Molecular Therapy
Nucleic Acids
Review

Exosomal noncoding RNA: A potential therapy for retinal vascular diseases

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Exosomes are extracellular vesicles that can contain DNA, RNA, proteins, and metabolites. They are secreted by cells and play a regulatory role in various biological responses by mediating cell-to-cell communication. Moreover, exosomes are of interest in developing therapies for retinal vascular disorders because they can deliver various substances to cellular targets. According to recent research, exosomes can be used as a strategy for managing retinal vascular diseases, and they are being investigated for therapeutic purposes in eye conditions, including glaucoma, dry eye syndrome, retinal ischemia, diabetic retinopathy, and age-related macular degeneration. However, the role of exosomal noncoding RNA in retinal vascular diseases is not fully understood. Here, we reviewed the latest research on the biological role of exosomal noncoding RNA in treating retinal vascular diseases. Research has shown that noncoding RNAs, including microRNAs, circular RNAs, and long noncoding RNAs play a significant role in the regulation of retinal vascular diseases. Furthermore, through exosome engineering, the expression of relevant noncoding RNAs in exosomes can be controlled to regulate retinal vascular diseases. Therefore, this review suggests that exosomal noncoding RNA could be considered as a biomarker for diagnosis and as a therapeutic target for treating retinal vascular disease.

INTRODUCTION

Abnormal growth of blood vessels in retinal diseases is mostly caused by ischemia or hypoxia and leads to retinal vascular diseases[1–3]; the progression of these diseases, which include age-related macular degeneration (AMD), diabetic retinopathy (DR), and retinopathy of prematurity (ROP), can cause permanent blindness.[4–6] Excessive neovascularization under hypoxic conditions upregulates the expression of hypoxia inducible factor 1 (HIF-1)[7–10] to increase the expression of angiogenic factors such as vascular endothelial growth factor (VEGF),[11–14] platelet-derived growth factor,[15–17] transforming growth factor (TGF),[18,19] and erythropoietin.[20,21] The main treatment for retinal neovascularization involves injecting anti-VEGF drugs such as bevacizumab, ranibizumab, aflibercept, and brolucizumab to suppress abnormal vascular development.[22–27] Treatments for retinal vascular diseases include intravitreal injections of anti-VEGF drugs, laser therapy, and surgery. However, these treatments may not be effective for all patients. Intravitreal injections may require frequent administration, which can lead to adverse effects such as bleeding, increased ocular pressure, intraocular inflammation, and cataracts.[28–32] Laser therapy has been reported to potentially cause vision loss due to iris damage, induce bleeding, and result in macular scarring.[33–35] Therefore, research on developing new and more effective therapies that can overcome the limitations of current treatments is needed.

Exosomes are extracellular vesicles ranging in size from 40 to 160 nm that are secreted by various types of cells and contain a range of cellular components, including DNA, RNA, proteins, and metabolites. They play a crucial role in regulating biological responses by modulating cell-to-cell communication, thereby contributing to physiological activities such as immune response, tissue regeneration, cancer, inflammation, and metabolic diseases.[36–41] Exosomes are generated in most cell types through the inward budding of the limiting membrane of multivesicular bodies, which contain intraluminal vesicles. Fusion of the multivesicular bodies with the plasma membrane enables the release of intraluminal vesicles as small extracellular vesicles into the extracellular space.[36,42] Exosomes play a vital role in intercellular communication and serve as important mediators of signal transduction. Exosomes can be found in body fluids (e.g., blood, urine, placenta) and are stable within the body, allowing for their easy collection and utilization as biomarkers.[43,44] Moreover, the functions and applications of exosomes can be modulated through various modifications.[45,46] Because exosomes are biologically derived substances, they have low toxicity, minimal immunogenicity, high biocompatibility, and enhanced stability.[47–49] In recent studies, exosomes have received attention because of their potential functions and as next-generation drug delivery vehicles in various diseases.[50–53] Furthermore, various substances can be carried as cargo by exosomes for delivery to treat human diseases.

