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REVIEW

Biogenesis, Composition and Potential Therapeutic Applications of Mesenchymal Stem Cells Derived Exosomes in Various Diseases

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Abstract: Exosomes are nanovesicles with a wide range of chemical compositions used in many different applications. Mesenchymal stem cell-derived exosomes (MSCs-EXOs) are spherical vesicles that have been shown to mediate tissue regeneration in a variety of diseases, including neurological, autoimmune and inflammatory, cancer, ischemic heart disease, lung injury, and liver fibrosis. They can modulate the immune response by interacting with immune effector cells due to the presence of anti-inflammatory compounds and are involved in intercellular communication through various types of cargo. MSCs-EXOs exhibit cytokine storm-mitigating properties in response to COVID-19. This review discussed the potential function of MSCs-EXOs in a variety of diseases including neurological, notably epileptic encephalopathy and Parkinson's disease, cancer, angiogenesis, autoimmune and inflammatory diseases. We provided an overview of exosome biogenesis and factors that regulate exosome biogenesis. Additionally, we highlight the functions and potential use of MSCs-EXOs in the treatment of the inflammatory disease COVID-19. Finally, we covered a strategies and challenges of MSCs-EXOs. Finally, we discuss conclusion and future perspectives of MSCs-EXOs.

Keywords: extracellular vesicle, biogenesis, mesenchymal stem cells, exosomes, autoimmune disease, angiogenesis

Introduction

Generally, extracellular vesicles (EVs) are a heterogeneous group of cell-derived membranous nanovesicles generated from cells that range in size from 30 to 1000 nm. Based on size and origin, EVs are classified into exosomes, microvesicles (MVs), and apoptotic bodies (ABs).[1,2] They are released from most cell types and bio-fluids such as blood, saliva, breast milk, semen, urine, cerebrospinal fluid (CSF), colostrum,[3] tears,[4] bronchoalveolar fluid,[5] epididymal fluid,[6] amniotic fluid,[7] bile,[8] blastocoel fluid,[9] middle ear effusion,[10] and ascites.[11] Exosomes are having with an average size between 30 and 150 nm, which are a subset of extracellular vesicles and are important messengers of paracrine activity. Tetraspanins (CD9, CD63, and CD81), heat shock proteins (HSPs), membrane transporters and fusion proteins, multivesicular bodies (MVBs) proteins, phospholipases, and lipid-related proteins are considered to be biomarkers found in exosomes.[12,13] The biogenesis and secretion of exosomes occurs by the formation of MVBs and fuse with the plasma membrane and eventually leads to secretion of cargoes in the extracellular milieu.[14] Exosomes are subset of EVs, which are playing vital role in physiological and pathological conditions, such as cellular junctions, integrins, and selectins.[15]

Exosomes are found abundantly in the secretome of many cell types such as embryonic stem cells, and induced pluripotent stem cells (iPSCs).[16–18] Exosomes are vesicles that carry a variety of bioactive substances, including proteins, DNA, soluble and membrane proteins, microRNAs (miRNAs), and nucleic acids. These exosomes are a reflection of the cell from which they were produced as well as of the biogenesis and release routes.[19,20] Exosomes are produced by nearly all forms of life and are present in a variety of bodily fluids. They have a variety of roles in cellular processes such

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as intercellular communication, immunological regulation, senescence, proliferation, and differentiation.[21–24] Exosomes produced from iPSCs are believed to be therapeutic agents as targeted delivery agents and are safer than parental cells. They can promote a variety of functions, including angiogenesis, extracellular matrix (ECM) remodelling, and immune response regulation.[25–29] Exosomes can transport exogenous bioactive substances and can pass the blood-brain barrier. Exosomes, for instance, are employed as indicators or therapy options for a number of diseases, such as cancer, neurological disorders, and immune-related illnesses.[30]

MSC-derived exosomes (MSC-EXOs) are nanosized vesicles that have demonstrated therapeutic efficacy in the treatment of a number of diseases, including liver diseases,[31] kidney diseases,[32] brain diseases,[33] and cardio vascular diseases (CVDs),[34] through interaction with their target cells through a variety of mechanisms, such as interaction, fusion, and internalisation of exosomes with the plasma membrane of recipient cells and these vesicles are necessary for cell-cell communication. The exosome cargoes that are released into physiological fluids mediate cell-cell contacts and regulate a variety of cellular processes. These mediators are crucial for the regulation of a variety of vital functions of their target cells to maintain homeostasis.[35,36]

Recent research suggests that active exosomes produced by stem cells can prevent heart and blood vessel illnesses by carrying a variety of payloads, including as proteins, miRNAs, and lncRNAs, to nearby or distant target cells. According to studies, the payloads and functions of exosomes produced by various types of cells varies greatly.[37] For instance, EVs produced from cancer stem cells (CSCs) carry out a variety of biological activities, such as metastasis, angiogenesis, immunosuppression, and resistance to treatment.[38,39] In order to maintain tumour heterogeneity, CSCs release EVs that communicate certain proteins and transcription factors to nearby cells.[40] Recent research suggests that MSC-EXOs could be used to treat inflammatory and autoimmune illnesses since MSCs have immunosuppressive qualities. Through the transport of parental cell cargo, MSCs' paracrine characteristics play a crucial role in cell-to-cell communication and are also implicated in the innate and adaptive immune response.[41] MSC-EXOs are capable of triggering the necessary response in the event of injury, inflammation, or repair due to their dynamic immuno-modulatory function.[42] According to numerous research, MSC-EXO's bioactive chemicals and anti-inflammatory molecules interact with immune effector cells to play a vital role in immune response and control. These properties can be used to treat autoimmune illnesses.[43] Exosomes produced by neurons, astrocytes, oligodendrocytes, and microglia and found in serum are thought to be early indicators of CNS illnesses, particularly neurodevelopmental disorders.[44–46] Exosomes may be able to stop the loss of neurons by specifically attaching to target cells in the central nervous system.[47] Pilocarpine-induced epilepsy was shown to reduce inflammation and memory impairment by MSC-EXOs by targeting hippocampus astrocytes in a mouse in vivo investigation.[48] Particularly, Parkinson's disease (PD), which affects about 1% of persons over,[49] is the second most common neurodegenerative disease in the world. Among these paracrine effectors, MSC-EVs are a significant contributor and have the property of becoming a directed anti-tumor drug delivery platform or agent.[50,51] The MSC-EXOs cargo has positive cardioprotective effects as a result of transporting and distributing a range of substances to the wounded cells.[18,19] MSC-EXOs have demonstrated efficacy as minimally invasive agents for the repair, regeneration, and protection of human organs against a variety of bodily injuries. Stem cell secretome (SCS) released exosomes shows significant anti-fibrotic, anti-inflammatory, immunomodulatory, and anti-angiogenic actions.[52–55]

Considering all the literatures into account, in this review, we discuss general aspects of biogenesis and factors involved in promotion of biogenesis and secretion of exosomes and we also discuss in detail account about the role of MSC-EXOs in various diseases including neurological diseases, epileptic encephalopathy and Parkinson's. Further, we discuss the involvement of MSC-EXOs in cardiovascular, cancer, angiogenesis and autoimmune and inflammatory diseases and specifically multiple sclerosis, rheumatoid arthritis, type 1 diabetes mellitus, uveitis, systemic lupus erythematosus, inflammatory bowel disease and COVID-19. Besides, this review summarizes the current advances of potential therapeutic benefits, underlying mechanisms, diagnosis, treatment, challenge and strategies of use of MSC-EXOs and limitations of mesenchymal stem cell-derived exosomes in various types of diseases.

Biogenesis of Exosomes

Exosomes are a subset of EVs that typically range in size from 30 to 180 nm and are important for intercellular communication between cells and organs.[56] Almost all types of cells secrete exosomes, which contain a variety of

biomolecules including DNA, RNA, and proteins.[57–59] Exosomes are created by the double invagination of the plasma membrane, which also produces early endosomes that develop into intraluminal vesicles (ILVs) before maturing gradually and being delivered into multivesicular bodies (MVBs) by inward budding, preventing cytoplasmic lysosomes from degrading them.[60–62] (Figure 1) The endosomal sorting complex required for transport (ESCRT), a separate mechanism made up of roughly 30 proteins that assemble into four complexes (ESCRT-0, -I, -II, and -III), controls the development of ILVs. In addition, two significant proteins, TSG101 and ALIX, are involved in the synthesis of exosomes, and syndecan and syntenin are typically found as a biomarker in exosomes produced from tumour cells. Exosome secretion can also take place by means of an ESCRT-independent mechanism. Rab GTPase family, cytoskeleton, molecular motors, and membrane fusion devices (SNARE complex) all play a role in controlling MVBs transports.[63–65] Exosomes releases are influenced by several physiological factors and cellular conditions such as lipopolysaccharide, tumor necrosis factor-α, interferon comma and hypoxia. Some others, which are secreted from injured organs, contain healing RNAs and protein-containing exosomes and induce stem cells, facilitate the maintenance of tissue homeostasis.[49]

Exosome secretion is affected by a number of variables, such as intracellular calcium concentrations, cellular energy levels, composition of membrane phospholipids, membrane-acting enzymes, cytoskeleton-membrane interactions, other exocytosis effectors, hypoxia, and oxidative stress.[66,67] Exosomes in circulation are picked up by recipient cells by three separate methods, including endocytosis, ligand-receptor uptake, and fusion. Exosomes were carefully targeted and internalised by ligand-receptors to deliver bioactive substances to the cells.[68–70] Exosomes are internalized into target cells through particular receptors such as integrins, CD9, CD63, and CD81.[71] The fusion of the exosome with the cell membrane releases the cargos produced from exosomes into the cytoplasm of the target cells.[72] For example, MSC-EXOs express markers CD9, CD63, and CD81 which are involved in accelerate skeletal muscle regeneration.[73] The structure, functions, delivery potential of cargos into target cells and protective nature of exosomes from cytosolic enzymes and cargos depends on composition of high levels of lipid species including ceramides, sphingomyelins (SM), cholesterol, gangliosidesphosphatidylserine, phosphatidylethanolamines, phosphatidylcholines, lyso-phosphatidylcholines, and phosphatidylinositols.[13,74] There are no proteins from the nucleus, mitochondria, endoplasmic reticulum, or Golgi complex in exosomes that are derived from endosomes.

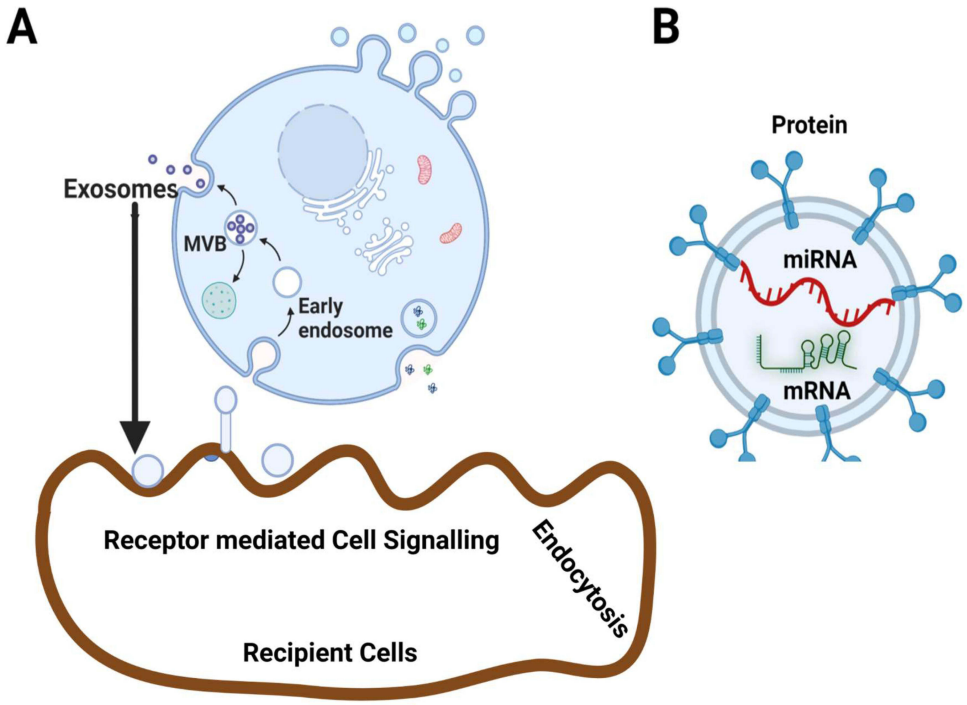

Figure 1 Biogenesis, secretion and cargoes of the mesenchymal stem cell derived exosomes. (**A**) Exosome biogenesis, secretion and uptake by recipient cells. (**B**) MSCs-derived exosomes are enriched with various cargoes such as proteins, mRNA and miRNA with multiple functions. Created with BioRender.com.

