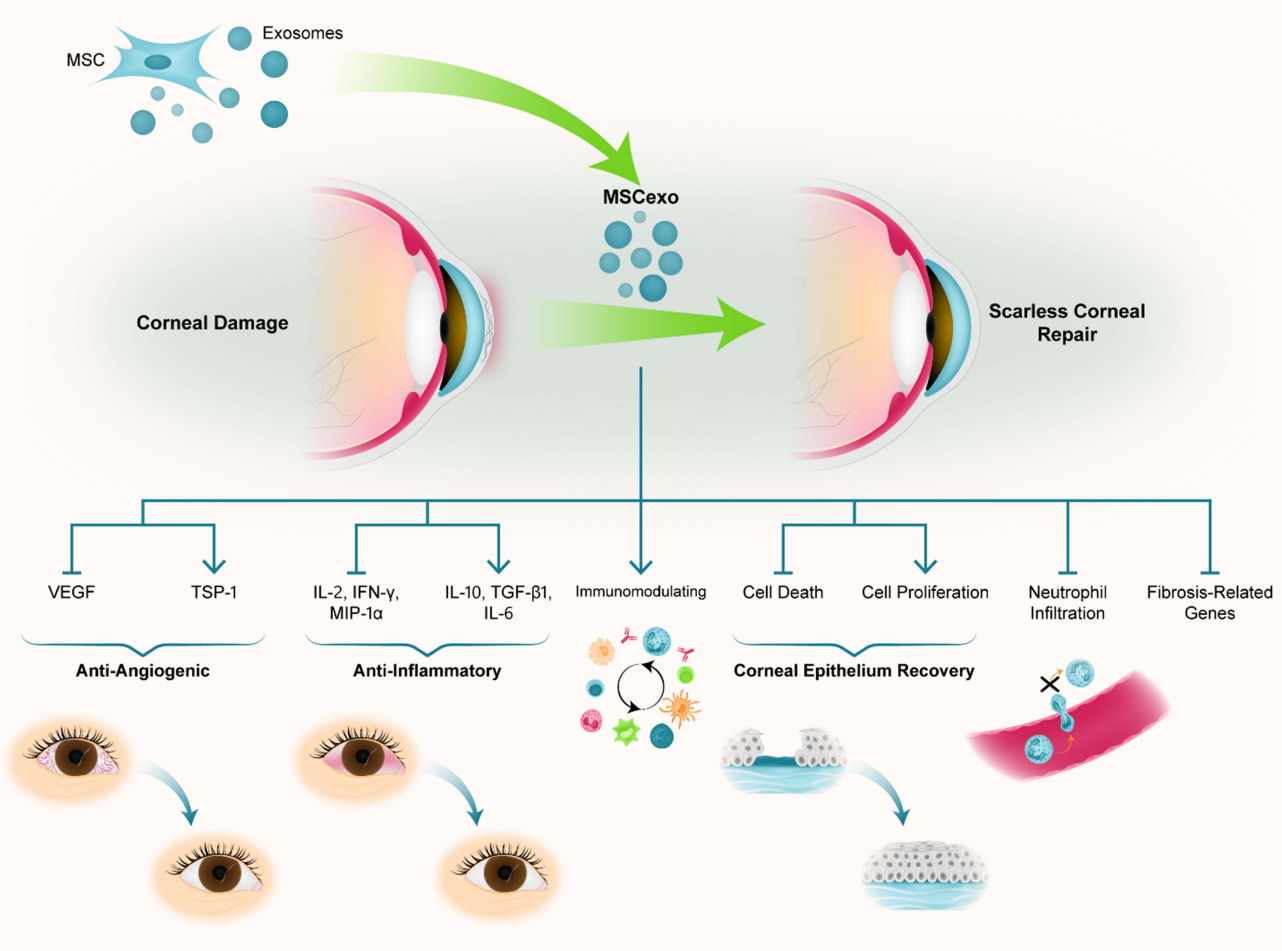


Figure 2 MSC-derived exosomes as a treatment for corneal injury. They help reduce inflammation and repair the epithelium. They also prevent abnormal blood vessel growth in the cornea.

promise in the treatment of corneal injuries due to their anti-inflammatory, anti-angiogenic, and immunomodulating capabilities. EXOs can improve corneal wound healing by increasing cell proliferation, decreasing cell death, and boosting corneal epithelium recovery. They can also reduce inflammation and scarring by decreasing neutrophil infiltration and fibrosis-related gene activation. Furthermore, MSC-derived EXOs (MSC_{exo}) can reduce corneal angiogenesis by inhibiting pro-angiogenic factors and speed up corneal wound healing by decreasing inflammatory cytokine expression. These features make MSC_{exo} a promising treatment for a variety of corneal illnesses and disorders.[73] see Figure 2 for MSC-derived exosomes' role in reducing inflammation, promoting epithelial repair, and inhibiting corneal neovascularization.

EXO-Based Targeted Therapy for Eye Cancer

EXOs as Drug Delivery Systems: Advantages and Limitations

EXOs represent a promising category of natural drug carriers owing to their structural composition, multifaceted roles, and distinctive origin. Research indicates that EXOs can transport a diverse array of pharmaceuticals through both passive and active mechanisms.[74] EXOs can enhance the stability and efficacy of medications by conjugating them to tetraspanins on their membrane. EXOs can contain beneficial compounds, including foreign proteins, facilitating their traversal across barriers such as the blood-brain barrier, so presenting possible therapies for neurological illnesses.[75] Moreover, EXOs can transport CRISPR/Cas9 components for gene editing, facilitating the transfer of gene-editing functionality between cells.[76] In addition to direct effects, autologous EXOs can augment drug distribution and efficacy in vivo.[74]

They can work as nanocarriers for functional RNA strands, DNA molecules, peptides, or synthetic pharmaceuticals.[77] EXOs derived from AAV-2-producing 293 T cells demonstrated superior efficiency in retinal transduction compared to standard AAV-2 following intravitreal injection. This illustrates the capability of EXOs in ocular pharmacotherapy. Nonetheless, there is a paucity of studies regarding the incorporation of external functional payloads into EXOs for the treatment of ocular illnesses, highlighting the necessity for substantial advancements in the development of such therapies within ophthalmology.[77]

Additionally, it has been observed that MSC-EXOs loaded with exogenous miRNA-126 reduce retinal inflammation brought on by hyperglycemia by inhibiting the high-mobility group box 1 (HMGB1) signal pathway.[78]

EXOs, with their biological properties, can encapsulate and deliver small chemotherapeutic drugs and biological molecules to recipient tissues or organs. They have better organotropism, homing capacity, cellular uptake, and cargo release ability than other synthetic nano-drug carriers. EXOs secreted in tumors can be used as nontoxic and non-immunogenic drug delivery vehicles for various cancers, especially in hypoxic and acidic tumor microenvironments.[79]

They can aid tumor cells in evading immune surveillance and fostering immunological tolerance, but immune cell-derived EXOs can also prevent tumor cell growth, proliferation, and metastasis.[48]

Like immune cells, cancer cells can produce EXOs that are immunologically active, which can alter the immune regulatory system. Tumor antigen-carrying EXOs exhibit anti-tumor properties. These EXOs can eradicate malignancies by utilizing CD8+ and CD4+ T lymphocytes. Additionally, they have the ability to immediately stop tumor growth and development.[80]

EXOs, on the other hand, have also been linked to resistance to a number of anti-cancer treatments. The function of EXOs in cancer progression, resistance, and the possible application of EXOs as a delivery system for cancer treatments must thus be thoroughly assessed.[81]

Effectively loading exogenous medicines into EXOs is essential for employing them as drug carriers; yet, this job presents a hurdle when researching the functionalization of EXOs as drug carriers. These medications have now been loaded into EXOs by sonication, electroporation, transfection, incubation, extrusion, transgenesis, saponin-assisted loading, freeze-thaw cycles, thermal stress, pH gradient technique, and hypotonic dialysis.[82]

Eye cancers are complex diseases requiring careful management to save the patient's life and preserve vision. The most prevalent intraocular cancers are malignant neoplasms in both children and adults. Retinoblastoma is a common pediatric IOC, with recent advances in treatment through intra-arterial chemotherapy. Uveal melanoma is the most frequent adult IOM, with management mainly based on proton beam therapy or iodine-125 plaque brachytherapy.[83]

A conceptual overview linking exosome sources, cargo profiles, mechanisms of action, and ocular target cells is summarized in Table 1.

