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Role of extracellular vesicles in mitochondrial eye diseases

Sushma Anand[1,2] | **Ian A. Trounce**[1,2] | **Lahiru Gangoda**[1,2,3,4]

[1]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia

[2]Opthalmology, Department of Surgery, University of Melbourne, Melbourne, Victoria, Australia

[3]The Walter and Eliza Hall Institute of Medical Research (WEHI), Melbourne, Victoria, Australia

[4]Department of Medical Biology, University of Melbourne, Melbourne, Victoria, Australia

Correspondence
Lahiru Gangoda and Sushma Anand, Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, VIC, Australia.
Email: l.gangoda@unimelb.edu.au and anand@unimelb.edu.au

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Abstract

Extracellular vesicles (EVs) are small packages that are released by almost all types of cells. While the role of EVs in pathogenesis of certain diseases such as cancer is well established, EVs role in ocular health and disease is still at early stages of investigation. Given the significant role of EVs in pathological development and progression of diseases such as cancer, EVs present a similar opportunity for investigation in ocular pathophysiology. Studies have shown the presence of EVs in fluids from the ocular environment have close links with ocular health and disease. Hence, the cargo carried in EVs from ocular fluids can be used for monitoring disease phenotypes or therapeutic outcomes in eye-related disorders. Furthermore, in recent times EVs have increasingly gained attention as therapeutics and drug-delivery vehicles for treatment of eye diseases. There is a close relationship between EVs and mitochondria functioning with mitochondria dysfunction leading to a significant number of ophthalmic disorders. This review discusses the current knowledge of EVs in visual systems with a special focus on eye diseases resulting from dysfunctional mitochondria.

KEYWORDS

disease biomarkers, extracellular vesicles, mesenchymal stem cells, mitochondria/reactive oxygen species, mitochondrial disorders, ophthalmology, retina

1 | INTRODUCTION TO EXTRACELLULAR VESICLES

Extracellular vesicles (EVs) (Table 1) are membrane bound vesicles released by virtually all types of cells.[1] EVs are packed with proteins, DNA, RNA, lipids, and metabolites which are a unique signature of their cells of origin. EVs are released into the extracellular space by various cell types during both normal and disease conditions.[2] Strong evidence of EVs' role in intercellular communication was established in 2007 in a study that showed exosomes packed with mRNAs and microRNAs are transferred to the recipient cells to regulate biological function of the target cells.[3] These crucial functions of EVs in cell–cell communication have stimulated researchers to better understand on EV biogenesis.

EVs are secreted into the extracellular environment in a variety of ways. Based on their biogenesis pathways, they are classified into exomeres (<50 nm), exosomes (30–150 nm), ectosomes/shedding microvesicles (100–1,000 nm), apoptotic bodies (1000–5,000 nm), migrasomes (500–3,000 nm), and oncosomes (1000–10,000 nm).[4,5] Ectosomes and apoptotic bodies are released from cell membrane budding of live and dead cells, respectively.[6,7]

TABLE 1 List of abbreviations

Abbreviation	*Full term*
EVs	Extracellular vesicles
MVBs	Multivesicular bodies
ESCRT	Endosomal sorting complex required for transport
OXPHOS	Oxidative phosphorylation
mtDNA	Mitochondrial DNA
ROS	Reactive oxygen species
RGCs	Retinal ganglion cells
RPE	Retinal pigment epithelial
DOA	Dominant optic atrophy
LHON	Leber hereditary optic neuropathy
CPEO	Chronic progressive external ophthalmoplegia
PR	Pigmentary retinopathy
MELAS	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
NARP	Neuropathy, ataxia, and retinitis pigmentosa
DR	Diabetic retinopathy
MMP2	Matrix metalloproteinase-2
AMD	Age-related macular degeneration
OPA1	Optic atrophy 1
DAMPs	Damage-associated molecular patterns
MSC	Mesenchymal stem cell