Tetraspanins, adhesion proteins, antigen presentation proteins, membrane transport proteins, and fusion proteins are four different types of proteins that make up exosomes and act as biomarkers for exosome characterization.[75] Adhesion proteins are playing a role in exosome maturation and target cell binding. Major Histocompatibility Complex (MHC) classes I and II and other antigen presentation proteins are involved in immune regulation, energy, and priming. Synaptosomal associated protein (SNAP), annexins, and Ran5b are examples of membrane transport and fusion proteins that are involved in exosome synthesis, secretion, and downstream cell fusion.[76] Furthermore, exosomes are characterized by the expression of various surface markers including CD9, CD63, CD81, ALIX, TSG101, Hsc70, and MHC class II.[77] Exosomes contain various types of cargoes with various sizes such as mRNA and miRNA. For example, dendritic cell-derived exosomes contain miR-451 are involved in an attenuation of the innate immune response to whole virus vaccines and monocyte-derived EVs contain miR-223 play essential role in suppressing macrophage activation and lung inflammation.[78] EVs derived from MSC were found to be enriched with miR-16 that targets expression of vascular endothelial growth factor (VEGF).[79] The functions of EVs are regulated by the compositions of EVs such as lipopolysaccharide (LPS), tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and hypoxia. According to Nakamura et al, adiponectin increases exosome release to improve MSCs-driven heart failure therapy. This increased exosome synthesis was strongly correlated with an increased amount of circulating hMSC-derived exosomes.[80] The spreading areas of BMSCs on the titanium surface are enhanced by physicochemical characteristics like roughness and hydrophilicity of micro/nanotextured hierarchical titanium topographies, which facilitate a stronger promotion of BMSC proliferation. It also promoted the synthesis, transport, and secretion of BMSCs-derived exosomes into the extracellular milieu.[81] Cortical spheroids made from human stem cells were subjected to iron oxide nanoparticles, which not only caused cytotoxicity but also greatly increased the number of extracellular vesicles.[82] Peng et al investigated the processes behind the regulation of multivesicular body (MVB) trafficking, exosome secretion, invadopodia formation, and tumour invasion by long noncoding RNA LINC00511 (LINC00511).[83] According to the findings of these studies, abnormal LINC00511 causes the formation of invadopodia in HCC cells by controlling the colocalization of two proteins, vesicle associated membrane protein 7 (VAMP7) and synaptosome associated protein 23 (SNAP23). Invadopodia are important secretion sites for MVBs and regulate the release of exosomes. Tetraspanin proteins found in MSC-EXOs, including CD63, CD9, CD81, CD29, CD73, CD90, CD44, and CD105, are MSC-specific and have a significant impact on exosome formation and secretion.[84] Collectively, these investigations offered proof of the molecular process underlying exosome formation.

Factors Influences Biogenesis and Secretion of Exosomes from Stem Cells

The biogenesis of the exosomes are complex process and regulated by various conditions may lead to discrepant therapeutic outcomes.[85–87] Biogenesis and secretion of exosomes are regulated by various factors including cell type, cell confluency, serum conditions, soluble factors, and the presence and absence of cytokines and growth factors and also sites of exosomes, protein sorting, physico-chemical aspects, and transacting mediators are playing significant role in biogenesis and secretion.[88] Biogenesis and secretion of exosomes of stem cells can be increased by addition of certain soluble cytokines directly into the culture medium. Bioactive molecules such as lipopolysaccharide,[89] N-methyldopamine,[90] noradrenaline,[90] and adiponectin[91] shows SuxiaoJiuxin pills increased the level of exosome secretion by stem cells.[92] Exosomes biogenesis and secretion can be increased by serum starvation, exogenous stress, nanoparticles and small molecules (Figure 2). Platelet-derived growth factor (PDGF) is an important factor for the selective expansion and recruitment of undifferentiated mesenchymal stem cells.[93–95] PDGF induces the migration and proliferation of mural progenitor cells during vascular development,[95] stimulates endothelial cells[96] and induces mesenchymal cell transdifferentiation into vessel cells.[97,98] The vascular niche in the tumor microenvironment (TME) also releases growth factors through adjacent and paracrine pathways to support the growth of cancer stem cells (CSCs) and maintain its stemness.[99,100] Exosomes were produced when human endothelial cells were exposed to low-level laser irradiation (LLLI) at an energy density of 80 J/cm2. Irradiation of the cells causes an increase in exosome release as well as enhanced gene expression, including CD63, Alix, Rab27a, and Rab27b. The increased levels of exosomes were associated with an enhanced acetylcholine esterase activity, pseudopodia formation, and reduced zeta potential value 24 h post-irradiation.[101] C1q-TNF-α related protein-9 (CTRP9) polypeptide that upregulates SOD2/SOD3 expression and improves cortical bone-derived mesenchymal stem cell (CBSC) CBSC survival/retention, similar to gCTRP9. Moreover, CTRP9-281 stimulates VEGFA-rich exosome production by CBSC, exerting superior pro-angiogenic, anti-fibrotic, and

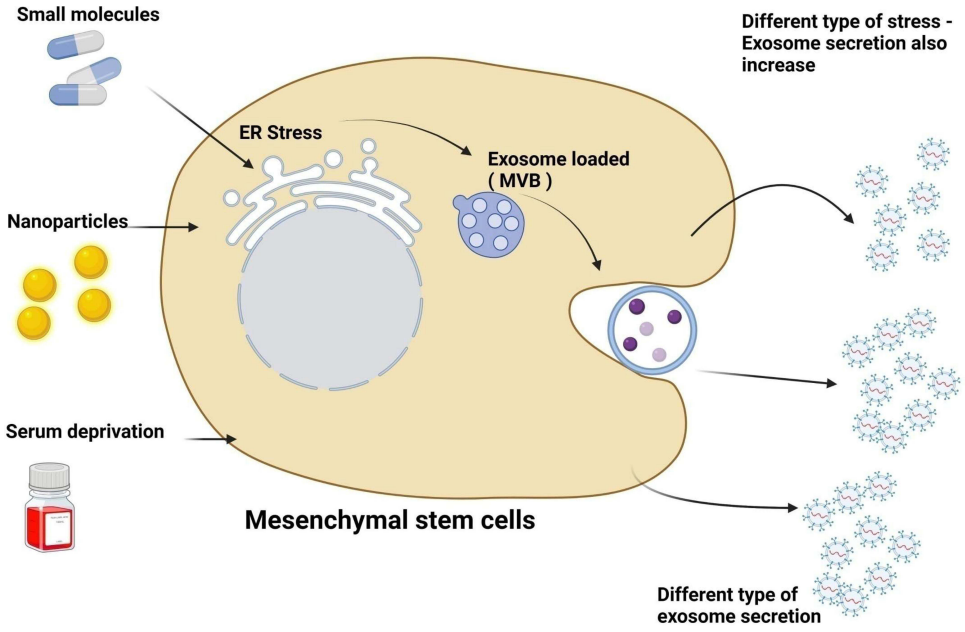

Figure 2 Effect of various factors on biogenesis and secretion of mesenchymal stem cell derived exosomes. Factors such as cell types, culture conditions, cell confluency, serum conditions, serum deprivation, preconditioning media and modified media, soluble factors, and cytokines and growth factors sites of exosomes, protein sorting, physico-chemical aspects, and transacting mediators influences biogenesis and secretion. Created with BioRender.com.

cardioprotective actions.[102] Lopatina et al reported that adipose mesenchymal stem cells (ASCs) derived EVs induced formation of vessel-like structure in human microvascular endothelial cells (HMEC).[103] Treatment of ASCs with platelet-derived growth factor (PDGF) stimulated the secretion of EVs, changed their protein composition and enhanced the angiogenic potential. Further, the authors described that PDGF treatment of ASC changed protein and RNA composition of released EVs by enhancing the expression of anti-inflammatory and immunomodulatory factors.[103] Mesenchymal stem cell-derived exosomes (MSC-EXOs) improves osteoarthritis through long non-coding RNA KLF3-AS1. Chondrocytes were treated with IL-1β to induce chondrocyte injury, followed by MSC-EXOs treatment enhanced KLF3-AS1 expression. MSC-EXOs-derived exosomes containsKLF3-AS1 promotes cell viability and inhibits apoptosis of IL-1β-treated chondrocytes. MSC-EXOs-mediated KLF3-AS1 inhibits autophagy and apoptosis of IL-1β-treated chondrocyte through PI3K/Akt/mTOR signaling pathway.[104] TNF-α-stimulated gingival MSC (GMSC)-exosomes (TG-EXOs), modulates inflammatory microglia and alleviates apoptosis.[105] A study using a mouse model of acute graft-versus-host disease (aGVHD) suggested that epidermal growth factor (EGF)-stimulated microRNA-21 (miR-21) in bone marrow-derived mesenchymal stem cells (BMSCs). As a result, the stimulated miR-21 promoted the proliferation, invasion, and migration of BMSCs. Furthermore, miR-21 in BMSC-EXOs inhibited phosphatase and tensin homolog (PTEN), but enhanced AKT phosphorylation and Foxp3 expression in Tregs.[106] The treatment of MSCs with a combination of N-methyldopamine and norepinephrine robustly increased exosome production by three-fold without altering the ability of the MSC exosomes.[90]

Physicochemical factors alter environment and eventually influences the biogenesis and secretion of exosomes. For example, stem cells exposed to chemical stimulations such as hypoxia can influence the secretion of exosomes. Hypoxia condition enhances of MSCs and also the derived exosomes enhanced therapeutic effect.[11,107,108] Serum deprivation stimulated the secretion of exosomes by the stem cells.[109,110] Furthermore, mechanical forces such as flow and stretching factors enhance the secretion of stem cells up to 37 folds via bioreactors.[111,112] Similarly, other mechanical factor such as high-frequency ultrasound increases biogenesis and secretion of exosomes up to 10 folds.[113] Interestingly, stimulations of exosomes secretion were observed and dependent on type of cells.[114] The 3D culture plays significant role in biogenesis and secretion of exosomes and increases surface area and continuous supply of shear force.[115] While the level of secretion increases 100 fold when cells are cultured on a hollow fibrillar scaffold that was 3D printed.[116] Studies showed that compared to BMSCs and adipose tissue-derived stem cells (ADSCs), human umbilical cord mesenchymal stem cells

(HUMSCs) generated from Wharton's jelly had the highest exosome output. Biomaterials including ferroferric oxide-coated PLGA nanoparticles, NO-releasing polymer, lithium-incorporated bioactive glass ceramic, and bioglass enhance exosome secretion and biogenesis.[116–120] In mesenchymal stem/stromal cells (MSCs), adiponectin enhanced exosome formation and secretion through binding to T-cadherin.[80] Mice model showed that internalization of exosomes contained small RNA isolated from neuron-CMinto astrocytes improved its signalling in amyotrophic lateral sclerosis.[121] MSCs exposed to ischemic brain extracts had increased levels of miR-133b in its released exosomes.[122] Scaffold contains nitric oxide (NO) and chitosan induces biogenesis of exosomes from placenta with pro-angiogenic and pro-migratory factors compared to the normal human placenta MSCs.[117] Endothelial cells exposed to hypoxia-mimetic agent desferrioxamine (1% O_2) produced higher levels of EVs compared to cells exposed to normoxia. Conversely, treatment of cells with sodium nitrite ($NaNO_2$) reduced the hypoxic enhancement of EVs production.[123] TNF-α can promote the release of EVs in astrocytes through upregulation of glutaminase expression. TNF-α treatment significantly upregulated protein levels of glutaminase and increased the production of glutamate, suggesting that glutaminase activity is responsible for biogenesis and secretion of exosomes. Glutaminase inhibitor blocked TNF-α-mediated generation of reactive oxygen species in astrocytes. TNF-α-mediated increased release of EVs can be blocked by either the glutaminase inhibitor, antioxidant N-acetyl-L-cysteine, or genetic knockout of glutaminase, suggesting that glutaminase plays an important role in astrocyte EVs release during neuroinflammation.[124] MSCs treated with small molecules such as combination of N-methyldopamine and norepinephrine strongly increased exosome production up to three-fold without altering the ability of the MSC exosomes to induce angiogenesis, polarize macrophages to an anti-inflammatory phenotype, or downregulate collagen expression.[90]

Recently, several studies reported that the effect of various types of nanoparticles on biogenesis and secretion of exosomes. For example, Gurunathan et al reported that platinum nanoparticles (PtNPs) enhance biogenesis and secretion of exosomes in A549 cells by generation of oxidative stress.[125] While culturing A549 cells with PtNPs enhance exosome secretion by altering various cellular and physiological processes. These studies found that A549 cells treated with PtNPs increase total protein concentration, which is associated with PtNPs-induced oxidative stress. The molecular mechanism of enhanced secretion of exosomes were substantiated with acetylcholinesterase (AChE) inhibitor such as GW4869, which inhibits PtNPs induced biogenesis and release of exosomes and alsoacetylcholinesterase (AChE), neutral sphingomyelinase activity (n-SMase), and exosome counts. Conversely, A549 cells pre-treated with N-acetylcysteine significantly inhibited PtNPs induced exosome biogenesis and release. These findings confirmed that PtNPs-induced exosome release was due to the induction of oxidative stress and the ceramide pathway. The same group further investigated that how PdNPs enhance exosome release in human leukemia monocytic cells (THP-1). Exosome production was associated with increased level of total protein concentration, exosome counts, acetylcholinesterase activity, and neutral sphingomyelinase activity. The exosomes were spherical in shape and had an average diameter of 50–80 nm. The expression levels of TSG101, CD9, CD63, and CD81 were significantly higher in PdNPs-treated cells than in control cells. Further, cytokine and chemokine levels were significantly higher in exosomes isolated from PdNPs-treated THP-1 cells than in those isolated from control cells. THP-1 cells pre-treated with N-acetylcysteine or GW4869 showed significant decreases in PdNPs-induced exosome biogenesis and release.