EXOs in UM Diagnosis and Treatment

Metastatic liver disease, which is typically deadly within a year, develops in about 50% of UM patients. Since metastases are less susceptible to immune checkpoint inhibitors or chemotherapy, a better understanding of tumor immunology and metabolism may result in new treatments.[3]

One study examines vitreous humor (VH) and extracellular matrix (EXOs) in relation to miRNA dysregulation in UM. It was discovered that the main cause of the changed miRNA profiles in VH EXOs is miRNAs, indicating their involvement in oncogenic signaling. The possibility of miRNA profiling for UM diagnosis was demonstrated by the elevated levels of miR-146a in VH, serum, and EXOs. The work highlights EXO-based miRNAs as therapeutic targets and biomarkers in UM, emphasizing their function in intercellular communication and UM pathogenesis.[84]

Furthermore, it was recently shown by Achberger et al that UM patients' plasma and CD3+, CD56+, and CD15+ cells have greater levels of miR-146a than controls.[85]

According to one study, UM-EVs—which are produced from UM cell lines—have the ability to convert and cause cancer in NOD-SCID mice in vivo. Target cells exhibited malignant transformation with exposure to UM-EVs in human BRCA1-deficient fibroblasts (Fibro-BKO). Additionally, the study discovered that UM-EVs are essential for target cell phenotypic change. Their melanocytic origin was validated by proteomics profiling, which showed elevated proteins associated with liver

Table 1 Conceptual Framework of EXO-Based Mechanisms in Ocular Cancers and Regenerative Ophthalmology

EXO Source	Cargo Type	Mechanism of Action	Targeted Ocular Cell Type	References
Mesenchymal stem cell-derived EXOs (MSC-EXOs)	miRNAs, proteins	Anti-inflammatory, anti-apoptotic, neuroprotective, promote tissue repair and immune regulation	Retinal cells, corneal epithelium	[60–63,72,73]
MSC-EXOs loaded with miR-126	miRNA	Inhibit HMGB1 pathway, reduce hyperglycemia-induced retinal inflammation	Retinal endothelial cells	[76]
Uveal melanoma-derived EXOs (UM-EXOs)	miR-146a, MIF, oncogenic proteins	Promote metastasis, tumor invasion, and microenvironment remodeling; miR-146a acts as biomarker	Melanoma cells, hepatic cells, fibroblasts	[82–85]
UM plasma/cell EXOs	miRNAs, proteins	Induce prometastatic signaling, enhance cell motility via cytokine and growth factor release	Melanoma cells, macrophages	[83–85]
Retinoblastoma-derived EXOs (RB-EXOs)	miRNAs (eg, miR-9, miR-494), proteins (TLN, β3 integrin, GSTM1, ABI2)	Regulate gene expression, alter ECM remodeling, promote tumor growth and chemoresistance	Retinoblastoma cells	[86–90]
Corneal MSC-EXOs	Cytokines, TSP-1, IL-10, TGF-β1	Suppress inflammation and neovascularization, promote scarless healing	Corneal fibroblasts, epithelial cells	[72,73]
Pancreatic β-cell EXOs (comparative context)	miR-29 family	Regulate glucose metabolism, demonstrate systemic communication pathways	Retinal and systemic vascular cells	[33]
Tumor-derived EXOs (general)	Oncogenic proteins, miRNAs	Mediate angiogenesis, immune modulation, and pre-metastatic niche formation	Fibroblasts, endothelial and immune cells	[50–56]

metastasis and carcinogenesis. The proteomic profile of primary UM-EVs differs from that of metastatic UM-EVs, indicating that the formers are involved in the creation of metastatic niches, invasion, migration, and proliferation of tumor cells.[91]

UM cell EXOs play a critical role in the development and spread of tumors. They encourage UM cell motility and invasion by inducing growth factor release, cytokine production, and cell signaling pathways. One important mediator in this process is macrophage migration inhibitory factor (MIF). Melanoma cell movement is inhibited by blocking MIF, underscoring its significance in metastasis. According to these results, a treatment approach to stop metastases in UM may involve focusing on EXO cargo, especially MIF.[86]

It is important to recognize that EXOs exhibit a dual and context-dependent nature. While melanoma-derived EXOs (such as those from uveal or cutaneous malignant melanoma) can promote tumor growth, angiogenesis, and metastasis through the transfer of oncogenic miRNAs and proteins, mesenchymal stem cell–derived exosomes (MSC-EXOs) demonstrate the opposite behavior, supporting anti-inflammatory and regenerative responses. These contrasting effects arise primarily from differences in their cellular origin and molecular cargo, including tumor-associated versus reparative signaling molecules. Therefore, the therapeutic application of EXOs in ocular malignancies requires careful characterization and bioengineering to minimize oncogenic risk while harnessing their regenerative and targeted delivery potential.[60–63,82–85] see Figure 3 for a schematic overview of EXO-mediated diagnostic and prognostic mechanisms.