Exosomes are small membrane extracellular vesicles that are secreted by the inward budding of the late endosome resulting into the progressive accumulation of intraluminal vesicles within large multivesicular bodies (MVBs). MVBs then fuse with the plasma membrane and release its intraluminal vesicles into the extracellular environment as exosomes.[7,8] Migrasomes are released by migrating cells and cytoskeleton polarisation.[9] Large oncosomes are cancer cell-derived vesicles that carry oncogenic cargos.[10] Exomeres are the newest addition to the EV family and are the smallest non-membranous vesicles and the exact pathway involved in their biogenesis still unknown.[4]

The cargo carried by EVs can facilitate molecular changes in the recipient cells upon their uptake.[11] The cargo enclosed in lipid bilayer bound EVs are highly stable in various harsh conditions. For example, orally administered bovine milk-derived EVs survive the harsh, degrading conditions of the gut in mice, and are subsequently detected in multiple organs.[12] Sorting of the cargo into EVs is a controlled and regulated process. Post-translational modifications such as ubiquitination, SUMOylation, and ISGylation have been reported in cargo sorting into EVs.[13] Various EV biogenesis mechanisms such as endosomal sorting complex required for transport (ESCRT), lipids, and tetraspanins also regulate EV protein sorting.[5,7] The variation in EV cargo largely indicates the normal versus diseased condition of the cell. EVs provide a unique and unswerving source for disease biomarkers.[14] They are present in biological fluids such as blood, milk, amniotic fluid, and urine and cell culture conditioned medium.[12,15] Thus, EVs are considered as non-invasive samples, derived from bodily fluids for disease analysis by evaluating their biomarkers. Besides their potential as diagnostics, EVs are now studied for their role as drug delivery vehicles. For example, the anti-inflammatory agent curcumin, has been shown to be delivered via exosomes with enhanced stability to the target inflammatory cells.[16] The innate capability of EVs to carry biomacromolecules, proteins, nucleic acids, lipids, metabolites, virus particles, or organelles from parent cells to regulate the function of the receiver cells upon uptake has made them an indispensable therapeutic tool.[17]

2 | MITOCHONDRIAL DYSFUNCTION IN EYE DISEASES

Mitochondrial diseases are a diverse group of disorders that affect energy metabolism pathways. They can present at any age with a wide range of neurological symptoms, often including ophthalmic symptoms.[18,19] The oxidative phosphorylation (OXPHOS) machinery in mitochondria which is encoded by both nuclear and mitochondrial DNA (mtDNA) genes is the principal generator of cellular energy in the form of ATP. Hence mitochondrial diseases can result from mutations of mtDNA or nuclear genes. In addition, mitochondria are a major producer of reactive oxygen species (ROS). In normal physiological conditions the cell counterbalances ROS production to maintain cellular homeostasis. However, dysfunctional mitochondrial can lead to a dramatic increase of ROS levels and decreased ATP production, resulting in substantial damage to cells' integrity and oxidative stress.[20]

The eye is one of the most impacted organs in mitochondrial diseases, with overwhelming consequences in permanent vision loss or blindness. As the retina and the optic nerve are highly energetic tissues, it is not surprising for vision to be affected by mitochondrial diseases. Cells with high mitochondrial densities (such as found in the retina) are uniquely vulnerable to bioenergetic failure. The retina consists of various types of cells including photoreceptors, bipolar cells, amacrine cells, horizontal cells, retinal ganglion cells (RGCs), Müller glial cells, and

retinal pigment epithelial (RPE) cells. Retinal cells are densely packed with mitochondria to provide metabolic energy in the form of ATP (Figure 1). These cells of the retina are interconnected to work together to capture light in the form of photons, convert the light stimulus to neuronal action potentials which are transmitted via the optic nerve to the visual cortex of the brain to allow visual experience.[21] Mutations in either mtDNA or nuclear DNA leading to mitochondrial dysfunction can cause primary mitochondrial ophthalmic diseases.[20] However, mitochondrial dysfunction caused by environmental or iatrogenic toxins can result in secondary mitochondrial ophthalmic diseases.