The endoplasmic reticulum stress, oxidative stress, apoptosis, and immunomodulation are all involved in the process of PdNPs increased exosome secretion. Exosome release and biogenesis in SH-SY5Y cells treated with silver nanoparticles.[125] While cells treated with N-acetylcysteine in the presence of AgNPs reduced the level of oxidative stress-induced exosome biogenesis and release, the expression levels of some key exosome biomarkers were significantly increased as a result ofAgNPs-induced oxidative stress. The authors also discovered that the ceramide pathway was involved in the exosome release caused by AgNPs. Exosome secretion and enhanced biogenesis can both be used therapeutically to treat a variety of illnesses.

Role of MSC-EXOs in Neurological Disease

Human pluripotent stem cell-derived EVs are essential for several biological functions, including the protection of tissue homeostasis.[126] The recipient cells experience protective benefits, reduced oxidative stress, and apoptosis after receiving EVs produced from stem cells. In addition to forming myelin, releasing neurotransmitters, and providing glia-mediated trophic

support to axons, the EVs released by neuronal cells like oligodendrocytes are also capable of communicating with other cells via miR-219.[127,128] In AD mice, EVs from hippocampal neuronal cells reduce amyloid beta (Ab) load and restore synaptic activity.[129,130] According to Haney et al, EVs produced from mouse macrophages boost the survival of brain cells while lowering ROS levels.[131] EVs carrying active neprilysin are also able to degrade Ab and eventually reduce the burden of Ab plaques and the amounts of dystrophic neurites in both the cortex and hippocampus of AD mice. EVs carrying active neprilysin are derived from MSCs and exhibit neuroprotective properties and suppressed 6-hydroxydopamine-induced apoptosis in dopaminergic neurons.[132,133] Exosomes produced by BM-MSCs demonstrated therapeutic effects in a mouse stroke model, including the enhancement of angio-neurogenesis and long-term neuro-protective properties.[134] Exosomes also contain miR-133b, which, when delivered to astrocytes and neurons, aids in neurite remodelling and, in turn, stroke recovery.[135] The miR-17-92 cluster is carried by exosomes and is involved in oligodendrogenesis, neurogenesis, and other neurological processes in the ischemia boundary zone.[136] According to Drommelschmidt et al, exosomes produced by bone marrow-derived mesenchymal stem cells (BM-MSCs) prevent reactive astrogliosis, microgliosis, and brain degeneration.[137] Exosomes from BM-MSCs demonstrated neuroprotective properties, including a decrease in neurological aftereffects and restoration of brain function.[138] Signal transducer and activator of transcription 3 (STAT3), c-Jun N-terminal kinase, and p53 are only a few of the signalling pathways that are modulated by exosomes generated from mice, which include different angiogenesis-related proteins, to improve angiogenesis and directly boost endothelial cell growth.[139] Exosomes from BM-MSCs demonstrated neuroprotective effects by lowering the extent of the lesion, restoring neurobehavioral function, upregulating the anti-apoptotic protein Bcl-2 expression, and modifying microglia/macrophage polarisation.[140] Exosomes made from BM-MSCs shown anti-inflammatory characteristics by repairing injured cord tissue and enhancing locomotor function by disorganizing astrocytes and microglia.[141] In an APP/PS1 mouse model of Alzheimer's disease (AD), hypoxia-preconditioned BM-MSCs generated exosomes restored synaptic dysfunction and encouraged anti-inflammatory actions.[142] Exosomes containing the enzyme neprilysin, which can break down -amyloid peptides in the brain tissue, were secreted by AD-MSCs. By generating 6-hydroxy-dopamine in a 3D culture, exosomes produced from dental pulp MSCs (DP-MSCs) protected dopaminergic neurons from apoptosis.[132] Exosomes of bone marrow stromal cells from Type 1 diabetes mellitus rats and normal rats were compared in terms of their impacts.[143] According to the study, when compared to Nor-BMSCs, DM-BMSCs and their derived exosomes boosted survival and angiogenesis processes while decreasing miR-145 expression. Additionally, in vivo research revealed that DM-BMSC treatment enhanced functional outcomes and white matter and vascular remodelling, which in turn reduced serum miR-145 expression and raised expression of miR-145 target genes ABCA1 and IGFR1. The therapeutic effects of extracellular vesicles produced from differentiated PC12 cells and MSCs on the treatment of spinal cord injury (SCI) were the subject of a study. According to the findings, miR-21 and miR-19b expression was elevated, PTEN mRNA expression was downregulated, and cell apoptosis was reduced. When miR-21/miR-19b precursors were transfected into the cells, cell apoptosis was inhibited.[144] According to Zhao et al, delivery of MSC-EXOs to rats through the tail vein had an anti-inflammatory impact and may have a role in the treatment of acute cerebral ischemia.[145] The findings demonstrated that MSC-EXOs treatment greatly enhanced the motor, learning, and memory abilities of MCAO/R rats seven days after treatment. Pro-inflammatory factors may be reduced by the treatment, whereas anti-inflammatory cytokines and neurotrophic factors may be increased in the cortex and hippocampus of the ischemic hemisphere that has received OGD and NMLTC4. Treatment with MSC-EXOs also significantly reduced the polarisation of M1 microglia and increased M2 microglia cells, while downregulating the expression of CysLT2R and ERK1/2 phosphorylation. By reversing CysLT2R-ERK1/2 driven microglia M1 polarisation, MSC-EXOs reduced brain damage and suppressed microglial inflammation. It's interesting to note that a study discovered down-regulation of miR-133b expression and up-regulation of EZH2 in glioma tissues and cells. It was revealed that miR-133b targets and inhibits the expression of EZH2. Furthermore, glioma cell proliferation, invasion, and migration were decreased by EZH2 knockdown via the Wnt/-catenin signalling pathway.[146] Lee et al observed that at how ADSC-EXOs prevented the disease phenotypes brought on by the A cascade in an AD.[147] The study found that treatment with ADSC-EXOs decreased the levels of A-42, A-40, and the A-42/40 ratio in AD cells and enhanced apoptotic molecules such p53, Bax, pro-caspase-3, and cleaved-caspase-3 while decreasing the level of Bcl-2 protein. In addition, Aβ impaired neurite development in the brains of AD patients, which was improved by ADSC-EXOs therapy. When combined, ADSC-EXOs may act as a therapeutic drug to slow the development of AD and Aβ-induced neuronal death. According to Sun et al, human umbilical cord mesenchymal stem cells (hucMSC) efficiently cause bone marrow-derived

macrophages (BMDM) to polarise from an M1 to an M2 phenotype, which enhances functional recovery following spinal cord injury by suppressing inflammatory cytokines like TNF-α, MIP-1, IL-6, and IFN-γ.[148] These results show that hucMSC-derived exosomes promote SCI repair by reducing inflammation in the area of the lesion. The effect of cerebral ischemia/reperfusion (I/R) on exosomal miR-150-5p from bone marrow-derived mesenchymal stromal cells (BMSCs) was investigated. Neurological performance was enhanced by exosomal microRNA-150-5p from mesenchymal stromal cells in bone marrow. In rats with middle cerebral artery occlusion (MCAO), the pathogenic modifications slow down neuronal death and lessen inflammatory factors. By suppressing TLR5, enriched miR-150-5p strengthens BMSC-EXOs' ability to protect against cerebral I/R damage. New therapeutic targets for the treatment of cerebral I/R injury were presented by this study.[149] By encouraging autophagy and preventing neuronal apoptosis, exosomes with miR-455-5p found in bone marrow mesenchymal stem cells demonstrated neuroprotective effects against spinal cord ischemia reperfusion injury.[150] In both normal and oxygen-glucose deprivation (OGD) culture conditions, exosomes isolated from NSCs (NSCs-EXOs) inhibited apoptosis while promoting the proliferation of SH-SY5Y cells. Additionally, NSC-EXOs facilitate the neuroprotective effects via transfer of miR-150-3p, which targets caspase-2, thereby suppressing neuronal apoptosis after brain injury.[151] An investigation was made into the mechanisms by which TNFα-stimulated gingival MSC (GMSC)-exosomes (TG-EXOs) modulate inflammatory microglia and reduce apoptosis. As compared to G-EXOs (GMSC-exosomes), the results demonstrated that intraocular injection of TG-EXOs into animals with IRI significantly reduced inflammation and cell loss. miR-21-5p-containing exosomes were an essential component of TG-EXOs for neuroprotection and anti-inflammation.[152] Exosomes derived from BMSCs contain microRNA-124-3p, which reduces tumour necrosis factor receptor associated factor 6 in newborn rats to lessen hypoxic-ischemic brain damage (HIBD). These exosomes improved neurological functions, reduced pathological and structural damage to neurons, slowed down oxidative stress, and decreased neuronal apoptosis in newborn HIBD rats.[153] Exosome release from BM-MSCs is increased in cells treated under hypoxia/reoxygenation (H/R) conditions, and these exosomes contain high levels of miR-29c, which reduces cardiac ischemia/reperfusion injury by inhibiting excessive autophagy via the PTEN/Akt/mTOR signalling pathway.[154] Exosomes from myocardial ischemia patients stimulate angiogenesis through the miR-939-iNOS-NO pathway.[155] According to Zhao et al, human umbilical cord derived mesenchymal stem cells (HucM-SCs)-derived miR-206-knockdown exosomes significantly reduce neurological deficit and brain edema in subarachnoid haemorrhage induced early brain injury and suppress neuronal apoptosis targeting via BDNF/TrkB/CREB signalling.[156] When compared to therapy with ordinary exosomes, miR-206-knockdown exosomes produced from hucMSCs significantly protect against early brain damage (EBI) brought on by subarachnoid haemorrhage (SAH). The exosomes with miR-206 knockdown drastically reduced brain edema and neurological deficits while also suppressing neuronal death by targeting BDNF.[156]

Exosomes from hepatocytes have been shown in in vivo experiments to efficiently treat hepatic I/R damage, reduce hepatocyte apoptosis, lower levels of liver enzymes, and promote hepatocyte regeneration. In vitro and in vivo findings suggested that exosomes effectively enhanced hepatocyte tolerance to ischemia and decreased hepatocyte death.[157] The autophagy-related proteins LC3IIB and Beclin-1 are expressed more often by BMSC-EXOs, which also helped autophagosome formation. Pro-apoptotic protein cleaved caspase-3 expression was significantly reduced after treatment with BMSC-EXOs, although Bcl-2 expression was increased.[158] The function of MSC-EXOs in cerebral ischemia-reperfusion (I/R) injury was the subject of a study. The findings demonstrated that miR-26a-5p-carrying MSC-EXOs reduced I/R damage in mice by preventing microglia from apoptosizing by suppressing CDK6. According to this study, MSC-EXOs are being investigated as a potential therapeutic option for cerebral I/R injury.[159] A study was carried out to determine how hMSC-EXOs affected the suppression of I/R-induced apoptosis and autophagy. By upregulating Bcl-2, downregulating Traf6, and activating mTORC1, hMSC-EXOs dramatically reduced H/R damage as seen by enhanced cell survival, decreased lactate dehydrogenase (LDH), and decreased apoptosis.[160] Another study looked into the molecular mechanisms underpinning oridonin's role in the prevention and treatment of ischaemia/reperfusion (IR)-induced damage as well as the function of BM-MSC-EXOs in IR-induced damage. BM-MSC-EXOs inhibited the progression of IR-induced myocardial damage by down regulation of Beclin-1, ATG13 and Bcl-2, conversely Apaf1 and Bax were significantly up-regulated in IR rats.[161] Exosomes derived from cochlear spiral ganglion progenitor cells prevent cochlea damage from ischemia-reperfusion injury via inhibiting the inflammatory process.[162] An in vitro study showed that exosomes from BM-MSCs prevented acute SCI's rupture of the blood-spinal cord barrier by inhibiting the

