International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Biological Nanotherapeutics Derived From Human Umbilical Cord Mesenchymal Stem Cells: Mechanisms and Translational Potential in Multisystem Therapies for Regeneration and Oncology

Ruirui Zhang[1,2,*], Zhipeng Xu[3,*], Shijie Xu[1], Rong Li[1], Hui Qian[1]

[1]Jiangsu Province Key Laboratory of Medical Science and Laboratory Medicine, Department of Laboratory Medicine, School of Medicine, Jiangsu University, Zhenjiang, Jiangsu, 212013, People's Republic of China; [2]Department of Anatomy, School of Medicine, Jiangsu University, Zhenjiang, 212013, People's Republic of China; [3]Department of Urology, Affiliated People's Hospital of Jiangsu University, The First People's Hospital of Zhenjiang, Zhenjiang, Jiangsu, 212002, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ruirui Zhang; Hui Qian, Email zrr812124246@163.com; lstmmmlst@163.com

Abstract: Extracellular vesicles derived from human umbilical cord mesenchymal stem cells (hucMSCs-EVs) represent a promising cell-free therapeutic strategy in regenerative medicine and oncology. These vesicles exhibit low immunogenicity, are non-invasively sourced, and possess multiple regenerative properties. This review examines the biogenesis of EVs and distinctive features of hucMSCs-EVs compared to other MSC-derived EVs. We explore their molecular mechanisms and preclinical efficacy across multiple organ systems, including nervous, locomotor, respiratory, circulatory, digestive, urinary, reproductive, and hormonal. HucMSCs-EVs demonstrate a dual role: promoting tissue repair through immunomodulation, angiogenesis, and anti-apoptosis in regenerative contexts, while exerting microenvironment-dependent pro- or anti-tumor effects in oncology. Despite promising preclinical results, clinical translation requires overcoming challenges such as standardized production, delivery optimization, and safety evaluation. As multifunctional biological nanotherapeutics, hucMSCs-EVs show transformative potential for treating multisystem diseases. However, their universal applicability is constrained by heterogeneity, biodistribution limitations, and environment-dependent efficacy. Future work should focus on scalable manufacturing, targeted delivery strategies, and rigorous clinical trials to realize their full therapeutic potential.

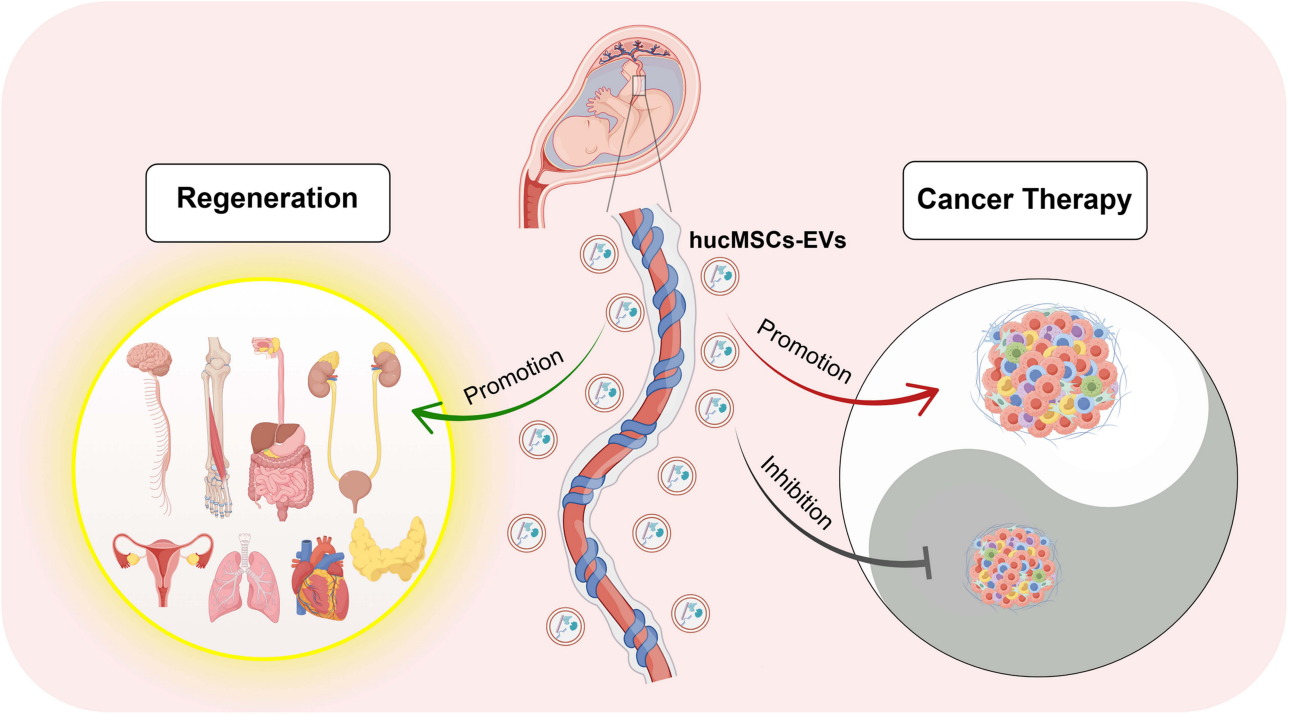
Keywords: human umbilical cord mesenchymal stem cells, hucMSCs, extracellular vesicles, EVs, multisystem therapeutics, regenerative medicine, cancer therapy, biogenesis, translational challenges

Introduction

Regenerative medicine and oncology are vital fields in the fight against the global burden of chronic diseases and cancers. Regenerative medicine aims to repair or replace tissues and organs damaged by severe injuries or chronic disease, while oncology focuses on combating the complex pathophysiology of cancers. With the aging population and rising incidence of chronic diseases such as cardiovascular diseases, neurodegenerative diseases and osteoarthritis, alongside the continued prevalence of cancers, the demand for innovative treatment plans has intensified.[1–4] Conventional therapeutic approaches such as pharmacological interventions, surgical transplantation, and chemotherapy can alleviate symptoms but often fail to restore tissue function, and frequently associated with adverse effects and high costs. For instance, organ transplantation faces limitations due to donor shortages and immune rejection risks,[5] while chemotherapies and targeted therapies face challenges such as systemic toxicity, drug resistance, and tumor recurrence.[6,7] These limitations emphasize the urgent need for therapies that can restore tissue integrity, regulate the disease microenvironment, and precisely target multifactorial pathology.

Received: 29 June 2025
Accepted: 23 September 2025
Published: 5 October 2025

Graphical Abstract



Mesenchymal stem cells (MSCs) are recognized as a cornerstone therapeutic agent in regenerative medicine due to their trilineage differentiation capacity, immunomodulatory properties, and paracrine signaling capabilities.[8] Nevertheless, MSC-based therapies face critical translational challenges: poor post-transplantation survival rates, inefficient homing to injury sites,[9] potential tumorigenic risks,[10] and regulatory complexities.[11] These challenges have prompted a shift in research focus towards the utilization of extracellular vesicles (EVs), which are nanoscale lipid bilayer particles secreted by MSCs, as a cell-free alternative.[12] EVs are generated through distinct biogenesis pathways, such as the endosomal sorting complex required for transport (ESCRT)-dependent mechanism and ESCRT-independent processes that involve tetraspanin-rich microdomains, which decide their molecular composition and functional specificity.[13] EVs inherit therapeutic cargo from parent cells, including proteins, nucleic acids, lipids, and metabolites, while avoiding risks associated with whole cell therapy. Their low immunogenicity, stability, and ability to traverse biological barriers position EVs as versatile vectors for both regenerative and oncological applications.[14] It is important to note that while EVs are not devoid of challenges related to limited targeting efficiency, potential pro-tumorigenic effects in certain environments, and regulatory hurdles, they present distinct advantages: their nanoscale size offers more favorable biodistribution and penetration, and their synthetic flexibility makes them highly suitable for enhancing homing engineering strategies;[15] their anucleate nature prevents them from proliferating, thus significantly reducing the risk of tumorigenesis;[16] and they are subject to a different, although still evolving, regulatory pathway as biological products rather than live cells.

Human umbilical cord-derived MSCs-EVs (hucMSCs-EVs) are particularly promising because they can be obtained non-invasively from medical waste, proliferate rapidly, have low immunogenicity, and do not raise ethical issues.[17] In regenerative medicine, hucMSCs-EVs demonstrate efficacy in different systems such as the nervous system, locomotor system, and respiratory system by modulating inflammation, promoting angiogenesis, and stimulating tissue repair.[18–22] At the same time, their role in cancer therapy is being increasingly recognized: hucMSCs-EVs deliver tumor-suppressive miRNAs, reverse chemoresistance, and remodel tumor microenvironments (TME) in cancers such as gastric, prostate,

and ovarian malignancies.[23–27] The dual therapeutic strategies of regeneration and cancer therapy empower hucMSCs-EVs to serve as a "multi-treatment tool" for combating various disease.

Despite the promising therapeutic potential of hucMSCs-EVs, several critical unknowns remain. The precise mechanisms controlling their biodistribution, cellular uptake, and cargo sorting are not fully elucidated. Additionally, the heterogeneity of EVs populations due to variations in isolation methods and source conditions poses challenges for standardization. The long-term safety profile, including potential off-target effects and immunogenic responses, especially in immunocompromised patients, requires further investigation. Moreover, the influence of the parental cell's physiological state on EVs functionality is poorly understood. Finally, while preclinical models demonstrate efficacy, the extension to human diseases is limited by species-specific differences and complex disease microenvironments. Addressing these gaps is essential for the rational design and clinical translation of hucMSCs-EVs-based therapies. We focus on the latest progress in hucMSCs-EVs for regenerative medicine and oncology, while also critically discussing the above challenges and future perspectives necessary to advance this booming field.

Mechanisms of EVs Biogenesis

EVs are mainly divided into two categories according to the biological mechanism: ectosomes (also known as microvesicles, microparticle) and exosomes (<200 nm in diameter).[16] Ectosomes are formed by direct budding through the plasma membrane. The biogenesis process involves three coordinated mechanisms: (1) phospholipid bilayer reorganization driven by phosphatidylserine externalization, (2) calcium influx-triggered cytoskeletal disassembly through cofilin activation,[28] and (3) arrestin domain-containing protein 1 (ARRDC1) mediated the recruitment of the ESCRT-I subunit tumor susceptibility gene 101 (TSG101), which promotes the assembly of vacuolar protein sorting-associated protein 4 (Vps4) ATPase to finalize vesicle scission.[14] In contrast, exosomes originated from endosomes and multivesicular bodies (MVBs), formed early endosomes through endocytosis, and were released after fusion of MVBs with plasma membrane. Their cargo was loaded using mechanisms that were both dependent and independent of ESCRT.[14]

Furthermore, distinct categories of EVs emerge during particular cellular processes. For instance, apoptotic vesicles originate from apoptotic cells.[29,30] Migrasome biogenesis is a mechanochemical process caused by tension from cell migration, stabilized by tetraspanin 4 (TSPAN4)-cholesterol complexes,[31] and regulated by the PI (4,5) P_2/Rab35/integrin pathway[32] (Figure 1). Some EVs also contain special cargo, such as mitochondria, called mitochondria-contained EVs (EV-Mito), which contain intact mitochondria or mitochondrial derived vesicles. EV-Mito is released through the exosomal pathway mediated by multivesicular bodies or the ectosomal pathway involving vesicle formation from the plasma membrane.[33] Mechanisms of EVs biogenesis are described in detail in the articles by Andrew Dixson et al.[13] It is worth noting that at present, there is a lack of specific molecular markers and standardized separation technology, so this paper uses EVs as a generalized term.

Although we have a preliminary understanding of the biogenesis pathways of EVs, the specific biogenic processes of hucMSCs-EVs and their precise regulatory mechanisms for cargo sorting remain a "black box".[34] The lack of this knowledge directly leads to our inability to artificially and efficiently produce hucMSCs-EVs carrying specific therapeutic agent. The functional specificity of different subtypes of EVs is also difficult to define due to limitations in their isolation techniques, which poses fundamental challenges for standardized production and large-scale applications.[35]

Characteristics of MSC-EVs

MSCs can be obtained from different tissues, such as umbilical cord, bone marrow, and adipose tissue and so on. These MSC-EVs from different sources share both common and unique characteristics.

Shared Characteristics of hucMSCs-EVs with Other MSC-EVs

HucMSCs-EVs share basic molecular and functional similarities with EVs derived from other MSC sources, such as adipose tissue (ADSC-EVs), bone marrow (BMSC-EVs), and placenta (PMSC-EVs). All MSC-EVs contain essential EVs markers, including CD9, CD63, CD81, TSG101, and Alix,[36,37] as well as MSC-specific surface markers like CD73, CD90, and CD105.[38] These EVs usually carry bioactive molecules such as growth factors like VEGF and HGF, cytokines, and regulatory miRNAs, which contribute to their roles in anti-apoptosis, immunomodulation, and tissue repair.[39–41]

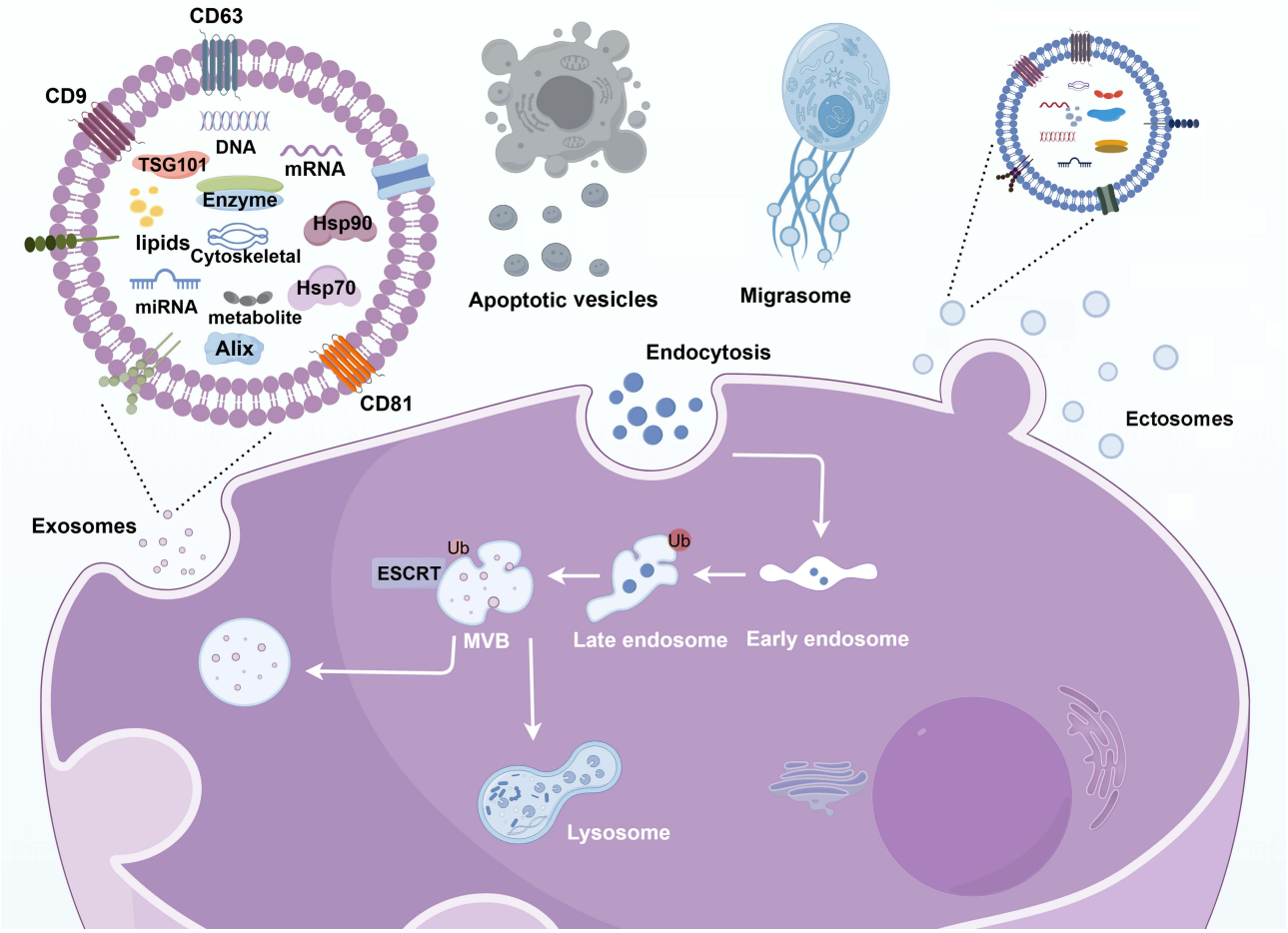


Figure 1 EVs classification and biogenesis. Ectosomes originate by directly budding outward and separating from the plasma membrane, while exosomes are released into the extracellular space through a three-step process: Initially, early endosomes are formed through the inward budding of the plasma membrane. These early endosomes then transform into late endosomes, eventually leading to the creation of MVBs. Subsequently, MVBs combine with the plasma membrane, causing the release of exosomes or they fuse with lysosomes, which leads to degradation. While apoptotic bodies are released by cells undergoing programmed cell death, migrasomes are vesicles that appear on the retraction fibers of migrating cells. These EVs are encased in a phospholipid bilayer and act as carriers for transporting a variety of cargoes such as lipids, proteins, nucleic acids, and metabolites. (Figure created with Figdraw).

The analysis of Reactome pathways reveals common roles in essential biological processes, including platelet degranulation, extracellular matrix (ECM) organization, and insulin-like growth factor (IGF) transport, which support their regenerative abilities across various tissue types.[40] For example, all MSC-EVs promote angiogenesis, reduce inflammatory responses, and improve cell survival through conserved signaling pathways such as PI3K-AKT and TGF-β.[42,43]

MSC-EVs from all sources also present organizational advantages, including stable phenotypes, lower immunogenicity than parental cells, and suitability for expandable production methods. These common characteristics highlight their shared potential as cell-free therapeutics, while tissue-specific molecular differences improve their applications for targeted diseases. While MSC-EVs from different sources have core therapeutic functions, hucMSCs-EVs exhibit great efficacy in specific situations because of their unique molecular signatures and tissue origin.

Different Characteristics of hucMSCs-EVs Compared to Other MSC-EVs

Despite shared core markers, MSC-EVs exhibit tissue-specific molecular features. Proteomic and transcriptomic analysis identified uniquely expressed proteins and miRNAs in MSC-EVs from different tissues. Among them, hucMSCs-EVs possess a greater number of identified protein markers (n=1393) compared to those from adipose tissue (n=21) and bone marrow (n=56). The protein markers of hucMSCs-EVs displayed in Figure 2B were further screened through bioinformatics analysis and are involved in key signaling pathways, highlighting a functionally distinct molecular signature.