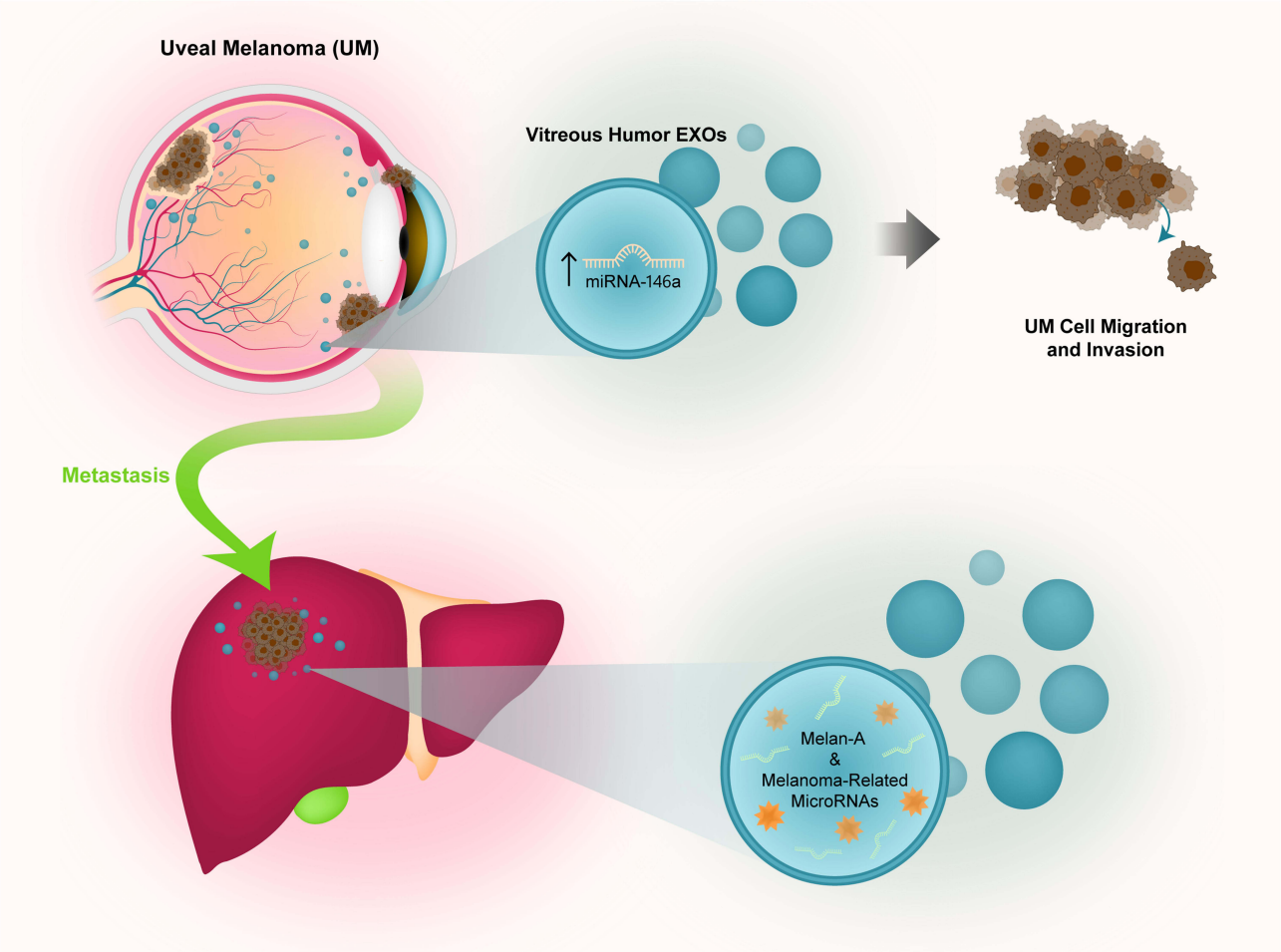


Figure 3 Exosomes in the diagnosis and progression of uveal melanoma.

In patients with hepatic metastatic UM who received hepatic perfusion, Eldh et al isolated EXOs from the liver perfusate. When melanoma-derived EXOs are released for hepatic circulation in metastatic UM, they include Melan-A and melanoma-related microRNAs, which further identify their source.[87]

EXOs in RB Diagnosis and Treatment

Regular tissue biopsy is not suitable for RB because of the possibility of metastasis and dissemination of extraocular tumors. Because liquid biopsies, like blood, are noninvasive, simple to remove, and known to have tumor markers, they are therefore used in modern research in EVs and tumor cells in circulation. By penetrating the microenvironment, EVs, particularly EXOs, have been implicated in the growth of RB tumors by several research group Exosomal cargo, which includes proteins and miRNA, has been demonstrated to be dysregulated in RB and may be used as a predictive and diagnostic marker as well as a possible target for treatment.[88]

Remarkably, 23 proteins found in RB tumor EXOs share targets with both the downregulated hsa-miR-9 and the upregulated hsa-miR-494 in RB tumor and serum. This even demonstrates how intricately miRNA regulation plays a role in RB carcinogenesis. New diagnostic and treatment techniques will be aided by extensive research on EXO formation and its role in the pathophysiology of RB and other eye malignancies. Finding relevant disease-specific EXOs or their constituents in the blood can greatly aid in the diagnosis of RB that requires invasive procedures. Simplifying the medications and dosages will also be aided by the minute variations in EXOs throughout treatment. EXOs in RB and other eye tumors have not been thoroughly studied, in contrast to other malignancies. The proteome of tears is not well understood.[89]

https://doi.org/10.2147/EB.S563110

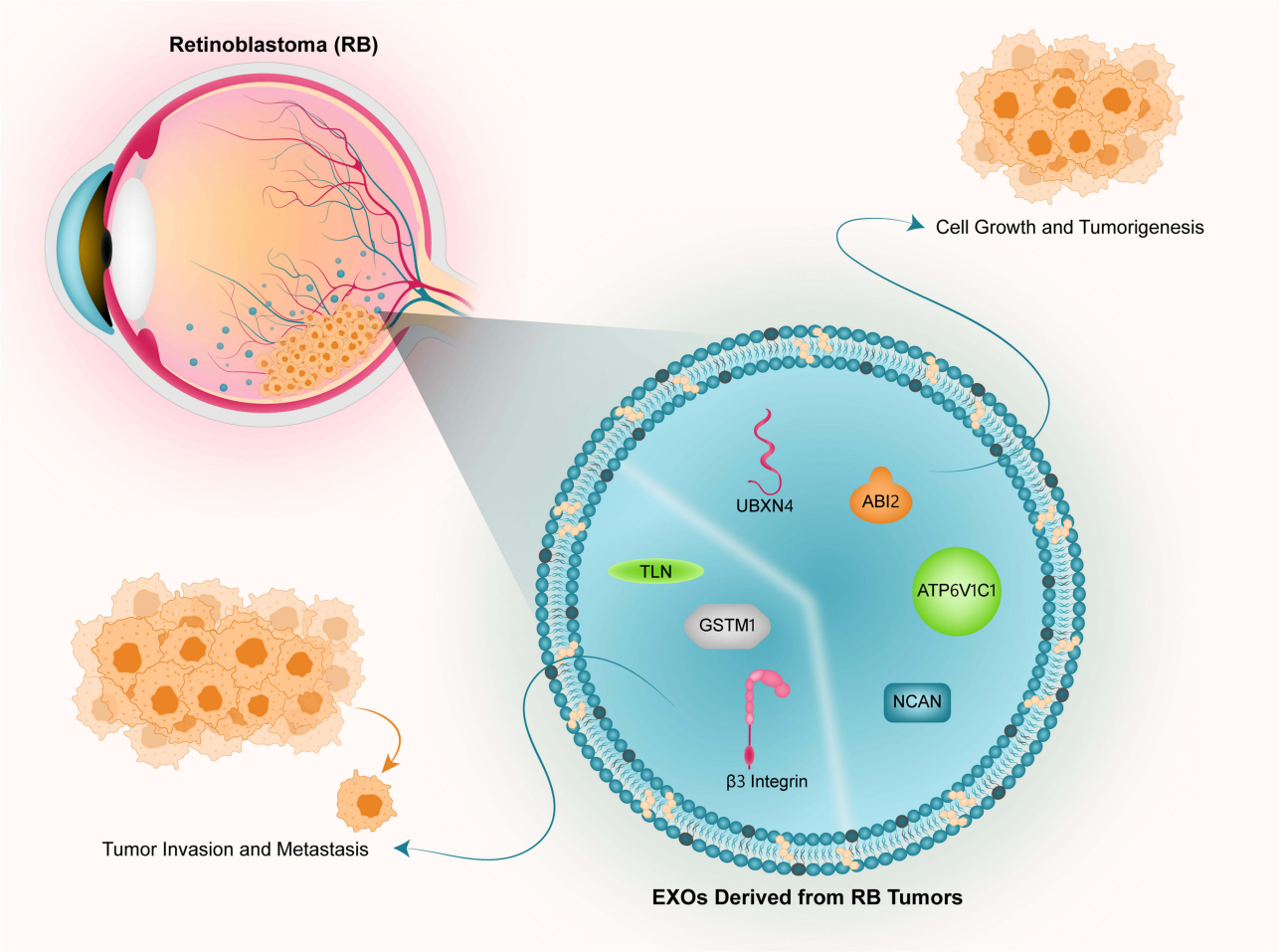


Figure 4 Exosomes act as both diagnostic indicators and functional players in retinoblastoma. Their molecular cargo contributes to tumor development. They also offer a promising source of biomarkers for early detection.