TIMP2/MMP pathway.[163] Ke et al studied the effect and potential mechanism on retinal Müller cells and retinal function using rat retinal tissues. Human embryonic stem extracellular vesicles (hESEVs) were injected into the vitreous cavity of RCS rats. The findings showed that RCS rats had more dedifferentiated Müller cell-like retinal progenitor cells at the postnatal 30-day.[164] The presence of many CHX10-positive cells in the retinal inner layer of RCS rats after hESEV injection is proof that hESEVs encouraged Müller cells to dedifferentiate and retrodifferentiate into retinal progenitor cells. By controlling the expression of Oct4 in Müller cells through HSP90 mediation in MVs, hESEVs also facilitated the retrodifferentiation of Müller cells into retinal progenitor cells. Exosomes containing hypoxia-inducible factor 1-alpha were implanted into the damaged spinal cord by encapsulation in a peptide-modified adhesive hydrogel to create a pro-angiogenic treatment for SCI models. The local delivery of exosomes was made possible by the sticky peptide PPFLMLLKGSTR-modified hyaluronic acid hydrogel, which also supplied the spinal cavity left vacant by spinal cord injury.[165] The function of hBMSCs-exosomes in controlling immune response and neuronal function.[166] Human MSCs-EXOs were discovered to protect against nerve injury by modulating the immune microenvironment in a model of neonatal hypoxic-ischemic brain damage. Exosomal miR-145 generated from MSCs was discovered to be able to change the polarisation of microglia towards the anti-inflammatory M2 phenotype in OGD/R-stimulated BV2 cells. Additionally, exosomal miR-145 significantly reduced the expression of FOXO1 while significantly suppressing apoptosis, cell cycle arrest, and oxidative stress in OGD/R-treated BV2 cells.Through the downregulation of FOXO1, MSCs-EXOs enriched with miR-145 were able to have neuroprotective effects in brain damage following ischemic stroke (IS).[167] Moreover, exosomal miR-145 markedly suppressed the apoptosis, cell cycle arrest and oxidative stress in OGD/R-treated BV2 cells and decreased the expression of FOXO1 in BV2 cell exposed to OGD/R and in brain tissues of middle cerebral artery occlusion (MCAO) rats.[167] Exosomes derived from umbilical cord mesenchymal stem cells (UCMSCs) have been shown in rat models of traumatic brain injury (TBI) to promote functional recovery, reduce neuronal apoptosis, and increase functional recovery of brain injury by inactivating microglia and astrocytes.[168] All of these findings provide a fresh viewpoint and treatment plan for the application of MSC-EXOs in regenerative medicine.

Role of MSC-EXOs in Epileptic Encephalopathy

Multiple factors contribute to epilepsy, which is a highly synchronised aberrant discharge of brain neurons that affects both health and behaviour. Epilepsy affects over 65 million people worldwide.[169,170] Exosomes were often isolated from a variety of physiological fluids, including cerebrospinal fluid, blood, urine, and other biological fluids.[48,171] MSC-EXOs have demonstrated positive effects on several neurological conditions, including stroke,[137] multiple sclerosis,[172] Alzheimer's disease (AD),[173] SCI,[174] ischemia,[134] traumatic brain injury,[175] hypoxic-ischemia produced prenatal brain injury,[138,176] and preterm brain injury. The microRNAs found in exosomes from patients with epilepsy and depression's CSF fluid may be able to traverse the blood-brain barrier.[177,178] By specifically connecting with target nervous system cells, exosomes control neuroinflammation of the central nervous system. Targeting hippocampal astrocytes, stem cell-derived exosomes reduced inflammation and corrected status epilepticus-induced learning and memory deficits in mice.[48] Micro RNAs including miR-27a-3p, miR-328-3p, and miR-654-3p are found in exosomes produced from plasma, which are thought to be possible indicators for people with epilepsy.[179] According to an in vitro study, overexpression of miR-132 in hippocampal neuronal culture dramatically increases the frequency of epileptic discharge in epileptic neurons and is associated with the onset of epilepsy.[180] The epileptogenic factors generated by transforming growth factor beta 1 (TGF-1) and interleukin-1 beta (IL-I) are thought to be negatively regulated by miR-132.[181] MicroRNAs found in exosomes, namely miR-219 and miR-338, have been shown to be resistant to demyelination.[182,183] Exosome-mediated transfer of microRNAs like miR-219 and miR-338 into oligodendrocytes was demonstrated in an in vivo investigation to result in a larger number of Olig2 than in the control group. According to this study, administration of miR-219/miR-338 improves myelination following spinal cord injury (SCI) and also improves axonal remyelination following nerve damage in the central nervous system to cure epileptic depression.[184] Inflammation in the brain plays a role in the complex process of epilepsy, and the activity of the seizure can encourage the synthesis of inflammatory molecules, affecting the severity of the epilepsy and the frequency of recurrence.[185,186] For instance, the patients cerebrospinal fluid had much greater levels of the pro-inflammatory cytokine IL-1.[187,188] The elevated level of IL-1 exhibits a favourable connection with depression.[189] Furthermore, according to another study, IL-1 knock-down in the hippocampus can

significantly improve memory deficits, anxiety, and depressive-like behaviour in mice induced by lipopolysaccharide (LPS), which is caused by downregulation of the neuropeptides brain-derived neurotrophic factor (BDNF) and LPS-induced neuropeptide (VEGF).[190] According to a therapeutic investigation, the expression of IL-1 was dramatically elevated after therapy with MSC-EXOs for retinal detachment.[191] According to an animal study, MSC-EXOs revealed anti-inflammatory action by reducing the amount of proinflammatory cytokines and inflammatory indicators in cerebrospinal fluid from sepsis syndrome (SS) animals as compared to the control group. It is well known that IL-1β disrupts blood brain barrier and this dysfunction leads to epilepsy. This theory is supported by an in vitro model study that found that overexpressing miR-132 lowers IL-I production, which in turn lowers blood-brain barrier disruption.[192] After the seizure and expression of miR-132 reduce the expression of MMP-9 to protect the integrity of the blood-brain barrier by lowering tight junction protein degradation, blood-brain barrier malfunction results in an elevated level of MMP-9 concentration.[193–197] All of these research came to the conclusion that miR-132 is important in the treatment of epilepsy because it increases anti-inflammatory effects and safeguards the blood-brain barrier's integrity. An in vivo investigation utilising a mouse model showed that intranasal (IN) delivery of hMSC-derived EVs twice within 24 hours effectively suppressed "cytokine storm" in the hippocampus. Reduced levels of pro-inflammatory proteins were linked to cytokine storm blockage. Reduced levels of pro-inflammatory cytokines including TNF- and IL-1 and elevated levels of the anti-inflammatory protein IL-10 were seen in the hippocampus as a result of cytokine storm blockade.[198] The advancement of epileptogenic alterations is slowed down by the administration of hMSC-EVs, as is the case with chronic epilepsy. Intra nasal delivery of EVs modifying abnormal long-term plasticity, such as aberrant mossy fibre sprouting, the activation of mTOR pathway, or psychiatric comorbidities, linked to epilepsy.[199–206]

Role of MSC-EXOs in Parkinson's Disease

The second most prevalent neurological disease in the world is Parkinson's disease (PD).[207] Nearly 0.3% of the population has PD, and those over the age of 65 make up 1% of those who are affected.[208,209] Clinical signs of Parkinson's disease (PD) patients include bradykinesia, postural instability, and resting tremor. Dopaminergic neurons in the SNpc are still dying, which is one of many mechanisms that contribute to the pathophysiology of PD.[210] The histological development of Lewy bodies, which predominately contain misfolded α-synuclein, is a hallmark of Parkinson's disease.[211] The misfolding, aggregation, and lewybody-induced deposition of α-syn cause neurotoxicity in PD. The neurotoxicity caused by non-cell autonomous mechanisms and the transmission of α-synuclein from cell to cell are the fundamental causes of Parkinson's disease (PD).[212] Parkinson's disease aetiology significantly depends on the level of α-synuclein. A key factor in the development of Parkinson's disease is cell dysfunction in those that contain α-synuclein.[213] By delivering essential biological molecules to neurons via exosomes, astrocytes shield dopaminergic neurons from the oxidative stress and iron-mediated toxicity brought on by dopamine metabolic products in PD patients. Therefore, protection of astrocyte-neuron contact is a crucial step in eliminating the PD's root cause.[214] MiR-200a-3p, which is found in exosomes produced from astrocytes, inhibits the mitogen-activated protein kinase kinase 4 (MKK4) pathway to stop MPP(+)-induced apoptotic cell death.[215] There are currently no proven and viable treatments for PD. Therefore, the development of novel medications or therapeutic techniques to treat PD is imperative. The majority of medications on the market are unable to pass through the blood-brain barrier (BBB).[216] Exosomes, on the other hand, can act as natural nanoscale vesicles that can carry drugs over the BBB.[217,218] According to rat models of Parkinson's disease (PD), exosomes made from MSCs appear to be a viable therapeutic approach for the treatment of a number of diseases including Parkinson's disease.[219,220] The motor and histological symptoms of 6-hydroxydopamine (6-OHDA) may be partially reversed by injection in the SNpc-STR route.[221] Exosomes containing dopamine, for instance, showed potential therapeutic effects and decreased toxicity in the PD mouse model.[222] MSC-EXOs may be able to restore dopaminergic neurons in the 6-OHDA animal model of PD, suggesting that this may be a possible treatment for the disease.[223] Studies using animal models showed that MSC-EXOs carry miRNAs that enhance neurogenesis and neuroinflammation. In MSC-EXOs, miR-21, miR-143, and miR133 are significantly influencing immunological regulation, neuronal apoptosis, and neuerite outgrowth.[224] According to Xin et al, MSC-EXOs administered intravenously increased neurogenesis, neurite remodelling, and angiogenesis while reducing neuroinflammation, oxidative stress, and cell death (Figure 3). MSC-EXOs administrations in a brain model diminish inflammation.[225] Additionally, MSC-EXO injection demonstrated

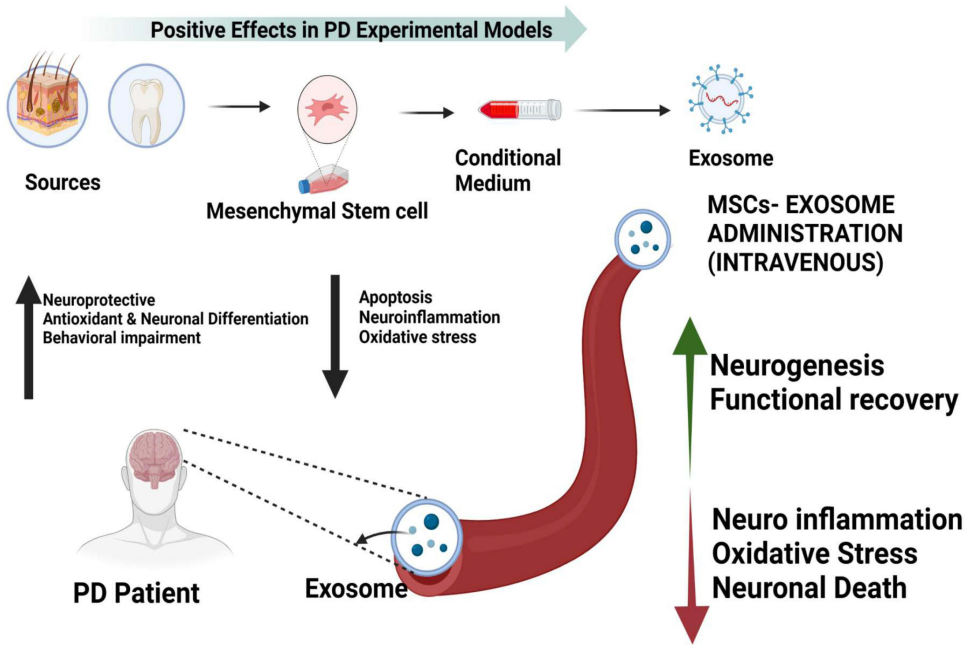

Figure 3 Neuroprotective and other beneficial effects of MSC-EXOs in PD patients. Intravenous administrations of exosomes are able to cross the blood-brain barrier (BBB) and protects neurons by exhibiting reducing inflammation, oxidative stress and cell death. Created with BioRender.com.

effective treatment for SCI by lowering inflammation and encouraging neuro-regeneration in injured rats.[226,227] In in vitro (6-OHDA) models of PD, MSC-EXOs were discovered to be able to rescue DAn, offering a possible regenerative treatment for this condition.[132] According to a study, exosomes from neurons, astrocytes, and oligodendrocytes may be beneficial as a biomarker for Parkinson's disease (PD).[228] MSCs-EXOs expressing miRNAs work in concert with neuronal cells to reduce neuroinflammation and promote neurogenesis in PD animal models, and they also offer a potential treatment for PD.