HucMSCs-EVs also demonstrate a unique miRNA expression profile (n=94), which is different from that of BMSC-EVs (n=134) and ADSC-EVs (n=689) (Figure 2A and B).[40,44] These specific molecular features determine their applications. BMSC-EVs are mainly used in diseases such as osteoporosis and osteolysis. ADSC-EVs are mainly used for osteoarthritis and other joint diseases. HucMSCs-EVs are mainly used in female reproductive system diseases, diabetes (Figure 2B and C).[40] The relevant content is described in detail in the articles by Zuo Ding et al and Sungho Shin et al[40,44] Unfortunately, the source of these tissue-specific molecular features is not yet fully understood. Is it due to

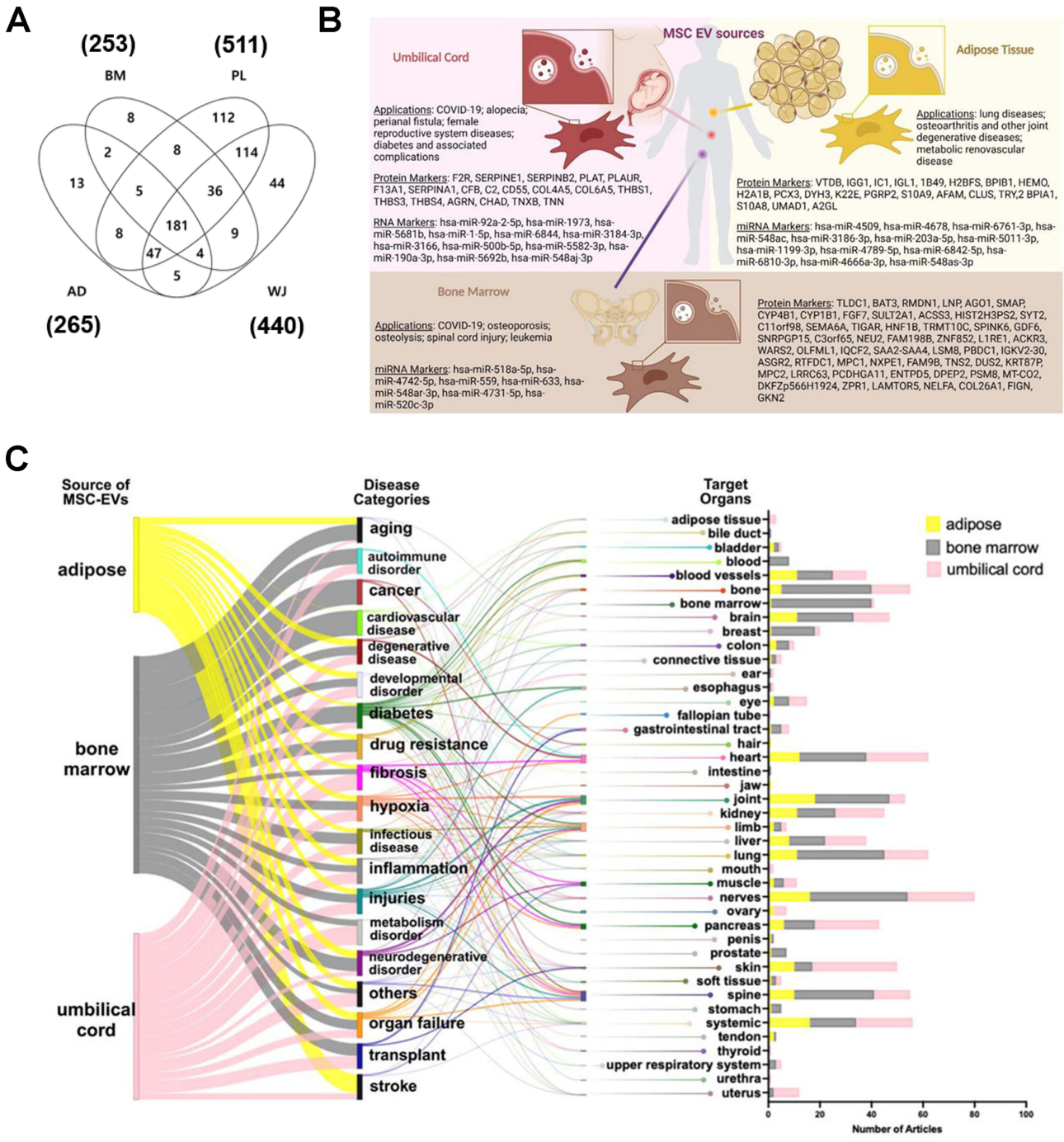


Figure 2 Molecular characteristics and applications of MSC-EVs from different sources. (**A**) The Venn diagram of proteins in MSC-EVs derived from adipose (AD), bone marrow (BM), placenta (PL), and Wharton's-jelly (WJ). Reproduced with permission from reference.[44] Copyright 2021, MDPI; (**B**) Applications, protein and miRNA markers of each MSC-EVs. Reproduced with permission from reference.[40] Copyright 2024, Elsevier; (**C**) The Sankey visualization of the effects of each MSC-EVs on different diseases and their target organs. Reproduced with permission from reference.[40] Copyright 2024, Elsevier.

https://doi.org/10.2147/IJN.S550390

inherent differences in parental cells or the influence of extraction and culture conditions? This heterogeneity is not only the basis for its unique therapeutic potential, but also the main source of inter batch differences and unpredictable efficacy. At present, there is a lack of gold standard biomarkers that can clearly distinguish EVs from different tissue sources or functional subtypes, which seriously hinders the development of precision treatment strategies based on EVs.

Applications of hucMSCs-EVs

MSCs-derived EVs show unique biological properties depending on their tissue origin. Although all MSC-EVs share common therapeutic functions, a growing body of evidence suggests that hucMSCs-EVs exhibit superior efficacy in tissue damage repair and certain oncology therapies. This prominence can be attributed to their parent cells, which have higher proliferation, lower immunogenicity, and better angiogenesis and immune regulatory abilities compared to other adult MSC sources.[17,19,45] These inherent advantages make hucMSCs-EVs a particularly promising candidate for clinical translation. HucMSCs-EVs exert therapeutic potential through multiple common core mechanisms and unique mechanisms in different disease models.[19,25,27,46–49] These core mechanisms include immunomodulation, autophagy regulation, regulation of cell survival, proliferation, and migration, metabolic regulation, and angiogenesis. This unified mechanism framework emphasizes the multifunctionality of hucMSCs-EVs as "biological nano-therapeutics" and provides information for the rational design of future EV-based solutions. These findings not only provide a theoretical foundation for understanding the regenerative medicine and anti-tumor value of hucMSCs-EVs, but also establish a mechanistic basis for their clinical translation. The following sections will present the therapeutic applications of hucMSCs-EVs across organ systems, dissecting their mechanisms in regenerative medicine and oncology (Figure 3).

Nervous System

Regenerative Effects

Traumatic Brain Injury

Traumatic brain injury (TBI) remains a leading cause of global morbidity and mortality, with an estimated annual incidence of 27–69 million cases.[50] It involves immediate mechanical damage to the brain, followed by secondary damage caused by inflammation, oxidative stress, and neuronal apoptosis, which worsens brain function.[51] Despite advances in acute care, survivors often face cognitive impairment, motor dysfunction, and psychiatric disorders, imposing substantial socioeconomic burdens.[51,52] Current therapies mainly focus on symptom alleviation and surgical interventions (eg, decompressive craniectomy), but these approaches fail to repair brain damage or promote functional recovery.[52] Pharmaceuticals like anti-inflammatory drugs, neurotrophic factors such as NGF, and antioxidants, face challenges including poor blood-brain barrier (BBB) penetration, systemic toxicity, and short therapeutic windows. Moreover, advanced monitoring techniques (eg, microdialysis, cerebral oxygenation) are complicated and not yet standardized for personalized care.[53–55] The emergence of hucMSCs-EVs has brought hope to TBI patients because of their small size, natural BBB permeability, and ability to modulate neuroinflammation, angiogenesis, and neuroprotection properties that make them ideal candidates for TBI repair.[56,57]

HucMSCs-EVs demonstrate strong neuroprotective and regenerative effects in TBI by combining anti-inflammatory, anti-apoptotic, pro-neurogenic, and angiogenic mechanisms. A key pathway suppresses neuroinflammation: hucMSCs-EVs inhibit NF-κB signaling, reduce the expression of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and shift microglial and astrocyte activation from a pro-inflammatory (M1/A1) to an anti-inflammatory (M2/A2) phenotype, thereby limiting secondary neuronal damage.[18,46] Concurrently, hucMSCs-EVs prevent cell apoptosis and enhance neurogenesis, promoting neuronal survival.[46] Moreover, hucMSCs-EVs have been found to promote angiogenesis.[19] This capability facilitates blood supply restoration in the injured brain tissue, which is essential for supporting tissue repair and neurological recovery. The bioactive cargo within hucMSCs-EVs play a crucial role in these effects. For instance, miR-21 helps to suppress excessive activation of microglia, thus reducing neuroinflammation,[58] while miR-146a-5p maintains neuronal integrity by specifically silencing pathways in neurotoxic astrocytes.[59,60] Additionally, hucMSCs-EVs carry functional proteins like PINK1, which enhances mitophagy to alleviate oxidative stress and stabilize cellular homeostasis.[61] Complementing these pathways, hucMSCs-EVs alleviate intracranial pressure and prevent further damage by reducing cerebral edema.[61] Together, these effects create a

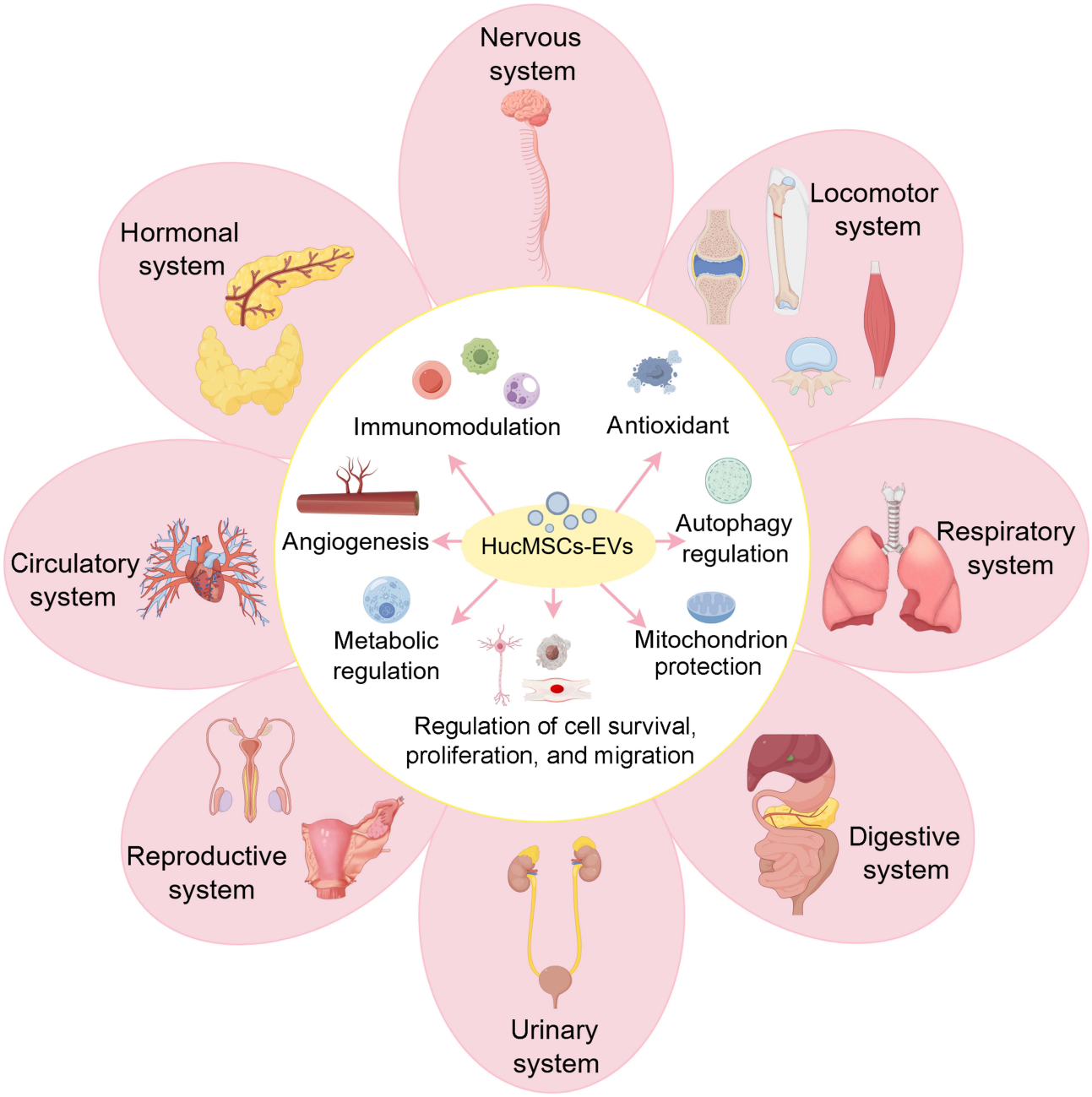


Figure 3 HucMSCs-EVs exert therapeutic effects across various organ systems through diverse mechanisms. HucMSCs-EVs exhibit therapeutic effects on diseases related to eight systemic organ systems, including the nervous, locomotor, respiratory, digestive, urinary, reproductive, circulatory, and hormonal systems. These effects are mediated through multiple mechanisms that contain immunomodulation, antioxidant activity, autophagy regulation, mitochondrial protection, regulation of cell survival, proliferation, and migration, metabolic regulation, and angiogenesis. (Figure created with Figdraw).

healing microenvironment in the brain, leading to better recovery in TBI models. Unfortunately, the treatment of hucMSCs-EVs for TBI has only animal trials, not yet entered the human stage.

Stroke

Stroke remains a leading global cause of mortality and disability, with approximately 11.9 million new cases and 7.3 million deaths each year.[62] According to the Global Burden of Disease Study, stroke imposes a significant socioeconomic burden because of its high incidence, recurrence rates, and long-term disabilities.[63] Current therapeutic strategies like intravenous thrombolysis (eg, recombinant tissue plasminogen activator, rt-PA) and endovascular thrombectomy, are restricted by narrow

https://doi.org/10.2147/IJN.S550390

treatment windows (≤4.5 hours for rt-PA) and low recanalization rates (30% for large vessel occlusions).[64–66] Additionally, rt-PA has a significant risk of causing hemorrhagic transformation, occurring in 8.94–46% of cases, which limits its use in clinical.[67–69] These therapies also fail to manage post-ischemic secondary neurodegeneration, BBB disruption, or neuroinflammation, resulting in survivors having ongoing neurological deficits.[70] To bridge this gap, researchers are exploring hucMSCs-EVs, which show promise in repairing stroke induced damage through different mechanisms.

HucMSCs-EVs exert neuroprotective and regenerative effects in stroke through various molecular mechanisms. For example, they reduce neuroinflammation by delivering miR-146a-5p, which inhibits the IRAK1/TRAF6/NF-κB inflammatory pathway. This reduces pro-inflammatory cytokines like IL-6 and TNF-α and shifts microglia to the protective M2 state, which helps to prevent more neuronal damage.[47] HucMSCs-EVs also inhibit ferroptosis by transferring miR-214-3p, which targets key regulators like GPX4 and ACSL2. This preserves mitochondrial integrity, reduces oxidative stress in neurons, and restores BBB integrity in hemorrhagic stroke models.[71] Besides, through miR-664a-5p, hucMSCs-EVs regulate Adaptor-Associated Kinase 1 (AAK1), a kinase involved in clathrin-mediated endocytosis and NF-κB signaling pathway. By suppressing AAK1, they inhibit NF-κB-driven inflammatory cascades, leading to smaller infarct volumes and better functional recovery in ischemic stroke models.[72] Animal experiments demonstrate that hucMSCs-EVs injections via veins or the nose reduces brain damage and enhances neurological function. According to a meta-analysis of 38 randomized controlled animal experiments, hucMSCs-EVs markedly enhance both movement and cognitive scores.[73] In a rat model of focal cerebral ischemia, MSC-EVs enhance neurogenesis and angiogenesis along the edge of the infarct. They can also improve synaptic transmission, long-term potentiation, and cognitive impairment after transient cerebral ischemia in mice. In a mouse model of focal cerebral ischemia, the administration of BMSC-EVs induced long-term neuroprotection, enhanced angiogenesis and neurogenesis, and facilitated better recovery of motor coordination. HucMSCs-EVs may have a similar effect as they can also promote angiogenesis and neurogenesis, thereby repairing damaged brain tissue.[19,46,74] The diverse therapeutic capabilities of hucMSCs-EVs enable the possibility of functional recovery after stroke. Thus, hucMSCs-EVs have emerged as a groundbreaking therapeutic candidate. To date, research on hucMSCs-EVs for stroke has not progressed beyond the preclinical phase, with efficacy data derived exclusively from animal experiments.

Alzheimer's Disease

Alzheimer's disease (AD), affecting over 55 million people globally, is the most prevalent neurodegenerative disorder, characterized by progressive cognitive decline associated with β-amyloid (Aβ) plaque accumulation, neurofibrillary tau tangles, and chronic neuroinflammation.[75] The therapies approved by the FDA, such as acetylcholinesterase inhibitors like donepezil and NMDA receptor antagonists like memantine, only relieve symptoms without altering disease progression.[76,77] Although new anti-Aβ monoclonal antibodies such as aducanumab show plaque removal, their clinical advantages are debated due to limited BBB penetration and inability to tackle issues like synaptic loss and neuroinflammation.[78–80] The absence of effective treatments has spurred research into novel strategies aimed at the complex pathophysiology of AD.

HucMSCs-EVs emerge as promising candidates, utilizing their innate ability to cross the BBB, immunomodulatory and neuroprotective properties. They demonstrate multifaceted therapeutic mechanisms against AD, targeting its core pathological hallmarks, including Aβ plaque accumulation, neuroinflammation, mitochondrial dysfunction, and neuronal apoptosis. The regulation of Aβ metabolism is a key mechanism, with hucMSCs-EVs enhancing the production of Aβ-degrading enzymes like neprilysin (NEP) and insulin-degrading enzyme (IDE) to promote plaque clearance.[48,81] They also modulate secretase activity by upregulating α-secretase and downregulating β-secretase (BACE1), thereby reducing Aβ production.[48,82] These effects are further amplified in engineered EVs, such as those transfected with miR-29c mimics or loaded with NEP, which show enhanced Aβ degradation in animal models.[48] By reprogramming microglial activation, hucMSCs-EVs also demonstrate significant immunomodulatory effects. They reduce brain inflammation by changing microglia from M1 phenotype to M2 phenotype, suppressing pro-inflammatory cytokines like TNF-α and IL-1β, while upregulating anti-inflammatory mediators such as TGF-β and IL-10.[48,81] This immunomodulation is mediated by EVs with miR-146a and TGF-β1, which attenuate neuroinflammatory cascades and protect neurons from damage.[48] Mitochondrial dysfunction, a critical contributor to AD progression, is addressed through EV-mediated mitochondrial transfer. HucMSCs-EVs deliver functional mitochondria to neurons, restoring membrane potential, enhancing ATP

production, and reducing oxidative stress, thereby preventing apoptosis and improving neuronal survival.[83] In addition, suppressing miR-211-5p in hucMSCs-EVs increases NEP expression, which facilitates Aβ clearance and protects neurons.[84] Other miRNAs target pathways linked to synaptic plasticity, apoptosis, and inflammation, further amplifying therapeutic efficacy.[48,82] Studies show that delivering hucMSCs-EVs through the nose helps them reach brain areas like the hippocampus, improving memory in animals.[85] By acting as a "multi-action therapy", hucMSCs-EVs target Aβ, tau proteins, inflammation, mitochondrial dysfunction, and synaptic loss, which makes them superior to traditional single-target treatments. It is encouraging that hucMSCs-EVs have not only undergone animal trials for the treatment of AD, but have also entered human clinical trials and are in Phase I (Table 1).

Parkinson's Disease

Parkinson's disease (PD), the second most prevalent neurodegenerative disorder globally, affects over 11.77 million people and is characterized by progressive dopaminergic neuron loss in the substantia nigra and pathological α-synuclein aggregation.[86,87] The clinical hallmarks—tremor, bradykinesia, rigidity, and postural instability—are compounded by non-motor symptoms such as cognitive decline and autonomic dysfunction, which collectively reduce quality of life.[88] Pharmacological interventions, mainly focus on dopamine replacement (eg, levodopa), which can provide transient relief, but are plagued by motor fluctuations (eg, dyskinesias and "on-off" phenomena) and non-motor side effects, such as orthostatic hypotension and neuropsychiatric complications.[89–91] Long-term use of dopamine agonists, although reducing reliance on levodopa, can bring risks such as impulse control disorders and cardiac valvulopathy.[92,93] Surgery (eg, deep brain stimulation) offer sustained symptom control but is invasive, costly, and unsuitable for advanced patients with cognitive impairments.[94] No treatments yet slow or reverse PD progression, highlighting the need for new strategies.

HucMSCs-EVs fight PD by targeting dopaminergic neuron loss, neuroinflammation, and α-synuclein aggregation. They cross the BBB and accumulate in damaged regions, such as the substantia nigra and olfactory bulb, where they are internalized by neurons, microglia, and astrocytes to exert localized repair.[95–97] Neuroprotection is achieved through multiple pathways: hucMSCs-EVs enhance the viability of dopaminergic neurons by increasing tyrosine hydroxylase-positive cells in the substantia nigra pars compacta, and restore olfactory function by improving neuronal activity in the olfactory bulb.[95,96] They also induce autophagy, upregulating LC3B-II/I and Beclin-1 while downregulating p62, thereby clearing toxic protein aggregates and alleviating 6-hydroxydopamine (6-OHDA)-induced apoptosis.[98]

The anti-inflammatory properties of hucMSCs-EVs are critical in modulating PD-associated neuroinflammation. By attenuating microglial and astrocytic activation, these EVs reduce pro-inflammatory cytokines (eg, TNF-α, IL-1β) and inhibit the PI3K/Akt-mediated NF-κB/NLRP3 pathway, thereby suppressing pyroptosis and creating a neuroprotective microenvironment.[96,97] Additionally, engineered hucMSCs-EVs hybridized with antioxidants like baicalein or oleuropein disrupt α-synuclein fibrillation, reduce reactive oxygen species (ROS) and nitric oxide (NO) levels, and protect BBB integrity, fighting against oxidative stress and neurotoxicity.[99,100]

HucMSCs-EVs further enhance neuronal survival by modulating multiple signaling pathways. SATB1 upregulation triggers the Wnt/β-catenin pathway, which promote neurogenesis and neurite outgrowth while inhibiting excessive autophagy.[96] Engineered EVs loaded with brain-derived neurotrophic factor (BDNF) maintain neuronal cytoskeletons by regulating microtubule-associated protein 2 (MAP2) and phosphorylated tau, and activate the Nrf2 antioxidant pathway to combat ferroptosis and oxidative damage.[100,101] Through the combination of autophagy induction, α-synuclein clearance, oxidative stress reduction, and pathway modulation, hucMSCs-EVs present a powerful multi-target approach to combat PD. Current therapeutic applications of hucMSCs-EVs for PD remain confined to animal models, with no clinical trials reported to date.