Serum exosomal miRNAs were examined in one study as possible RB indicators. Even after confirmation with a larger cohort, the expression of certain miRNAs, such as hsa-miR-301b-3p and hsa-miR-216b-5p, was not detected in the serum EXOs of RB patients, although they were found to be considerably increased in RB tissues. According to these results, serum exosomal miRNAs might not be accurate indicators of RB prognosis. The study suggests investigating other fluids instead, such as vitreous or cerebrospinal fluid (CSF), which demonstrated encouraging outcomes for specific miRNAs[90] (Figure 4).

Galardi et al recently studied the protein composition of exosomes derived from both primary retinoblastoma tissues and vitreous seeding cell lines. Their goal was to identify biomarkers and therapeutic candidates linked to the process of vitreous seeding. The analysis revealed higher levels of several proteins, such as TLN, β3 integrin, and GSTM1. These molecules play roles in reshaping the extracellular matrix, altering glucose and amino acid metabolism, and driving tumor invasion and metastasis. They are also connected with stem cell traits and resistance to chemotherapy. In addition, the exosomes carried other proteins, including ABI2, NCAN, ATP6V1C1, and UBXN4, which are closely tied to cell growth and tumor development, highlighting their relevance in retinoblastoma progression.[92] Additionally, ABI2 (Abl-interactor 2 protein) may function as a tumor suppressor in retinoblastoma (RB), as research indicates that it suppresses cellular proliferation and that its truncated variant facilitates the progression of malignancy.[93] In both UM and RB, current diagnostic biomarkers face important limitations that restrict early and minimally invasive detection. In UM, fine-needle aspiration biopsy (FNAB), although informative, carries risks such as tumor seeding, insufficient sampling, and procedure-related complications, which limits its routine use. Similarly, in RB, reliable tissue acquisition is difficult

Table 2 Conventional and Novel Exosome-Based Therapies for Eye Cancers

Eye Cancer Type	Conventional Treatments	Novel Exosome-Based Therapies	Study Outcomes	References
UM	Iodine-125 plaque brachytherapy, Proton beam therapy, Enucleation	Profiling of miRNAs in vitreous humor and serum exosomes as diagnostic and therapeutic biomarkers; Targeting exosomal MIF to inhibit metastasis.	Elevated exosomal miR-146a correlates with UM; vitreous/serum exosome profiling enables minimally invasive diagnosis; MIF-positive exosomes enhance metastasis, and their targeting reduces invasion.	[17,83,86]
RB	Intravenous chemotherapy (IVC), Intra-arterial chemotherapy (IAC), Intravitreal melphalan injection, Enucleation	Identification of exosomal proteins and miRNAs as early diagnostic biomarkers and therapeutic targets; Exosome manipulation to inhibit tumor growth.	Increased levels of miR-301b and miR-3613-3p in RB vitreous exosomes enable early and minimally invasive diagnosis	[17,89,92]
Intraocular lymphoma	Chemotherapy, Radiotherapy	To date, no exosome-based therapeutic approaches have been developed.	No data available	[17]
Conjunctival Tumors	Surgery, Cryotherapy, Topical chemotherapy	To date, no exosome-based therapeutic approaches have been developed.	No data available	[17]

because vitreous sampling is inherently restricted and may not fully represent tumor heterogeneity. Furthermore, serum biomarkers often lack sensitivity and specificity, making them unreliable for early diagnosis or monitoring. Exosome profiling helps overcome these issues by enabling the detection of tumor-derived miRNAs and proteins in accessible biofluids such as serum, plasma, or vitreous humor, providing a minimally invasive and repeatable platform with higher molecular stability and diagnostic precision compared with conventional approaches.[71–75,80–85,91]

Table 2 provides a summary of conventional and emerging exosome-based therapeutic strategies for eye cancers.

Challenges in Clinical Translation

One of the most significant problems in employing EXOs in clinical settings for ocular illnesses is the lack of a recognized standard for their separation and purification.[74] Isolation presents a significant challenge. A consistent approach for manufacturing clinical-grade EVs is currently lacking, despite the existence of diverse processes. Targeting EVs to specific cells provides another challenge. Although the parameters driving the targeting process are not entirely understood, surface chemicals, the physiological state of the target cells, and the route of administration are significant influences.[94] Several technologies for delivering nucleic acids using EXO mimics have been developed. One strategy is to generate size-controllable EXO mimics by progressively extruding non-tumorigenic MCF10A (Human breast epithelial cells that have been immortalized but not transformed), cells through filters with varying pore diameters, followed by encapsulating small interfering RNAs (siRNA) via electroporation.[95,96]

Recent advances have further highlighted the distinct advantages and remaining limitations of engineered exosomes and EV-mediated CRISPR delivery in ophthalmic drug development. While CRISPR-Cas9 enables precise gene editing, its safe and efficient transport across ocular cell membranes remains a major challenge due to off-target risks, immunogenicity, and the limited tumor affinity of viral and nanoparticle vectors. Engineered exosomes provide important improvements in these areas: their biocompatibility, inherent targeting capability, and high loading capacity support more efficient transfer of gene-editing complexes. Moreover, surface-modified exosomes have demonstrated enhanced internalization and improved resistance to the restrictive tumor microenvironment. Exosome mimetics also address key translational obstacles by offering scalable production and reduced batch variability compared to natural vesicles. However, despite these advantages, critical issues—including delivery efficiency, potential immune interactions, cargo

stability, and manufacturing reproducibility—remain unresolved, indicating that technologies, although promising, still require substantial optimization for reliable clinical use in ophthalmic gene therapy.[75]

The absence of industrial standards constrains the commercialization of EXOs originating from various sources exhibit different characteristics, which demands specific manufacturing protocols and quality control standards.[97] Furthermore, the stability, safety, potency, and general quality of EXOs must be closely monitored during production and delivery. As a result, they propose a set of standards to handle all of these issues, which will necessitate technological breakthroughs and regulatory collaboration between the government and industry.[97] A group of researchers suggested that standardizing EXO dosage and potency across investigations would increase data dependability, allowing the government to establish rules in the event of standardization.[98] Despite production efficiency, they acknowledge that evolving federal standards continue to pose a difficulty for clinical translation. However, as the variability of EXOs becomes evident, they predict EXOs will become more reproducible and easier to use in biological therapies.[98]

Future Perspectives and Challenges

EXO biology research could move the science forward, make EXO-based drugs work, and figure out how to make synthetic EXOs. Synthetic EXOs, while not thoroughly investigated, provide a means to generate EXOs with specific structure, content, and activity, thereby facilitating clinical translation and reverse engineering.[42]

EXOs, despite their advantages, face challenges in clinical application, like low targeting efficiency and easy immune system phagocytosis. The separation and purification method is time-consuming and laborious, and their heterogeneity depends on the cell type produced.[48]

Therapeutic EXOs loaded with specific molecules like miRNA, siRNA, and recombinant proteins can provide optimal bioavailability and minimal immune rejection. However, their complex composition and functional activity may limit their clinical applications.[99]

For every milliliter of culture media, less than 1 μg of EXOs are made. Using standard cell culture methods, EXOs can be made for 12 hours. However, bioreactors can boost the amount made. It's crucial to store EXOs properly; for instance, storing them at −80°C keeps them in better shape than storing them at higher temperatures. Post-administration biodistribution is highly important.[100]