Role of MSC-EXOs in Cardiovascular Diseases

Cardiovascular diseases (CVDs) are a major cause of mortality worldwide and have become a public health priority. The main causes of CVDs are low levels of cardiac progenitor cell proliferation and insufficient myocyte proliferation in existing myocytes.[229] Recent research has shown that MSC-EXOs are important in cardio-protective functions. Stem/progenitor cell transplantation is regarded as an effective therapeutic approach that can replace missing cardiomyocytes and enhance contractility.[230] A rat myocardial infarction (MI) model research that used vesicles from hBM-MSCs showed that these substances had cardioprotective properties.[231] Signal transducer and activator of transcription 3 (STAT3) pathways are inactivated by MSC-EXOs, and miR-204 is increased in the lung cells, which reduces vascular remodelling and hypoxic pulmonary hypertension in mice.[232] Tube formation, T cell inhibition, the reduction of infarct size, and the restoration of cardiac systolic and diastolic performance were all facilitated by BM-MSC-EXOs.[233,234] BM-MSC-EXOs harbouring miR-221 demonstrated anti-apoptotic and cardioprotective effects by suppressing PUMA expression.[235] Exosomes from BM-MSC containing miR-19a decreased the infarct size and restored cardiac function in a rat model of acute MI by downregulating PTEN and activating the Akt and ERK signalling pathways.[236] When cardiac MSC-EXOs are delivered, cardiac function is improved by encouraging cardiac angiogenesis and triggering cardiomyocyte (CMC) proliferation through the production of chemokines and growth factors.[237] Different miRNAs enriched in MSC-EXOs, such as miR-221 and miR-19a, are capable of producing stronger protective effects on CMC and also the regeneration of ischemia injury by boosting the survival of myocytes in ischemic injury by lowering the expression of the p53-upregulated apoptosis modulator (PUMA).[238,239] The survival and bioenergetics of cardiac cells were directly impacted by MSC-EXOs. The findings showed a decrease in oxidative stress and an increase in the creation of molecules high in energy, such ATP and NADH.Additionally, the modification of pro- and anti-apoptotic pathways is a function of exosomes.[240]

Exosomal miR-210 was shown to stimulate angiogenesis and maintain heart function in an in vitro and in vivo model study.[241] By inhibiting PTEN, activating Akt, and upregulating Bcl-2 and VEGF, endometrium-derived MSC exosomes have demonstrated cardioprotective actions, which ultimately result in the recovery of cardiac function. Exosomes produced by stem cells have been proven in studies to have cardioprotective benefits by delivering a range of cargos to damaged cells.[242] Stem cell-based therapies have been shown in both animal and human studies to be effective in treating CVDs by replacing lost cardiomyocytes and enhancing contractility.[243] Exosomes made from stem cells were able to repair and protect after transplantation.[244] Human umbilical vein endothelial cells ability to form tubes was considerably improved by MSC-EXOs. They also reduced infarct size; degrade T-cell activity by preventing cell proliferation.[233] In vivo murine auricle ischemic injury model revealed that exosomes produced from human placenta-derived mesenchymal stem cells may induce angiogenesis by factors of both angiogenic and angiostatic factors, which improved endothelial tube formation.[245] Comparing hucMSCs to hucMSCs with Akt transfection, angiogenesis is dramatically increased. Additionally, Akt-Exo showed dramatically increased levels of platelet-derived growth factor D (PDGF-D) expression.[246] Exosomes from mouse bone marrow mesenchymal stem cells (BMSCs) expressing Mir9-3hg were used to treat HL-1 mouse cardiomyocytes with hypoxia/reoxygenation (H/R), which promoted cell proliferation, increased glutathione (GSH) content, and decreased iron ion concentration, reactive oxygen species (ROS) level, and ferroptosis marker protein levels. Additionally, the administration of BMSC-EXOs to animals receiving I/R therapy improved their cardiac function by preventing cardiomyocyte ferroptosis by altering the Pum2/PRDX6 axis.[247] According to Gong et al angiogenesis is boosted by nano-sized EVs generated from genetically altered MSCs that overexpress GATA-4.[248] When compared to exosomes from the cells of origin, those produced from multiple myeloma BM mesenchymal stromal cells (BM-MSCs) had larger concentrations of oncogenic proteins, cytokines, and adhesion molecules, which hindered the proliferation of MM cells.[249] Exosomes from FNDC5-preconditioned BM-MSCs have been shown to have anti-inflammatory properties and to enhance M2 macrophage polarisation through the NF-B signalling pathway and Nrf2/HO-1 Axis.[250] Exosomes from BM-MSCs, has been shown to have protective effects against myocardial ischemic injury. It also plays a significant role in the regulation of the process by inhibiting the expression of PTEN, activating the PI3K/AKT signalling pathway, and subsequently preventing the apoptosis of injured cardiomyocytes. Exosomes generated by human trophoblast stem cells (TSC) and miR-200b inhibitor both reduced primary cardiomyocyte death. Similar improvements in cardiac function were shown in mice treated with TSC-EXOs and AAV-miR-200b inhibitor, together with a decrease in inflammation and apoptosis. TSC-EXOs reduced the heart damage caused by doxorubicin by acting as antiapoptotic and anti-inflammatory agents.[251] Hypoxia-conditioned and normoxic-conditioned generated exosomes were injected intramyocardially in a study to determine the mechanism of cardiomyocyte survival. The study discovered that the presence of encapsulated lncRNA-UCA1 in exosomes protected cardiomyocytes and elevated levels of the anti-apoptotic protein BCL2.[252] The processes attenuating mitochondrial fission and cellular senescence of cardiomyocytes generated by SD/H were attenuated by exosomes obtained from Hemin-pretreated MSCs, which markedly enhanced cardiac function and decreased fibrosis. By controlling the HMGB1/ERK pathway, Hemin-MSC-EXOs prevented SD/H-induced cardiomyocyte senescence in recipient cardiomyocytes.[253] The impact of Nrf2-overexpressing BMSC-EXOs on rats with atrial fibrillation (AF) was investigated. According to the study's findings, injecting Lv-Nrf2 exosomes into AF-affected mice significantly reduced AF durations, decreased cardiomyocyte apoptosis, decreased AF-driven atrial fibrosis, and inhibited inflammatory responses. By activating the Nrf2/HO-1 pathway, exosomes containing overexpressed Nrf2 prevented AF-induced arrhythmias, myocardial fibrosis, apoptosis, and inflammation.[254] Bax and caspase expression were shown to be downregulated in exosome-overexpressing cells, whilst Bcl-2 expression was found to be upregulated. After intramyocardial injection of exosomes overexpressing miR-338 in rats, cardiac function was noticeably improved.[255] A study using a rat model showed that exosomes containing miR-146a greatly reduced AMI-induced apoptosis, an inflammatory response, and fibrosis by suppressing EGR1 expression, which in turn reversed the activation of TLR4 or the NF-B signal caused by hypoxia or AMI.[256] Apoptosis and fibrosis levels were dramatically lowered in mice treated with differentiated cardiomyocytes from induced pluripotent stem cells (iCM-Ex), suggesting a considerable improvement in the heart's function following myocardial infarction.[257] Circulating exosomal lncRNA-UCA1 may be a promising new biomarker for the detection of AMI, as shown by intramyocardial injection of lncRNA-UCA1-knockdown-Hypo-Exo in a rat model. Hypo-Exo lncRNA-UCA1

has a cardioprotective effect via the miR-873-5p/XIAP axis VEGF-targeting miR-16, miR-24, miR-29, miR-146 that binds to and inhibits EGFR mRNA-27, miR-294, and miR-494 are all present in enhanced levels.[73,79,252,258] According to in vitro and in vivo research, BMSC-EXOs efficiently reduced intestinal pathological injury, decreased intestinal cell apoptosis, relieved oxidative stress, and controlled the PTEN/Akt/Nrf2 pathway. Additionally, the oxygen and glucose deprivation/reperfusion drastically decreased the exosomes carrying miR-144-3p, and miR-144-3p directly targets PTEN to control its expression.[259] BMSC-derived exosomes containing lncRNA were cultured with HL-1 mouse cardiomyocytes that had been subjected to hypoxia/reoxygenation (H/R). By regulating cell proliferation, elevating glutathione (GSH) content, and lowering iron ion concentration, reactive oxygen species level, and ferroptosis marker protein levels, Mir9-3hg inhibits cardiomyocyte ferroptosis in ischemia-reperfusion mice via the Pum2/PRDX6 axis.[260] A study was created to look at the cardioprotective effects of MSCs-EXOs in a model of cardiotoxicity caused by DOX/Trz. By altering the NRG-1/HER2, MAPK, PI3K/AKT, PJNK/JNK, and PSTAT/STAT signalling pathways, the intraperitoneal delivery of MSCs-EXOs reduced cardiac damage in both protective and curative conditions.[247] Treatment of Exo/NC, Exo/miR-183-5p-Exo/anti-miR-183-5p-Exo increased left ventricular end-diastolic pressure (LVEDP), myocardial infarct size, and apoptosis index (AI) but decreased left ventricular ejection fraction (LVEF), left ventricular fraction shortening (LVFS), and left ventricular systolic pressure (LVSP) by altering the expression of FOXO1 and through the miR-15a/15b/16/NFATc3/OCN axis and osteogenic transdifferentiation.[261] BM-MSC-EXOs prevent the calcification of human aortic vascular smooth muscle cells.[261] According to the available research, MSC-EXOs can potentially protect against cardiovascular illnesses by reducing oxidative stress, inflammation, and apoptosis (Figure 4).

Role of MSC-EXOs in Angiogenesis

MSC-EXOs are important in the process of angiogenesis. Studies have shown that COVID-19 and other intractable illnesses can be effectively treated using stem cell-based therapies.[262,263] Exosomes may be helpful in reducing damage, enhancing neurological recovery, and promoting wound healing.[264] The efficacy of iMSC-EXOs to lessen limb ischemia and increase angiogenesis after being transplanted into mice with femoral artery excision. In rat ischemic limbs, intramuscular injection of iMSC-EXOs markedly improved microvessel density and blood perfusion. Additionally, iMSC-EXOs induced the expression

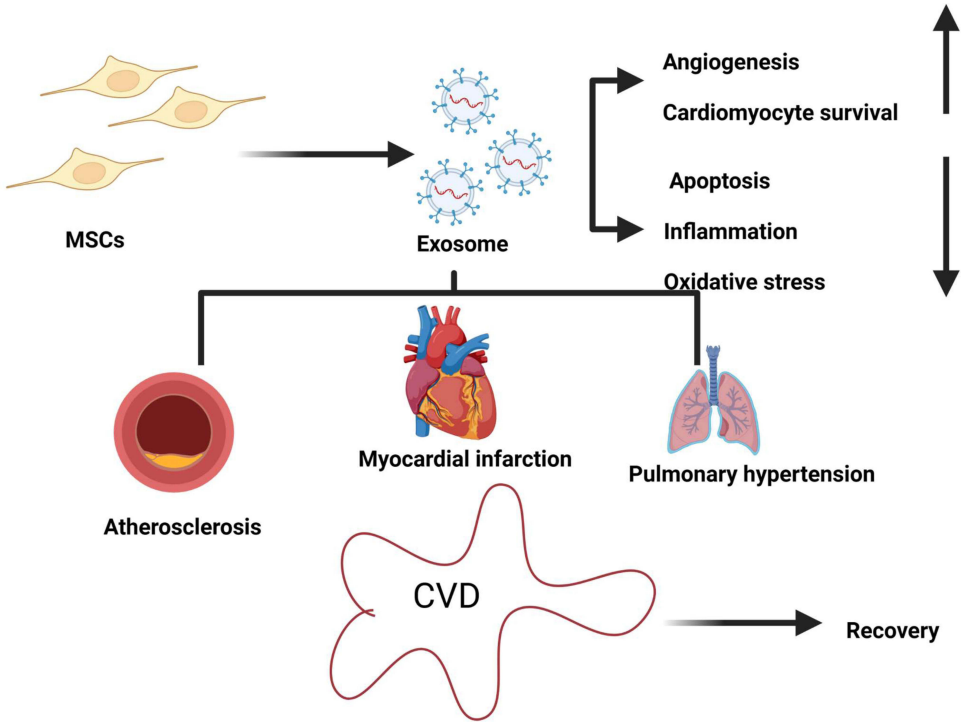

Figure 4 Mesenchymal stem cells derived exosomes exhibits potential therapy for CVDs. MSC-EXOs protects the damaged tissues by inducing angiogenesis and survival of cells through different mechanisms including reducing oxidative stress, inflammation and apoptosis. Created with BioRender.com.