Multiple Sclerosis

Multiple sclerosis (MS), a chronic autoimmune disorder affecting 2.8 million people globally, is characterized by demyelination, neuroinflammation, and axonal damage in the central nervous system (CNS), leading to progressive neurological disability.[102] Current disease-modifying therapies (DMTs) such as β-interferons, dimethyl fumarate, and anti-CD20 monoclonal antibodies, mainly target peripheral immune activation to reduce recurrence rates, but have limited efficacy in progressive MS and fail to promote CNS repair or remyelination.[103] Furthermore, long-term

Table 1 Registered Clinical Trials with hucMSCs-EVs Interventions on Clinicaltrials.gov (http://www.clinicaltrials.gov/)

NCT Number	Study Title	Conditions	Interventions	Phases	Last Update Posted
NCT06607900	HUC-MSC-sEV-001 Nasal Drops for Neurodegenerative Diseases	Alzheimer Disease|Parkinson Disease|Lewy Body Dementia|Multiple System Atrophy|Fronto-temporal Dementia	HucMSCs-EVs	PHASE1	2024/9/25
NCT05808400	Safety and Efficacy of Umbilical Cord Mesenchymal Stem Cell Exosomes in Treating Chronic Cough After COVID-19	Long COVID-19 Syndrome	HucMSCs-EVs	EARLY_PHASE1	2023/4/14
NCT05787288	A Clinical Study on Safety and Effectiveness of Mesenchymal Stem Cell Exosomes for the Treatment of COVID-19.	COVID-19 Pneumonia	HucMSCs-EVs	EARLY_PHASE1	2023/4/7
NCT04399889	hCT-MSCs for COVID19 ARDS	COVID|Corona Virus Infection|COVID 19	HucMSCs-EVs	PHASE1|PHASE2	2022/12/20
NCT06813027	Use of Allogeneic Extracellular Secretomes (EV)Derived from Umbilical Cord Mesenchymal Stromal Cells: a Phase I Open-label Safety Trial.	Vitiligo	HucMSCs-EVs	PHASE1	2025/2/6
NCT06431152	Intra-articular Injection of UC-MSC Exosome in Knee Osteoarthritis	Osteo Arthritis Knee	HucMSCs-EVs	EARLY_PHASE1	2024/5/29
NCT06697080	Umbilical Cord-derived Mesenchymal Stem Cell Exosomes on Hair Growth in Patients with Androgenetic Alopecia	Androgenic Alopecia	HucMSCs-EVs	NA	2024/11/20
NCT06896747	Evaluating Mechanically Engineered Stem Cell Exosomes for Treating Endometrial Injury: A Clinical Study	Thin Endometrial Lining|Female Infertility|Intrauterine Adhesions	HucMSCs-EVs	PHASE1|PHASE2	2025/3/26
NCT04356300	Exosome of Mesenchymal Stem Cells for Multiple Organ Dysfuntion Syndrome After Surgical Repair of Acute Type an Aortic Dissection	Multiple Organ Failure	HucMSCs-EVs	NA	2020/5/6
NCT05871463	Effect of Mesenchymal Stem Cells-derived Exosomes in Decompensated Liver Cirrhosis	Decompensated Liver Cirrhosis	HucMSCs-EVs	PHASE2	2023/5/23
NCT05413148	The Effect of Stem Cells and Stem Cell Exosomes on Visual Functions in Patients with Retinitis Pigmentosa	Retinitis Pigmentosa	HucMSCs-EVs	PHASE2|PHASE3	2022/9/7
NCT06764004	The Effect of Human Umbilical Cord Mesenchymal Stem Cells and Exosomes on the Healing of Postoperative Pain and Periapical Lesions in the Treatment of Apical Periodontitis: Randomized Controlled Clinical Study	Apical Periodontitis	HucMSCs-EVs	PHASE1|PHASE2	2025/1/8
NCT06853522	HucMSCs Exosomes for the Treatment of Active Ulcerative Colitis	Ulcerative Colitis (UC)	HucMSCs-EVs	EARLY_PHASE1	2025/3/3
NCT06245746	UCMSC-Exo for Chemotherapy-induced Myelosuppression in Acute Myeloid Leukemia	Acute Myeloid Leukemia|Neutropenia|Anemia|Thrombocytopenia|Infections|Bleeding	HucMSCs-EVs	PHASE1	2025/3/21
NCT06632470	Clinical Utility and Safety of Human Umbilical Cord Mesenchymal Stem Cell Secretome in Moderate Neurocognitive Impairment (Dementia)	Dementia|Moderate Dementia	HucMSCs-EVs	PHASE1	2024/10/9
NCT05777213	Potential Injection of Human Umbilical Cord Secretome in the Case of Trophic Ulcers (Pre-post Intervention)	Trophic Ulcer; Leprosy	HucMSCs-EVs	PHASE1	2023/3/21
NCT06812637	Efficacy and Safety of Wharton's Jelly-Derived Mesenchymal Stem Cell Exosomes in the Treatment of Diabetic Foot Ulcers: a Double-blinded Randomized Controlled Clinical Trial	Diabetic Foot Ulcer (DFU)	HucMSCs-EVs	PHASE1	2025/2/19
NCT05813379	Mesenchymal Stem Cells Derived Exosomes in Skin Rejuvenation	Anti-Aging	HucMSCs-EVs	PHASE1|PHASE2	2023/4/14

NCT06629909	Safety and Feasibility of Human Umbilical Cord Mesenchymal Stem Cell-Derived Secretome in the Treatment of Liver Cirrhosis: a Comprehensive Evaluation of Fibrosis Reduction, Immunomodulation, and Hepatic Regeneration: a Single Center, Randomized, Phase I Clinical Trial	Liver Cirrhosis	HucMSCs-EVs	PHASE1	2024/10/8
NCT04213248	Effect of UMSCs Derived Exosomes on Dry Eye in Patients With cGVHD	Dry Eye	HucMSCs-EVs	PHASE1| PHASE2	2022/2/11
NCT06600529	Combined Photo-Biomodulation at Acupuncture Points, Autologous PRP, and Umbilical Cord-Derived Exosome Therapy in Autism Spectrum Disorder	Autism Spectrum Disorder	HucMSCs-EVs	NA	2024/9/19
NCT06677931	Umbilical Cord Mesenchymal Stem Cell-Derived Exosomes in the Treatment of Melasma	Melasma	HucMSCs-EVs	NA	2024/11/7

https://doi.org/10.2147/IJN.S550390

immunosuppression increases infection risks, while high-dose corticosteroids used for acute recurrence can cause metabolic and osteoporotic complications.[104–106] These unsatisfied needs fully demonstrate that there is an urgent need to develop therapies that can combine immunomodulation with neuroprotection and regeneration.

In MS, hucMSCs-EVs demonstrate therapeutic potential by targeting autoimmune dysregulation, neuroinflammation, and demyelination. The core of its efficacy lies in immunomodulation: hucMSCs-EVs suppress pathogenic T-cell proliferation, particularly $CD4^+CD25^-$ conventional T cells, while enhancing regulatory T cell (Treg) expansion, including $CD4^+CD25^+Foxp3^+$ populations, to restore immune tolerance.[107,108] This is achieved through dual cytokine regulation, which downregulate pro-inflammatory mediators (IFN-γ, IL-17, TNF-α, IL-1β, IL-6) and upregulate anti-inflammatory cytokines (IL-10, TGF-β, IL-4). This rebalances the Th17/Treg axis and reduces neuroinflammation in both in vitro MS models and experimental autoimmune encephalomyelitis (EAE) mice.[107–109]

It is crucial that hucMSCs-EVs promote remyelination by delivering miR-23a-3p, which activates the PI3K/Akt pathway and suppresses Tbr1/Wnt pathway in oligodendrocyte precursor cells (OPCs), which promotes their differentiation into mature myelinating oligodendrocytes.[110] Meanwhile, these EVs enhance myelin basic protein (MBP) expression, reduce demyelinated lesions in spinal cord tissues, and improve neurological function in EAE models.[15,109] By modulating microglial polarization to anti-inflammatory M2 phenotype, this approach enhances their regenerative potential, helping to resolve chronic inflammation and promote tissue repair.[15]

In addition, hucMSCs-EVs enhance the inhibitory function of Treg by upregulation lymphocyte-activation gene 3 (Lag-3) in $Foxp3^+CD4^+$ T cells, thereby inhibiting immune cell proliferation and cytokine storm in EAE.[111] Unlike traditional DMTs that lack remyelination or neuroprotective effects, hucMSCs-EVs are a "multi-drug platform" that can simultaneously inhibit autoimmune attacks, reduce neuroinflammation, and stimulate CNS repair. Preclinical studies have emphasized their superior efficacy compared to whole MSCs, with peptide modified EVs targeting the CNS showing enhanced biodistribution and BBB penetration.[15] Despite promising results in animal studies, hucMSCs-EVs-based interventions for MS have not yet advanced to human clinical trials.

Spinal Cord Injury

Spinal cord injury (SCI), a severe condition impacting over 27 million people worldwide, causes permanent loss of movement, sensation, and autonomic dysfunction. This occurs not only from primary mechanical damage but also from secondary pathological cascades involving inflammation, glial scar formation, and axonal degeneration.[112–114] Beyond physical disability, SCI patients face heavy mental stress, with suicide risks 2–37 times higher than healthy individuals.[115] Current clinical interventions, such as surgical decompression, methylprednisolone pulse therapy, and rehabilitation mainly manage early-stage problems but cannot address neural regeneration or functional recovery.[116] Although steroids like methylprednisolone reduce swelling, long-term use can cause serious side effects (eg, immunosuppression, osteoporosis) without healing nerves.[117] New approaches using stem cells show limited promise in animal studies but struggle with poor survival, uncontrolled differentiation, and tumorigenic risks.[118] These challenges bring attention to the urgent need for innovative strategies to repair damaged nerve environments.

HucMSCs-EVs exhibit diverse therapeutic potential in SCI repair by simultaneously addressing inflammation, angiogenesis, neurogenesis, apoptosis, autophagy, and microenvironment modulation.

Immunomodulatory. HucMSCs-EVs alleviate neuroinflammation by switching macrophage/microglia from the M1 to M2 phenotype. This shift decreases pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IFN-γ) and increases anti-inflammatory mediators (IL-4, IL-10).[119–124] The conversion of AMP to adenosine is limited by CD73 (ecto-5′-nucleotidase), which is the rate-limiting ecto-enzyme in extracellular AMP hydrolysis. $CD73^+$ hucMSCs-EVs, promote adenosine production via ATP hydrolysis, which activates the A2bR/cAMP/PKA pathway to enhance M2 polarization.[120] The 4D-culture, which characterized by extended 3D-culture time and enhanced cell-microenvironment interaction that forms an MSC-favorable niche generates EVs that upregulate IGFBP2/EGFR, activate STAT3, and suppress neuroinflammation.[121] IL-4-engineered EVs inhibit PDCD4 by delivering miR-21-5p, further promoting M2 polarization.[122] Quercetin-loaded EVs suppress TLR4/NF-κB signaling, reducing cytokine release.[123] A supportive regenerative microenvironment is created through immunomodulatory.

Angiogenesis. HucMSCs-EVs enhance vascular repair by stimulating endothelial cell migration and tube formation. By transferring miR-27a-3p, $CD146^{+}CD271^{+}$ EVs decrease DLL4 expression, which promote angiogenesis and functional recovery in vivo.[125] Hypoxia-preconditioned EVs further amplify angiogenic signaling in MSCs, restoring blood supply to injured tissue.[126] The increase in $CD31^{+}$ endothelial cell proliferation and vascular density at lesion sites confirm their pro-angiogenic efficacy.[125,126]

Neurogenesis and Axonal Regeneration. HucMSCs-EVs enhance the expression of neuronal markers such as NF200, MBP, GAP43, synaptophysin and PSD95, which promote remyelination, synaptogenesis, and axonal growth.[124,127–130] miR-126-modified EVs enhance neurogenesis by increasing neural progenitor cells and neurons,[131] while miR-29b-3p targets PTEN to activate the Akt/mTOR pathway, promoting nerve repair.[132] EVs also activate endogenous neural stem cells (NSCs) via ERK1/2 signaling, driving their proliferation and differentiation.[128] Scaffold-coupled EVs, such as collagen-paclitaxel hybrids, synergistically recruit NSCs and enhance neural network reconstruction.[133]

Anti-Apoptotic and Pro-Autophagic Effects. HucMSCs-EVs inhibit apoptosis by downregulating Bax, cleaved caspase-3, and p75NTR while upregulating Bcl-2.[124,126–129,131,134] Under the influence of micro electrical fields, hucMSCs-EVs transport lncRNA-MALAT1 to target miR-22-3p, elevating SIRT1 and AMPK phosphorylation to inhibit apoptosis.[134] In addition, EVs maintain cell homeostasis and survival by enhancing autophagy.[134]

Microenvironment Regulation and Barrier Repair. HucMSCs-EVs restore blood-spinal cord barrier (BSCB) integrity by downregulating endothelin-1 (ET-1) and upregulating junction proteins (ZO-1, β-catenin, occludin, claudin-5).[135,136] $RGD^{-}CD146^{+}CD271^{+}$ hucMSCs-EVs modulate endothelial cells by suppressing the miR-501-5p/MLCK axis, stabilizing tight junctions and reducing vascular leakage.[136] HucMSCs-EVs also attenuate oxidative stress and glial scarring through miR-138-mediated NLRP3-caspase1 and Nrf2-keap1 pathway.[137] Quercetin-loaded EVs limit scar formation by inhibiting JAK2/STAT3 and A1 astrocyte activation.[123]

Targeted Delivery and Clinical Translation. After intranasal administration, functionalized EVs like RGD-modified EVs specifically accumulate, improving therapeutic accuracy.[136] Tannic acid hydrogels enable sustained EVs release, reducing ROS and inflammation while preserving motor and urinary function.[138] Early-phase trials demonstrate intrathecal hucMSCs-EVs safety and functional improvement in subacute SCI, highlighting translational potential.[129] Encouragingly, hucMSCs-EVs therapy for SCI has advanced beyond animal studies to initiate clinical trials in humans (Table 2).

Peripheral Nerve Injury

Peripheral nerve injury (PNI), commonly caused by physical trauma from accidents, natural disasters, wars, or surgical complications, affecting over one million individuals worldwide each year.[139] Damage often results in permanent motor and sensory deficits due to slow axonal regeneration rates, Wallerian degeneration, and inadequate Schwann cell (SC) remyelination, particularly in large injury gaps (1 cm in rodents and 3 cm in humans).[140,141] Current treatments include microsurgical suturing, autologous nerve grafting, and nerve conduits. While autografts remain the "gold standard" for bridging nerve gaps, they face limitations such as donor site damage, limited availability, and poor efficacy for long-gap injuries (>15 mm).[139] Synthetic nerve conduits, such as BDNF-loaded chitosan-based biomimetic polymers, have shown promise in preclinical models by enhancing axonal regeneration and myelination. However, their efficacy as independent therapies is still limited by insufficient bioactivity and incomplete microenvironmental modulation.[139] Complementary approaches, including electrical stimulation and traditional Chinese medicine techniques (eg, acupuncture, tuina), aim to accelerate nerve repair by promoting neurotrophic factor expression and reducing inflammation.[142–144] However, these methods lack standardized protocols and exhibit variable outcomes depending on injury type and severity. These challenges highlight the urgent need for therapies that simultaneously enhance axonal regeneration, modulate the inhibitory microenvironment, and prevent muscle atrophy during prolonged recovery.

For PNI, hucMSCs-EVs show multifaceted regenerative potential, resolving critical challenges such as slow axonal regeneration, SC dysfunction, neuroinflammation, and muscle atrophy. HucMSCs-EVs promote SC proliferation, migration, and differentiation by upregulating migration-related genes (MMP9, MMP13), adhesion molecules (N-cadherin, Integrin β1), and cell cycle regulators (PCNA, Cyclin E1).[145–147] This process is achieved through transferring miR-21, which activates cell growth pathways (PI3K/Akt/mTOR) while blocking stress signal (MAPK), enhancing SC-mediated axonal elongation and remyelination.[145,146] HucMSCs-EVs also stimulate SC to secrete neurotrophic factors like NT-3

Table 2 Registered Clinical Trials with hucMSCs-EVs Interventions on Irct.behdasht.gov.ir (https://irct.behdasht.gov.ir/)

IRCTID	Study Title	Conditions	Interventions	Phases	Last Update Posted
IRCT20200502047277N1	Safety and Efficacy Assessment of Combination of Artificial Dura and Umbilical Cord and Placenta Mesenchymal Stem Cell-Derived Exosomes in Patients with Acute, Sub-acute and Chronic Complete Spinal Cord Injury: A Single-blinded Controlled Clinical Trial	SCI	HucMSCs-EVs	NA	2023/3/25
IRCT20201202049568N3	Evaluation of the Safety and Efficiency of human Umbilical Cord Derived Mesenchymal Stem Cell Exosomes in patients with ARDS of COVID-19; An interventional randomized double-blind controlled clinical trial: phase I and II	ARDS due to COVID-19	HucMSCs-EVs	PHASE1| PHASE2	2021/3/5
IRCT20160422027520N23	Investigating the effect of intrauterine injection of Extracellular vesicles derived from human umbilical cord Wharton's Jelly mesenchymal stem cells in the healing process of women with intrauterine adhesions (Asherman syndrome)	Asherman syndrome (intrauterine adhesions)	HucMSCs-EVs	NA	2024/2/21
IRCT20240317061316N1	Evaluation of safety and efficacy of using exosome harvested from human umbilical cord mesenchymal stem cells (hucMSCs) in diabetic foot ulcer patients (Clinical trial Phases I, II)	Diabetic Foot Ulcer	HucMSCs-EVs	PHASE1| PHASE2	2024/7/11

and BDNF, creating a regenerative microenvironment.[147,148] The repair process is further supported by immunomodulation, as hucMSCs-EVs reduce pro-inflammatory cytokines (IL-6, IL-1β) while elevate anti-inflammatory IL-10, resolving chronic inflammation that impedes regeneration.[149,150] They also enhance angiogenesis, as evidenced by increased $CD31^+$ endothelial cells in regenerated nerves, improving oxygen and nutrient delivery to injury sites.[150] To combat muscle atrophy, hucMSCs-EVs suppress muscle-specific ubiquitin ligases (Fbxo32, Trim63) by delivering miR-23b-3p, maintaining muscle mass and function during long-term recovery.[151] Through hypoxic pretreatment, hucMSCs-EVs are enriched with factors that promote regeneration, enhance SC migration, and neurotrophic factor secretion.[147] Engineered delivery systems, such as dual-responsive hydrogels or 3D-printed nerve conduits loaded with decellularized ECM (dECM)-encapsulated EVs, enable sustained release and spatial targeting, improving functional recovery in rodent sciatic nerve models.[145,150,152] Combinatorial methods, such as combining hucMSCs-EVs with olfactory ensheathing cells (OECs), can synergistically promote BDNF secretion and SC survival in hypoxic conditions, accelerating axonal reconnection.[148] These studies highlight the potential of hucMSCs-EVs as a cell-free, multi-targeted therapy for PNI. HucMSCs-EVs improve neurological diseases through multiple mechanisms such as immune regulation, angiogenesis, and nerve regeneration. HucMSCs-EVs treatment for PNI is currently supported only by animal-level evidence, human trials are lacking. The specific molecular pathways are summarized in Figure 4 and Table 3.

Anti-Tumor Effects

Glioblastoma

Glioblastoma (GBM) is the most invasive primary brain tumor, and despite standard treatments such as surgery, radiation therapy, and chemotherapy, the prognosis is still poor. The BBB restricts drug delivery, tumor heterogeneity promotes therapy resistance, and the immunosuppressive microenvironment further limits treatment efficacy.[153–156]

HucMSCs-EVs have emerged as promising nanocarriers for GBM therapy due to their tumor accumulation, biocompatibility, and ability to cross the BBB. These vesicles mediate therapeutic effects through multiple mechanisms, including direct induction of apoptosis, cell cycle arrest, immunomodulation, and targeted delivery of therapeutic nucleic acids or drugs. Yueh et al demonstrated that miR-124-loaded hucMSCs-EVs downregulate CDK4 and CDK6, leading to G1 phase arrest and apoptosis in GBM cells. Additionally, these EVs modulate the tumor microenvironment by enhancing T-cell activation and dendritic cell maturation, while suppressing regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thereby promoting an anti-tumor immune response.[153] Moreover, hucMSCs-EVs serve as efficient vehicles for enzyme/prodrug systems. Tibensky et al showed that EVs derived from hucMSCs expressing the yeast cytosine deaminase::uracil phosphoribosyl transferase (yCD::UPRT) gene can convert the prodrug 5-fluorocytosine (5-FC) into cytotoxic 5-fluorouracil (5-FU) within tumor cells, leading to significant tumor growth inhibition and even complete regression in rodent GBM models.[155] Del Fattore et al reported that hucMSCs-EVs inhibit GBM cell proliferation and induce apoptosis. When hucMSCs-EV are loaded with chemotherapy drugs such as vincristine, this anti-tumor effect is further enhanced and drug delivery and cytotoxicity are improved.[156] However, the dual role of MSC-EVs in GBM must be carefully considered. Pavon et al highlighted that although hucMSCs exhibit strong bias toward $CD133^+$ GBM stem cells through chemokine signaling pathways such as MCP-1/CCL2 and SDF-1/CXCL12, their subsequent recruitment may inadvertently support tumor proliferation and invasion through EVs mediated intercellular communication.[154] In summary, hucMSCs-EVs represent a multifunctional platform for GBM therapy through targeted RNA interference, enzyme/prodrug activation, and immunomodulation. The specific molecular pathways are summarized in Figure 4 and Table 3.