Noncoding RNA (ncRNA) refers to RNA that is not translated into proteins, and it includes microRNA (miRNA), circular RNA (circRNA), and long noncoding RNA (lncRNA).[54,55] These ncRNAs play a critical role in various biological processes, including the regulation of signal transduction, cell division, and gene expression. They are reported to act as important regulators in various diseases.[56–60] Many

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studies investigated ncRNAs for their roles in retinal vascular diseases, including retinal vascular formation, inflammation, and cell death.[61–66] miRNAs, one of the small ncRNAs, have been the most extensively studied among ncRNAs in the development and progression of retinal vascular diseases.[63,67–74] In particular, miR-204-5p inhibits SMAD family member 2/3 (*SMAD2/3*) mRNA in DR, suppressing vascular endothelial cell proliferation.[75] miR-21 regulates VEGF signaling, activating the AKT serine/threonine kinase (*AKT*) signaling pathway, thus promoting the survival and growth of retinal vascular endothelial cells in DR. It plays a role in controlling vascular angiogenesis and migration.[76,77] circRNA refers to circular-shaped RNA as opposed to linear RNA, which is the more common form. circRNA lacks exposed 3′ and 5′ ends, which provides protection from degradation by ribonucleases, endowing circRNA with more stability than linear RNA.[78–80] Recently, circRNA has gained attention due to its involvement in regulating gene expression, signal transduction, cell proliferation and apoptosis, and other biological processes.[81–87] Reports on the regulatory functions of circRNA in retinal vascular diseases showed that circRNA *CDR1* acts as an miR-7 sponge in DR and retinal neuropathy.[88,89] It regulates expression and controls retinal neurocyte and vascular endothelial cell damage by modulating the *VEGFR2* and phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathways, upregulating cell growth and survival.[90] lncRNAs are linear RNA with a length of >200 nt. Similar to mRNAs, lncRNAs are transcribed but do not encode proteins and are subject to various regulatory mechanisms within cells.[91–93] lncRNAs are being extensively studied in retinal vascular diseases and are reported to have effects on the function and regulation of retinal vasculature.[94,95] lncRNA *MALAT1* is known to contribute to the progression of DR by regulating vascular endothelial cadherin through miR-125a-5p. This regulation consequently activates *HIF-1α*, inducing retinal endothelial cell neovascularization and aggravates the disease.[96,97] As demonstrated by previous instances, ncRNA may play a crucial role in retinal vascular diseases and may serve as promising novel therapeutic strategies to treat these diseases. Consequently, regulating ncRNA in the treatment of retinal vascular diseases is anticipated to significantly affect favorable outcomes. Through this review, we aim to discuss the potential of exosomal ncRNAs as a novel therapeutic approach to modulate retinal vascular disease.

In this review, we summarize relevant studies concerning the function of exosomal ncRNA in retinal vascular diseases. We conducted literature searches in databases such as PubMed and ClinicalTrials.gov using terms associated with exosomal ncRNA, including miRNA, circRNA, and lncRNA. We also used various disease-related terms, including conditions such as coronavirus disease 2019 (COVID-19), cardiovascular disorder, dry eye syndrome, cancer, and others. In addition, we used retinal vascular disease-related terms, such as DR, ROP, AMD, and diabetic macular edema (DME) to identify papers relevant to our topic. Subsequently, we then manually reviewed the papers to confirm their direct relevance to our topic and included papers that met the criteria for addressing function of exosomal ncRNA in the context of retinal vascular diseases. Furthermore, we aimed to adhere to established nomenclature conventions for ncRNA gene names.

CLINICAL APPLICATION OF EXOSOME THERAPIES IN DIVERSE DISEASES

Exosomes are known to play a significant role in infectious disease, cardiovascular disease, and cancer.[98–101] Various cell-derived exosomes are being researched for therapeutic purposes. Exosomes derived from immune cells such as dendritic cells, T cells, macrophages, and natural killer cells are known to be effective in cancer treatment.[102–107] Specifically, exosomes derived from stem cells, including bone marrow-derived stem cells, and mesenchymal stem cells (MSCs), are known to be involved in various mechanisms that regulate immune response, tissue regeneration, and cell growth.[108,109] Since exosomes are biogenic molecules, they exhibit low toxicity and provoke minimal immune reactions. Due to the low immunogenicity, exosomes have been extensively studied for the treatment of inflammatory diseases.[110–113] In particular, the number of clinical trials regarding exosome therapy to treat COVID-19 has increased rapidly. These trials were conducted with the aim of treating acute respiratory distress syndrome associated with COVID-19. A Phase II clinical trial using MSC-derived exosomes revealed that exosomes can regulate inflammation and regenerative processes by altering the secretion of anti-inflammatory cytokines, thereby promoting the regenerative functions of immune cells.[114–116] Furthermore, the delivery of exosomes could reduce inflammation and tissue damage in the lungs, while simultaneously stimulating regenerative processes in patients with COVID-19 (the trials were registered at ClinicalTrials.gov: NCT04798716, NCT04491240, and NCT04602104).[117,118] Thus, exosomes exhibit considerable potential in the realm of disease management, particularly in the development of vaccines and drug delivery systems that exert regulatory effects on inflammation and intercellular communication.