of angiogenesis-related molecules and angiogenic parameters, which are thought to be potential therapeutic strategies for the treatment of ischemic disorders.[265] MiR-185-enriched MSC-EXOs decreased inflammation, blocked angiogenesis and cell growth, and induced cell death.[266] Through the release of anti-apoptotic and pro-angiogenic proteins, extracellular vesicles generated from endometrial mesenchymal stromal cells (endMSCs) demonstrated cardioprotective activity. The results of these investigations showed a marked rise in the overall number of blastomeres in enlarged murine blastocysts. Additionally, EV-endMSCs caused embryos to secrete pro-angiogenic molecules, showing a concentration-dependent rise in VEGF and PDGF-AA. The overall number of cells in the blastocyst rises as a result of pro-angiogenic substances, which also promote endometrial angiogenesis, vascularization, differentiation, and tissue remodelling.[267] According to Gong et al, MSCs produced from mouse embryos carry vascular precursor receptors (such as miR-30b) that are transferred to human umbilical vein endothelial cells (hUVECs), which encouraged the development of the hUVECs' tube-like structure.[268] Human induced pluripotent stem cell-derived endothelial cell exosomes (hiPS-EC-Exos) enriched with miR-199b-5p were shown to dramatically promote neovascularization in a mouse model of hind limb ischemia. A further in vitro study demonstrates how miR-199b-5p induces overexpression of the vascular endothelial growth factor receptor 2 (VEGFR-2) by altering the Jagged1/Notch1 signalling pathway. This transcriptional upregulation of VEGFR-2 positively regulates HUVEC migration and proliferation.[269] Exosomes are said to have anti-inflammatory and pro-angiogenic effects by targeting the ROCK1/PTEN pathway and delivering miR-132 and miR-146a.[270] These results imply that exosomes are thought to be interesting treatment candidates for conditions linked to angiogenesis and inflammation. HuR's impact on VEGF expression and angiogenesis in human umbilical vein endothelial cells (HUVECs) grown with exosomes produced from ADSCs. Through the stabilisation and overexpression of VEGF, human antigen R (HuR) encourages the angiogenesis of HUVECs co-cultured with exosomes produced from ADSCs.[271] Exosomes produced by cancer stem cells were examined to determine their contribution to the growth of tumours.[272] In order to achieve this, fibroblasts (FBs) were used as recipient cells and Piwil2 induced cancer stem cells (Piwil2 iCSCs) as exosome producing cells. The exosomes produced by Piwil2 iCSC were found to be uniformly sized (30–100 nm in diameter), oval or spherical, membrane-coated vesicles. The findings showed that MMP2 and MMP9 expression levels were elevated in Piwil2 iCSC EXOs, which boosted angiogenic capabilities. By down-regulating VEGFA, MMP-9, and ANGPT1, human deciduous exfoliated teeth (SHED-EXOs) prevent cell proliferation and migration and cause death in HUVECs. When miR-100-5p and miR-1246 are delivered from SHED-EXOs to endothelial cells, tube formation is reduced due to the down-regulation of VEGFA expression.[273] While VEGFR signaling, inhibitors reduce endothelial cell permeability, glioblastoma stem-like cell-derived EVs enriched in VEGF-A showed improved angiogenesis and vascular permeability. In a rat model, human induced pluripotent stem cell-derived exosomes (hiPSC-MSC-EXOs) were administered subcutaneously near wound sites.[274] Histological and immunofluorescence tests were performed to determine the effectiveness of the hiPSC-MSC-EXOs. The findings showed that hiPSC-MSC-EXO transplantation to wound sites led to rapid re-epithelialization, decreased scar widths, and the promotion of collagen maturity, as well as promoted numerous angiogenic processes.[225] The function and probable mechanism of MALAT1-201 in preeclampsia (PE) model demonstrated that exosomes from MSCs that overexpressed MALAT1-201 were collected, and a number of angiogenic experiments were subsequently carried out. The findings suggested that MSC-EXOs expressing MALAT1-201 increased proliferation and migration while inhibiting trophoblast death. MSC-EXOs work as an anti-angiogenic agent in addition to being involved in angiogenic processes as a whole.

Role MSC-EXOs in Cancer

Exosomes produced by MSCs are crucial for both drug resistance and pro-angiogenesis. MSCs have the power to trigger immunological responses, tissue healing, cell proliferation, and tumour progression control.[275] As regulators of the tumour niche, MSCs release exosomes, and their involvement in tumorigenesis and metastasis is controlled by a number of growth factor receptors, including EGFR and PDGFR. Through the AKT (protein kinase B), PKC, and MAP kinase pathways, the activation of these receptors by intracellular kinases causes downstream pro-growth signals to be released, which promotes the growth of tumour cells by activating the AKT/ERK1/2 signalling pathway.[276] Through the activation of pathways like p53, AKT, and c-Jun N-terminal kinase (JNK), BM-MSC-EXOs promoted proliferation and migration.[277] BM-MSC-EXOs contains miR-221 potentially accelerating their growth and increasing their invasive capacity.[278] MSC-EXOs promote the growth and spread of breast cancer by activating Wnt signalling and establishing

a favourable microenvironment.[279] MSC-EXOs promote VEGF production in tumour cells, promoting the development of the tumour by stimulating the ERK1/2 pathway. Exosomes from AT-MSCs that contained platelet-derived growth factor encouraged angiogenesis.[103] MSC-EXOs are involved in angiogenesis and promote it by transferring miR-NA-30b to endothelial cells, among other chemicals like miRNAs, IL-6, IL-8, and TGFB. Through the stimulation of the AKT/eNOS pathway and upregulation of miR-221-3p expression, MSC-EXOs promote angiogenesis.[268,280,281] According to Liang et al, increasing expression of miR-144 reduced the amount of S phase-arrested cells, colony formation, and cell proliferation in NSCLC via down-regulating CCNE1 and CCNE2.[282] Exosomal miR-144 produced by BM-MSCs also resulted in limited NSCLC cell growth and colony formation. MiR-21-5p transfected MSC-EXOs could greatly increase osteosarcoma cell proliferation and invasion and significant levels of human bone marrow MSCs produced miR-21-5p-exosomes stimulated the PI3K/Akt/mTOR pathway by inhibiting the expression of PIK3R1 in osteosarcoma cells.[283] By transporting several microRNAs, the exosomes released by BM-MSC-EXOs encourage the growth of lung cancer and osteosarcoma cells.[284,285] Human umbilical cord MSC-EXOs carrying microRNA-375 down regulated ENAH to retard esophageal squamous cell carcinoma progression, and AD-MSC-EXOs promote the differentiation of Th17 and Treg from naive CD4+ T cell to exert anti-tumor ability by carrying miR-10a.[286,287]

Cancer stem cells, also known as tumor-initiating cells, are the small population of cells in a tumor bulk, which represent a critical subset of the tumor population.[288] EVs actively participate in cell-to-cell interactions by shutting cellular components and these EVs are promoted non-CSCs to acquire stem-like properties, leading to the enhanced tumorigenicity.[289–291] EVs derived from CSCs carry the stemness markers of parent cells, which possess the ability to reprogram non-CSCs to obtain a stem-like phenotype.[292] Exosomes derived from CSCs are wrapped with proteins and related to activation of tumor stemness signaling pathways, which may directly activate the stemness-related signaling pathways on non-CSCs, thereby facilitating their stem-like phenotype.[290] Exosomes derived from clear cell renal cell carcinoma (CCRCC) stem cells accelerated the process of EMT and promoted lung metastasis and these exosomes containing miR-19b-3p strongly promoted tumor cell EMT through targeting PTEN signaling pathway.[292] Similarly, a microvesicle shed by renal CSCs significantly increases the lung metastasis of renal cancer cells in mice.[293] CSCs derived EVs carrying pro-angiogenic molecules, which promoted tumor angiogenesis through cross talk with endothelial cells and other stromal cells in the microenvironment.[38,274,294] Exosomes derived from CSCs contains miR-26a significantly enhanced tumor angiogenesis and increased the expression levels of VEGF, MMP-2, and MMP-9.[294] Collectively, multiple lines of evidence suggest that MSC-EXOs can modulate the tumour microenvironment and play important roles in tumour development, particularly, cancer resistance to chemotherapy agents, radiotherapy and immunotherapy.

Role of MSC-EXOs in Autoimmune and Inflammatory Diseases

Studies have been focused on EVs, which are utilized as a cell-free therapy and elucidate its potential significance of MSC-EXOs in the treatment of autoimmune diseases. Autoimmune diseases are potentially influencing multiple organs and systems, such as circulatory, respiratory, the motor and digestive system. Compared to men, women are more affected. Glucocorticoids and immunosuppressive medications are the only therapy for autoimmune illness that are currently accessible. However, using steroids frequently results in undesirable side effects.[295] Increasing evidence indicates that MSC-EXOs play a crucial role in autoimmune disorders by decreasing immunological responses that are driven by immune cells. Exosomes from MSCs have a paracrine route that can modify innate and adaptive immune cells.[296,297] MSC-EVs encourage M1 macrophage polarisation to M2 macrophages, which are associated with lower levels of VEGF-A, IFN-g, IL-12, and TNF-alpha and increased levels of IL-10.[298–302] By establishing an immunosuppressive M2 phenotype shown by colonic macrophage polarisation, MSC-EXOs reduces dextran sodium sulphate (DSS)-induced colitis. Mice treated with exosomes produced more IL-10-producing M2 macrophages than those in the control group.[302] Mice treated with exosomes containing miR-146a from human umbilical cord-derived MSCs (hUC-MSCs) successfully promote macrophage polarisation into an anti-inflammatory M2 phenotype, increasing survival.[303] According to Zhao et al, AD-MSC-EXOs increased the production of IL-10 and Arg-1 in macrophages while also promoting an M2 macrophage polarisation by activating STAT3 transcription.[304] Olfactory ectomesenchymal stem cell-derived exosomes (OE-MSC-EXOs) activate the JAK2/STAT3 pathway in myeloid-derived suppressor cells (MDSCs) and enhance their inhibitory function by increasing the levels of arginase, ROS, and NO. Additionally, these exosomes produced IL-6, which promoted the immunosuppressive function of MDSC.NK cells experience an immunosuppressive effect

from MSC-EVs, which inhibits their growth, activation, and cytotoxicity.[305] Through the surface expression of TGF-β, human foetal liver (FL) MSC-derived exosomes (hFL-MSCEXOs) mediated downstream TGF-β/Smad signal transduction to prevent the proliferation and activation of NK cells.[306] Internalization of MSC-EVs through $CD19^{+}$/$CD86^{+}$ B cells inhibited B cell proliferation, differentiation, and antibody production, as well as inhibited memory B cell maturation.[307] MSC-EVs exert dose-dependent anti-inflammatory effects by inhibiting B cell maturation and inducing Bregs in lymph nodes in a murine model of collagen induced arthritis (CIA) and delayed-type hypersensitivity (DTH). A study suggests that MSC-EVs carrying miR-155-5p inhibited B cell proliferation and reduced the activation capacity through downregulate the PI3K/Akt signaling pathway.[308] Tavasolian et al investigated the therapeutic effect of miR-146a/miR-155 transduced MSC-EXOs on the immune response in collagen-induced arthritis (CIA) mice.[309] MiR-146a-transduced MSC-EXOs increased expression of forkhead box P3 (Fox-P3), TGF-β and IL-10 and miR-155 further increased the gene expressions of RORγt, IL-17, and IL-6 in these mice.