Locomotor System

Regenerative Effects

Bone-Related Disorders

Bone-related disorders, including osteoporosis, fracture nonunion, and osteonecrosis, affect over 200 million people worldwide and impose a significant global health burden.[157] These conditions are often exacerbated by dysregulated bone metabolism, where imbalances in osteoblast-osteoclast activity and impaired energy metabolism pathways disrupt bone remodeling, leading to structural fragility and delayed healing.[158,159] Current therapeutic strategies, such as

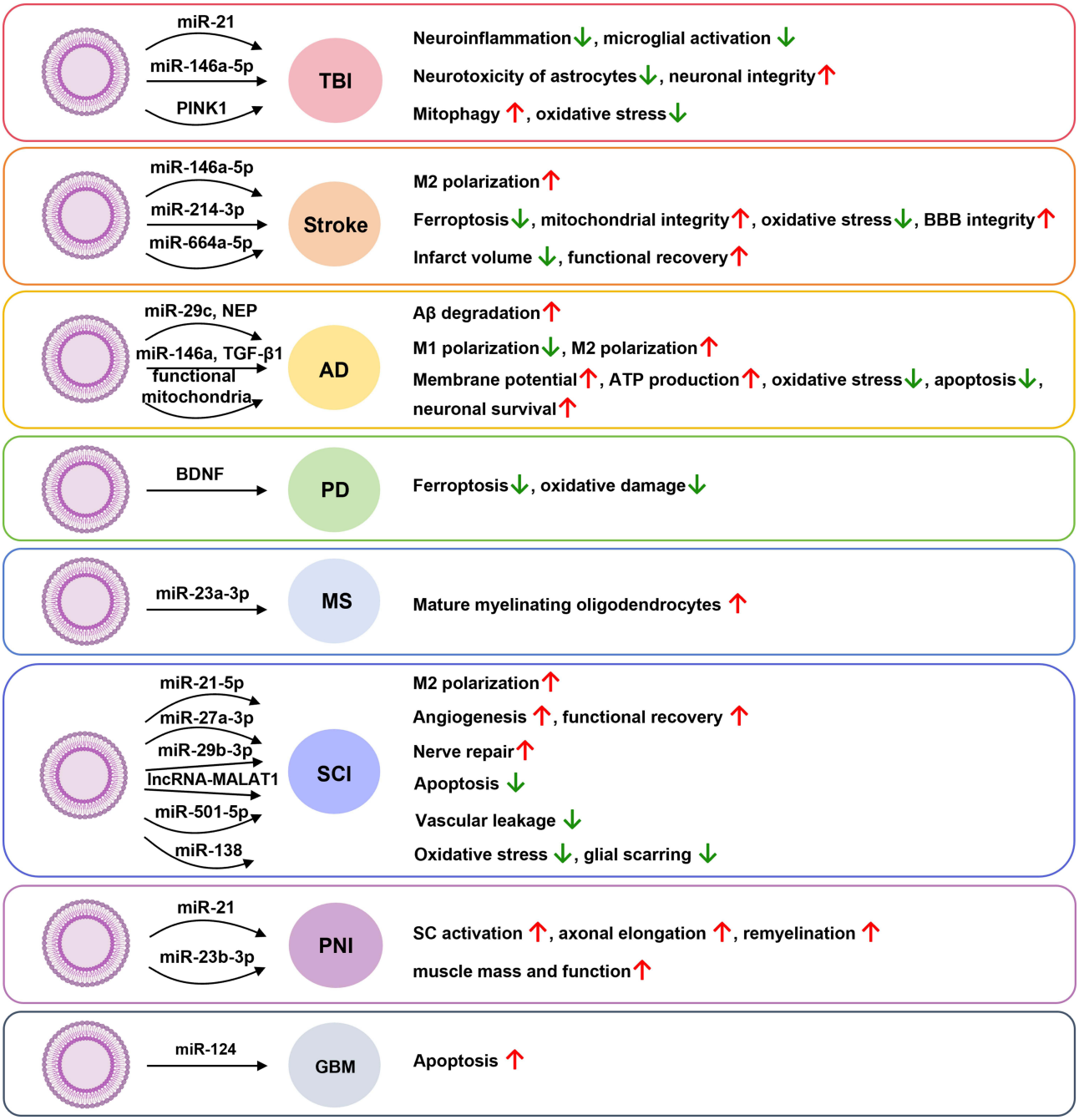


Figure 4 The effects of hucMSCs-EVs carrying different cargoes on different nervous system diseases. The red colored upward arrows indicate promotion or upregulation, while the green colored downward arrows indicate inhibition or downregulation.

bisphosphonates, parathyroid hormone analogs, and surgical interventions, remain limited.[160] Drugs can cause systemic side effects and fail to address the underlying metabolic dysfunction,[161] while surgeries like bone grafts may struggle with poor tissue integration or infections.[162,163] Using a patient's own stem cells for treatment shows potential but faces hurdles like poor cell survival, inconsistent differentiation, and ethical concerns.[164] This highlights the urgent need for therapies that enhance osteogenesis, suppress pathological osteoclast activity, and modulate the inflammatory microenvironment.

HucMSCs-EVs for Osteoporosis. In osteoporosis, hucMSCs-EVs inhibit BMSC apoptosis via the miR-1263/Mob1/Hippo signaling pathway, restore osteoblast-adipocyte differentiation balance, and maintain bone homeostasis.[165,166]

Table 3 Molecular Mechanism of hucMSCs-EVs in Treating Different Diseases in the Nervous System

HucMSCs-EVs Cargo	Target/signaling	Conditions/ Diseases	Action[a]	Reference
None reported	NF-κB	TBI	M1/A1 polarization↓, M2/A2 polarization↑, cell apoptosis↓, neurogenesis↑	[18,46]
miR-21	NF-κB	TBI	Neuroinflammation↓, microglial activation↓	[58]
miR-146a-5p	Neurotoxic astrocyte pathways	TBI	The effects of neurotoxic astrocytes↓, neuronal integrity↑	[59,60]
PINK1	Mitophagy pathways	TBI	Mitophagy↑, oxidative stress↓	[61]
miR-146a-5p	IRAK1/TRAF6/NF-κB	Stroke	M2 polarization↑	[47]
miR-214-3p	GPX4, ACSL2	Stroke	Ferroptosis↓, mitochondrial integrity↑, oxidative stress↓, BBB integrity↑	[71]
miR-664a-5p	AAK1/ NF-κB	Stroke	Infarct volume↓, functional recovery↑	[72]
miR-29c, NEP	None reported	AD	Aβ degradation↑	[48]
miR-146a, TGF-β1	None reported	AD	M1 polarization↓, M2 polarization↑	[48,81]
functional mitochondria	None reported	AD	Membrane potential↑, ATP production↑, oxidative stress↓, apoptosis↓, neuronal survival↑	[83]
None reported	None reported	PD	the viability of dopaminergic neurons↑, olfactory function↑	[95,96]
None reported	LC3B-II/I, Beclin-1, p62	PD	α-synuclein aggregation ↓, apoptosis↓,	[98]
None reported	PI3K/Akt/NF-κB/NLRP3	PD	Pyroptosis↓	[96, 97]
None reported	SATB1/ Wnt/β-catenin	PD	Neurogenesis↑, neurite outgrowth↑, autophagy↓,	[96]
BDNF	MAP2, tau, Nrf2 antioxidant pathway	PD	Ferroptosis↓, oxidative damage↓	[100,101]
None reported	None reported	MS	Immune tolerance↑	[107,108]
miR-23a-3p	PI3K/Akt, Tbr1/Wnt	MS	Mature myelinating oligodendrocytes↑	[110]
None reported	MBP	MS	Demyelinated lesions↓, neurological function↑	[15,109]
None reported	Lag-3	MS	Immune cell proliferation↓, cytokine storm↓	[111]
None reported	A2bR/cAMP/PKA	SCI	M2 polarization↑	[120]
miR-21-5p	PDCD4	SCI	M2 polarization↑	[122]
miR-27a-3p	DLL4	SCI	Angiogenesis↑, functional recovery↑	[125]
None reported	NF200, MBP, GAP43, synaptophysin, PSD95	SCI	Remyelination↑, synaptogenesis↑, axonal growth↑,	[124,127–130]
miR-29b-3p	PTEN, Akt/mTOR	SCI	Nerve repair↑	[132]
None reported	ERK1/2	SCI	The proliferation and differentiation of NSCs↑	[128]
None reported	Bax, caspase-3, p75NTR, Bcl-2	SCI	Apoptosis↓	[124,126–129,131,134]
lncRNA-MALAT1	miR-22-3p/ SIRT1 /AMPK	SCI	Apoptosis↓	[134]
None reported	ET-1, ZO-1, β-catenin, occludin, claudin-5	SCI	BSCB integrity↑	[135,136]
miR-501-5p	MLCK	SCI	Vascular leakage↓	[136]
miR-138	NLRP3-caspase1, Nrf2-keap1	SCI	Oxidative stress↓, glial scarring↓	[137]
miR-21	PI3K/Akt/mTOR, MAPK	PNI	SC activation↑, axonal elongation ↑, remyelination↑	[145,146]
miR-23b-3p	Fbxo32, Trim63	PNI	Muscle mass and function↑	[151]
miR-124	CDK4, CDK6	GBM	Apoptosis↑	[153]

Notes: [a] ↑ indicates promotion or upregulation; ↓ indicates inhibition or downregulation.

These EVs also carry proteins like CLEC11A, which is a pro-osteogenic protein that push BMSC to become osteoblasts instead of adipocytes, while suppressing the formation of osteoclasts, effectively reducing bone resorption and bone marrow fat accumulation.[167] Although some potencies have been achieved in animal studies, hucMSCs-EVs-based interventions for osteoporosis have not yet entered to human clinical trials.

HucMSCs-EVs for Fracture. For bone regeneration and fracture healing, hucMSCs-EVs enhance osteogenesis by upregulating osteogenic proteins such as RUNX2, ALP, BMP-2, and OCN, which promote the deposition of mineralized

matrix and the formation of calcified nodules in BMSC and osteoblast progenitor.[45,168,169] They also promote angiogenesis by activating HIF-1α and VEGF in endothelial cells, stimulating proliferation, migration, and tube formation, which improves oxygen and nutrient supply to injured areas.[169–171] Notably, hucMSCs-EVs derived miR-23a-3p targets PTEN to activate the AKT pathway and linking osteogenesis with osteogenesis and angiogenesis for vascularized bone repair.[169] By integrating hucMSCs-EVs with biomaterials, including hyaluronic acid hydrogels and nanohydroxyapatite scaffolds, the delivery efficiency of osteoinductive factors like rhBMP-2 is enhanced, accelerating regeneration in osteoporotic defects.[172–174] So far, researches on hucMSCs-EVs therapy for fracture have remained limited to animal models and lack human trials.

HucMSCs-EVs for Cartilage and Intervertebral Disc Repair. In cartilage and intervertebral disc repair, hucMSCs-EVs modulate immune microenvironments by reducing inflammation and suppressing ECM degradation. They enhance mitochondrial function in chondrocytes via transferring glycolytic enzyme and alleviate endoplasmic reticulum stress in nucleus pulposus cells by activating AKT/ERK pathway, thus reducing apoptosis and fibrosis.[171] HucMSCs-EVs treatment for cartilage and intervertebral disc repair is currently supported only by animal-level evidence, human trials are lacking.

HucMSCs-EVs for Periapical Periodontitis. The anti-inflammatory properties further contribute to bone repair in inflammatory environments, such as periapical periodontitis, where hucMSCs-EVs reduce osteoclast activity and inflammatory cell infiltration, promoting alveolar bone regeneration.[45] Notably, therapeutic development of hucMSCs-EVs for periapical periodontitis has transitioned from animal validation to active Phase II human clinical evaluation (Table 1).

These studies indicate that hucMSCs-EVs are effective multi-target treatment for osteoporosis, fracture non-unions, cartilage and intervertebral discs, but strict trials are needed to verify long-term efficacy and safety.

Joint-Related Disorders

Joint-related disorders like osteoarthritis (OA), rheumatoid arthritis (RA) impact billions worldwide,[175,176] leading to chronic pain, disability, and irreversible cartilage loss caused by imbalanced inflammatory cascades, chondrocyte apoptosis, and ECM degradation.[177,178] Existing treatments for joint diseases remain inadequate. Pharmacological interventions, including nonsteroidal anti-inflammatory drugs (NSAIDs), can alleviate symptoms but cannot prevent disease progression. Long term use carries risks of gastrointestinal, cardiovascular, and renal toxicity.[179] Intra-articular injections of corticosteroids or hyaluronic acid offer transient benefits but require frequent administration due to rapid clearance, reducing patient compliance.[180] Although total knee arthroplasty and other surgeries are effective for end-stage OA, they are invasive, costly, and associated with complications such as infection and incomplete functional recovery.[181] These shortcomings emphasize the urgent need for therapies that simultaneously resolve inflammation, restore cartilage integrity, and modulate the synovial microenvironment.

HucMSCs-EVs for OA. HucMSCs-EVs show multiple healing abilities for OA by addressing inflammation, angiogenesis, cartilage regeneration, synovial microenvironment modulation.

Immunomodulation and Inflammation Resolution

HucMSCs-EVs reprogram immune cells to relieve synovial inflammation. They polarize macrophages from M1 to M2 phenotypes by suppressing NLRP3 inflammasome activation via miR-223 binding to NLRP3 mRNA[20] and reducing METTL3-mediated m6A modification of NLRP3.[21] This shift decreases synovial TNF-α, IL-1β, and IL-6 while elevating IL-10 and TGF-β, creating a regenerative microenvironment.[20,21,182,183] EVs also inhibit T-cell proliferation and NF-κB signaling, further attenuating inflammatory cascades.[184,185]

Chondrocyte Protection and Cartilage Matrix Homeostasis

HucMSCs-EVs directly protect chondrocytes from oxidative stress and apoptosis. miR-100-5p in EVs targets NOX4 to reduce ROS levels, while miR-7704 silences MMP13 to inhibit matrix degradation.[186,187] They upregulate COL2A1 and aggrecan, activate ITGB1/TGF-β/Smad2/3 pathway,[188,189] and downregulate ADAMTS5 and MMP13 through miRNA-mediated pathways,[190,191] thereby rescuing IL-1β-damaged chondrocytes. Compared to EVs from 2D cultures, those from 3D cultures show superior efficacy in suppressing ADAMTS5 and enhancing COL2 synthesis.[191]

Promotion of Cartilage Regeneration

In cartilage regeneration, hucMSCs-EVs enhance BMSC proliferation, migration, and chondrogenic differentiation. By suppressing SMAD7, miR-181c-5p promotes BMP2-induced BMSC differentiation into chondrocytes,[192] miR-23a-

3p activates the PTEN/AKT pathway to stimulate glycosaminoglycan and collagen II deposition.[193] Engineered EVs, such as siRNA loaded EVs with IGF-1, adhere to cartilage through charge interactions to ensure their sustained therapeutic effect at the defect site.[194] Hydrogel-encapsulated EVs, including alginate/hyaluronic acid and Gelma/nanoclay systems, achieve complete cartilage regeneration in rodent models by spatially controlling EV release.[191,193]

Synovial Microenvironment Regulation

HucMSCs-EVs modulate synovial homeostasis by reducing pyroptosis via miR-223/NLRP3 axis inhibition[20] and suppressing NF-κB-induced cytokine storms.[184] They enhance ECM synthesis in aging chondrocytes by continuously delivering miR-29b-3p, which targets FoxO3 to restore mitochondrial function.[195] Clinical-grade EVs demonstrate safety and efficacy in early trials, reducing synovial inflammation and improving joint function.[183,196]

Angiogenesis and Tissue Repair Coordination

For blood vessel support, hucMSCs-EVs promote vascularization by upregulating HIF-1α/VEGF in endothelial cells.[21,197] When combined with acellular cartilage matrix, this synergistic effect of angiogenesis can promote osteochondral defect healing.[197]

Engineering Innovations

Advanced delivery systems optimize EVs efficacy: IL-1β-preconditioned EVs selectively enrich anti-inflammatory miRNAs like miR-148a and miR-29b to enhance cartilage repair.[184,198] Decellularized Wharton's jelly hydrogels loaded with $CD56^+$ EVs promote meniscus healing and safeguard articular cartilage.[199] Encouragingly, based on strong animal experimental evidence, hucMSCs-EVs intervention in OA has now entered phase I human clinical trials (Table 1).

HucMSCs-EVs for RA. RA, a severe autoimmune disorder, is caused by synovial inflammation and joint destruction. HucMSCs-EVs are employed in treatment due to their immunomodulatory and regenerative capabilities. The core of their efficacy is to restore immune homeostasis: hucMSCs-EVs rebalance Th17/Treg cell dynamics by downregulating RORγt (a Th17 transcription factor) and upregulating Foxp3 (a Treg marker), thus reducing IL-17-induced inflammation while promoting immune tolerance.[200–202] The adjustment leads to a reduction in inflammatory proteins like IL-17 and TNF-α and an increase in anti-inflammatory molecules like TGF-β, creating a better environment for healing.[201–203] HucMSCs-EVs also silenced ATF2 by delivering miR-45a, directly inhibiting pathogenic synovial fibroblasts, which are key driving factors for synovial proliferation and cartilage erosion. ATF2 is a key regulatory factor for synovial fibroblasts proliferation and invasion.[204] EVs help maintain cartilage integrity by delivering miR-140-3p, which inhibits chondrocyte apoptosis by targeting SGK1, a kinase associated with oxidative stress and matrix degradation.[205] Emerging evidence also highlights their systemic effects: hucMSCs-EVs restore gut microbiota balance in RA models, enriching beneficial bacteria like *Candidatus Saccharibacteria* and inhibiting systemic inflammation.[203] HucMSCs-EVs pretreated with pro-inflammatory cytokines exhibit stronger anti-inflammatory properties and better immunosuppressive effect.[206] Animal studies confirm their capacity to reduce synovial hyperplasia, inflammatory infiltration, and cartilage damage, emphasizing their potential as a holistic therapy.[201,202] Regrettably, the application of hucMSCs-EVs in treating RA has only undergone animal trials and has not yet advanced to human clinical trials.

Muscle-Related Disorders

HucMSCs-EVs show promise for treating muscle-related disorders by targeting both muscle atrophy and fibrotic degeneration. In age-related and dexamethasone-induced muscle atrophy models, hucMSCs-EVs alleviate muscle atrophy by delivering miR-132-3p, which directly silences FoxO3, a transcriptional regulator of muscle atrophy markers MuRF1 and atrogin-1. By suppressing the miR-132-3p/FoxO3 axis, EVs restore muscle mass, enhance grip strength, and preserve muscle fiber integrity, offsetting the catabolic pathways that cause atrophy.[207] Beyond atrophy prevention, hucMSCs-EVs promote muscle regeneration and inhibit fibrosis by delivering Follistatin, a key regulatory protein. HucMSCs-EVs derived Follistatin binds to TGF-β family ligands like Myostatin, blocking Smad2 activation, a pro-fibrotic pathway, and enhancing AKT signaling, which stimulates myoblast differentiation and myotube formation. This dual modulation reduces collagen deposition and fibrotic scarring while promoting functional muscle repair, as evidenced by improved regeneration in murine models.[208] hucMSCs-EVs provides a comprehensive treatment for muscle disorders by inhibiting atrophy and promoting regeneration. Unfortunately, the current status of hucMSCs-EVs for muscle disorders treatment remains limited to animal experiments, and there has been no progress in research at the human stage.

Tendon-Related Disorders

Tendon injury-related diseases present significant challenges because of their limited natural healing ability. HucMSCs-EVs demonstrate multifaceted therapeutic potential in tendon repair by addressing the complex interplay of cellular regeneration, inflammatory dysregulation, and structural degeneration. Their effectiveness primarily lies in enhancing the proliferation and tenogenic differentiation of tendon-derived stem cells by delivering miR-29a-3p, which targets PTEN to activate the mTOR/TGF-β1 signaling pathway. This activation enhances collagen deposition and upregulates tendon-specific markers (COL1A1, SCXA, TNMD), driving functional tendon regeneration.[209] In animal models, hucMSCs-EVs regulate the inflammatory microenvironment by suppressing T-cell proliferation and attenuating excessive immune responses that cause fibrosis and tissue damage.[185] Beyond cellular repair, these EVs prevent tendon fatty degeneration—a common post-injury sequela—by delivering paracrine factors that regulate muscle cell metabolism and differentiation. As proved by the rotator cuff repair study, collagen gel loaded with EVs reduces fat accumulation in rotator cuff muscles.[210] Furthermore, hucMSCs-EVs enhance the biomechanical integrity of healed tendons, improving ultimate tensile strength and stiffness in Achilles tendon models, which may be achieved by optimizing matrix remodeling and collagen alignment.[209] Unfortunately, the treatment of tendon-related disorders with hucMSCs-EVs is still in the animal trial stage and has not yet entered human studies.