In addition, exosomes are associated with cardiovascular disorders such as atherosclerosis and heart failure.[99–101] Clinical trials are investigating the therapeutic potential of stem cell-derived exosomes for their cardiovascular protection properties. The addition of exosomes derived from MSCs has been reported to improve functional impairment in patients with acute ischemic stroke following brain injury in a Phase II clinical trial (the trial was registered at ClinicalTrials.gov: NCT03384433).[119] Moreover, in cases of acute myocardial infarction due to heart failure, MSC-derived exosomes were shown to limit the inflammatory damage and suppress oxidative stress in a Phase II clinical trial (the trial was registered at ClinicalTrials.gov: NCT05669144).[120–122]

Limited reports are available on clinical trials using exosomes in ophthalmology (Table 1). An evaluation was conducted to assess whether exosomes derived from MSCs could alleviate dry eye symptoms. This study evaluated patients with dry eye conditions after refractive surgery and those associated with blepharospasm (Table 1; the trial was registered at ClinicalTrials.gov: NCT05738629),[123,124] as well as dry eye syndrome resulting from chronic graft-versus-host disease (cGvHD) (Table 1; the trial was registered at ClinicalTrials.gov: NCT04213248).[125,126] In addition, clinical trials are under way to evaluate the safety and efficacy of MSC exosomes in treating vision loss caused by retinitis pigmentosa (Table 1; the trial was registered at

Table 1. Clinical trials of exosome treatments in eye disease

Disease	Origin of exosomes	Study population	Assessment	Phase	NCT no.	Reference
Dry eye disease	PSC-MSC	Patients experiencing dry eye symptoms after refractive surgery or blepharospasm	Safety and efficacy of PSC-MSC-exosome eye drop treatment	II	NCT05738629	N/A
	UMSC	cGvHD patients experiencing dry eye symptoms	Symptom improvement of dry eye symptoms in cGvHD patients after UMSC exosome treatment	II	NCT04213248	Zhou et al.[125]
Retinitis pigmentosa	UMSC	Patients diagnosed with retinitis pigmentosa	Efficacy of UMSCs and UMSC exosomes	III	NCT05413148	Ozmert et al.[127]
Macular holes	MSC	Patients with macular holes after undergoing vitrectomy	Safety and efficacy of MSCs and MSC-derived exosomes	I	NCT03437759	Bai et al.[132]

PSC-MSC, pluripotent stem cell-derived MSC; UMSC, umbilical MSC.

ClinicalTrials.gov: NCT05413148)[127] and macular holes associated with vitrectomy and internal limiting membrane peeling (Table 1; the trial was registered at ClinicalTrials.gov: NCT03437759).[128–132] Consequently, based on the important characteristics of MSCs, including their immunomodulatory and inflammatory disease-controlling properties, the patients' symptoms improved, highlighting the potential of exosomes as a promising alternative therapy.

Furthermore, several exosomal RNA therapies have been investigated in clinical trials. For cancer treatment, a Phase I clinical trial is under way to test the therapeutic effects of exosomes loaded with *KRASG12D*-specific small interfering RNA (siRNA) targeting the cancer gene kirsten rat sarcoma viral oncogene homolog (*KRAS*), aiming to reduce *KRAS* expression (the trial was registered at ClinicalTrials.gov: NCT03608631). This trial focuses on patients with pancreatic cancer who have the *KRASG12D* mutation.[133] Exosomes carrying *KRASG12D* siRNA derived from MSCs were investigated in the Phase I clinical trial in patients with pancreatic cancer. The study aimed to determine the maximum tolerated dose and overall survival and to evaluate the dose-limiting toxicity. In addition, a Phase I clinical trial is under way for a cell-derived exosome therapeutic agent tagged with signal transducer and activator of transcription 6 (*STAT6*) antisense oligonucleotide targeting hepatocellular carcinoma, gastric cancer, and secondary liver metastasis. The exosome therapeutic agent has undergone safety and pharmacokinetic assessments. Moreover, this trial evaluated the anticancer effects of *STAT6* antisense oligonucleotide through the inhibition of *STAT6* and the repolarization of macrophages from the M2 to M1 phenotype.[134,135] Therefore, exosomal RNA therapy has shown potential to regulate cancer cell growth and oncogenes.