Multiple Sclerosis (MS)

The central nervous system (CNS) is affected by the chronic autoimmune and inflammatory disease known as multiple sclerosis.[310] The most widely utilised animal model of MS is called experimental autoimmune encephalomyelitis (EAE).[311] The CNS is the primary pathogenic component in MS, and it is activated and recruited by auto-aggressive CD4+ and CD8+ T cells. Therapies that treat diseases might have undesirable side effects. MSC-EXOs were used to create an alternate manner of treatment.[312–314] By delivering the tolerogenic molecules to the autoreactive immune cells, MSC-EXOs establish peripheral tolerance towards autoreactive T cells.[315,316] MSC-derived extracellular vesicles have immunomodulatory effects on splenic mononuclear cells (MNCs) of EAE mice, such as reducing proliferation and increasing the quantity of IL-10, and these immunomodulatory effects are controlled by PD-L1, galectin-1, and TGF-β.[317] Intravenous administration of MSC-EXOs recovered Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease.[172,318] MSC-EXOs polarize microglia cells mainly into the M2 phenotype and consequently improve clinical scores of EAE. MSC-EXOs improved proliferation of oligodendroglia cell line (OLN93) through reduction of both inflammatory responses and demyelinated lesions in the CNS of EAE mice.[319,320] Microglia are prevented from acquiring an M1 phenotype by BM-MSC-EXOs-mediated treatment, which also encourages M2 phenotypic polarisation and the release of anti-inflammatory cytokines. Treatment with MSC-EXOs and BM-MSC-EXOs dramatically reduced the neurobehavioral symptoms of EAE rats, as well as inflammation, demyelination, and polarisation of CNS microglia.[321] MSC-EXOs can transport mRNA, miRNA, and proteins and control the polarisation of microglia. MSC-EXOs can transport mRNA, miRNA, and proteins and control the polarisation of microglia and significantly encouraged the establishment of Tregs and slowed the progression of EAE.[322] MSC-EXOs therefore exhibit a lot of promise for the treatment of MS.

Rheumatoid Arthritis (RA)

RA is a long-lasting, inflammatory, and systemic autoimmune condition characterised by symptoms of joint degeneration and eventual loss of function brought on by both genetic and environmental causes.[323,324] Disorders of innate and adaptive immunity, which lead to immune complex-mediated complement activation, are defining characteristics of RA.[325,326] Antibodies or soluble decoy receptors are used to combat pro-inflammatory cytokines such GM-CSF, TNF-, and IL-6.[325,326] Recent research suggests that MSC-EXOs decrease the immune system's response to RA.[327,328] Injection of co-gene DBA/1 fibroblasts secreting GAL-1 slowed the progression of arthritis by preventing proliferation and lowering the proportion of mature T and B cell subsets.[329] MSC-EXOs have been shown to have anti-inflammatory effects on T and B lymphocytes in the collagen-induced arthritis (CIA) mouse model.[330] The induction of TGF-β and IL-10 by vesicles derived from MSCs are less effective compared to MSCs alone.[331] Chen et al reported that MSC-EXOs carrying miRNA-150-5p, target the matrix metalloproteinase 14 (MMP14) and subsequently, decrease migration and invasion of fibroblast-like synoviocytes (FLS) and downregulated the process of angiogenesis responsible proteins like MMP14 and VEGF in HUVECs.[332] The serum and synovial fluid levels of the autoreactive infiltrating chemokines CCL2 and CXCL12 were considerably reduced after intraarticular injection of hUCMSC-derived exosomes.[333] Pigs receiving intra-articular injections of BM-MSC-EVs saw a decrease in the number of synovial lymphocytes and a down-regulation of TNF-α production, which served to reduce inflammation.[334] Altogether, MSC-EVs exhibited potential beneficial effects for the treatment of RA. Exosome-derived lncRNA affected the migration of activated macrophages and significantly decreased the levels of MMP-2 and MMP-13.[335]

MiR-17 suppresses regulatory T cells by targeting TGFBR II in RA. Exosome-derived lncRNA altered the movement of activated macrophages and drastically reduced the levels of MMP-2 and MMP-13. miR-155 and miR-146-a are found in exosomes generated from DCs have a significant role in regulating immunological response and inflammatory response in RA.[336–339] Exosomal ncRNAs collectively contribute to the onset and progression of RA through controlling immunological and inflammatory cells.

Type 1 Diabetes Mellitus (Insulin-Dependent Diabetes Mellitus)

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease influenced by genetic, immune, and environmental factors. Insulin resistance and low insulin levels are caused by the autoimmune loss of pancreatic cells that produce insulin.[340] The cause of type 1 diabetes and its contributing variables are the loss of immunological tolerance in autoreactive B cells, CD4+T cells, and CD8+.[341] Ezquer et al demonstrated that anti-diabetic effects of MSC by normalized Th1/Th2 response in diabetic group compared to control and its restore immune response balance in pancreas by modulation of endocrine activity.[342] MSC-EXOs improved diabetic rat's cognitive deficits and restored damaged astrocytes and neurons.Co-administration of MSC-EXOs and islet transplantation increased regulatory T cell activities, T cell populations, and upregulation of IL-4, IL-10, and TGF- cytokines while downregulating IL-17 and IFNγ- cytokines and suppressing PBMC proliferation. By suppressing the growth of Th1 cells, it improves graft survival in a syngeneic mouse model of T1DM and delays the onset of autoimmune diabetes.[343,344] Exosomes from BM-MSCs alleviated cognitive impairment in diabetic rats by mending damaged neurons and astrocytes.[345] When ADMSC-EXOs are administered, anti-inflammatory factors (such IL-10) are expressed more frequently, the Treg population grows, and the immune system is suppressed, resulting in autoimmune damage.[346] According to a study, MSC-EVs reduced islet inflammation, which increased plasma insulin levels and prevented mice from developing type 1 diabetes.[347]

Uveitis

Uveitis is an autoimmune condition that severely impairs vision.[348] Corticosteroids were employed to overcome the vision impairment. However, prolonged steroid use results in glaucoma. Consequently, a fresh approach to treatment is required. For instance, Bai et al showed that MSC-EXOs from the human umbilical cord lessened the severity of EAU by preventing inflammatory leukocyte infiltration into the eyes.[349] Exosomes containing CD73 interact with CD39 on activated immune cells to inhibit proliferation through an increase in adenosine synthesis. Using EAU mice, an in vivo investigation showed the exosome-treated EAU mice showed eyes that resembled normal mouse retinas, free of structural damage and inflammatory infiltration. As a result, the retinal photoreceptors and other organs in the untreated mice suffered serious damage.[347,349] According to a different study, mice treated with MSC-EXOs demonstrated significantly lower CD3+ T cell infiltration into the retina and lower levels of macrophage migration to the retina than EAU mice treated with PBS.[349] MSC-EVs improved EAU by directly inhibiting the development of Th1 and Th17 cells rather than inducing Tregs to inhibit T cell proliferation.[347]

Systemic Lupus Erythematosus (SLE)

SLE is a systemic, persistent autoimmune illness that is impacted by a number of variables. Multi-organ damage results from SLE's increased inflammation and complicated autoimmune diseases.[350–352] Profound T and B lymphocyte activation, elevated levels of pro-inflammatory cytokines, and immune complex material sedimentation are the causes of SLE.[353] Immune complex triggers cause nephritis, which is brought on by an influx of sizable inflammatory cells.[354] The administration of hBM-MSCs increased survival rates by lowering autoantibodies and reduced glomerulonephritis by preventing the growth of Tfh in animals.[354] Additionally, allogeneic bone marrow mesenchymal stem cell transplantation (MSCT) may be able to treat various organ dysfunctions.[355] The MSC-EXOs' cargoes have a crucial role in the immunological and inflammatory control of SLE.[356,357] Proinflammatory cytokines including TNF-α, IL-1, IL-6, and other inflammatory mediators can be induced by exosomes generated from SLE patients.[357]

Inflammatory Bowel Disease (IBD)

IBD is a chronic, nonspecific, relapsing inflammatory gastrointestinal disease.MSC- EXOs components have potential targets for the diagnosis and treatment of IBD. For instance, an in vivo study using mouse model of IBD revealed that hUC-MSC-EXOs treatment decreased the infiltration of macrophages in colon tissue and inhibited the expression of IL-7.[358] MSC-EXOs carrying miR-146a, effectively down-regulated TNF receptor-associated factor 6 (TRAF6) and IL-1 receptor associated kinase 1 (IRAK1) expression, inhibited pro-inflammatory cytokine and enhanced the expression of IL-10.[359] hUC-MSC-EXOs protects intestinal barrier by down regulation of pro-inflammatory cytokines in colon tissue, and up-regulated the levels of anti-inflammatory cytokines.[360] Mice study revealed that OEMSC-EXOs significantly enhanced the colitis by modulating the immune response of Th-cells.[361] AD-MSC-EXOs significantly recovered the percentage of Treg in the spleen and improved inflammation in DSS induced acute colitis.[362] hBM-MSC-EXOs protects intestinal barrier integrity by down regulation of inflammatory responses, polarized M2b macrophages.[363] Dextran sulphate sodium induced mouse model study suggests that inflammatory responses are significantly controlled by inducing the production of M2 macrophages.[302,364] Mice treated with MSC-EVs promote repair and regeneration of damaged epithelial cells by production of higher levels of immunosuppressive factors (IL-10 and TGF-β) and low level of IL-1β, NO, and IL-18 by depressing NF-κB and iN-OS-driven signaling in 2,4,6-trinitrobenzene sulfonic acid induced colitis.[359,364,365] According to the results of all these findings, MSC-EXOs can act as a significant regulator and novel therapeutic agent by reducing inflammatory responses. They can also successfully block immune responses and promote the survival and regeneration of wounded cells. Although MSC-EXOs play a key role in IBD, further research is still required to pinpoint the molecular basis of MSC-EXOs participation in autoimmune disease.

Role of MSC-EXOs on COVID-19

Patients who had immune-mediated inflammatory diseases were impacted by COVID-19 and were thought to be at a high risk of contracting SARS-CoV-2 and developing severe COVID-19. An overwhelming host immunological response, or "cytokine storm", caused by COVID-19 is characterised by an overproduction of growth factors, chemokines, and pro-inflammatory cytokines like TNF and IL-6.[366,367] Targeting pro-inflammatory cytokines are the best tools and are therapeutic targets in the treatment of patients affected by immune-mediated inflammatory diseases and also involved in re-generation.[368,369] Hence, to find out effective therapies for the treatment of patients with severe stages of the disease like COVID-19 is inevitable MSC-EXOs can promote the survival of alveolar macrophages and change their phenotype from pro-inflammatory (M1) into the anti-inflammatory (M2) polarization, which has been confirmed by at least two studies.[370,371] MSC-EXOs could improve some complications of COVID-19 such as cytokine storm, acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). The stem cell secretome (SCS) showed multifarious activities against ant-fibrotic, anti-inflammatory, immunomodulatory, and angiogenic biological activities.[372–374] MSC exosomes have the capacity to control inflammation through cytokines and immunological response through immune cells.[375,376] According to a study on mice, MSC-EXOs can treat liver damage by reducing the formation of collagen (type I/III) and hepatocytes' shift from epithelial to mesenchymal state. MSC-EXOs significantly modulate immunological responses. MSC-EXOs also include microRNAs (miRNAs), which control key biological processes such cell division, death, and host immune responses.[377] MSC-EXOs are regarded as a suitable vector for the administration of tailored antiviral medications for the treatment of COVID-19 because of their distinct properties.[378] Exosomes produced by MSCs are paracrine effectors that are comparable to the parental cell and have the capacity to sustain healing capabilities, making MSC-EXOs an appealing replacement for MSCs in the treatment of a variety of disorders.[379] Bone marrow derived exosomes, a complex mixture of signalling nanovesicles produced by BM-MSC-EXOs, have the ability to reverse the inhibition of host antiviral defences and down-regulate the cytokine storm that characterise COVID-19.[380] A variety of chemokines, growth factors, mRNA, and miRNA found in BM-MSC-EXOs have anti-inflammatory, regenerative, and immunomodulatory properties. The paracrine and endocrine mediators known as exosomes provide BM-MSCs their ability to repair, making them a good candidate for treating COVID-19.[381] Intravenous administration of bone marrow-derived exosomes reduced alveolar inflammation, enhanced edema clearance, restoration of leaky epithelial membranes, and other sequelae of

cytokine storm.[382,383] BM-MSC-EXOs were used in the first known clinical research to treat severe COVID-19.[384] In patients hospitalised with severe COVID-19, it was found that a single intravenous dosage of bone marrow-derived exosomes corrected hypoxia, immunological reconstitution, and downregulation of cytokine storm without causing any negative consequences. In addition to SARS-CoV-2 ARDS and COVID-19, exosomes from BM-MSCs may be used in a variety of inflammatory disease states, including traditional ARDS, chronic obstructive pulmonary disease, sepsis, autoimmune illness, and cancer.[385–388] In numerous preclinical models, MSC-EXOs demonstrated immunomodulatory and antiinfection properties that had therapeutic potential. Patients with moderate to severe ARDS brought on by COVID-19 may benefit from MSC-EXOs because they can improve oxygenation and reduce cytokine storm.[389] Due to their special abilities to modulate the immune system and reduce inflammation; MSC-EXOs are an intriguing treatment approach for the ongoing COVID-19 epidemic. Most likely, MSC-EXOs can stimulate endogenous repair of wounded lungs as well as prevent the cytokine storm brought on by excessive immune responses. Immune deficiency, inflammation, ARDS, and other lung illnesses may all be treated using MSC-EXOs.[390,391] MSC-EXOs can therefore be utilised to treat pneumonia caused by COVID-19. To combat COVID-19, MSC-EXOs can be used as a nanoplatform for therapies and drug delivery.