Anti-Tumor Effects

Osteosarcoma

Osteosarcoma (OS) is a highly malignant bone tumor that mainly affects children and adolescents, accounting for approximately 60% of all bone sarcomas. It is characterized by aggressive local invasion and early metastasis, particularly to the lungs, which significantly contributes to its poor prognosis. Current standard treatments include surgical resection combined with chemotherapy. However, therapeutic efficacy is often limited by chemoresistance and tumor heterogeneity.[211,212] These challenges underscore the urgent need for novel therapeutic strategies that can specifically target tumor cells while minimizing systemic toxicity.

In recent years, hucMSCs-EVs have emerged as promising biological nanocarriers for targeted cancer therapy. Study has demonstrated that hucMSCs-EVs can efficiently accumulate within osteosarcoma tumors over a sustained period (24–48 hours) post-systemic administration, and they outperform synthetic nanoparticles in both retention and specificity.[212] They demonstrate a multifaceted mechanism of action against OS, including effective tumor targeting, cellular internalization, and dose-dependent proliferation inhibition without inducing cell apoptosis.[212] HucMSCs-EVs exhibit targeted repair potential in bone, joint, muscle, and tendon diseases, with key mechanisms summarized in Figure 5 and Table 4.

Respiratory System

Regenerative Effects

Covid-19

The outbreak of COVID-19 has brought challenges to global health. HucMSCs-EVs show diverse potential by targeting viral pathogenesis, hyperinflammation, and tissue damage. Central to their efficacy is the suppression of cytokine storms, a hallmark of severe COVID-19, through immunomodulatory. HucMSCs-EVs inhibit NF-κB pathway activation, reducing nuclear translocation of p65 and downregulating pro-inflammatory cytokines, even under hyperglycemic and uremic toxin conditions, thus reducing systemic inflammation and organ damage.[22] Meanwhile, their anti-inflammatory properties are enhanced by miRNA cargo such as miR-126 and miR-30b, which attenuate pulmonary fibrosis and remodel airway. Patients treated with nebulized EVs have improved lung lesion absorption and shortened hospitalization time.[213] Beyond inflammation control, hucMSCs-EVs directly combat viral replication via antiviral miRNAs like miR-125b, which suppress influenza and seasonal coronavirus proliferation. This suggests that their broad-spectrum antiviral capacity potentially applicable to SARS-CoV-2.[214] Furthermore, these EVs promote tissue repair by delivering regenerative factors such as angiopoietin-1 and HGF, which promote alveolar regeneration, angiogenesis, and cell survival, improving COVID-19-induced lung injury.[214,215] Identify more miRNA candidates in EVs, such as miR-148a and miR-21-5p, which could synergistically target viral entry receptors like ACE2 and TMPRSS2, as well as inflammatory

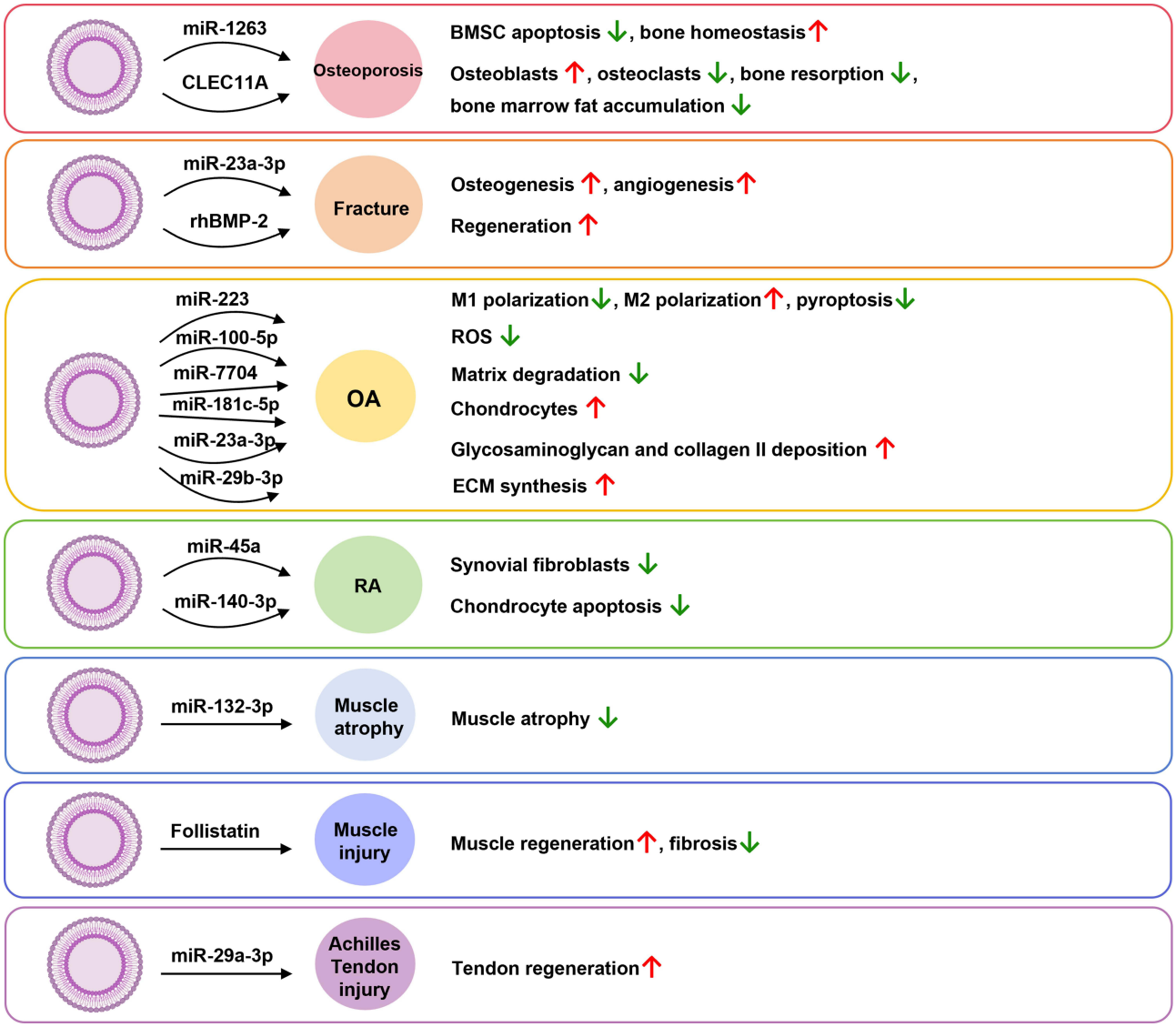


Figure 5 The effects of hucMSCs-EVs carrying different cargoes on different locomotor system diseases. The red colored upward arrows indicate promotion or upregulation, while the green colored downward arrows indicate inhibition or downregulation.

pathways, offering a multi-targeted therapeutic strategy.[216] Notably, hucMSCs-EVs for treating COVID-19 are not only being studied in animal studies, but have also undergone phase II clinical trials in humans (Table 1).

Acute Lung Injury/Acute Respiratory Distress Syndrome

HucMSCs-EVs show multifaceted therapeutic efficacy in acute lung injury/acute respiratory distress syndrome (ALI/ARDS) by anti-inflammatory, antioxidant, and regenerative pathways. The mechanism primarily relies on the regulation of key signaling pathways mediated by miRNA to achieve the inhibition of hyperinflammation, which is the cornerstone of their therapeutic efficacy. In sulfur mustard and burn-induced ALI, EVs enriched with miR-146a-5p and miR-451 target TRAF6 to inhibit TLR4/NF-κB and MIF-PI3K-AKT pathway to promote macrophage M2 polarization, thereby attenuating pro-inflammatory cytokine storms.[217–219] In sulfur mustard-exposed models, hucMSCs-EVs deliver miR-199a-5p to silence CAV1 and activate the NRF2/HO-1 axis, which reduces ROS and lipid peroxidation, and enhances antioxidant enzymes such as SOD, GSH.[220] This antioxidant synergy is enhanced by ferroptosis inhibition, where EVs upregulate SLC7A11 and GPX4, activate the NRF2 pathway, and rescue lung epithelial cells from iron-dependent death.[221,222] Beyond inflammation resolution, hucMSCs-EVs promote tissue repair by restoring alveolar fluid clearance.

https://doi.org/10.2147/IJN.S550390

Table 4 Molecular Mechanism of hucMSCs-EVs in Treating Different Diseases in the Locomotor System

HucMSCs-EVs Cargo	Target/Signaling	Conditions/Diseases	Action[a]	Reference
miR-1263	Mob1/Hippo	Osteoporosis	BMSC apoptosis↓, bone homeostasis↑	[165,166]
CLEC11A	NF-κB, microglial activation	Osteoporosis	Osteoblasts ↑, osteoclasts↓, bone resorption↓, bone marrow fat accumulation↓	[167]
None reported	RUNX2, ALP, BMP-2, OCN	Fracture	Osteogenesis↑	[45,168,169]
None reported	HIF-1α, VEGF	Fracture	Angiogenesis↑	[169–171]
miR-23a-3p	PTEN / AKT	Fracture	Osteogenesis↑, angiogenesis↑	[169]
rhBMP-2	None reported	Fracture	Regeneration↑	[172–174]
None reported	AKT/ERK	Cartilage and intervertebral disc repair	Apoptosis↓, fibrosis↓	[171]
None reported	None reported	Periapical periodontitis	Osteoclast activity↓, inflammatory cell infiltration↓, alveolar bone regeneration↑	[45]
miR-223	NLRP3	OA	M1 polarization↓, M2 polarization↑, pyroptosis↓	[20]
None reported	NF-κB	OA	T-cell proliferation↓, inflammatory cascades↓	[184,185]
miR-100-5p	NOX4	OA	ROS↓	[186]
miR-7704	MMP13	OA	Matrix degradation↓	[187]
None reported	ITGB1/TGF-β/Smad2/3	OA	Chondrocytes protection↑	[188,189]
miR-181c-5p	SMAD7	OA	Chondrocytes↑	[192]
miR-23a-3p	PTEN/AKT	OA	Glycosaminoglycan and collagen II deposition↑	[193]
miR-29b-3p	FoxO3	OA	ECM synthesis↑	[195]
None reported	HIF-1α/VEGF	OA	Vascularization↑	[21,197]
None reported	RORγt, Foxp3	RA	Inflammation, immune tolerance↑	[200–202]
miR-45a	ATF2	RA	Synovial fibroblasts↓	[204]
miR-140-3p	SGK1	RA	Chondrocyte apoptosis↓	[205]
miR-132-3p	FoxO3	Muscle atrophy	Muscle atrophy↓	[207]
Follistatin	Myostatin, Smad2, AKT	Muscle injury, myotubes atrophy	Muscle regeneration↑, fibrosis↓	[208]
miR-29a-3p	PTEN/mTOR/TGF-β1	Achilles tendon injury	Tendon regeneration↑	[209]
None	None reported	OS	Proliferation↓	[212]

Notes: [a] ↑ indicates promotion or upregulation; ↓ indicates inhibition or downregulation.

They also preserve endothelial barrier integrity to reduce edema in ischemia-reperfusion and bacterial pneumonia models.[223–225] Engineered EVs further amplify efficacy: IFN-γ-loaded EVs suppress NLRP3 activation via miR-199b-5p/AFTPH-mediated NF-κB inhibition,[226] while miR-486-5p-modified EVs target SMAD2 to alleviate radiation-induced fibrosis and enhance Akt phosphorylation to promote epithelial regeneration.[222] It is worth noting that SARS-CoV-2-S-RBD-engineered EVs achieve lung-specific delivery, optimizing the biodistribution of anti-fibrotic miR-486-5p to reduce collagen deposition and improve alveolar architecture.[222] Autophagy modulation is another important mechanism, with miR-377-3p in EVs activating RPTOR-targeted autophagy to alleviate LPS-induced injury, while miR-451 suppresses alveolar macrophage autophagy via TSC1/mTOR to balance tissue repair and inflammation resolution.[227,228] These mechanisms collectively weaken the pathological features—inflammatory infiltration, epithelial apoptosis, and fibrotic remodeling—in ALI/ARDS models, leading to improved histopathology, reduced BALF cytokines, and enhanced survival.[229–232] In addition to these animal studies, hucMSCs-EVs for the treatment of ARDS have entered phase II clinical trials in humans (Table 2).

Chronic Obstructive Pulmonary Disease

HucMSCs-EVs display diverse therapeutic potential in chronic obstructive pulmonary disease (COPD) by targeting its key pathological features—chronic inflammation, alveolar apoptosis, ECM remodeling, and vascular degeneration. In cigarette smoke-induced COPD models, hucMSCs-EVs alleviate airway and parenchymal inflammation by suppressing NF-κB signaling and pro-inflammatory cytokines like TNF-α and IL-6. HucMSCs-EVs also attenuate neutrophil and macrophage infiltration and goblet cell hyperplasia.[233] These EVs counteract alveolar destruction by restoring ECM homeostasis: they inhibit MMP-9 activity to prevent elastin degradation and upregulate TIMP-1 to stabilize lung architecture, thereby preserving alveolar integrity.[233] In papain-induced emphysema models, hucMSCs-EVs inhibit endothelial apoptosis via activating the VEGF-VEGFR2 axis, which triggers downstream survival pathways (AKT and MEK/ERK) to suppress apoptosis and maintain alveolar septal structure.[234] This anti-apoptotic effect synergizes with their promote angiogenesis capacity, as VEGF-VEGFR2 signaling stimulates endothelial proliferation and microvascular network regeneration, improving gas exchange in emphysematous lungs.[234] miRNA profiling shows that hucMSCs-EVs deliver key regulatory molecules such as miR-146a-5p and miR-10a-5p, which coordinate these effects by silencing pro-inflammatory mediators and enhancing cell survival pathways, respectively.[234] By reducing inflammation, preventing apoptosis, remodeling ECM, and promoting vascular repair, hucMSCs-EVs serve as cell-free regenerative strategy to address various pathology of COPD. Unfortunately, hucMSCs-EVs for COPD treatment have only been tested in animal models and have not yet entered human clinical trials.

Asthma

In asthma, hucMSCs-EVs display diverse therapeutic efficacy by targeting chronic inflammation, airway remodeling, and epithelial barrier dysfunction. The key aspect of their function is the reprogramming of immune responses, achieved through macrophage polarization and the modulation of innate lymphoid cells. In severe steroid-resistant asthma models, hucMSCs-EVs play a crucial role in modulating the immune environment. They shift pro-inflammatory M1 macrophages to anti-inflammatory M2 phenotypes. By suppressing NF-κB activation and enhancing PI3K/AKT signaling, reducing neutrophil infiltration and pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), while increasing IL-10 levels.[235] This immunomodulation also affects group 2 innate lymphoid cell-dominant allergic airway inflammation. Here, EV-delivered miR-146a-5p inhibits IL-13 production and eosinophil recruitment, while simultaneously enhancing Treg immunosuppressive capacity through TGF-β1 and IL-10 upregulation.[236,237] HucMSCs-EVs preserve airway epithelial integrity via hypoxia-preconditioned EVs (Hypo-EVs) that transfer caveolin-1 (CAV-1) to inhibit STAT6 phosphorylation, thereby restoring tight junction proteins (ZO-1, E-cadherin) and reducing allergen penetration.[238] Administering these Hypo-EVs via nebulization improves therapeutic delivery, enhancing lung bioavailability to attenuate goblet cell metaplasia, subepithelial collagen deposition, and α-SMA-induced fibrosis by inhibiting the TGF-β1/Smad2/3 pathway.[239] EVs with overexpressed miR-146a-5p enhance these effects by targeting TRAF6 and IRAK1, which inhibits the activation of NF-κB/NLRP3 and pro-inflammatory cytokines like IL-1β, IL-18, while reducing epithelial barrier disruption.[240] HucMSCs-EVs alleviates asthma by synergistically resolving inflammation, restoring epithelial integrity, and preventing fibrotic remodeling. Regretfully, the therapeutic effect of hucMSCs-EVs on asthma has not been confirmed by clinical trials yet.

Silicosis

Silicosis is a weakened fibrotic lung disease caused by silica-induced inflammation and fibroblast activation. More and more studies have found that hucMSCs-EVs treat silicosis through anti-fibrotic and immunomodulatory. EVs inhibits the transition of fibroblasts to myofibroblasts by downregulating profibrotic markers (α-SMA, collagen I, fibronectin) through delivery of miRNA. For instance, miR-148a-3p enriched EVs inhibit heat shock protein 90 beta member 1 (Hsp90b1), suppressing collagen synthesis and fibroblast activation,[241] while let-7i-5p targets TGFβ receptor 1 (TGFBR1) to block TGF-β1/Smad3 signaling, reducing ECM deposition.[242] HucMSCs-EVs also inhibit the PWWP2A/NLRP3 axis by transmitting miR-223-3p, suppressing NLRP3 activation and pro-inflammatory cytokine (IL-1β, IL-18), thereby addressing chronic inflammation that promotes fibrosis.[243] Furthermore, these EVs silence the protease Adam17 on the Notch pathway by delivering miR-26a-5p, counteracting epithelial-mesenchymal transition (EMT), which is a critical source of fibroblasts.[244] The synergistic effects of these mechanisms—fibroblast inhibition,

EMT blockade, and NLRP3-driven inflammation resolution—are amplified by the 3D culture of hucMSCs, which enhances EVs yield and therapeutic potency in reducing collagen deposition and improving lung architecture in murine silicosis models.[245] Collectively, hucMSCs-EVs address silicosis pathology at molecular, cellular, and tissue levels, although optimizing delivery pathways and scaling up production remain key challenges for clinical translation. It is worth noting that these effects of hucMSCs-EVs have only been achieved in animal models and have not yet been validated in clinical trials.

Anti-Tumor Effects

Lung Cancer

Lung cancer remains one of the most common and deadly malignant tumors in the world. Current treatments, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, are often constrained by late diagnosis, drug resistance, metastasis, recurrence, and systemic toxicity, contributing to unsatisfactory long-term survival rates.[246,247] These limitations emphasize the critical need for innovative treatment strategies that can selectively target cancer cells while minimizing damage to healthy tissues.

Research into the role of hucMSCs-EVs in lung cancer has revealed context-dependent functions, with evidence supporting both anti-tumor and pro-tumor effects. On one hand, several studies demonstrate that engineered or selectively loaded hucMSCs-EVs can suppress tumor progression. For example, Zhao et al showed that EVs derived from TGF-β1-silenced hucMSCs inhibited EMT, migration, and invasion of lung cancer cells through the inactivation of Smad2/3, Akt/GSK-3β/β-catenin, MAPK, and NF-κB signaling pathways.[248] Similarly, Xie and Wang reported that miR-320a-enriched hucMSCs-EVs suppressed proliferation and metastasis by targeting SOX4 and inhibiting the Wnt/β-catenin axis.[249]

On the other hand, certain studies indicate that native hucMSCs-EVs may promote tumor growth and metastatic under specific conditions. For instance, Dong et al found that hucMSCs-EVs transferred miR-410 to lung adenocarcinoma cells, resulting in downregulation of the tumor suppressor PTEN, thereby enhancing proliferation and inhibiting apoptosis.[247] Liu et al also observed that both hucMSCs and their EVs could enhance the proliferation and migration of A549 lung cancer cells, though without significant effects on invasiveness.[250] These different outcomes highlight the importance of factors such as EVs cargo composition, cancer subtype, and the tumor microenvironment in determining functional consequences.

Notably, some investigations report a neutral or even protective role of hucMSCs-EVs. Patel et al indicated that hucMSC-derived secretomes did not stimulate lung cancer cell proliferation or confer resistance to chemotherapeutic agents such as doxorubicin, indicating its good safety.[251] Beyond direct tumor modulation, hucMSCs-EVs may also facilitate immunoregulation and enhance chemosensitivity, offering multifaceted therapeutic opportunities.[246,251]

In summary, hucMSCs-EVs represent a promising avenue for lung cancer treatment, capable of delivering tumor-suppressive miRNAs and proteins to modulate key oncogenic pathways. However, their dual nature requires careful evaluation of source cells, isolation methods, and engineering strategies. HucMSCs-EVs alleviate respiratory system diseases through anti-inflammatory, antioxidant, anti-fibrotic and other pathways, with specific molecular targets shown in Figure 6 and Table 5.