RESEARCH ON EXOSOMAL ncRNA THERAPIES FOR RETINAL VASCULAR DISEASES

Exosomes have been studied in ophthalmic diseases such as glaucoma, dry eye syndrome, retinal ischemia, DR, and AMD.[136–139] Recent studies suggest that exosomes can be used as a strategy for managing retinal vascular diseases. For example, exosomes can regulate cell proliferation by interacting with VEGFs secreted from endothelial cells. Exosomal miR-21-5p derived from endothelial precursor cells suppressed the expression of thrombospondin-1, an angiogenesis inhibitor, thereby promoting endothelial cell repair.[140] In addition, a significant increase in cytokines and angiogenic factors was observed in exosomes of patients with diabetes. Exosomes isolated from the blood of patients with diabetes revealed elevated levels of angiogenic factors, such as fibroblast growth factor, VEGFR2, and cytokines, including tumor necrosis factor α.[141] Consequently, exosomes appear to play the role of carriers of cytokines and angiogenic factors. Recent studies have increasingly revealed a close association between exosomal ncRNAs and retinal diseases, including the impairment of retinal endothelial cells and the development of retinal neovascularization.[142] Exosomal ncRNAs are implicated in the initiation and progression of retinal disorders through various pathways, offering novel approaches for early diagnosis and treatment.[143,144] There are several reports that investigated the role of exosomal ncRNAs in retinal diseases (Table 2), with most studies focusing on miRNAs and DR.

Among these reports, exosomal miR-15a is reported to play an important role in retinal damage in DR. miR-15a targets *AKT3*, thereby inhibiting the PI3K signaling pathway, resulting in an increase in reactive oxygen species in retinal Müller cells. This process triggers oxidative stress and promotes cell apoptosis, which ultimately culminates in retinal damage. However, the inhibition by exogenously introduced endogenous miR-15a has demonstrated the potential to mitigate oxidative stress and reduce damage in retinal Müller cells, suggesting a potential treatment for retinal diseases.[145]

In DR, exosomal miR-202-5p secreted from a human retinal pigment epithelial cell line, ARPE-19, targets TGF-β receptor 2 to regulate the TGF/SMAD signaling pathway and reduce the growth, tube formation, and migration of human umbilical vein endothelial cells. In addition, it suppresses the endothelial-to-mesenchymal transition (EMT). This indicates that exosomal miR-202-5p and the TGF-β signaling pathway are involved in the interaction between retinal pigment epithelium (RPE) cells and endothelial cells.[146] These discoveries offer potential targets for the treatment of DR.

The role of serum exosomal miR-377-3p in DME progression has been investigated among patients with type 2 diabetes. The differentially regulated miRNAs were identified from patients with and without

Table 2. Research on exosomal ncRNA therapies for retinal vascular diseases

Disease type	Exosomal ncRNAs	Expression	Major finding	Reference
DR	miR-15a	Up	Increased exosomal miR-15 targets AKT3, inducing oxidative stress and promoting apoptotic cell death	Tengku et al.[145]
	miR-202-5p	Down	Exosomes containing miR-202-5p suppress cell growth, migration, and tube formation by delivering miR-202-5p through the TGF/SMAD pathway	Gu et al.[146]
	miR-377-3p	Down	Exosomal miR-377-3p suppresses VEGF expression, thereby inhibiting RPE proliferation	Jiang et al.[147]
	circ_0005015	UP	Exosomal circ_0005015 inhibits miR-519d-3p activity, causing increased expression of MMP-2, XIAP, and STAT3, thereby promoting angiogenic function	Zhang et al.[148]
	circPWWP2a	Up	Exosomal circPWWP2A functions as a sponge for endogenous miR-579, causing increased expression of angiopoietin 1, occludin, and SIRT1, thereby alleviating retinal vascular dysfunction	Liu et al.[149]
	lncRNA SNHG7	Down	Exosomal lncRNA SNHG7 inhibits EMT and angiogenesis in vascular endothelial cells by suppressing the miR-34a-5p/XBP1 pathway	Cao et al.[150]
ROP	miR-24-3p	Down	Exosomal miR-24-3p inhibits IRE1α expression and suppresses the secretion of proangiogenic factors during ROP, reducing photoreceptor damage	Xu et al.[151]
AMD	miR-486-5p	Up	miR-486-5p regulates multiple pathways such as IGF1/AKT/mTOR, CD40, and mTOR that control angiogenesis, inflammatory responses, and photoreceptor degeneration	Viñas et al.[152]
	miR-626	Up	miR-626 acts as a suppressor of the SLC7A5 gene, inhibiting neurodegeneration occurring in AMD	Elbay et al.[153]
	miR-126	Down	miR-126 expression in MSC-derived exosome reduces hyperglycemia-induced retinal inflammation by downregulating the HMGB1	Zhang et al.[154]
	miR-27b	Down	hucMSC-derived exosomal miR-27b repressed EMT in RPE cells induced by TGF-β2 via inhibiting HOXC6 expression	Li et al.,[155] He et al.[156]

IGF1, insulin-like growth factor 1; mTOR, mammalian target of rapamycin; hucMSC, human umbilical cord mesenchymal stem cell.