2.1 | Primary mitochondrial ophthalmic diseases

2.1.1 | Dominant optic atrophy

Dominant optic atrophy (DOA) is genetic mitochondrial disease that predominantly causes the degeneration of the RGCs and optic nerve with gradual vision loss mainly affecting the central vision.[22] It is most often caused by mutations in the nuclear gene OPA1, which encodes a mitochondrial protein that belongs to the dynamin family. The dynamin-associated GTPase coded by this gene is responsible for the mitochondrial outer membrane fusion. OPA1 is required for the OXPHOS pathway and overall mitochondrial quality control for cellular homeostasis. It primarily produces defects in complex I respiration. To completely understand RGC degeneration in DOA, different Opa1 mutant mouse models have been developed which have in part deciphered how mitochondrial dysfunction is responsible for the DOA pathophysiology.[23]

2.1.2 | Leber hereditary optic neuropathy

Leber hereditary optic neuropathy (LHON) is characterized by irreversible loss of central vision due to loss of RGCs leading to optic nerve degeneration.[24] Vision loss in LHON is most common in young adults (aged 18–32 years). It is a rare mitochondrial disease which affects 1 in 50,000 people worldwide. LHON is caused by mutations in the mtDNA. More than 95% of LHON cases result from one of three mtDNA mutations, all OXPHOS complex I genes: G3460A in ND1, G11778A in ND4, and T14484C in ND6. Additionally, males are more frequently affected with vision loss compared with females.[25] These mtDNA mutations result in substantial decrease in ATP production and enhanced ROS generation which leads to RGC dysfunction. MtDNA mutations in LHON are typically *homoplasmic*, occurring in all mtDNA molecules in affected patients' cells, while in many other syndromic mtDNA diseases the causative mutations occur in a *heteroplasmic* state where various levels of mutant and wild type mtDNA co-exist in cells.