Circulatory System

Regenerative Effects

Cardiac Diseases

HucMSCs-EVs display diverse therapeutic capabilities in the process of cardiac repair, relying on different molecular and cellular mechanisms. In viral myocarditis, hucMSCs-EVs reduce cardiomyocyte damage by modulating autophagy and ferroptosis pathways. For instance, let-7a-5p derived from hucMSCs-EVs targets SMAD2 to upregulate ZFP36, inhibiting coxsackievirus B3 (CVB3)-induced ferroptosis in cardiomyocytes.[49] Meanwhile, the activation of the AMPK/mTOR autophagy pathway reduces apoptosis and improves cardiac function by enhancing LC3II/I and BECLIN-1 expression.[252] Similarly, in myocardial infarction (MI), hucMSCs-EVs promote angiogenesis via microRNA-mediated pathways, such as miR-423-5p inhibits EFNA3 to enhance endothelial cell migration,[253] and miR-23a-3p targets DMT1 to inhibit ferroptosis.[254] Engineered EVs, like macrophage migration inhibitory factor (MIF)-enriched EVs, further amplify therapeutic effects by activating miR-133a-3p/AKT signaling to enhance endothelial proliferation and suppress

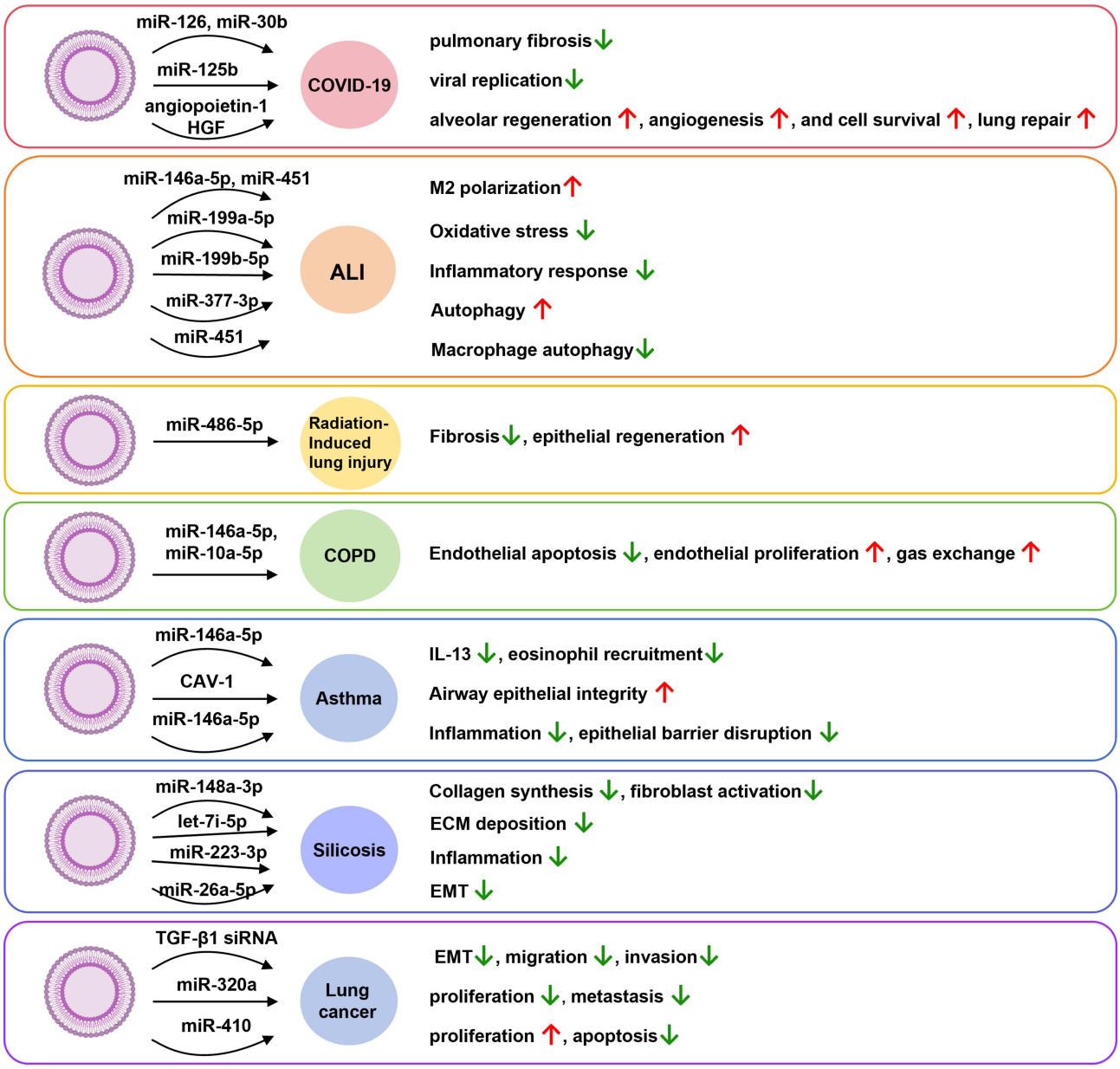


Figure 6 The effects of hucMSCs-EVs carrying different cargoes on different respiratory system diseases. The red colored upward arrows indicate promotion or upregulation, while the green colored downward arrows indicate inhibition or downregulation.

apoptosis.[255] Additionally, hucMSCs-EVs alleviate oxidative stress and apoptosis in cardiomyocytes exposed to doxorubicin or hypoxia/reoxygenation injury by modulating pathways like miR-100-5p/NOX4[256] and PI3K/Akt.[257] Moreover, mitochondrial protection regulates calcium homeostasis through PINK1-PKA-NCLX axis activation.[258]

Fibrosis and inflammation are key factors in cardiac remodeling, and hucMSCs-EVs inhibit them through miRNA delivery and signaling pathway regulation. EVs transmit miR-29b to reduce fibrosis-related proteins in cardiac fibroblasts.[259] By transmitting miR-125b-5p to inhibit Smad7 upregulation, EVs can weaken TGF-β-driven fibrosis.[260] Anti-inflammatory effects are mediated through NF-κB/TNF-α pathway suppression by lncRNA MALAT1[261] and p38/JNK MAPK inhibition to reduce cytokine production.[262] Furthermore, hucMSCs-EVs enhance tissue repair by promoting fibroblast-to-myofibroblast differentiation in inflammatory environments, improving infarct stability and attenuating apoptosis.[263] Moreover, advanced delivery systems like conductive hydrogels[264] or microneedle patches[259] prolong EVs retention and enhance localized efficacy.

https://doi.org/10.2147/IJN.S550390

Table 5 Molecular Mechanism of hucMSCs-EVs in Treating Different Diseases in the Respiratory System

HucMSCs-EVs Cargo	Target/Signaling	Conditions/ Diseases	Action[a]	Reference
None reported	NF-κB	COVID-19	Systemic inflammation↓	[22]
miR-126, miR-30b	None reported	COVID-19	Pulmonary fibrosis↓	[213]
miR-125b	interferon-stimulated genes	COVID-19	Viral replication↓	[214]
angiopoietin-1, HGF	None reported	COVID-19	Alveolar regeneration↑, angiogenesis↑, and cell survival↑, lung repair↑	[214,215]
miR-146a-5p, miR-451	TRAF6, TLR4/NF-κB, MIF-PI3K-AKT	ALI	M2 polarization↑	[217–219]
miR-199a-5p	CAV1/NRF2/HO-1	ALI	Oxidative stress↓	[220]
None reported	SLC7A11, GPX4, NRF2	ALI	Lung epithelial cells↑	[221,222]
miR-199b-5p	AFTPH, NF-κB	ALI	Inflammatory response↓	[226]
miR-486-5p	SMAD2, Akt	Radiation-induced lung injury	Fibrosis↓, epithelial regeneration↑	[222]
miR-377-3p	RPTOR	ALI	Autophagy↑	[227]
miR-451	TSC1/mTOR	ALI	Macrophage autophagy↓	[228]
None reported	NF-κB	COPD	Inflammation↓	[233]
None reported	MMP-9, TIMP-1	COPD	Alveolar destruction↓	[233]
miR-146a-5p, miR-10a-5p	VEGF-VEGFR2, AKT, MEK/ERK	COPD	Endothelial apoptosis↓, endothelial proliferation↑, gas exchange↑	[234]
None reported	TRAF1/ NF-κB, PI3K/AKT	Asthma	M2 polarization↑, neutrophil infiltration↓	[235]
miR-146a-5p	None reported	Asthma	IL-13↓, eosinophil recruitment↓	[236]
CAV-1	STAT6	Asthma	Airway epithelial integrity↑	[238]
None reported	TGF-β1/Smad2/3	Asthma	Goblet cell metaplasia↓, subepithelial collagen deposition↓, α-SMA-driven fibrosis↓	[239]
miR-146a-5p	TRAF6, IRAK1, NF-κB/NLRP3	asthma	Inflammation↓, epithelial barrier disruption↓	[240]
miR-148a-3p	Hsp90b1	Silicosis	Collagen synthesis↓, fibroblast activation↓	[241]
let-7i-5p	TGFBR1, TGF-β1/Smad3	Silicosis	ECM deposition↓	[242]
miR-223-3p	PWWP2A/NLRP3	Silicosis	Inflammation↓	[243]
miR-26a-5p	Notch	Silicosis	EMT↓	[244]
TGF-β1 siRNA	Smad2/3, Akt/GSK-3β/β-catenin, MAPK, and NF-κB	Lung cancer	EMT↓, migration↓, invasion↓	[248]
miR-320a	SOX4, Wnt/β-catenin	Lung cancer	Proliferation↓, metastasis↓	[249]
miR-410	PTEN	lung cancer	proliferation↑, apoptosis↓	[247]

Notes: [a] ↑ indicates promotion or upregulation; ↓ indicates inhibition or downregulation.

Importantly, hucMSCs-EVs can also restore the vitality of aged stem cells via miR-136/Apaf1 regulation[265] and activate PI3K/Akt to improve graft function in ischemic hearts,[266] demonstrating a regenerative synergistic effect. Their role in metabolic regulation, such as restoring energy metabolism and calcium transients in radiation-damaged cardiac organoids,[267] highlights their multifunctionality. Overall, these mechanisms—anti-apoptotic, pro-angiogenic, anti-fibrotic, anti-inflammatory, and mitochondrial protective—highlight the translational potential of hucMSCs-EVs in cardiac regenerative medicine. Although there is a large amount of animal data proving the efficacy of hucMSCs-EVs in cardiac diseases, there is a lack of clinical trial data.

Vascular Diseases

HucMSCs-EVs show great therapeutic potential in vascular diseases by targeting diverse pathological processes through cargo-mediated molecular regulation. In pulmonary hypertension (PH), hucMSCs-EVs alleviate right ventricular hypertrophy and pulmonary vascular remodeling by dual mechanisms: activating Wnt5a signaling in pulmonary arterial endothelial cells to inhibit hypoxia-induced apoptosis, and inhibiting endothelial-mesenchymal transition (EndMT) to attenuate vascular stiffening.[268,269] These effects are complemented by the ability of hucMSCs-EVs to reduce smooth

muscle cell proliferation, further stabilizing pulmonary hemodynamics.[268] Similarly, in abdominal aortic aneurysm (AAA), hucMSCs-EVs engineered with miR-147 suppress macrophage-driven inflammation and leukocyte infiltration, while restoring vascular integrity through increased smooth muscle α-actin expression, thereby limiting aneurysm progression.[270] For vein graft disease, hucMSCs-EVs enhance endothelial regeneration and inhibit intimal hyperplasia via miRNA-directed pathways. HucMSCs-EVs derived miR-126-3p promotes endothelial cell proliferation and migration by targeting SPRED-1 and PIK3R2, activating AKT/ERK1/2 signaling to accelerate reendothelialization and reduce neointimal formation.[271,272] At the same time, miR-148a-3p-enriched hucMSCs-EVs inhibit phenotype transition and proliferation of vascular smooth muscle cells (VSMCs) by downregulating Serpine1, thereby stabilizing contractile markers like SM22α and preventing pathological remodeling in injured arteries.[273] Therefore, hucMSCs-EVs modulate vascular homeostasis in multiple ways through anti-apoptotic, anti-inflammatory, endothelial regeneration, and stabilizing VSMCs, making them promising candidates for treating complex vascular diseases. Animal and cell experiments have shown that hucMSCs-EVs improve cardiovascular and cerebrovascular diseases through anti-apoptotic, pro-angiogenic, anti-fibrotic and other pathways, but there is no clinical trial support.

Anti-Tumor Effects

Leukemia

Leukemia is a group of hematological malignancies characterized by uncontrolled proliferation of immature white blood cells. Due to its heterogeneity, high recurrence rate, and development of treatment resistance, it remains a major clinical challenge.[274] The current treatment methods include chemotherapy, tyrosine kinase inhibitors like imatinib, targeted therapy, and hematopoietic stem cell transplantation. However, these methods are often limited by systemic toxicity, drug resistance, and poor specificity, emphasizing the need for new treatment strategies.[275]

HucMSCs-EVs exert multifaceted anti-leukemia effects through multiple synergistic mechanisms. HucMSCs-EVs loaded with miR-146a-5p can target USP6, a deubiquitinase overexpressed in imatinib-resistant chronic myeloid leukemia (CML) cells. By downregulating USP6, these EVs suppress GLS1 ubiquitination, increase glutaminolysis, and promote imatinib-induced apoptosis in K562-R cells.[274] Additionally, hucMSCs-EVs alone can enhance caspase-3 and caspase-9 activation, further sensitizing leukemia cells to chemotherapeutic agents.[275] For targeted therapy, hucMSCs-EVs can encapsulate and protect oncolytic reovirus from neutralizing antibodies. These EVs are internalized by acute myeloid leukemia (AML) cells, leading to viral release and subsequent tumor cell lysis. This approach effectively targets even reovirus-resistant AML cells.[276] By displaying thrombopoietin-mimetic peptides on their surface (like CD63-mTPO$_3$), hucMSCs-EVs can specifically bind to c-Mpl$^+$ AML cells. Loaded with daunorubicin, these engineered EVs significantly enhance drug delivery and cytotoxicity in vitro and in vivo, while reducing cardiotoxicity.[277] Through mechanisms such as miRNA-mediated gene regulation, delivery of oncolytic viruses, and engineered targeting of leukemia-specific antigens, hucMSCs-EVs offer a promising strategy to overcome drug resistance and reduce systemic toxicity. The molecular mechanisms are detailed in Figure 7 and Table 6.

Digestive System

Regenerative Effects

Liver Diseases

HucMSCs-EVs exert multiple hepatoprotective effects by targeting inflammation, oxidative stress, fibrosis, apoptosis, and metabolic dysregulation. In acute liver failure models, hucMSCs-EVs alleviate inflammatory cascades by suppressing NLRP3 activation in macrophages. As a result, they reduce pro-inflammatory cytokines (IL-1β, IL-6) and attenuate hepatocyte apoptosis.[278,279] This anti-inflammatory effect is also reflected in sepsis-related liver injury. HucMSCs-EVs promote polarization of M2 macrophages by inhibiting HIF-1α-mediated glycolysis.[280] Similarly, in acetaminophen-induced hepatotoxicity, hucMSCs-EVs combat oxidative stress by enhancing glutathione (GSH) and superoxide dismutase (SOD) activity. They also inhibit CYP2E1-mediated lipid peroxidation and activate the pro-survival ERK1/2 and IGF-1R/PI3K/AKT pathways.[281,282]

Liver fibrosis is a common sequela of chronic liver injury. By directly targeting activated hepatic stellate cells (HSCs), hucMSCs-EVs can improve liver fibrosis. These vesicles deliver anti-fibrotic miRNAs, such as miR-27b-3p and

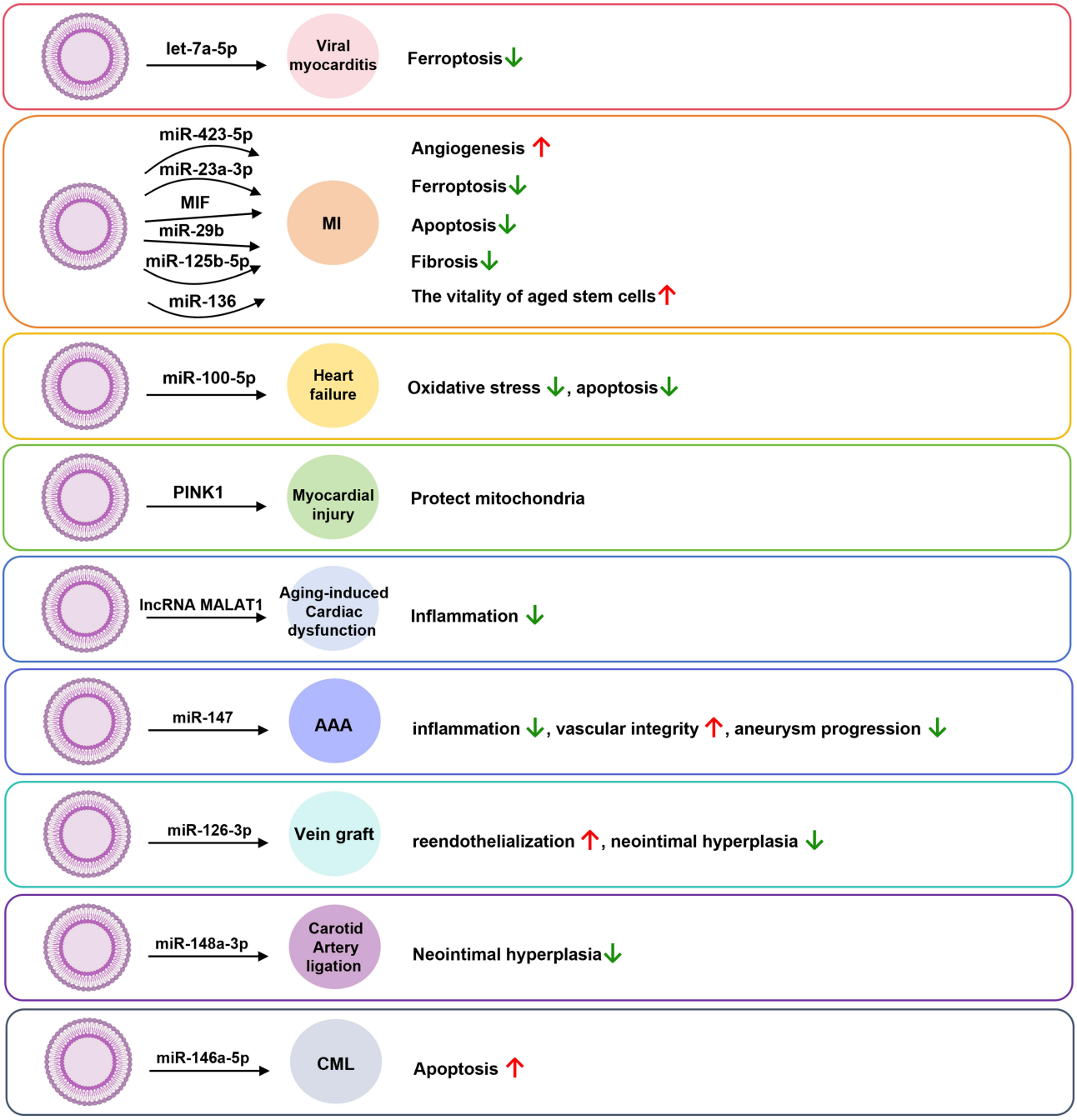


Figure 7 The effects of hucMSCs-EVs carrying different cargoes on different circulatory system diseases. The red colored upward arrows indicate promotion or upregulation, while the green colored downward arrows indicate inhibition or downregulation.

miR-148a-5p, which respectively inhibit YAP/LOXL2 and TGF-β1/Smad signaling, reducing collagen cross-linking and ECM deposition.[283,284] Engineered hucMSCs-EVs further enhance precision therapy. For example, HSTP1 peptide-modified EVs selectively bind to activated HSCs, reversing their fibrogenic phenotype and suppressing proliferation.[285] On the other hand, BMP7-loaded EVs promote HSCs quiescence by reactivating lipid droplet formation and down-regulating α-SMA and COL1A1.[286] In addition, hucMSCs-EVs inhibits xCT/GPX4 through BECN1, inducing ferroptosis of HSCs and enhancing collagen degradation.[287]

In metabolic liver disorders, such as non-alcoholic steatohepatitis (NASH), hucMSCs-EVs enhance fatty acid oxidation by upregulating PPARα and FABP5, while inhibiting SREBP-1c-driven lipogenesis, thereby restoring lipid

Table 6 Molecular Mechanism of hucMSCs-EVs in Treating Different Diseases in the Circulatory System

HucMSCs-EVs Cargo	Target/Signaling	Conditions/Diseases	Action[a]	Reference
let-7a-5p	SMAD2	Viral myocarditis	Ferroptosis↓	[49]
None reported	AMPK/mTOR	Viral myocarditis	Apoptosis↓, cardiac function↑	[252]
miR-423-5p	EFNA3	MI	Angiogenesis↑	[253]
miR-23a-3p	DMT1	MI	Ferroptosis↓	[254]
MIF	miR-133a-3p/AKT	MI	Angiogenesis↑, apoptosis↓	[255]
miR-100-5p	NOX4	Heart failure	Oxidative stress↓, apoptosis↓	[256]
None reported	PI3K/Akt	Hypoxia/reoxygenation injury	Apoptosis↓	[257]
PINK1	PKA/NCLX	Myocardial injury	Protect mitochondria	[258]
miR-29b	None reported	MI	Fibrosis↓	[259]
miR-125b-5p	Smad7	MI	Fibrosis↓	[260]
lncRNA MALAT1	NF-κB/TNF-α	Aging-induced cardiac dysfunction	Inflammation↓	[261]
None reported	p38/JNK MAPK	Atherosclerosis	Inflammation↓	[262]
None reported	None reported	MI	Inflammation↓, apoptosis↓	[263]
miR-136	Apaf1	MI	The vitality of aged stem cells↑	[265]
None reported	PI3K/Akt	Heart transplantation	Myocardial ischemia-reperfusion injury↓	[266]
None reported	Wnt5a	PH	Right ventricular hypertrophy↓, pulmonary vascular remodeling↓, apoptosis↓, vascular stiffening↓	[268,269]
miR-147	None reported	AAA	Inflammation↓, vascular integrity↑, aneurysm progression↓	[270]
miR-126-3p	SPRED-1, PIK3R2, AKT/ERK1/2	Vein graft	Reendothelialization↑, neointimal hyperplasia↓	[271,272]
miR-148a-3p	Serpine1	Carotid artery ligation	Neointimal hyperplasia↓	[273]
miR-146a-5p	USP6	CML	Apoptosis↑	[274]
None reported	caspase-3, caspase-9	Leukemia	Sensitivity to chemotherapy drugs↑	[275]

Notes: [a] ↑ indicates promotion or upregulation; ↓ indicates inhibition or downregulation.

homeostasis.[288] This metabolic reprogramming is complemented by Nrf2/NQO-1 pathway activation mediated antioxidant effects, which reduces ROS accumulation and lipid peroxidation.[288,289] Furthermore, miR-24-3p derived from EVs targets STING to inhibit macrophage-driven inflammation in NASH,[290] while miR-627-5p improves glucose metabolism by repressing FTO expression, alleviating insulin resistance and hepatic steatosis.[291]

In acute liver injury, hucMSCs-EVs enhance hepatocyte regeneration by transferring GPX1 to alleviate oxidative damage and activating anti-apoptotic signals such as ERK1/2 and Bcl-2.[282]

In general, hucMSCs-EVs repair the liver through immunomodulation, oxidative stress relief, fibrotic cascade inhibition, metabolic regulation, and direct cytoprotection, making them a multifunctional therapeutic platform for various liver diseases. Encouragingly, hucMSCs-EVs have not only completed animal trials for liver cirrhosis treatment but have also advanced to human clinical trials, currently in Phase II (Table 1).