DME through miRNA profiling. Exosomal miR-377-3p, one of the downregulated miRNAs, was found to suppress the proliferation of macular cells through the inhibition of *VEGF* expression.[147] Overexpression of VEGF induced proliferation in RPE by promoting angiogenesis and increasing vascular permeability in a high glucose condition, which ultimately resulted in DME.[157] The overexpression of miR-377-3p significantly inhibited RPE proliferation. Conversely, the reactivation of VEGF in miR-377-3p-overexpressing ARPE-19 cells significantly increased RPE proliferation. These findings imply that miR-377-3p-VEGF axis regulates RPE proliferation and shows the potential of miR-377-3p as a diagnostic biomarker for DME.

Furthermore, Zhang et al. demonstrated that elevated levels of circ_0005015 were observed in patients with DR. circ_0005015 in bodily fluids was verified to originate from exosomes. circ_0005015 functions as a suppressor of miR-519d-3p, leading to the subsequent upregulation of key regulators of retinal endothelial cell angiogenesis, including matrix metalloproteinase-2 (MMP-2), X-linked inhibitor of apoptosis protein (XIAP), and STAT3.[148] This discovery implies that exosomal circ_0005015 may serve as a candidate biomarker for DR and a potential target for therapeutic interventions.

Other ncRNAs including circRNA and lncRNA have been investigated in DR. Diabetes-related stress increases the secretion of exosomal circPWWP2A from pericytes, which works as a sponge for miR-579, causing the increased expression of angiopoietin 1, occludin, and Sirtuin 1 (SIRT1). The overexpression of circPWWP2A or inhibition of miR-579 suppresses retinal vascular dysfunction induced by diabetes, whereas silencing circPWWP2A or overexpressing miR-579 exacerbates retinal vascular dysfunction.[149]

lncRNA *SNHG7* was found to have inhibitory effects in DR. The overexpression of lncRNA *SNHG7* inhibits EMT and vascular formation in high glucose-induced human retinal microvascular endothelial cells (HRMECs). MSC-derived exosomal lncRNA *SNHG7* negatively regulates the miR-34a-5p/X-box binding protein 1 (XBP1) pathway inhibiting both EMT and vascular formation in HRMECs. Conversely, the overexpression of miR-34a-5p reverses these effects.[150]

In studies of exosomal ncRNA for treating ROP, the intravitreal injection of exosomes derived miR-24-3p from microglial cells into mice with oxygen-induced retinopathy (OIR) reduces the size of vascular tufts and the number of neovascular clusters in exosome-treated OIR mice. miR-24-3p inhibits the cascade associated with endoplasmic reticulum stress-related inositol-requiring enzyme 1α (IRE1α)-XBP1 induced by oxygen deprivation. In addition, it downregulates the expression of *VEGF* and *TGF-β* enhancing photoreceptor cell survival.[151]

Several studies investigated exosomal ncRNAs in AMD. Exosomal miR-486-5p was more highly expressed in patients with AMD than in the control group.[153] Exosomal miR-486-5p can induce cell death through the regulation of AKT-mediated signaling, causing photoreceptor degeneration, RPE damage, and the onset of AMD.[152,158] However, it also plays a crucial role in regulating immune and inflammatory responses by participating in the cluster of differentiation 40 (CD40) pathway, thereby promoting VEGF-A-dependent neovascularization and contributing to the endothelial cell proliferation process in patients with AMD.[159] In addition, the expression of miR-626 was upregulated in patients with AMD. miR-626 is reported to function as a suppressor of the solute carrier family 7 member 5 (*SLC7A5*) gene, which is associated with neuronal cell proliferation in the human brain. In human RPE cells, *SLC7A5* mediates L-leucine transport across the inner blood-retinal barrier and plays a protective role against ornithine cytotoxicity; mutations in *SLC7A5* cause severe retinal degeneration in mice. The observed neurodegenerative manifestations in AMD may be linked to the increased expression of miR-626, which possesses inhibitory properties targeting *SLC7A5*.[153]