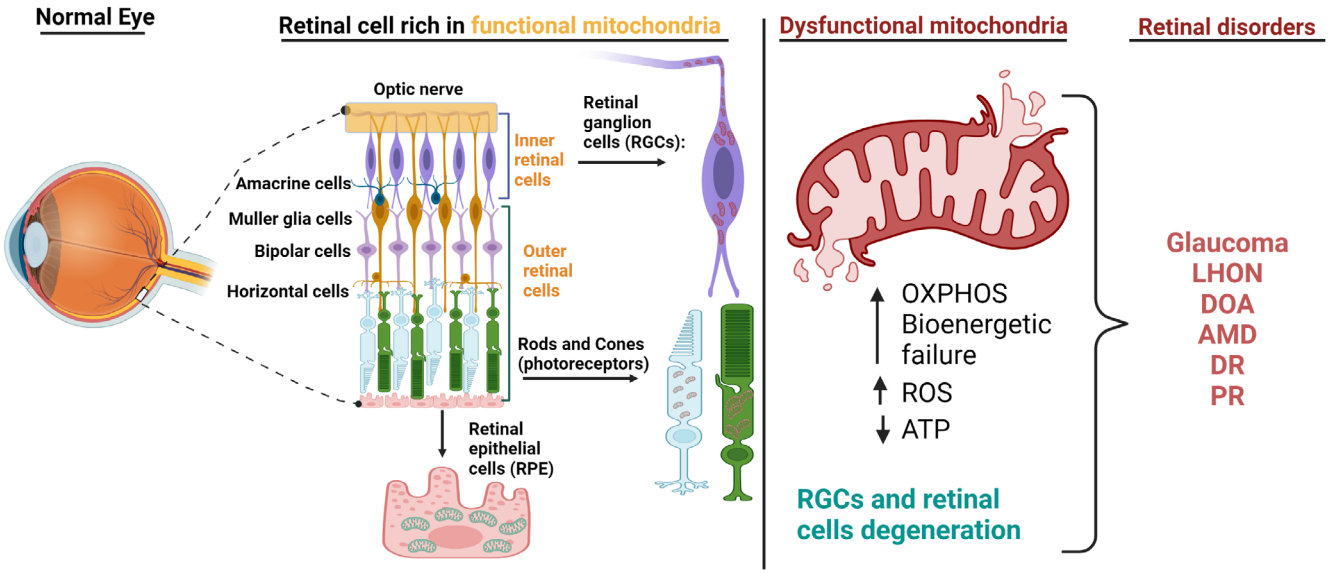

FIGURE 1 Retinal cells and mitochondrial dysfunction. Schematic illustration of the normal human retina. The dotted line indicates the magnified normal human retinal cells layers. Retinal ganglion cells (RGCs), photoreceptors, and retinal epithelial cells (RPE) are rich in mitochondria. A defect in mitochondrial activity causes loss of RGCs, RPE, and photoreceptor cells resulting in bioenergetic failure, increased ROS levels, and decrease of ATP production. This can contribute to the pathogenesis of LHON, DOA, Glaucoma, AMD DR, and PR. Image was created BioRender.com.

2.1.3 | Chronic progressive external ophthalmoplegia

Chronic progressive external ophthalmoplegia (CPEO) is another type of mitochondrial disease where extraocular muscle mobility is impaired resulting in restricted eye and eyebrow movement. CPEO can be caused by mutations in both nuclear and mtDNA genes and is diagnosed using skeletal muscle biopsies.[26] Heteroplasmic deletions of mtDNA are one cause of CPEO, which are less likely to be inherited by the offspring of affected patients. Nuclear encoded genes that are involved in mtDNA preservation can also lead to CPEO, including TYMP, ANT1, PEO1, POLG, POLG2, and OPA1.[20]

2.1.4 | Pigmentary retinopathy

Pigmentary retinopathy (PR) refers to the migration and proliferation of RPE cells or macrophages containing melanin pigments to the retina. Pigmentary changes in the retina may occur in patients with mitochondrial disease. The best explained are Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) and Neuropathy, ataxia, and retinitis pigmentosa (NARP). Affected individuals with MELAS or NARP can have frequent association of night blindness, reduce visual acuity and constricted visual fields. These signs and symptoms are typically manifested in childhood or early adulthood, with worsening over time. MELAS is most frequently associated with a mutation in the mtDNA tRNALeu gene (A3243G), while NARP is often caused by a mutation in the ATPase 6 gene (T8993G).[27,28]

2.2 | Secondary mitochondrial ophthalmic diseases

2.2.1 | Diabetic retinopathy

Diabetic retinopathy (DR) is the biggest cause of vision loss in young individuals. Mitochondrial dysfunction may predispose the development of diabetes mellitus with the accompanying risk for developing diabetic retinopathy or may contribute directly to the diabetic metabolic dysregulation and thereby increase the risk of diabetic late complications including retinopathy.[29,30] Diabetic retinopathy initiates microvascular changes that include retinal inflammation, increased vascular permeability, and atypical angiogenesis of the retina. The relation between mitochondrial disease and diabetic retinopathy can be influenced by epigenetics where factors in the environment modify the expression of regulatory proteins coding for the elimination of reactive oxygen species. Improper mitochondrial functioning gives rise to substantial production of reactive oxygen species (ROS) and death of retinal capillary and endothelial cells influencing diabetic retinopathy pathogenesis. Matrix metalloproteinase-2 (MMP2) is pro-apoptotic in the retinal cells of diabetic patients. Antioxidant therapies are proposed for the treatment of diabetic retinopathy. This includes excess protein expression of the mitochondrial superoxide scavenging enzyme, manganese superoxide dismutase, and inhibition of MMP2 protein expression.[20]

2.2.2 | Age-related macular degeneration

Age-related macular degeneration (AMD) is a prominent cause of permanent blindness that affects millions of elderly people globally. It is diagnosed by analyzing the dilated fundus on people over 55 years of age. There are two types of AMD: (a) non-neovascular or dry AMD, (b) neovascular or wet AMD. Retinal cells with dysfunctional mitochondria experience detrimental consequences upon exposure to light. As a result, the macula, a small area at the center of the retina which is responsible for color vision is damaged. The vision process is energy demanding hence, the macula is always under extensive oxidative stress with constant ROS production.[20,31] AMD pathogenesis includes low activity of mitochondrial dehydrogenase enzymes and increased ROS which ultimately causes damage to the RPE.[31]