Intestinal Diseases

In intestinal diseases, hucMSCs-EVs exhibit diverse therapeutic potential through immunomodulation, cellular repair, and molecular pathway regulation. In inflammatory bowel disease (IBD), hucMSCs-EVs alleviate inflammation by promoting M2 macrophage polarization. This leads to an increase in the secretion of TGF-β and IL-10, while suppressing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[292–294] This immunoregulatory effect is further enhanced by their ability to inhibit macrophage pyroptosis via the miR-378a-5p/NLRP3 axis, which reduces caspase-1 activation and IL-18/IL-1β release.[295,296] Additionally, hucMSCs-EVs alleviate IBD-associated ferroptosis in intestinal epithelial cells by delivering miR-129-5p, which targets ACSL4 to suppress lipid peroxidation.[297] Besides immunomodulation,

hucMSCs-EVs also restore intestinal barrier integrity by upregulating tight junction proteins (ZO-1, Occludin, Claudin-1) and TSG-6 expression. This enhances mucosal repair and reduces permeability.[298,299] EVs also regulate inflammation through some important signaling pathways: miR-326 inhibits NF-κB-driven inflammation,[300] while miR-302d-3p targets VEGFR3 to inhibit lymphangiogenesis via the AKT pathway, improving lymphatic drainage and reducing macrophage infiltration.[301] In colitis-associated carcinogenesis, hucMSCs-EVs prevent malignant transformation by downregulating SUMO1 and Wnt/β-catenin pathway via miR-146a.[302] Collectively, these effects highlight hucMSCs-EVs address intestinal inflammation, malignancy, and structural damage through a synergistic interaction of immunomodulation, epigenetic regulation, and tissue regeneration. A positive development is that hucMSCs-EVs have entered phase I human clinical trials for the treatment of ulcerative colitis (Table 1).

Pancreatitis

HucMSCs-EVs show multifaceted therapeutic effects in pancreatitis through targeting cell death, inflammation, and tissue regeneration. Among them, regulating the cell death process in pancreatic acinar cells is one of the key pathways. In severe acute pancreatitis (SAP), TNF-α-pretreated hucMSCs-EVs deliver bioactive metabolites such as 3,4-dihydroxyphenylglycol, which activates the mTOR pathway to inhibit excessive autophagy, thereby reducing acinar cell damage and pancreatic dysfunction.[303] Meanwhile, these EVs inhibit necroptosis by downregulating phosphorylated RIPK3 and MLKL, preventing the progression of pancreatic injury.[304] The regulation of cell death pathways synergizes with their powerful anti-inflammatory activity. HucMSCs-EVs rebalance cytokine networks, reducing pro-inflammatory mediators (eg, TNF-α, IL-1β, IL-6) while elevating anti-inflammatory factors (eg, IL-10, TGF-β), thereby attenuating systemic inflammation and creating a favorable microenvironment for repair.[305,306] This immunomodulatory effect is further enhanced by their ability to enhance cell survival. In traumatic pancreatitis (TP), hucMSCs-EVs suppress apoptosis by downregulating pro-apoptotic Bax and caspase-3 while upregulating anti-apoptotic Bcl-2, protecting acinar cell integrity and promoting tissue recovery.[305,306] Interestingly, although hucMSCs-EVs inhibit overactivated autophagy in SAP,[303] they promote protective autophagy through mTOR inhibition in TP, indicating that environment dependent regulation of autophagy can clear damaged organelles and restore cellular homeostasis.[307] This dual role emphasizes their adaptability in dealing with different pathological states. Overall, hucMSCs-EVs meet tissue-specific requirements by inhibiting cell death, alleviating inflammation, and promoting survival, while dynamically modulating autophagy. These integrated mechanisms define hucMSCs-EVs as a promising therapeutic strategy for pancreatitis, though further research is needed to reveal molecular differences in specific conditions and optimize translation applications.[303–307] Although hucMSCs-EVs has achieved certain results in animal models of pancreatitis, human trials have not yet been conducted.

Anti-Tumor Effects

Gastric Cancer

Gastric cancer (GC) is a highly prevalent and malignancy worldwide, ranking as the fifth most common cancer and the fourth leading cause of cancer-related deaths globally. Despite a general decline in incidence and mortality rates in some regions, GC remains a significant health burden, particularly in certain areas such as Asia, where it ranks third in both incidence and mortality among all cancer types.[308] Traditional therapies, such as continuous chemotherapy, have not been satisfactory for advanced GC, although immunotherapy has shown great therapeutic potential.[309]

HucMSCs-EVs have demonstrated significant therapeutic potential in GC through various mechanisms that target tumor progression and microenvironmental. One key pathway for its efficacy is regulating autophagy, which is a critical process in cancer cell survival. Wu et al revealed that hucMSCs-EVs delivering miR-13896 suppress ATG2A, a key mediator of autophagosome formation, thereby inhibiting autophagy in GC cells and shifting the balance toward apoptosis.[23] This effect is further supported by Tang et al, who demonstrated that ATG2A/B deficiency converts autophagy into apoptosis, highlighting the dual role of autophagy modulation in cancer therapy.[310] Beyond autophagy, hucMSCs-EVs exert direct anti-tumor effects by impairing proliferation, migration, and survival of GC cells. These EVs are enriched with tumor-suppressive miRNAs, including miR-122, miR-124, miR-143, miR-145, and miR-375, which collectively inhibit oncogenic signaling pathways and induce apoptosis, as evidenced by reduced tumor growth and metastasis in models.[23] Additionally, hucMSCs-EVs regulate TME by delivering bioactive molecules that alter cytokine

and chemokine expression, thereby disrupting stromal interactions and immune evasion that are critical for cancer progression.[24] However, the therapeutic application of hucMSCs-EVs requires cautious optimization, as emerging evidence suggests the potential transfer of pro-survival factors that could enhance drug resistance or tumorigenic signaling under specific conditions.[24] Overall, these findings emphasize the dual role of hucMSCs-EVs in GC therapy, driven by simultaneously targeting autophagy, tumor cell behavior, and TME remodeling. Further research is crucial for elucidating precise mechanisms, reducing risks, and fully utilizing its conversion potential. Please note that the curative effects of hucMSCs-EVs are limited to animal experiments and have not been validated through clinical human trials.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) progression is inhibited by hucMSCs-EVs through tumor-suppressive miRNAs and lncRNAs. miR-451a derived from EVs inhibits EMT by downregulating ADAM10, suppressing HCC cell proliferation and metastasis.[311] Meanwhile, lncRNA FAM99B induces cell cycle arrest and apoptosis through tumor-suppressive pathways.[312]

Colorectal Cancer

For colorectal cancer (CRC), hucMSCs-EVs deliver tumor-suppressive miRNAs, such as miR-486-5p and miR-431-5p that target NEK2 and PRDX1 respectively, to suppress glycolysis, metastasis, and angiogenesis.[313–315] These vesicles also inhibit TGF-β-induced ERK phosphorylation in fibroblasts,[316] resolve necrotizing enterocolitis through mTOR-mediated autophagy regulation,[317] and promote perianal fistulas healing via HIF-1α/TGF-β/Smad pathway activation, demonstrating their efficacy in alleviating intestinal fibrosis.[318] Furthermore, hucMSCs-EVs modulate gut microbiota composition and Treg/Th17 balance, enhancing IL-10 and TGF-β1 production, while reducing Th17-associated pathology in IBD.[319,320]

Pancreatic Ductal Adenocarcinoma

HucMSCs-EVs demonstrate a dual but promising role in the progression of pancreatic ductal adenocarcinoma (PDAC), primarily mediated by their cargo of miRNAs that modulate oncogenic and tumor-suppressive pathways. A key therapeutic mechanism involves the selective transfer of tumor-inhibitory miRNAs. For instance, hucMSCs-EVs deliver miR-145-5p, which suppresses PDAC cell proliferation, invasion, and EMT by directly targeting the central mediator Smad3 of the TGF-β signaling pathway. This inhibitory effect stabilizes epithelial markers such as E-cadherin, reduces mesenchymal markers such as N-cadherin, and induces apoptosis and cell cycle arrest, thus inhibiting tumor growth in xenografts.[321] Similarly, hucMSCs-EVs transport hsa-miRNA-128-3p, which inhibits Galectin-3 (a protein associated with tumor cell survival and metastasis), thereby suppressing proliferation, migration, and invasion in PDAC models.[322] Paradoxically, hucMSCs-EVs also harbor miRNAs with pro-tumorigenic effects, such as miR-100-5p, which enhances PDAC growth both in vitro and in vivo, highlighting the complexity of their regulation.[323] This duality highlights the environmental dependent nature of hucMSCs-EVs activity, where their therapeutic efficacy depends on miRNA composition and recipient cell interactions. While the tumor-suppressive roles of miR-145-5p and hsa-miRNA-128-3p make hucMSCs-EVs potential carriers for targeted therapy, the carcinogenic effects of miRNAs like miR-100-5p require rigorous cargo analysis to optimize their clinical application. Collectively, these findings illuminate the multifaceted role of hucMSCs-EVs in PDAC, offering new paths for miRNA-based interventions, while emphasizing the necessity of understanding the slight differences in mechanisms and improving vesicle engineering strategies to better exert their therapeutic potential. Similarly, the treatment of PDAC by hucMSCs-EVs has not yet undergone human trials. HucMSCs-EVs intervene in digestive system diseases through pathways such as regulating autophagy, immune microenvironment, and metabolic reprogramming. The detailed mechanism is shown in Figure 8 and Table 7.

Urinary System

Regenerative Effects

Kidney Diseases

HucMSCs-EVs exhibit multiple potency in kidney diseases through complex molecular and cellular mechanisms. In diabetic kidney disease (DKD), hucMSCs-EVs alleviate renal fibrosis and inflammation by delivering miR-23a-3p,

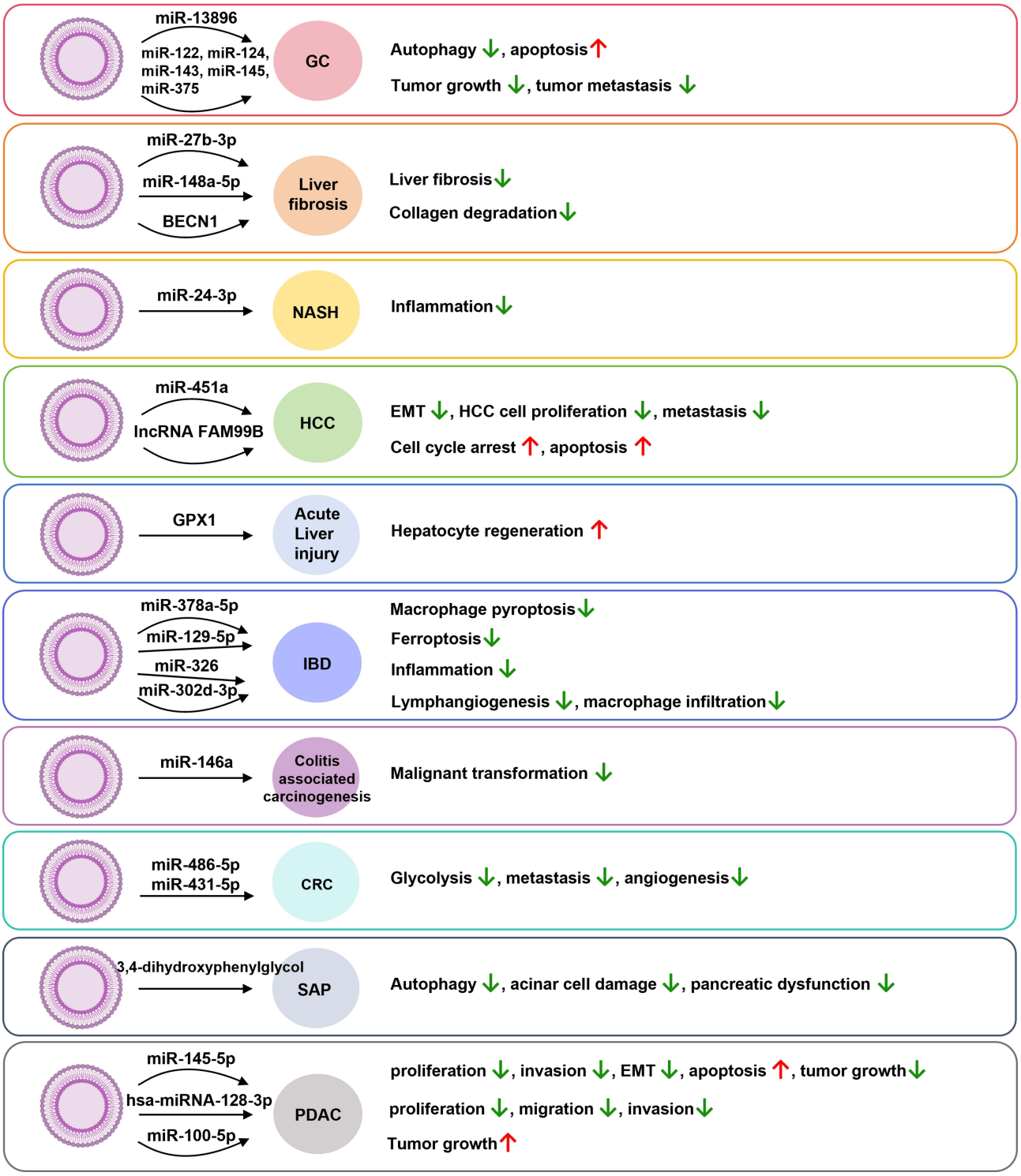


Figure 8 The effects of hucMSCs-EVs carrying different cargoes on different digestive system diseases. The red colored upward arrows indicate promotion or upregulation, while the green colored downward arrows indicate inhibition or downregulation.

which targets KLF3 to inhibit the STAT3 signaling pathway, thus reducing hyperglycemia-induced renal injury.[324] Similarly, miR-22-3p-enriched EVs attenuate NLRP3 activation, reducing inflammatory cytokine release (eg, IL-6, TNF-α) and protecting podocytes in DKD models.[325] For acute kidney injury (AKI), hucMSCs-EVs counteract the damage induced by cisplatin or ischemia-reperfusion through regulating necroptosis, pyroptosis, and apoptosis. miR-874-

Table 7 Molecular Mechanism of hucMSCs-EVs in Treating Different Diseases in the Digestive System

HucMSCs-EVs Cargo	Target/Signaling	Conditions/ Diseases	Action[a]	Reference
miR-13896	ATG2A	GC	Autophagy↓, apoptosis↑	[23]
miR-122, miR-124, miR-143, miR-145, miR-375	Oncogenic signaling pathways	GC	Tumor growth↓, tumor metastasis↓	[23]
None reported	NLRP3	Acute liver failure	Inflammation↓, hepatocyte apoptosis↓	[278,279]
None reported	HIF-1α	Sepsis-related liver injury	M2 polarization↑, inflammation↓	[280]
miR-27b-3p	YAP/LOXL2	Liver fibrosis	Liver fibrosis↓	[283]
miR-148a-5p	TGF-β1/Smad	Liver fibrosis	Liver fibrosis↓	[284]
BECN1	xCT/GPX4	Liver fibrosis	Collagen degradation↓	[287]
None reported	PPARα, FABP5, SREBP-1c, Nrf2/NQO-1	NASH	Fatty acid oxidation↑, lipogenesis↓	[288]
miR-24-3p	STING	NASH	Inflammation↓	[290]
miR-627-5p	FTO	Non-alcoholic fatty liver disease	Insulin resistance↓, hepatic steatosis↓	[291]
miR-451a	ADAM10	HCC	EMT↓, HCC cell proliferation↓, metastasis↓	[311]
lncRNA FAM99B	None reported	HCC	Cell cycle arrest↑, apoptosis↑	[312]
GPX1	ERK1/2, Bcl-2	Acute liver injury	Hepatocyte regeneration↑	[282]
None reported	None reported	IBD	M2 polarization↑, inflammation↓	[292–294]
miR-378a-5p	NLRP3	IBD	Macrophage pyroptosis↓	[295,296]
miR-129-5p	ACSL4	IBD	Ferroptosis↓	[297]
None reported	ZO-1, Occludin, Claudin-1, TSG-6	IBD	Mucosal repair↑, permeability↓	[298,299]
miR-326	IκB, NF-κB	IBD	Inflammation↓	[300]
miR-302d-3p	VEGFR3, AKT	IBD	Lymphangiogenesis↓, macrophage infiltration↓	[301]
miR-146a	Wnt/β-catenin	Colitis-associated carcinogenesis	Malignant transformation↓	[302]
miR-486-5p, miR-431-5p	NEK2, PRDX1	CRC	Glycolysis↓, metastasis↓, angiogenesis↓	[313–315]
None reported	TGF-β, ERK	IBD	Intestinal fibrosis↓	[316]
None reported	mTOR	Necrotizing enterocolitis	Autophagy↓	[317]
None reported	HIF-1α/TGF-β/Smad	Complex perianal fistulas	Healing of perianal fistulas↑	[318]
3,4-dihydroxyphenylglycol	mTOR	SAP	Autophagy↓, acinar cell damage↓, pancreatic dysfunction↓	[303]
None reported	RIPK3, MLKL	SAP	Necroptosis↓, pancreatic injury↓	[304]
None reported	Bax, caspase-3, Bcl-2	TP	Tissue recovery↑	[305,306]
miR-145-5p	TGF-β, Smad3	PDAC	Proliferation↓, invasion↓, EMT↓, apoptosis↑, tumor growth↓	[321]
hsa-miRNA-128-3p	Galectin-3	PDAC	Proliferation↓, migration↓, invasion↓	[322]
miR-100-5p	None reported	PDAC	Tumor growth↑	[323]

Notes: [a] ↑ indicates promotion or upregulation; ↓ indicates inhibition or downregulation.

3p inhibits RIPK1/PGAM5-mediated mitochondrial fission and necroptosis,[326] while miR-100-5p targets FKBP5 to activate the AKT pathway and reduce tubular apoptosis.[327] Additionally, hucMSCs-EVs suppress pyroptosis by down-regulating NLRP3, caspase-1, and gasdermin D, thereby alleviating renal inflammation.[328] In cisplatin-AKI, miR-13896-enriched EVs promote M2 macrophage polarization via TRAF6/NF-κB inhibition, and engineered EVs with elevated miR-13896 further enhance therapeutic efficacy.[329]

The anti-fibrotic properties of hucMSCs-EVs are mediated through multiple pathways. In renal fibrosis models, EVs deliver CK1δ and β-TRCP to promote YAP ubiquitination and degradation, thereby reducing collagen deposition.[330] miR-13474 targets ADAM17 to inhibit Notch1/TGF-β/Smad signaling, while miR-146b suppresses IRAK1/NF-κB activation, reducing fibrosis and inflammatory responses.[331,332] Hypoxia-pretreated hucMSCs-EVs enhance antioxidant capacity and alleviate oxidative stress through GSTO1 in ischemia-reperfusion injury.[333] miR-148b-3p targets PDK4 to inhibit endoplasmic reticulum stress via ATF-6 pathway.[334] Furthermore, hucMSCs-EVs counteract cellular senescence in aging kidneys by modulating Lamin A/C phosphorylation and p53-p21 axis, reducing senescence-associated secretory phenotypes (SASP) and DNA damage.[335]

Immunoregulation is another critical mechanism: hucMSCs-EVs restore Th1/Th17/Treg balance by inhibiting IL-6/STAT3/IL-17 signaling in lupus nephritis,[336] while miR-375 promotes autophagy and T cell survival via HDAC4 inhibition in sepsis-associated AKI.[337] Enhanced targeting strategies, such as neutrophil membrane-engineered EVs (NEX), improve renal uptake and reduce macrophage clearance, amplifying therapeutic effects in AKI.[338] 3D culture systems further boost EV yield and bioactivity, enhancing autophagy activation and mTOR pathway inhibition to alleviate cisplatin nephrotoxicity.[339,340] Overall, hucMSCs-EVs repair the kidneys through miRNA-mediated gene silencing, signaling pathway modulation, oxidative stress reduction, and immune reprogramming, making them a promising cell-free therapy for treating various kidney diseases. Regrettably, the application of hucMSCs-EVs in treating kidney diseases has only undergone animal trials and has not yet entered to human clinical trials.