By creating EXOs for controlled release under particular physiological conditions, EXO-based medicines might work better and have fewer negative effects if they develop EXOs that can be released in a controlled manner when certain physiological parameters are met. When storing products, it's vital to look at formulations that make them more stable, including stabilizing substances or better lyophilization methods. Researching shelf life and stability over the long term is also crucial. Targeting approaches, hybrid systems, and in vivo performance are also vital for progress.[101]

One of the biggest problems with EXO therapies is that there are not any standard ways to load them and make them in huge quantities. Natural EXOs have certain distinct biological benefits, but it is still hard, expensive, and unreliable to isolate and prepare them. A new option is the creation of artificial nanocarriers, like synthetic liposomes. They closely resemble the structure and function of natural EXOs. These synthetic systems have apparent business benefits, such as higher yield, better quality control, reproducibility, and the capacity to be used on a large scale in factories.[99] But even though more research is being done, large-scale EXO production still has a major problem. The problem is meeting the needs of preclinical studies, clinical trials, and eventual commercialization. To address these issues, researchers are investigating cell culture systems utilizing three-dimensional stirred-tank bioreactors. These investigations provide the regulated and continuous generation of EXOs appropriate for medicinal applications.[100] One of the most critical challenges in the development of EXO -based therapeutics is purification. Conventional approaches commonly used in research settings, such as ultracentrifugation or precipitation, often leave behind considerable amounts of process- and product-related impurities. Such contamination reduces the reliability and safety of the final preparation, so it becomes unsuitable for clinical-grade applications. To address this gap, there is an urgent demand for advanced purification techniques. These techniques are not only scalable but also highly precise, ensuring the production of exosomes with the purity required to meet regulatory standards for human use in clinical trials.[102]

Tissue culture bioreactors and other techniques have made it easier to manufacture EXOs that are good enough for use in hospitals. The fact that off-the-shelf EXO products can stay stable at −20°C is a good sign. EXOs made from

autologous dendritic cells have shown promise in clinical trials for safety and effectiveness, especially when it comes to treating cancer. However, challenges remain, such as safety assessments, uniform production guidelines, and ideal dosage suggestions.[103]

In a study, EVs made from Expi293F cells were safe for therapeutic application, showing no toxicity in vitro or in vivo, even at high dosages. The research finds that EVs can be used as efficient biodelivery vehicles for medicinal drugs.[104]

Numerous preclinical studies have evaluated the immunogenicity, safety, and effectiveness of EXOs derived from xenogeneic and allogenic sources in cellular treatments, although these aspects have not yet been thoroughly defined. It is encouraging that pre-clinical research employing EXOs from such cellular sources may more effectively get past regulatory obstacles when applied to a clinical environment, given studies demonstrating disease improvement in both allogeneic and autologous treatments.[98] EXOs can transport diverse pharmaceuticals, making them viable delivery platforms for anti-tumor medicines and genetic tools in cancer treatment. Also, several clinical studies on EXO molecular profiling are already underway, which may soon be helpful in precision medicine.[105]

Conclusion

Exosome-based approaches signify a revolutionary framework in ocular cancer and regenerative ophthalmology. Exosomes, as natural nanocarriers, have distinct benefits in targeted drug administration, immunomodulation, and intercellular communication, facilitating precision treatment of ophthalmic cancers including uveal melanoma and retinoblastoma while reducing systemic toxicity. Moreover, exosomes generated from mesenchymal stem cells exhibit significant regeneration capabilities in the restoration of retinal and ocular tissues due to their anti-inflammatory and neuroprotective characteristics. Despite these advances, the clinical translation of exosome-based therapies remains limited, primarily due to unresolved challenges such as large-scale production, standardized isolation techniques, control of heterogeneity, and regulatory complexities. Addressing these gaps through interdisciplinary collaboration and advanced bioengineering could unlock their full clinical potential. Future initiatives should concentrate on optimizing bioengineering methods to improve loading efficiency and targeting specificity, alongside developing strong manufacturing and quality assurance processes. With continued research, clinical validation, and technological progress, exosomes are expected to evolve from promising experimental tools into practical, safe, and effective components of individualized and regenerative therapies for ocular disorders.

Abbreviations

AAV-2, Adeno-associated Virus Type 2; ALIX, ALG2-interacting Protein X; AMD, Age-related Macular Degeneration; CAF, Cancer-associated Fibroblast; CNS, Central Nervous System; COMS, Collaborative Ocular Melanoma Study; CRISPR/Cas9, Clustered Regularly Interspaced Short Palindromic Repeats/Cas9; DR, Diabetic Retinopathy; ESCRT, Endosomal Sorting Complex Required for Transport; EVs, Extracellular Vesicles; EXO, Exosomes; HMGB1, High-Mobility Group Box 1; IAC, Intra-arterial Chemotherapy; IFN, Interferon Gamma; IL, Interleukin; ILVs, Intraluminal Vesicles; miRNA, microRNA; MSC, Mesenchymal Stem Cell; MSC-EXO, Mesenchymal Stem Cell-derived Exosome; MVB, Multivesicular Body; MVEs, Multivesicular Endosomes; ONC, Optic Nerve Crush; OSSN, Ocular Surface Squamous Neoplasia; RB, Retinoblastoma; sEVs, Small Extracellular Vesicles; siRNA, Small Interfering RNA; TAM, Tumor-associated Macrophages; TGF, Transforming Growth Factor Beta; TME, Tumor Microenvironment; TSG101, Tumor Susceptibility Gene 101; TSP-1, Thrombospondin-1; UM, Uveal Melanoma; VEGF, Vascular Endothelial Growth Factor; VH, Vitreous Humor.