2.2.3 | Glaucoma

Glaucoma is a leading cause of irreversible blindness globally.[32–34] It ranks fourth among the causes of permanent blindness in the world according to the World Health Organization. According to the BrightFocus Foundation, in 2020, around 80 million people were suffering from glaucoma worldwide, and this number is expected to increase to over 100 million in the next 20 years. According to Glaucoma Australia, 1 in 50 Australians will develop glaucoma in their lifetime with 50% of patients remaining undiagnosed. Glaucoma is a neurodegenerative disease that targets the optic nerve, and is often associated with elevated intraocular pressure which leads to the loss of RGCs and blindness.[35] RGCs are the distal eye neurons and are densely packed with mitochondria. These neurons deliver visual signals from the retina to the brain via their axons which form the optic nerve at the back of the eye. As discussed previously, impairment in mitochondrial quality control including

fission and fusion results in several detrimental consequences leading to high oxidative stress and decrease in ATP production which could potentially contribute to glaucoma pathogenesis. Furthermore, studies using primary open angle glaucoma patient samples have provided convincing evidence of mtDNA mutation and defects in respiratory complex I activity.[36–38] Additionally, glaucoma is also considered as an aging disease. Accumulation of dysfunctional mitochondria promotes the release of cytochrome c which plays an active role in the electron transport chain and this triggers cellular apoptosis.[39] All current standard treatments for glaucoma aim to reduce the fluid pressure within the eye to slow down the disease progression,[40] yet a significant fraction of patients develop vision loss despite this treatment. Hence, at present, there is no cure for glaucoma but, early diagnosis and standard treatment is advised to prevent the disease progressing into severe blindness. Hence, there is an urgent need to develop new treatments to prevent or reverse vision loss in glaucoma patients.[35]

3 | EVs IN MITOCHONDRIAL FUNCTION

Mitochondria are important organelles involved in several key cellular processes including energy production and cell death regulation. Hence, alterations of mitochondrial function and structure can lead to several pathological conditions such as cancer and neuronal diseases including the eye diseases discussed above. It has been found that some cells can secrete EVs containing mitochondria or mitochondrial components which can affect the function of the recipient cells including their metabolic outputs. Monocytes release proinflammatory microvesicles enriched in mitochondrial content and intact mitochondria which can exert inflammatory effects on endothelial cells.[41] Chronic alcohol consumption has been shown to result in an increase in the levels of circulating, mtDNA-enriched, microparticles which can cause neutrophilia and promote liver injury.[42] Thus, mitochondria may represent critical intercellular mediators in settings where EVs are used as a mode of mitochondrial communication.

Damaged mitochondria and mitochondrial components can be removed by EVs.[43,44] Research suggest that secretion of mitochondrial proteins could be a form of quality control where cells export their damaged mitochondria destined for degradation in distant cells. Neurons can release damaged mitochondria and transfer them to astrocytes for disposal and recycling.[45] Astrocytes in mice have also been shown to release functional mitochondria that enter neurons to amplify cell survival signals thereby contributing to neuroprotective and neurorecovery mechanisms after stroke.[46] The inclusion of mitochondrial content inside EVs requires mitochondria-derived vesicle formation. Optic Atrophy 1 (OPA1) and sorting nexin 9 (Snx9)-dependent mitochondria-derived vesicles are required to target mitochondrial proteins to EVs, while the Parkinson's disease-related protein Parkin blocks this process by directing damaged mitochondrial content to lysosomes.[47] This selective packaging of mitochondrial proteins into EVs prevents the release of mitochondrial damage-associated molecular patterns (DAMPs).