Furthermore, because stem cells are crucially involved in tissue repair, research on the treatment of AMD uses various stem cell-derived exosomes. Intravitreal injection of exosomes derived from MSCs was reported to improve retinal laser-induced damage by reducing injury, suppressing cell death, and inhibiting inflammation.[160] For instance, miRNA-126-containing exosomes derived from bone marrow MSCs exhibit anti-inflammatory effects in *in vivo*. These exosomes reduce high-glucose-induced high-mobility group box 1 (HMGB1) expression and NOD-like receptor pyrin domain-containing protein 3 inflammasome activation in human retinal endothelial cells. This effect is accompanied by suppression in the expression levels of caspase-1, interleukin-1β (IL-1β), and IL-18, thereby demonstrating anti-inflammatory effects.[154]

In addition, intravitreal injection of exosomes derived from human umbilical cord-derived MSCs that contain miR-27b effectively inhibit laser-induced choroidal neovascularization and subretinal fibrosis in RPE cells induced by TGF-β2 via the suppression of homeobox protein Hox-C6 (HOXC6). This inhibition reduces retinal fibrosis by suppressing the EMT. These findings suggest the potential significance of the exosomal miR-27b/HOXC6 axis in ameliorating subretinal fibrosis.[155,156] Therefore, exosomes have a significant effect on the progression of retinal vascular disorders, and the development of novel therapeutic strategies using exosomes could contribute to the prevention and treatment of retinal vascular disorders.

STRATEGIES TO MODULATE EXOSOME USING EXOSOME ENGINEERING

Exosome engineering involves manipulating exosomes to control intercellular communication or using exosomes themselves as therapeutic drugs or vaccines.[161,162] Delivering specific molecules or genes inside damaged tissue using exosomes can increase the therapeutic effect.[163,164] In exosome engineering, several methodologies are used, with the principal approaches falling into two categories: first, the modification of exosomal surface proteins, and second, the manipulation of exosomal contents, encompassing genes or molecules.[164–166] Manipulating the proteins expressed on the surface of exosomes can enable the selective receptor binding to specific cells or tissues. Protecting exosomes from uptake by nontarget cells can enhance the overall drug delivery efficiency of exosomes.[167–169] The manipulation of specific surface proteins of exosomes in vaccine development can facilitate the production of personalized vaccines and enhance vaccine safety.[162] Furthermore, in cancer immunotherapy, exosomes with enhanced cellular specificity alleviate side effects by modifying the surface epitopes of highly toxic antigenic exosomes.[161,170,171]

The manipulation of the exosomal contents can ensure the delivery of specific DNA and protein molecules to target cells or tissues to enhance therapeutic effects. The two major methods to manipulate exosomal contents are the parental cell-based approach and direct exosome engineering (Figure 1).[164] The parental cell-based approach involves genetically engineering cells to produce engineered exosomes, allowing functional molecules to be loaded into or displayed on the exosome surface through genetic manipulation of the parental cells.[172] Direct exosome engineering enables the introduction of small nucleic acid molecules, such as miRNAs, siRNAs, and other ncRNAs, as well as therapeutic molecules such as anticancer drugs into exosomes.[165] This method is technically less complex than the cell-based approach and is widely used for various applications. Techniques such as electroporation, extrusion, and sonication are commonly used to achieve this.[165,173] Since ncRNAs are highly expressed in exosomes, exosomes may serve as an ideal delivery method for RNA drugs. In addition, the Exo-Fect transfection system was recently developed by System Biosciences and allows for the insertion of RNA, DNA, and small molecules into isolated exosomes.[174–176] Thus, these methods allow drugs to be loaded into exosomes to maximize the accuracy and effectiveness of drug delivery.

CURRENT STATUS OF TREATMENT DEVELOPMENT USING EXOSOME ENGINEERING

Multiple studies have investigated the development of therapeutic agents through exosome engineering, including therapies for cancer,