Acknowledgement

We also extend our thanks to the Clinical Research Development Center of Imam Khomeini, Mohammad Kermanshahi, and Farabi Hospitals, affiliated with Kermanshah University of Medical Sciences, for their kind support.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Eagle R. The pathology of ocular cancer. *Eye*. 2013;27(2):128–136. doi:10.1038/eye.2012.237
2. Shields CL, Kalafatis NE, Gad M, et al. Metastatic tumours to the eye. Review of metastasis to the iris, ciliary body, choroid, retina, optic disc, vitreous, and/or lens capsule. *Eye*. 2023;37(5):809–814. doi:10.1038/s41433-022-02015-4
3. Jager MJ, Shields CL, Cebulla CM, et al. Uveal melanoma. *Nat Rev Dis Prim*. 2020;6(1):24. doi:10.1038/s41572-020-0158-0
4. Lorigan JG, Wallace S, Mavligit GM. The prevalence and location of metastases from ocular melanoma: imaging study in 110 patients. *Am J Roentgenol*. 1991;157(6):1279–1281. doi:10.2214/ajr.157.6.1950883
5. Spagnolo F, Caltabiano G, Queirolo P. Uveal melanoma. Cancer treatment reviews. *Cancer Treat Rev*. 2012;38(5):549–553. doi:10.1016/j.ctrv.2012.01.002
6. Reddy EK, Bhatia P, Evans RG. Primary orbital lymphomas. *Int J Radiat Oncol Biol Phys*. 1988;15(5):1239–1241. doi:10.1016/0360-3016(88)90210-6
7. Mochizuki M, Singh AD. Epidemiology and clinical features of intraocular lymphoma. *Ocul Immunol Inflamm*. 2009;17(2):69–72. doi:10.1080/09273940902957305
8. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an international primary central nervous system lymphoma collaborative group symposium. *oncologist*. 2011;16(11):1589–1599. doi:10.1634/theoncologist.2011-0210
9. Davis J. Intraocular lymphoma: a clinical perspective. *Eye*. 2013;27(2):153–162. doi:10.1038/eye.2012.250
10. Coupland SE, Damato B. Understanding intraocular lymphomas. *Clin Exp Ophthalmol*. 2008;36(6):564–578. doi:10.1111/j.1442-9071.2008.01843.x
11. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues: International Agency for Research on Cancer*. Lyon, France; 2008.
12. Chan -C-C, Buggage RR, Nussenblatt RB. Intraocular lymphoma. *Curr Opin Ophthalmol*. 2002;13(6):411–418. doi:10.1097/00055735-200212000-00012
13. Soussain C, Malaise D, Cassoux N. Primary vitreoretinal lymphoma: a diagnostic and management challenge. *Blood J Am Soc Hematol*. 2021;138(17):1519–1534.
14. Coupland SE, Heimann H, Bechrakis NE. Primary intraocular lymphoma: a review of the clinical, histopathological and molecular biological features. *Graefes Arch Clin Exp Ophthalmol*. 2004;242(11):901–913. doi:10.1007/s00417-004-0973-0
15. Saornil M, Becerra E, Méndez M, Blanco G. Conjunctival tumors. *Archivos de la Sociedad Espanola de Oftalmologia*. 2009;84(1):7–22. doi:10.4321/s0365-66912009000100003
16. Shields CL, Chien JL, Surakiatchanukul T, Sioufi K, Lally SE, Shields JA. Conjunctival tumors: review of clinical features, risks, biomarkers, and outcomes—the 2017 J. Donald M. Gass Lecture. *Asia-Pac J Ophthalmol*. 2017;6(2):109–120. doi:10.22608/APO.201710
17. Maheshwari A, Finger PT. Cancers of the eye. *Cancer Metastasis Rev*. 2018;37(4):677–690. doi:10.1007/s10555-018-9762-9
18. Abramson DH, Frank CM, Susman M, Whalen MP, Dunkel IJ, Boyd NW. Presenting signs of retinoblastoma. *J Pediatr*. 1998;132(3 Pt 1):505–508. doi:10.1016/S0022-3476(98)70028-9
19. Eagle RC. Ocular tumors: triumphs, challenges and controversies. *Saudi J Ophthalmol*. 2013;27(3):129–132. doi:10.1016/j.sjopt.2013.06.002
20. van den Boogaard WM, Komninos DS, Vermeij WP. Chemotherapy side-effects: not all DNA damage is equal. *Cancers*. 2022;14(3):627. doi:10.3390/cancers14030627
21. Kaneko A. Japanese contributions to ocular oncology. *Int J Clin Oncol*. 1999;4:321–326. doi:10.1007/s101470050078
22. Yamane T, Kaneko A, Mohri M. The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma. *Int J Clin Oncol*. 2004;9(2):69–73. doi:10.1007/s10147-004-0392-6
23. Eagle RC Jr, Shields CL, Bianciotto C, Jabbour P, Shields JA. Histopathologic observations after intra-arterial chemotherapy for retinoblastoma. *Arch Ophthalmol*. 2011;129(11):1416–1421. doi:10.1001/archophthalmol.2011.223
24. Shields CL, Demirci H, Materin MA, Marr BP, Mashayekhi A, Shields JA. Clinical factors in the identification of small choroidal melanoma. *Can J Ophthalmol*. 2004;39(4):351–357. doi:10.1016/S0008-4182(04)80005-X
25. Shields CL, Shields JA, Kiratli H, De Potter P, Cater JR. Risk factors for growth and metastasis of small choroidal melanocytic lesions. *Ophthalmology*. 1995;102(9):1351–1361. doi:10.1016/S0161-6420(95)30864-0
26. Deb A, Gupta S, Mazumder PB. Exosomes: a new horizon in modern medicine. *Life Sci*. 2021;264:118623. doi:10.1016/j.lfs.2020.118623
27. Dafe VN, Hatwar PR, Bakal RL, Bindod HV. Exploring the role of exosomes in modern medicine. *transportation*. 2025; 85(03):01–10.
28. Yang J, Wang X, Wang B, Park K, Wooley K, Zhang S. Challenging the fundamental conjectures in nanoparticle drug delivery for chemotherapy treatment of solid cancers. *Adv Drug Delivery Rev*. 2022;190:114525. doi:10.1016/j.addr.2022.114525
29. Zarbin MA, Montemagno C, Leary JF, Ritch R. Nanomedicine in ophthalmology: the new frontier. *Am J Ophthalmol*. 2010;150(2):144–62.e2. doi:10.1016/j.ajo.2010.03.019
30. Di Bella MA. Overview and update on extracellular vesicles: considerations on exosomes and their application in modern medicine. *Biology*. 2022;11(6):804. doi:10.3390/biology11060804
31. Jeppesen DK, Fenix AM, Franklin JL, et al. Reassessment of exosome composition. *Cell*. 2019;177(2):428–45.e18. doi:10.1016/j.cell.2019.02.029
32. Lai JJ, Chau ZL, Chen SY, et al. Exosome processing and characterization approaches for research and technology development. *Adv Sci*. 2022;9(15):2103222. doi:10.1002/advs.202103222
33. Li J, Zhang Y, Ye Y, et al. Pancreatic β cells control glucose homeostasis via the secretion of exosomal miR-29 family. *J Extracell Vesicles*. 2021;10(3):e12055. doi:10.1002/jev2.12055
34. Calvo V, Izquierdo M. Inducible polarized secretion of exosomes in T and B lymphocytes. *Int J Mol Sci*. 2020;21(7):2631. doi:10.3390/ijms21072631
35. Gurung S, Perocheau D, Touramanidou L, Baruteau J. The exosome journey: from biogenesis to uptake and intracellular signalling. *Cell Commun Signaling*. 2021;19(1):47. doi:10.1186/s12964-021-00730-1
36. Lenassi M, Cagney G, Liao M, et al. HIV Nef is secreted in exosomes and triggers apoptosis in bystander CD4+ T cells. *Traffic*. 2010;11(1):110–122. doi:10.1111/j.1600-0854.2009.01006.x