Given there are many ophthalmologic manifestations resulting from both primary and secondary mitochondrial disorders, EVs are likely to play an important role in these disease pathologies. Mutations in *OPA1* are the most common cause of autosomal DOA, which is a genetically heterogeneous, monogenic disorder, primarily caused by mutations in nuclear genes encoding mitochondrial proteins. Given the concurrent role of OPA1 in selective packaging of mitochondrial proteins into EVs, the inhibition of mitochondria-derived vesicle formation with mutations of OPA1[47] is likely to play a role in DOA disease progression, an area which warrants further investigation.

4 | EVs IN EYE DISEASES

4.1 | EVs as biomarkers of eye disease

The rate of secretion, type and the cargo composition of EVs change during certain conditions and can be leveraged as a way of monitoring disease phenotypes or therapeutic outcomes.[48] For example, cancer cells have been shown to secrete more EVs than normal cells and the amount of EVs secreted by cancer cells increase as the disease progresses.[49]

Ocular diseases such as age-related macular degeneration, glaucoma, and diabetic retinopathy present various challenges in their early diagnosis and treatments due to contributing factors such as delay in the onset of symptoms and difficulty in obtaining samples for biopsy. EVs have been detected in a wide range of bodily fluids including those in ocular environments. Human tears have been shown to contain high amounts of exosomes and present the most non-invasive method of collecting ocular EVs.[50] Furthermore, vitreous humor[51] and aqueous humor[52] have been shown to carry EVs which are mainly exosomes. The aqueous humor is a clear fluid located at the front part of the eye and is responsible for providing nutrients to the eye. The aqueous humor also drains out any excess material and waste from the eye. The vitreous humor is a colorless, transparent, gel-like material located between the retina and the lens.

miRNAs contained within exosomes from aqueous humor has been suggested to mediate communication between aqueous humor inflow and outflow tissues.[52] The cargo carried by these ocular fluid EVs can be potential biomarkers of eye diseases and can act as a prospective diagnostic test to support clinical decision-making (Figure 2). Blood is another avenue for identifying EV biomarkers associated with eye health. Blood is easier and less invasive to collect than aqueous humor and vitreous humor and can be collected in larger volumes. However, the disadvantage of using blood as a source of EVs from the eye is that these are likely to make up a very small fraction of the total EVs found in the systemic circulation and will therefore be difficult to detect and analyze as eye-specific EVs.[53] Progress is also being made in developing nanoscale devices for capturing even single EVs.[54] The ability to detect cell-type specific EVs will more rapidly advance the knowledge of EV biology in normal and pathogenic conditions and speed up therapeutic developments.[55]

miR-182 has been shown to be significantly higher in exosomes derived from human trabecular meshwork cells, and it has been suggested that miR-182 may be involved in the pathogenesis of primary open-angle glaucoma through regulation of aqueous humor dynamics and intraocular pressure.[56] Analysis of miRNA from the exosomes in AMD patients has revealed that these miRNAs may have critical roles in the apoptosis and neovascularization pathways and pathogenesis of wet AMD.[57] Exosomes released from stressed retinal pigment