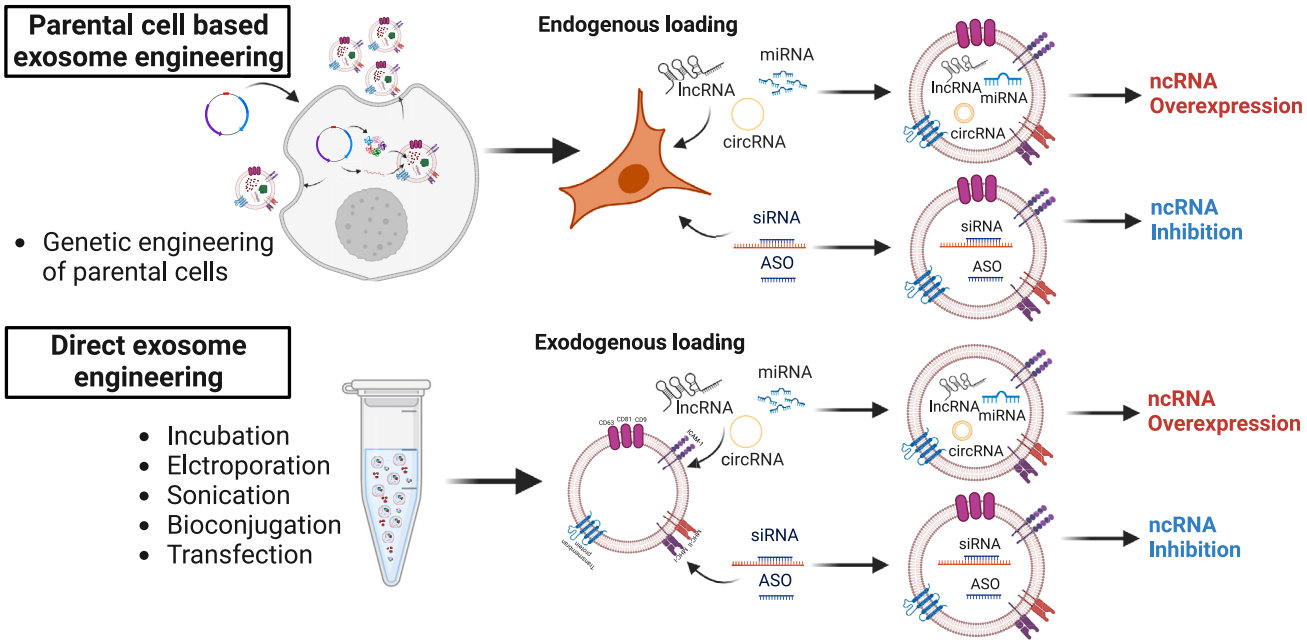

Figure 1. Methodologies of exosome engineering

Various molecules can be loaded into the lumen and can be displayed on the surface of exosomes for therapeutic purposes. Two main approaches are used in exosome engineering: the parental cell-based exosome engineering and the direct exosome engineering. During parental cell-based exosome engineering, the desired nucleic acids are loaded into exosomes using a transfection-based strategy. After transfection with vectors, the parental cells generate ncRNAs, and the products are then packaged into exosomes (endogenous loading). In the direct exosome engineering, physical treatments enable direct loading of cargoes into exosomes (exogenous loading). Electroporation, sonication, and other methods induce exosomal membrane disruption and recombination processes, facilitating cargo loading into exosomes. Loading ncRNAs or their inhibitors into exosomes holds significant therapeutic potential for human diseases.

immune enhancement, nervous system disorder, and tissue regeneration (Figure 2).[43,53,177]

To develop cancer therapies, Zhu et al. enhanced the specificity and circulation time of exosomes by incorporating glycosphingolipid supports onto their surface. These exosomes effectively target cancer cells, demonstrating the potential for their application in cancer treatment.[178] Zhang et al. used exosome engineering to display targeting ligands (anti-human epidermal growth factor receptor 2 antibody) on the surface of exosomes incorporating anticancer drugs (doxorubicin). This modification increased exosome specificity for cancer cells, enhanced their anticancer effects, and improved safety by reducing side effects, showing promise as an alternative treatment method in cancer therapy.[179] The development of immune-enhancing therapies involves the engineering of exosomes containing envelope glycoprotein 70, a specific melanoma antigen, to stimulate T cell activation and induce anticancer immune responses.[180] In addition, Viaud et al. developed dendritic cell-derived exosomes using CD40 and lysosomal associated membrane protein 2 as antigen targets, which promote interaction with cancer cells to induce T cell activation, thus effectively using anticancer immunotherapy.[181]

To develop therapies for nervous system disorders, Mizrak et al. used engineered exosomes to inhibit neuroendocrine tumors. Exosomes were used to deliver cell death genes, such as those encoding cytosine deaminase and uracil phosphoribosyltransferase, specific to neuroendocrine tumors, to suppress tumor growth.[182] Tian et al. applied exosome therapy for cerebral ischemia treatment and engineered MSC-derived exosomes with surface c(RGDyK) peptides that were loaded with curcumin to target brain endothelial cells.[183] This approach significantly inhibited inflammation and cellular apoptosis in the ischemic brain region. These studies demonstrate the potential of exosome engineering technology in various therapeutic fields.