37. Xu M, Ji J, Jin D, et al. The biogenesis and secretion of exosomes and multivesicular bodies (MVBs): intercellular shuttles and implications in human diseases. *Genes Dis*. 2023;10(5):1894–1907. doi:10.1016/j.gendis.2022.03.021
38. Palmulli R, van Niel G. To be or not to be. secreted as exosomes, a balance finely tuned by the mechanisms of biogenesis. *Essays Biochem*. 2018;62(2):177–191. doi:10.1042/EBC20170076
39. Sharma A. Role of stem cell derived exosomes in tumor biology. *Int J Cancer*. 2018;142(6):1086–1092. doi:10.1002/ijc.31089
40. Yates AG, Pink RC, Erdbrügger U, et al. In sickness and in health: the functional role of extracellular vesicles in physiology and pathology in vivo: part I: health and normal physiology. *J Extracell Vesicles*. 2022;11(1):e12151. doi:10.1002/jev2.12151
41. Zhao Y, Liu L, Sun R, et al. Exosomes in cancer immunoediting and immunotherapy. *Asian J Pharm Sci*. 2022;17(2):193–205. doi:10.1016/j.ajps.2021.12.001
42. Ferguson SW, Nguyen J. Exosomes as therapeutics: the implications of molecular composition and exosomal heterogeneity. *J Control Release*. 2016;228:179–190. doi:10.1016/j.jconrel.2016.02.037
43. Strybel U, Marczak L, Zeman M, et al. Molecular composition of serum exosomes could discriminate rectal cancer patients with different responses to neoadjuvant radiotherapy. *Cancers*. 2022;14(4):993. doi:10.3390/cancers14040993
44. Aheget H, Mazini L, Martin F, Belqat B, Marchal JA, Benabdellah K. Exosomes: their role in pathogenesis, diagnosis and treatment of diseases. *Cancers*. 2020;13(1):84. doi:10.3390/cancers13010084
45. Jafari A, Babajani A, Abdollahpour-Alitappeh M, Ahmadi N, Rezaei-Tavirani M. Exosomes and cancer: from molecular mechanisms to clinical applications. *Med Oncol*. 2021;38(4):45. doi:10.1007/s12032-021-01491-0
46. Brinton LT, Sloane HS, Kester M, Kelly KA. Formation and role of exosomes in cancer. *Cell Mol Life Sci*. 2015;72:659–671. doi:10.1007/s00018-014-1764-3
47. Kalluri R. The biology and function of exosomes in cancer. *J Clin Invest*. 2016;126(4):1208–1215. doi:10.1172/JCI81135
48. Liu J, Ren L, Li S, et al. The biology, function, and applications of exosomes in cancer. *Acta Pharmaceutica Sinica B*. 2021;11(9):2783–2797. doi:10.1016/j.apsb.2021.01.001
49. Xu B, Wang T. Intimate cross-talk between cancer cells and the tumor microenvironment of B-cell lymphomas: the key role of exosomes. *Tumour Biol*. 2017;39(6):1010428317706227. doi:10.1177/1010428317706227
50. Webber J, Steadman R, Mason MD, Tabi Z, Clayton A. Cancer exosomes trigger fibroblast to myofibroblast differentiation. *Cancer Res*. 2010;70(23):9621–9630. doi:10.1158/0008-5472.CAN-10-1722
51. Ruivo CF, Adem B, Silva M, Melo SA. The biology of cancer exosomes: insights and new perspectives. *Cancer Res*. 2017;77(23):6480–6488. doi:10.1158/0008-5472.CAN-17-0994
52. Maia J, Caja S, Strano Moraes MC, Couto N, Costa-Silva B. Exosome-based cell-cell communication in the tumor microenvironment. *Front Cell Dev Biol*. 2018;6:18. doi:10.3389/fcell.2018.00018
53. Al-Nedawi K, Meehan B, Micallef J, et al. Intercellular transfer of the oncogenic receptor EGFRvIII by microvesicles derived from tumour cells. *Nat Cell Biol*. 2008;10(5):619–624. doi:10.1038/ncb1725
54. Mohamed AH, Abaza T, Youssef YA, et al. Extracellular vesicles: from intracellular trafficking molecules to fully fortified delivery vehicles for cancer therapeutics. *Nanoscale Adv*. 2025;7(4):934–962. doi:10.1039/D4NA00393D
55. Steinbichler TB, Dudás J, Riechelmann H, I-I S. Therole of exosomes in cancer metastasis. In: *Seminars in Cancer Biology*. Elsevier; 2017.
56. Tai YL, Chen KC, Hsieh JT, Shen TL. Exosomes in cancer development and clinical applications. *Cancer Sci*. 2018;109(8):2364–2374. doi:10.1111/cas.13697
57. Chen B, Li Q, Zhao B, Wang Y. Stem cell-derived extracellular vesicles as a novel potential therapeutic tool for tissue repair. *Stem Cells Transl Med*. 2017;6(9):1753–1758. doi:10.1002/sctm.16-0477
58. Bjørge IM, Kim SY, Mano JF, Kalionis B, Chrzanowski W. Extracellular vesicles, exosomes and shedding vesicles in regenerative medicine - a new paradigm for tissue repair. *Biomater Sci*. 2017;6(1):60–78. doi:10.1039/C7BM00479F
59. Wan R, Hussain A, Behfar A, Moran SL, Zhao C. The therapeutic potential of exosomes in soft tissue repair and regeneration. *Int J Mol Sci*. 2022;23(7):3869. doi:10.3390/ijms23073869
60. Wu KY, Ahmad H, Lin G, Carbonneau M, Tran SD. Mesenchymal stem cell-derived exosomes in ophthalmology: a comprehensive review. *Pharmaceutics*. 2023;15(4):1167. doi:10.3390/pharmaceutics15041167
61. Niamprem P, Srinivas SP, Tiyaboonchai W. Penetration of Nile red-loaded nanostructured lipid carriers (NLCs) across the porcine cornea. *Colloids Surf B Biointerfaces*. 2019;176:371–378. doi:10.1016/j.colsurfb.2019.01.018
62. Blass S, Teubl B, Fröhlich E, et al. Permeability studies on the ocular absorbance of nanostructured materials across the cornea. *Scientia Pharmaceutica*. 2010;78(3):678. doi:10.3797/scipharm.cespt.8.PNM08
63. Mohammadpour M, Hashemi H, Jabbarvand M, Delrish E. Penetration of silicate nanoparticles into the corneal stroma and intraocular fluids. *Cornea*. 2014;33(7):738–743. doi:10.1097/ICO.0000000000000144
64. Yoles E, Schwartz M. Degeneration of spared axons following partial white matter lesion: implications for optic nerve neuropathies. *Exp Neurol*. 1998;153(1):1–7. doi:10.1006/exnr.1998.6811
65. Luan X, Sansanaphongpricha K, Myers I, Chen H, Yuan H, Sun D. Engineering exosomes as refined biological nanoplatforms for drug delivery. *Acta Pharmacol Sin*. 2017;38(6):754–763. doi:10.1038/aps.2017.12
66. Zhang L, Yu D. Exosomes in cancer development, metastasis, and immunity. *Biochim Biophys Acta Rev Cancer*. 2019;1871(2):455–468. doi:10.1016/j.bbcan.2019.04.004
67. Han C, Yang J, Sun J, Qin G. Extracellular vesicles in cardiovascular disease: biological functions and therapeutic implications. *Pharmacol Ther*. 2022;233:108025. doi:10.1016/j.pharmthera.2021.108025
68. Hill AF. Extracellular vesicles and neurodegenerative diseases. *J Neurosci*. 2019;39(47):9269–9273. doi:10.1523/JNEUROSCI.0147-18.2019
69. Zhang Z, Mugisha A, Fransisca S, Liu Q, Xie P, Hu Z. Emerging role of exosomes in retinal diseases. *Front Cell Dev Biol*. 2021;9:643680. doi:10.3389/fcell.2021.643680
70. Yu B, Shao H, Su C, et al. Exosomes derived from MSCs ameliorate retinal laser injury partially by inhibition of MCP-1. *Sci Rep*. 2016;6:34562. doi:10.1038/srep34562
71. Mead B, Tomarev S. Extracellular vesicle therapy for retinal diseases. *Prog Retin Eye Res*. 2020;79:100849. doi:10.1016/j.preteyeres.2020.100849