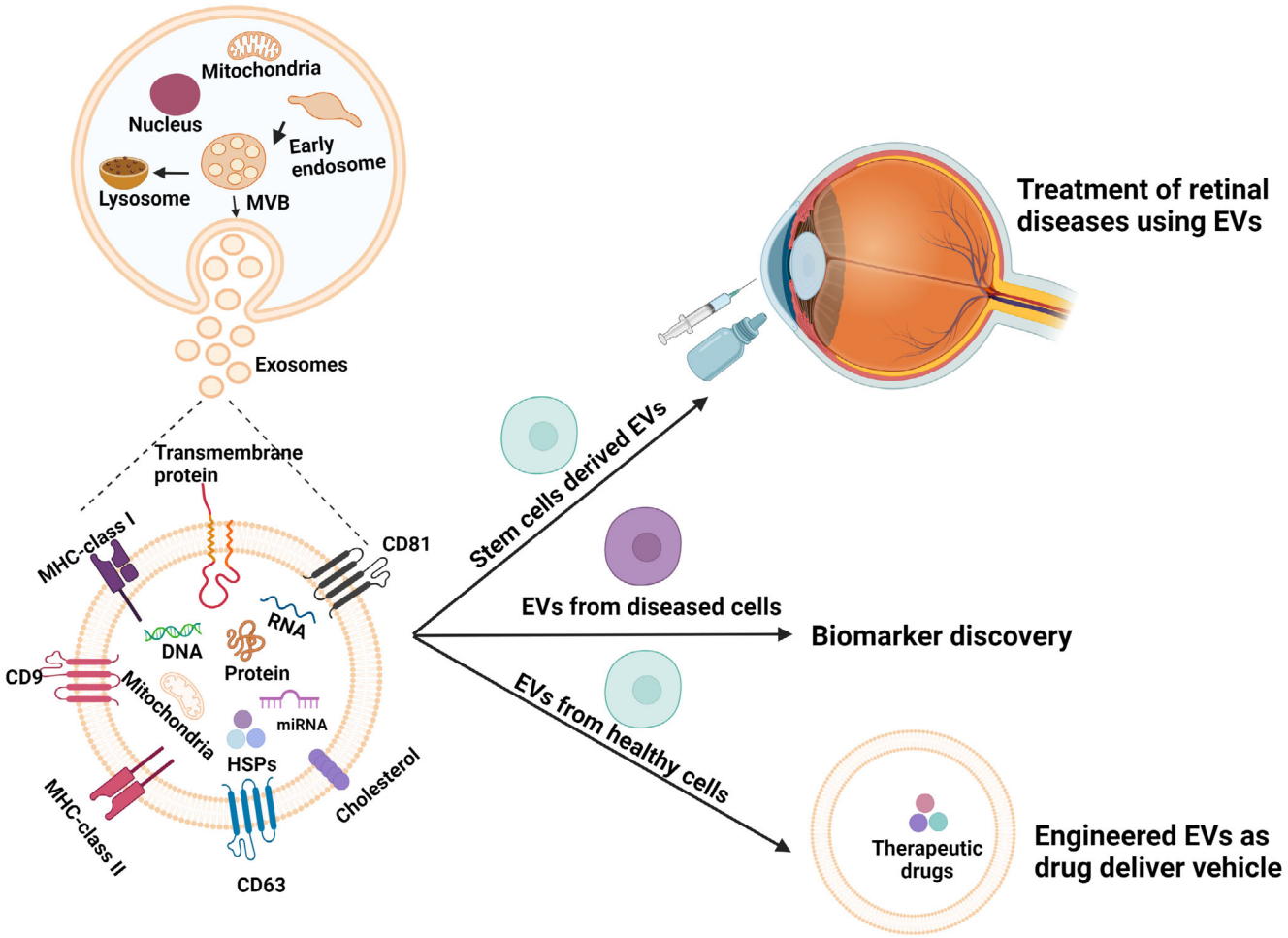

FIGURE 2 EVs and their therapeutic application in eye disease. Illustration of biogenesis of exosomes, a subtype of EVs. Plasma membrane invagination forms early endosomes which then mature into late endosomes. Inward budding of the late endosome results in the progressive accumulation of intraluminal vesicles within large multivesicular bodies (MVBs). MVBs either can fuse with lysosomes for degradation or can fuse with the plasma membrane to releases intraluminal vesicles into the extracellular environment as exosomes. Dotted line shows zoomed single exosomes and its cargos. Three black solid arrows indicate therapeutic application of EVs. Stem cell-derived EVs are rich with regenerative cargos. Hence, they can be used to treat eye disorders via either intravitreal injection or eye drop. EVs secreted from diseased cells can serve for biomarker discovery. In addition, EVs can be utilized as drug delivery vehicles to target specific delivery of the therapeutic drugs. Image was created BioRender.com.

epithelium (RPE) cells has been found to promote autophagy, which furthers the progression of AMD.[58] A study by Tumahai et al. showed vitreous EVs derived from photoreceptors were higher in the aqueous humor of patients after rhegmatogenous retinal detachment.[59] The photoreceptor-specific EVs were higher depending on the duration of the retinal detachment at the time of surgery and closely correlated to soluble factors, like MCP-1, a pro-inflammatory cytokine involved in photoreceptor apoptosis. Thus, the analysis of vitreous EVs may aid in the prognosis of retinal detachment surgery and visual recovery.