The Potential of MSC-EXOs in the Treatment of COVID-19

The primary pathogenesis of COVID-19 is overactivation of the immune system. MSCs are known to induce anti-inflammatory macrophages, regulatory T cells and dendritic cells. At present, the treatment for COVID-19 is mostly symptomatic and supportive, though anti-inflammatory and antiviral treatment has been employed.[392] MSC-exosomes are able to transfer cargoes to target cells and tissues, resulting in changes to gene expression and in the behavior of target cells. MSC-derived exosomes as cell-free therapeutics due to the unique properties of MSC-EXOs including high stability, low immunogenicity, easy storage, and ability to cross the blood-brain barrier compared to their counter parts.[393] MSC-secreted exosomes are shown to both regulate immunity through interacting with immune cells and inhibit the inflammatory response through cytokines.[375,394] Animal study revealed that MSC-derived exosomes potentially change the phenotype of alveolar macrophages (M1) toward an anti-inflammatory state (M2) with enhanced phagocytic activities. Macrophages treated with MSC-derived exosomes were able to reduce the alveolar inflammation in mice bearing the endotoxin-induced lung injuries.[395] MSC-EXOs acted as a TLR signaling mediator and enhanced the transfer of regulatory miR-451 to the macrophages, thereby ameliorating the TNF-α secretion and suppressing the excess inflammatory responses to the lung injury.[396] Exosomes derived from human amnion epithelial cells could suppress the activated neutrophils and T cells proliferation and decrease the percentage of interstitial macrophage in the lungs.[397] MSC-secreted exosomes may be employed in the treatment of immune deficiency, inflammation, ARDS, and other lung diseases.[390,391] Therefore, MSC-secreted exosomes play significant role for the treatment of COVID-19. A study observed that miR-21-5p delivery by the MSC-exosomes protected lung epithelial cells against oxidative stress-induced cell death.[398] In vivo study suggested that administration of MSC-exosomes increased the proliferation of lung epithelial cells. These exosomes contain growth factor FGF2, which has the regenerative capacity and is important in lung development.[399] Varderidou-Minasian et al reported that the quick entry into the blood, circulation, retention and clearance of MSC-EXOs is significantly potential compared to MSCs.[400] For example, the detection of MSCs in the lung parenchymal cells found that after 24 hrs of treatment, conversely MSC-Exos found that within 1 hrtreatment and remained there for up to 7 days compared to their counterparts. Intravenous injection of MSC-exosomes improved the conditions of COVID-19 patients via clinical symptoms, oxygenation, serum markers of acute inflammation, neutrophil and lymphocyte counts without any side effects.[384] The immunomodulatory effects of MSCexosomes inhibit IL-1, IL-6, NK cells, effector and cytotoxic T cells through antiinflammatory cargo, such as IDO, HLA-G, PD-L1, galectin-1, IL-10, TGF-β1 and HGF.[401,402] MSC-exosomes contains miRNAs that play a role in COVID-19, including miRNA-145, miRNA-126, miRNA199a, miRNA-221, miRNA-27 and Let-7f.[403,404] APCs produce less Ag/MHC molecules on their surface as a result of miRNAs delivered by MSC exosomes, which results in less effector T cell activation. The ability of macrophages, NK cells, T cells, and B cells to prevent infection is also mediated by miRNAs transported by MSC-exosomes.[405] Clinical study confirmed that exosomes derived from the amniotic fluid are highly effective in treating the respiratory failure of COVID-19 patients.[406] In silico analysis revealed that MSC-EVs miRNA potential to modulate COVID-19 induced increased cytokines, cell death and coagulation disturbance caused by

COVID-19.[407] EVs bearing hACE2 explicitly block the SARS-CoV-2 entry and thereby inhibit viral replication. MSC-EXOs bearing miR-7-5p, miR-24-3p, miR-145-5p and miR223-3p directly inhibit S protein expression and SARS-CoV-2 replication.[408] EVs from amniotic fluid-derived improved respiratory failure in a COVID-19 long hauler.[409] Wharton's jelly MSC-derived EVs showed significantly reduced the expression of nuclear NF-jB p65 and suppression of the cytokine storm in COVID-19 patients suffering from diabetes mellitus or renal disease.[410] All these studies concluded that MSC-EXOs potentially involved for the treatment COVID-19.

Challenges and Strategies of Use of MSC-EXOs

The important challenges for the application exosomes derived from stem cells is to identify the molecules involved in paracrine action of stem cells, which facilitate to open new therapeutics avenues using exosomes including the production, processing and manufacturing aspects, particularly isolation, purification and characterization.[411] Although, variety of isolation techniques/methods are available such as ultracentrifugation, size, immunoaffinity captured, precipitation and microfluidics, still to prepare clinical grade exosomes are critical factor. Another important factor is, there is no uniform method to separate exosomes, and also each and every method has its own advantages and disadvantages.[412] Therefore, MSC-EXOs separation methods must be uniform and standardized. For instance, the contents of cargoes are different among various separating methods.[412] For example, ultracentrifugation is well known and common method, which produces significant purity but the yield is low.[412] Therefore, it is required to explore a more efficient method for purification and yield and near future developments. The most important obstacle is the yield of exosomes, which can be improved using combination of currently available methods such as 3D microcarrier-based suspension culture promoted by certain bio-active materials. To increase the yield, engineering of full artificial exosomes is necessary which can be relatively controllable composition and clear therapeutic pathway.

The next challenge is source of EVs/exosomes. Physiological conditions and behavior of cells are important factor to provide consistent exosome quality and yield. Next, the important challenge is isolation and storage of exosomes, which are critical, adequate and appropriate technologies to produce quality exosomes for the safety of both donor and recipients. Although exosomes have great potential to treat various types of diseases, still several challenges are remained elusive. The important task is, the source and contents of the exosomes derived from various culture conditions must be determined using standardized protocol and also the conditions of storage, preservation, half-life of freshly isolated and cryopreserved exosomes and also transportation of exosomes needs to be solved.[103] Further challenges are warranted to understand and precise determination of exact components involved to treat neurological, particularly epileptic encephalopathy, Parkinson's, cancer, angiogenesis and autoimmune and inflammatory diseases. Further, several challenges are required to probe the therapeutic effect of MSC-EXOs to maintain the long-term effect, and know the facts of negative effect, which are very important criteria for the correct use of exosomes to treat various diseases. Furthermore, although MSC-EXOs are superior to MSCs, to increase the efficacy, and purification and the scale-up technology needs to be improved before it can be used in clinical practice.

Conclusion and Future Perspectives

The exosomes released from stem cells have been utilized for numerous therapeutic purposes and to develop novel regenerative approaches. The EVs from stem cells exert protective effects in the treatment of various diseases by regulating various pathological conditions. MSC-EXOs offer a more possibility of cell-free therapy than parental MSCs due to the regenerative and anti-inflammatory effect. The unique properties MSC-EXOs such as immunomodulatory effects allow treating different inflammatory and autoimmune diseases. Finding from several studies indicated that exosomes secreted by MSCs play significant role in cancer progression. Conversely, MSC-EXOs can also suppress tumors through regulating immune responses and intercellular signaling. MSC-EXOs used as drug delivery systems are considered to deliver targeted tumor therapy. MSC-EXOs shows potential effects on suppression of several autoreactive cells in autoimmune diseases. Due to their ability to modulate DAn survival, MSC-secretome considered as a promising therapeutic tool for several neuro-degenerative diseases.

The future perspectives need to be concentrated on various aspects including stability, long-term preservation, purification processes and the precise molecular contents are essential; it would help produce ready-to-use batches of

exosomes, which could be easily transported. Culture conditions such as cell density, passage number, hypoxia, extracellular matrix, and mechanical stress can influence the production. Hence, the derived exosomes must be characterized by various analytical techniques including size distribution, TEM, SEM, Nanotrack, proteomics, and miRNA profiling, which are essential parameters for therapeutic purposes for various diseases. However, the exact mechanisms of the effects of MSC-EXOs on cancer need to be explored and tested and the utility of exosomes as a delivery vehicle. Hence, additional studies of MSC-EXOs are required to determine their roles in the pathogenesis of cancer and to provide a new tool for cancer diagnosis and therapeutics. More studies are required to illuminate unclear aspects of cell-free therapy using MSC-EXOs. Thus, understanding the complexity of MSC-EXOs, and how its miRNA content interacts with cells involved in the molecular, cellular and functional mechanisms is of great importance in all kinds of diseases. More studies are necessary to explore the molecular mechanisms of those exosomes harboring lncRNAs in the pathogenesis, potential pathways, and development of multi-target-based strategies for RA. Since exosomes are derived from various types of stem cells and may provide different response in target cells, thus detailed investigations are necessary to identify the optimal cell types, functional status, and molecular contents and engineering of exosomes are essential to provide platforms for durable retention and prolonged release of cargos in the injured myocardium. Standards and guidelines should be established for isolation, purification, and identification of surface biomarkers from the samples of diseases patients for the use of the clinical setting. Another important issue needs to resolve is to reduce the lot-to-lot variation regarding primary naive MSCs. Collectively, findings from various studies imply that MSC-derived exosomes possess promising therapeutic capacity and these can be exploited as exosome-based therapy for the treatment of a variety of diseases as drug delivery vehicle and biomarkers (Figure 5). However, many efforts are required towards determining standards methods to enhance effective, efficacy and safety therapy, which will speed up clinical trials and patients speed recovery by implementation of MSC-EXOs as therapeutic agents. Finally, determination of optimal dose and safety measurements are inevitable parameters for the development of an effective exosome-based nanoplatform to expand the therapeutic potential.

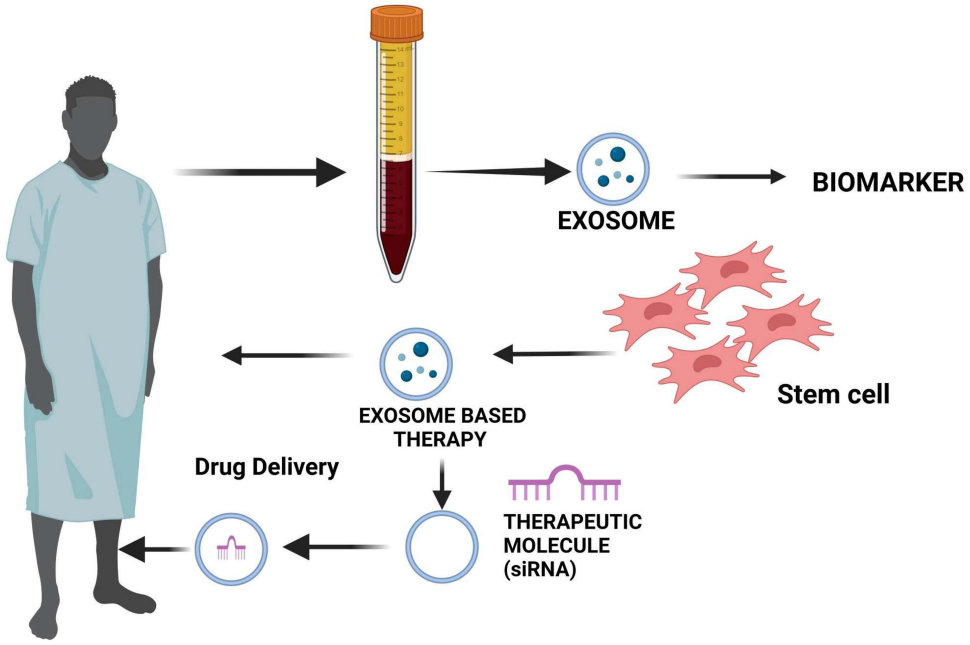

Figure 5 Potential therapeutic applications of MSC-EXOs as biomarkers and drug delivery vehicle. MSC-EXOs have enormous potential as a biomarker and drug delivery vehicle for various diseases such as neurological, autoimmune and inflammatory, cancer, ischemic heart disease, lung injury, and liver fibrosis due to enhanced biocompatibility, excellent payload capability, and reduced immunogenicity compared to alternative polymeric-based carriers. Created with BioRender.com.

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Disclosure

The authors declare no conflicts of interest in this work.

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