72. Tiwari A, Singh A, Verma S, Stephenson S, Bhowmick T, Sangwan VS. Mini review: current trends and understanding of exosome therapeutic potential in corneal diseases. *Front Pharmacol*. 2021;12:684712. doi:10.3389/fphar.2021.684712
73. Bhujel B, Oh S-H, Kim C-M, et al. Mesenchymal stem cells and exosomes: a novel therapeutic approach for corneal diseases. *Int J Mol Sci*. 2023;24(13):10917.
74. Liu J, Jiang F, Jiang Y, et al. Roles of Exosomes in Ocular Diseases. *Int J Nanomed*. 2020;15:10519–10538.
75. Balaraman AK, Babu MA, Moglad E, et al. Exosome-mediated delivery of CRISPR-Cas9: a revolutionary approach to cancer gene editing. *Pathol Res Pract*. 2025;266:155785.
76. Chen R, Huang H, Liu H, et al. Friend or foe? Evidence indicates endogenous exosomes can deliver functional gRNA and Cas9 protein. *Small*. 2019;15(38):1902686. doi:10.1002/smll.201902686
77. Li N, Zhao L, Wei Y, Ea VL, Nian H, Wei R. Recent advances of exosomes in immune-mediated eye diseases. *Stem Cell Res Ther*. 2019;10 (1):278. doi:10.1186/s13287-019-1372-0
78. 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 Visual Sci*. 2019;60(1):294–303. doi:10.1167/iovs.18-25617
79. Gebeyehu A, Kommineni N, Meckes DG, Singh MS. Role of Exosomes for Delivery of Chemotherapeutic Drugs. *Crit Rev Ther Drug Carrier Syst*. 2021;38(5):53–97. doi:10.1615/CritRevTherDrugCarrierSyst.2021036301
80. Greening DW, Gopal SK, Xu R, Simpson RJ, Chen W. Exosomes and their roles in immune regulation and cancer. In: *Seminars in Cell & Developmental Biology*. Elsevier; 2015.
81. Chinnappan M, Srivastava A, Amreddy N, et al. Exosomes as drug delivery vehicle and contributor of resistance to anticancer drugs. *Cancer Lett*. 2020;486:18–28. doi:10.1016/j.canlet.2020.05.004
82. Xi X-M, Xia S-J, Lu R. Drug loading techniques for exosome-based drug delivery systems. *Die Pharmazie*. 2021;76(2–3):61–67.
83. Hazazi A, AlShehah AA, Khan FR, et al. From diagnosis to therapy: the transformative role of lncRNAs in eye cancer management. *Pathol Res Pract*. 2024;254:155081.
84. Ragusa M, Barbagallo C, Statello L, et al. miRNA profiling in vitreous humor, vitreal exosomes and serum from uveal melanoma patients: pathological and diagnostic implications. *Cancer Biol Ther*. 2015;16(9):1387–1396.
85. Achberger S, Aldrich W, Tubbs R, Crabb JW, Singh AD, Triozzi PL. Circulating immune cell and microRNA in patients with uveal melanoma developing metastatic disease. *Mol Immunol*. 2014;58(2):182–186. doi:10.1016/j.molimm.2013.11.018
86. Ambrosini G, Rai AJ, Carvajal RD, Schwartz GK. Uveal melanoma exosomes induce a prometastatic microenvironment through macrophage migration inhibitory factor. *Mol Cancer Res*. 2022;20(4):661–669. doi:10.1158/1541-7786.MCR-21-0526
87. Eldh M, Olofsson Bagge R, Lässer C, et al. MicroRNA in exosomes isolated directly from the liver circulation in patients with metastatic uveal melanoma. *BMC Cancer*. 2014;14:1–10. doi:10.1186/1471-2407-14-962
88. Manukonda R, Attem J, Yenuganti VR, Kaliki S, Vemuganti GK. Exosomes in the visual system: new avenues in ocular diseases. *Tumor Biol*. 2022;44(1):129–152. doi:10.3233/TUB-211543
89. Lande K, Gupta J, Ranjan R, et al. Exosomes: insights from retinoblastoma and other eye cancers. *Int J Mol Sci*. 2020;21(19):7055. doi:10.3390/ijms21197055
90. Ravishankar H, Mangani AS, Phoebe Moses GL, et al. Serum exosomal miRNA as biomarkers for retinoblastoma. *Exp Eye Res*. 2020;199:108184. doi:10.1016/j.exer.2020.108184
91. Tsering T, Laskaris A, Abdouh M, et al. Uveal melanoma-derived extracellular vesicles display transforming potential and carry protein cargo involved in metastatic niche preparation. *Cancers*. 2020;12(10):2923. doi:10.3390/cancers12102923
92. Galardi A, Colletti M, Lavarello C, et al. Proteomic profiling of retinoblastoma-derived exosomes reveals potential biomarkers of vitreous seeding. *Cancers*. 2020;12(6):1555. doi:10.3390/cancers12061555
93. Dai Z, Pendergast AM. Abi-2, a novel SH3-containing protein interacts with the c-Abl tyrosine kinase and modulates c-Abl transforming activity. *Genes Dev*. 1995;9(21):2569–2582. doi:10.1101/gad.9.21.2569
94. Habib S, Mansour AM, Baban B, Elmasry K. Extracellular vesicles and diabetic retinopathy: nano-sized vesicles with mega-sized hopes. 2024.
95. Yang Z, Xie J, Zhu J, et al. Functional exosome-mimic for delivery of siRNA to cancer: in vitro and in vivo evaluation. *J Control Release*. 2016;243:160–171. doi:10.1016/j.jconrel.2016.10.008
96. Yusuf R, Frenkel K. Morphologic transformation of human breast epithelial cells MCF-10A: dependence on an oxidative microenvironment and estrogen/epidermal growth factor receptors. *Can Cell Inter*. 2010;10(1):30. doi:10.1186/1475-2867-10-30
97. Dai X, Ye Y, He F. Emerging innovations on exosome-based onco-therapeutics. *Front Immunol*. 2022;13:865245. doi:10.3389/fimmu.2022.865245
98. Popowski K, Lutz H, Hu S, George A, Dinh P-U, Cheng K. Exosome therapeutics for lung regenerative medicine. *J Extracell Vesicles*. 2020;9 (1):1785161. doi:10.1080/20013078.2020.1785161
99. Wang X, Tian L, Lu J, Ng IO-L. Exosomes and cancer - Diagnostic and prognostic biomarkers and therapeutic vehicle. *Oncogenesis*. 2022;11 (1):54. doi:10.1038/s41389-022-00431-5
100. Yamashita T, Takahashi Y, Takakura Y. Possibility of exosome-based therapeutics and challenges in production of exosomes eligible for therapeutic application. *Biol Pharm Bull*. 2018;41(6):835–842. doi:10.1248/bpb.b18-00133
101. Palakurthi SS, Shah B, Kapre S, et al. A comprehensive review of challenges and advances in exosome-based drug delivery systems. *Nanoscale Adv*. 2024;6(23):5803–5826. doi:10.1039/D4NA00501E
102. Ahn S-H, Ryu S-W, Choi H, You S, Park J, Choi C. Manufacturing therapeutic exosomes: from bench to industry. *Mol Cells*. 2022;45 (5):284–290. doi:10.14348/molcells.2022.2033
103. Willis GR, Kourembanas S, Mitsialis SA. Toward exosome-based therapeutics: isolation, heterogeneity, and fit-for-purpose potency. *Front Cardiovasc Med*. 2017;4:63. doi:10.3389/fcvm.2017.00063
104. Saleh AF, Lázaro-Ibáñez E, Forsgard -MA-M, et al. Extracellular vesicles induce minimal hepatotoxicity and immunogenicity. *Nanoscale*. 2019;11(14):6990–7001. doi:10.1039/C8NR08720B
105. Paskeh MDA, Entezari M, Mirzaei S, et al. Emerging role of exosomes in cancer progression and tumor microenvironment remodeling. *J hematol oncol*. 2022;15(1):83.