4.2 | EVs as therapeutics for eye diseases

Treatment of eye diseases mainly relies on surgery and drug intervention. Due to the risk of serious side effects, there is a need for novel therapeutic approaches. Studies have indicated that stem cell-based transplantation exerts reparative functions in several eye diseases; however, there are some safety issues around this method such as tumorigenicity.[60,61] Therefore, compared with cell-based therapies EVs are attractive alternatives for ocular diseases. Mesenchymal stem cell (MSC) derived EVs are promising candidates for the treatment of ocular diseases and mediate the therapeutic effects of MSCs such as self-renewal and regeneration abilities.[62] Purified EVs can be easily stored and loaded with small molecules, proteins, and nucleic acids, like miRNAs or viral vectors (Figure 2). EVs can target and deliver diverse cargo to recipient cells. Bone marrow-derived mesenchymal stem cells-derived exosomes have been shown to promote survival of RGCs through miRNA-dependent mechanisms.[63] Adipose MSC exosomes induced repair of diabetic retinal degeneration and mediated tissue repair by transporting specific miRNAs.[64] MSC exosomes reduced the hyperglycemia-induced retinal inflammation in diabetic retinopathy.[65] Human MSC exosomes have been shown to inhibit the autoimmune response, protect the retinal structure and rescue retinal function in uveitis.[66] Umbilical code-MSC derived exosomes has been shown to promote RGC survival and glial cell activation in rats with optic neuropathy.[67] Corneal stromal-MSCs, within the human limbus have the potency of multilineage differentiation. Corneal stromal-MSC-derived EVs have been shown to reduce stromal scarring and promote regeneration of normal corneal collagen in a mouse model of mechanical stromal wounding.[68]

Recent studies have tried to overcome the effects of glaucoma in animal models using exosomes isolated from bone marrow stem cells. Use of intravitreal bone marrow stem cell exosomes promoted neuroprotection of RGCs of rodents injured using intracameral microbeads or laser photocoagulation of the trabecular meshwork.[69] It has been shown that non-pigmented ciliary epithelium cell-derived EVs accumulate in trabecular meshwork cells and affect Wnt signaling, a pathway involved in intraocular pressure regulation.[70] These findings suggest that EVs and their cargoes can serve as biomarkers for glaucoma, potentially serving as an early diagnostic marker, and may also contribute directly to the progression of the disease.[55]

The recent finding that MSC-derived EVs in treatment of eye diseases serves as a proof of concept of EV-based therapy. Yet, developing a robust, scalable, good manufacturing practice (GMP)-compliant EV purification method for EV therapy to be translated from bench to bedside remains a challenge. Although GMP-compliant protocols for the purification of exosomes including the use of ultracentrifugation and density gradient separation have been reported, the protocols are labor- and time-intensive and are not feasible for large-scale production. EV-based therapy is a relatively new concept that has gained increasing interest in the vision community however therapeutic development of EVs is at an early stage and warrants further preclinical study.

5 | CONCLUDING REMARKS

EVs carry a wide range of biological cargo that contributes to their broad functions including intercellular communication. Several studies have shown the importance of EVs in the pathological process of ocular diseases, including inflammation, neuronal degeneration, oxidative stress, and neovascularization. Using EVs as disease biomarkers or carriers of therapeutic molecules may improve diagnosis and treatment options for patients with eye diseases. Yet, the role of EVs in eye diseases are still at early stages of investigation and significant studies are needed to develop EV based therapeutic treatments in ocular diseases.

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CONFLICT OF INTEREST

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ORCID

Sushma Anand https://orcid.org/0000-0003-0848-6618
Ian A. Trounce https://orcid.org/0000-0002-1070-8892
Lahiru Gangoda https://orcid.org/0000-0003-1931-6809

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