CONCLUSIONS

Recently, exosomes have been highly evaluated in fields such as intercellular communication, disease diagnosis, and treatment. Furthermore, exosome engineering technology can be used to control the characteristics and improve the functions of exosomes to maximize the effectiveness of therapies. Exosomes have been actively studied in therapeutic drug development. In particular, recent studies revealed that RNA contained within exosomes can play an important role in diagnosing and treating various diseases, including ocular disease.[142,143,184] Exosomes are easy to transport within the body because of their small size, simplifying the delivery of therapeutic agents, and RNA therapy agents can be inserted into exosomes to treat the retina. Current pharmacologic treatments for retinal vascular diseases, such as anti-VEGF drugs, need frequent injections and may cause adverse effects, including increased ocular pressure and cataracts. In addition, laser therapy may cause vision loss and macular scarring. Therefore, further research is necessary to

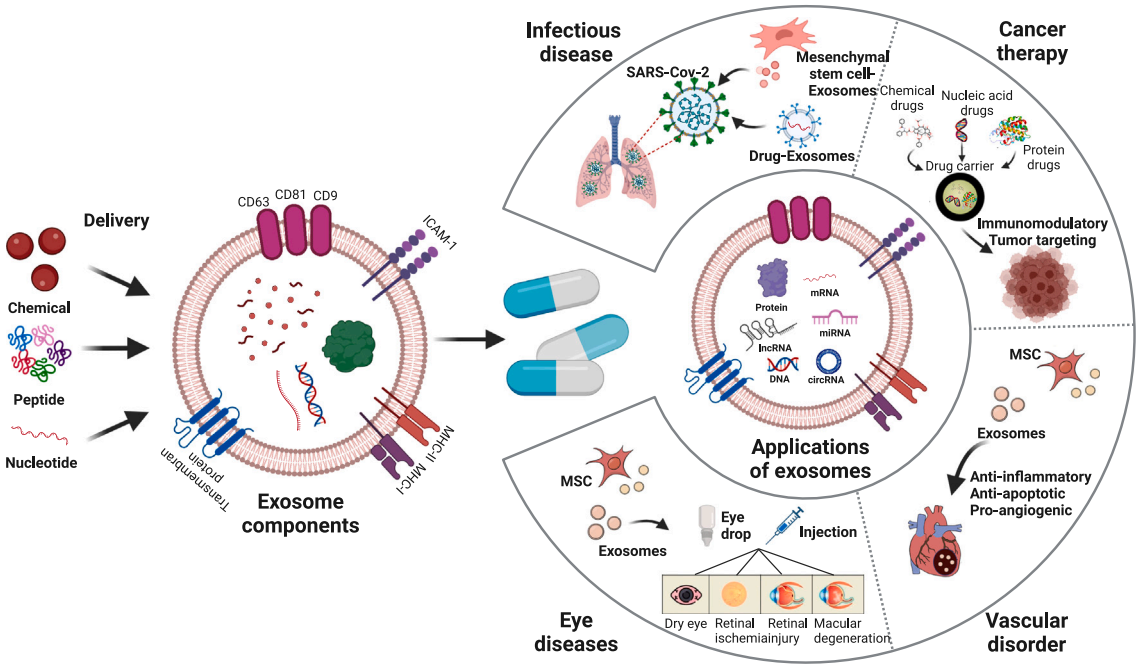

Figure 2. Application of exosomes in the development of therapeutics for various diseases

Exosomes are small vesicles derived from cells that contain a diverse range of molecules, including proteins and nucleic acids. They can be bioengineered to display antibodies and peptides on their surfaces and can be designed to efficiently carry small molecules and active biological substances. Exosomes offer significant promise in targeting specific diseases because of their targeting capabilities and specificity and may be used as a potential drug delivery vehicle.

overcome the limitations of current therapy and alleviate adverse effects associated with existing therapies for retinal vascular disease to effectively treat these diseases. Exosomal ncRNAs can be promising therapeutic agents since they can act directly on specific areas and enhance the therapeutic effect. Although the development of a therapy for retinal vascular disease using exosomes and ncRNA is still in its early stages, this approach is attracting attention as a new alternative that can overcome the limitations of existing treatment methods. As research progresses, it is expected that a therapy with high efficacy and safety will be developed.

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AUTHOR CONTRIBUTIONS

J.-I.H. collected the available literature. J.-I.H. and J.R. analyzed and interpreted the literature. J.-I.H. wrote the first draft. J.R. revised the manuscript. J.R. acquired funding.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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