Urethral Stricture

Urethral stricture is a common urological disorder characterized by pathological fibrosis and lumen narrowing. Due to the limitations of conventional therapies, this poses significant challenges to clinical practice. TNF-α-pretreated hucMSCs-EVs have shown promise in addressing fibrosis and inflammation. In a TGF-β1-induced rat model, these EVs reduced α-smooth muscle actin (αSMA) and collagen deposition, while suppressing myofibroblast differentiation and pro-inflammatory cytokines like IL-6 and IL-1β. Mechanistically, TNF-α pretreatment enriched EVs with miR-146a, which targeted TRAF6 and IRAK1 to inhibit NF-κB signaling, thereby attenuating fibroblast activation and fibrosis. This dual modulation of fibrotic and inflammatory pathways highlights the therapeutic advantage of engineered hucMSCs-EVs, offering a cell-free strategy to disrupt fibrosis and restore urethral function.[341] The treatment of urethral stricture with hucMSCs-EVs has not yet entered human clinical trials.

Anti-Tumor Effects

Wilms Tumor

Wilms tumor (WT) is the most common pediatric kidney malignancy. It is characterized by aggressive local invasion, frequent metastasis, making it a major clinical challenge. Current treatments, including surgery, chemotherapy, and radiation, often lead to substantial long-term morbidity and functional impairments in developing children. These limitations highlight the critical need for more targeted and less toxic therapeutic strategies. A compelling study by Huang et al demonstrated that hucMSCs-EVs can serve as efficient vehicles for delivering tumor-suppressive microRNAs to Wilms tumor cells.[342] Specifically, the researchers found that hucMSCs-EVs carrying miR-15a-5p inhibit WT progression by directly targeting and downregulating SEPT2, a protein overexpressed in WT that promotes tumor growth. This targeted delivery system significantly reduced tumor cell proliferation, migration, and invasion while inducing apoptosis in both in vitro and in vivo models.[342] HucMSCs-EVs may overcome the limitations of traditional therapies for WT by targeting specific molecules and reducing off target effects. HucMSCs-EVs improve kidney and urinary tract diseases through miRNA mediated gene silencing and signaling pathway regulation, as summarized in Figure 9 and Table 8.

Reproductive System

Regenerative Effects

Male Infertility

Male infertility, particularly nonobstructive azoospermia (NOA), is a significant clinical challenge, with environmental

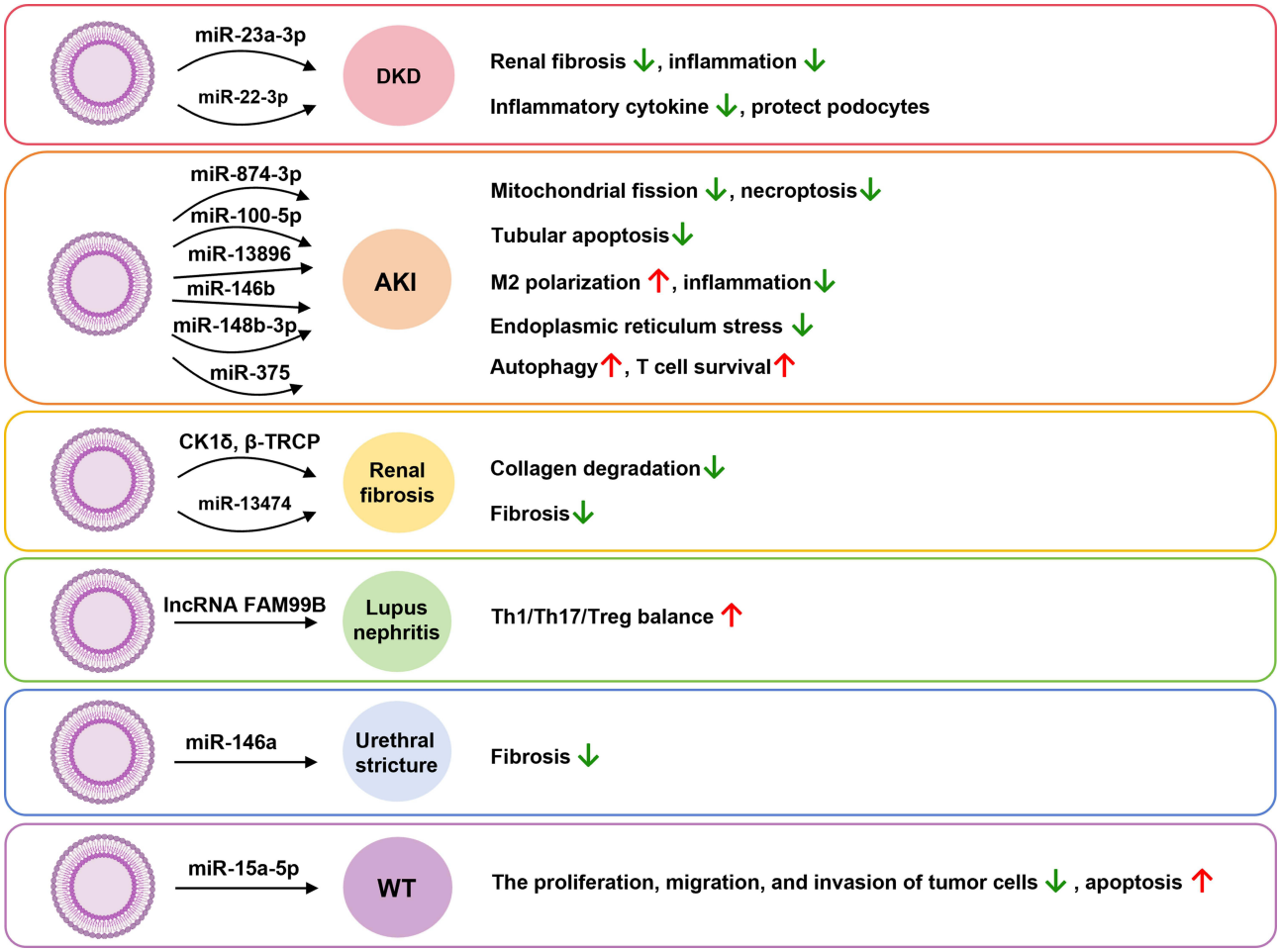


Figure 9 The effects of hucMSCs-EVs carrying different cargoes on different urinary system diseases. The red colored upward arrows indicate promotion or upregulation, while the green colored downward arrows indicate inhibition or downregulation.

and chemotherapeutic damage exacerbating germ cell loss and testicular dysfunction. HucMSCs-EVs demonstrate promising reparative effects, which can be demonstrated by their ability to restore spermatogenic function in busulfan-induced injury models.[343] HucMSCs-EVs enhance the proliferation and migration of germ cell lines GC-1 while

Table 8 Molecular Mechanism of hucMSCs-EVs in Treating Different Diseases in the Urinary System

HucMSCs-EVs Cargo	Target/Signaling	Conditions/ Diseases	Action[a]	Reference
miR-23a-3p	KLF3, STAT3	DKD	Renal fibrosis↓, inflammation↓	[324]
miR-22-3p	NLRP3	DKD	Inflammatory cytokine↓, protect podocytes	[325]
miR-874-3p	RIPK1/PGAM5	AKI	Mitochondrial fission↓, necroptosis↓	[326]
miR-100-5p	FKBP5, AKT	AKI	Tubular apoptosis↓	[327]
None reported	NLRP3, caspase-1, gasdermin D	AKI	Pyroptosis↓, inflammation↓	[328]
miR-13896	TRAF6/NF-κB	AKI	M2 polarization↑, inflammation↓	[329]
CK1δ, β-TRCP	YAP	Renal fibrosis	Collagen degradation↓	[330]
miR-13474	ADAM17/Notch1/TGF-β/Smad	Renal fibrosis	Fibrosis↓	[331]
miR-146b	IRAK1/NF-κB	AKI	Inflammation↓	[332]

(*Continued*)

https://doi.org/10.2147/IJN.S550390

Table 8 (Continued).

HucMSCs-EVs Cargo	Target/Signaling	Conditions/ Diseases	Action[a]	Reference
miR-148b-3p	PDK4/ATF-6	AKI	Endoplasmic reticulum stress↓	[334]
None reported	Lamin A/C, p53-p21	Renal aging	Cellular senescence↓	[335]
lncRNA FAM99B	IL-6/STAT3/IL-17	Lupus nephritis	Th1/Th17/Treg balance↑	[336]
miR-375	HDAC4	AKI	Autophagy↑, T cell survival↑	[337]
miR-146a	TRAF6, IRAK1, NF-κB	Urethral stricture	Fibrosis↓	[341]
miR-15a-5p	SEPT2	WT	The proliferation, migration, and invasion of tumor cells↓, apoptosis↑	[342]

Notes: [a] ↑ indicates promotion or upregulation; ↓ indicates inhibition or downregulation. Molecular mechanism of hucMSCs-EVs in treating different diseases in the reproductive system.

improving oxidative stress and apoptosis through downregulation of Bax and caspase-3 and upregulation of Bcl-2. Intratesticular administration in mice can restore spermatogenesis, improve the structure of seminiferous tubule, upregulate germ cell markers (Vasa, Miwi, Stra8, Dazl) and junctional proteins (connexin 43, β-catenin), thereby stabilizing the testicular microenvironment. These effects are mediated by EVs cargo that suppress oxidative damage and activate transcriptional networks critical for germ cell maturation. Further research is needed to define the bioactive components of hucMSCs-EVs and optimize their clinical translation for NOA treatment,[343] but unfortunately, clinical human trials have not yet been conducted.

Female Infertility

HucMSCs-EVs possess a multiple potential for treating female infertility. They target the diverse pathological mechanisms of reproductive disorders. In intrauterine adhesions (IUAs), collagen scaffolds loaded hucMSCs-EVs promote endometrial regeneration by polarizing $CD163^+$ M2 macrophages, thereby reducing inflammation and enhancing estrogen/progesterone receptor expression, restoring fertility in rat models.[344] This immunomodulatory effect is enhanced by RNAs in EVs, which remodel the uterine microenvironment to support tissue repair and embryo implantation. For ovarian dysfunction, hucMSCs-EVs alleviate premature ovarian insufficiency (POI) by suppressing oxidative stress and granulosa cell apoptosis through circBRCA1/miR-642a-5p/FOXO1 signaling[345] and enhancing estrogen production via miR-21-mediated downregulation of LATS1/LOXL2/YAP pathways.[346] In chemotherapy-induced ovarian damage, hucMSCs-EVs activate PI3K/AKT pathway to induce angiogenesis and restore follicular development.[347] In polycystic ovary syndrome (PCOS), EVs reduce granulosa cell inflammation by inhibiting NF-κB-driven TNF-α and IFN-γ production while promoting progesterone synthesis, thereby improving ovarian microenvironment.[348] Age-related fertility decline is combated by hucMSCs-EVs through the activation of PI3K/mTOR signaling in primordial oocytes, which reduces oxidative stress and enhances mitochondrial function, thereby improving follicular quality and yield in aged mice.[349] For tubal inflammatory infertility, hucMSCs-EVs resolve Chlamydia trachomatis-induced damage by inhibiting NF-κB and shifting macrophages from M1 to M2 phenotype.[350] In addition, thermosensitive hydrogel-EVs complexes cooperatively inhibit TGF-β/Smad-mediated fibrosis and inflammation in IUAs, and enhance endometrial repair and fertility.[351] In a word, hucMSCs-EVs coordinate tissue regeneration through miRNA-mediated gene regulation, immunomodulation, oxidative stress reduction, and pro-angiogenic signaling, offering a multifunctional cell-free approach to restore reproductive function. It is heartening that hucMSCs-EVs are not limited to animal models for female infertility treatment, they have progressed to Phase II clinical trials (Table 1).

Cervical Inflammation

HucMSCs-EVs demonstrate continuous therapeutic effects in cervical pathology from inflammation to precancerous lesions and invasive cancer by targeting stage-specific molecular. In cervical inflammation, hucMSCs-EVs attenuates tissue damage by rebalancing inflammatory mediators, suppressing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and elevating anti-inflammatory IL-10, thereby resolving LPS-induced inflammatory cascades. At the same time, these EVs restore epithelial

integrity through E-cadherin upregulation and N-cadherin downregulation, effectively preventing early pathological remodeling and inhibiting EMT—a precursor to dysplasia.[352] Notably, the treatment of intrauterine adhesions with hucMSCs-EVs has entered the clinical stage (Table 1), and I believe this has reference value for cervical diseases as well.

Anti-Tumor Effects

Prostate Cancer

Prostate cancer (PCa) is a common and lethal malignancy in men, and the search for effective treatment strategies is crucial. Emerging evidence highlights the multiple therapeutic potential of hucMSCs-EVs in PCa. A pivotal study by Gan et al demonstrated that miR-375 antisense oligonucleotides (e-375i) engineered hucMSCs-EVs effectively suppress PCa progression by targeting the miR-375/PTPN4/STAT3 axis. Elevated miR-375 in PCa tissues promotes tumor aggressiveness and enzalutamide resistance by directly inhibiting PTPN4, thereby stabilizing phosphorylated STAT3—a key driver of oncogenic signaling. The e-375i-loaded EVs counteract this pathway, restoring PTPN4 expression, downregulating p-STAT3, and inhibiting proliferation while inducing apoptosis.[25] As a supplement, Yuan et al revealed that interferon-β (IFN-β)-modified hucMSCs-EVs exert potent anti-tumor effects by arresting PCa cells in the G0/G1 phase through modulation of cyclin D/E levels, thereby suppressing proliferation and promoting apoptosis.[353] This IFN-β-mediated cell cycle disruption synergizes with the regulatory effects of DHRS2-enriched hucMSCs-EVs, as shown by Wu et al. DHRS2-modified hucMSCs-EVs inhibit malignant behaviors of PCa cells by downregulating the cyclin D/E, inducing G0/G1 phase arrest and apoptosis.[354] Together, these studies emphasize the capacity of engineered hucMSCs-EVs to simultaneously target oncogenic signaling, dysregulated cell cycle checkpoints, and apoptotic resistance, which are key hallmarks of PCa progression. By delivering therapeutic miRNAs, cytokines, or tumor-suppressive proteins like DHRS2, hucMSCs-EVs offer a multimodal platform to disrupt critical pathways in PCa while minimizing off-target effects. Sadly, hucMSCs-EVs for PCa treatment have only been tested in animal models, without having entered clinical trials.

Ovarian Cancer

HucMSCs-EVs demonstrate dual therapeutic efficacy in ovarian cancer (OC) by targeting tumor chemoresistance and reducing ovarian damage caused by chemotherapy. Qiu et al revealed that hucMSCs-EVs enriched with miR-146a suppress OC cell proliferation and chemoresistance by directly targeting laminin γ2 (LAMC2), a regulator of the PI3K/Akt signaling pathway.[26] Meanwhile, Tang et al demonstrated that hucMSCs-EVs exhibit protective effects against chemotherapy-induced ovarian dysfunction in cisplatin (CDDP)-treated models. Their study showed that hucMSCs-EVs alleviate CDDP-induced POI by transferring anti-apoptotic miRNAs, including miR-26a-5p, miR-222-3p, and let-7i-5p, to granulosa cell. These miRNAs suppress pro-apoptotic gene expression, reduce caspase activation, and maintain ovarian follicle integrity, thereby counteracting CDDP-induced granulosa cell apoptosis and ovarian atrophy.[27] This dual effect—simultaneously targeting malignant cells while protecting reproductive function—highlights the potential of hucMSCs-EVs in improving the treatment efficacy and quality of life in OC patients. Although there is animal data support for the treatment of OC by hucMSCs-EVs, more efforts are needed to bring them into clinical trials.

Cervical Precancerous and Cervical Cancer

Progressing to cervical precancerous lesions, hucMSCs-EVs deliver miR-370-3p suppresses lesion progression by inhibiting DHCR24, a protein overexpressed during carcinogenesis.[355] Advancing to cervical cancer, hucMSCs-EVs combat tumorigenesis through a dual strategy. First, hucMSCs-EVs activate the NOTCH pathway via surface Jagged1, inducing squamous differentiation of CaSki cancer cells, which suppresses their proliferation and migration.[356] Second, engineered hucMSCs-EVs loaded with paclitaxel exhibit synergistic effects with chemotherapy drugs, enhancing HeLa cell apoptosis and inhibiting EMT protein even at low doses, demonstrating their potential as precision drug carriers.[357]

In summary, hucMSCs-EVs have effectively managed cervical pathology by immunomodulation, miRNA-mediated gene regulation, differentiation induction, and enhanced drug delivery mechanisms—resolving inflammation, arresting premalignant progression, and directly targeting cancer cells. This graded treatment strategy highlights their adaptability in managing the dynamic spectrum of cervical diseases. HucMSCs-EVs repair reproductive system function through mechanisms such as immune regulation, differentiation induction, and angiogenesis. The specific effects are shown in Figure 10 and Table 9.

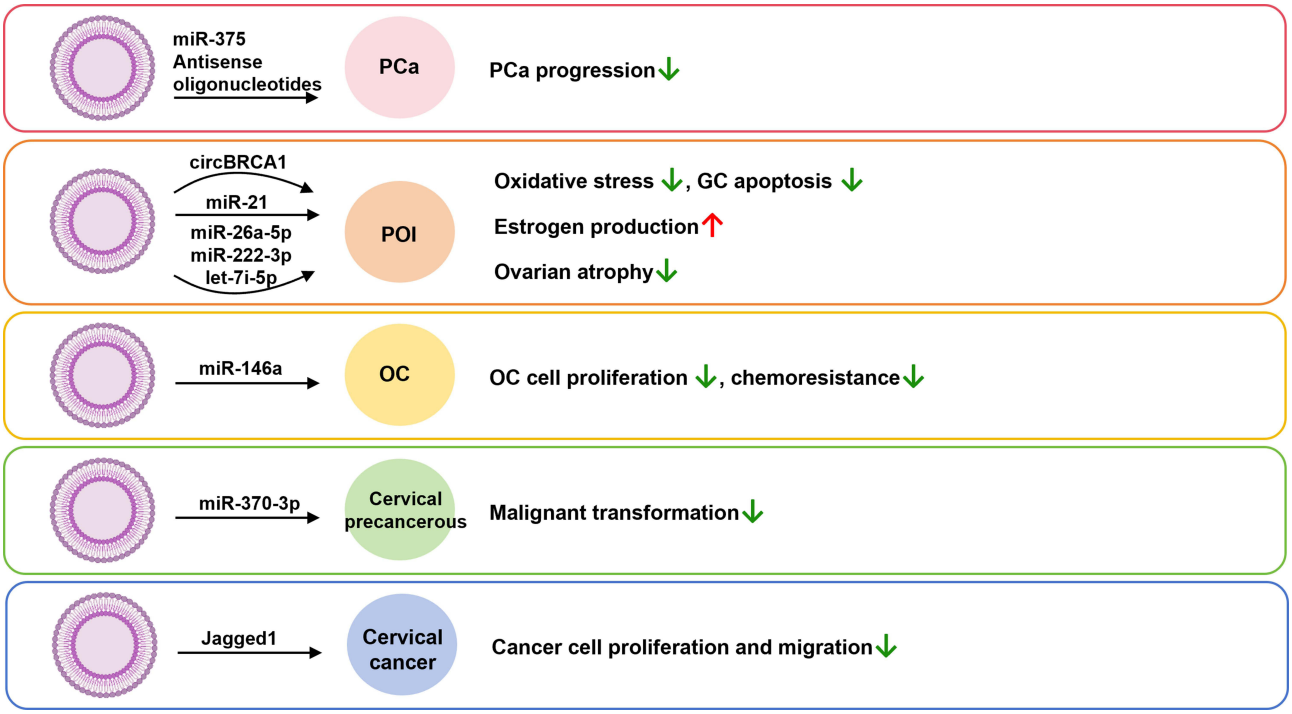


Figure 10 The effects of hucMSCs-EVs carrying different cargoes on different reproductive system diseases. The red colored upward arrows indicate promotion or upregulation, while the green colored downward arrows indicate inhibition or downregulation.

Hormonal System

Regenerative Effects

Diabetes

Diabetes is a multifactorial metabolic disorder that has reached epidemic level globally. The prevalence of diabetes and its associated complications continues to rise, posing significant public health challenges.[358] HucMSCs-EVs demonstrate remarkable therapeutic efficacy in a series of diabetes-related complications.

Table 9 Molecular Mechanism of hucMSCs-EVs in Treating Different Diseases in the Reproductive System

HucMSCs-EVs Cargo	Target/signaling	Conditions/ diseases	Action[a]	Reference
None reported	Bax, caspase-3, Bcl-2	Male infertility	Spermatogenic function↑	[343]
miR-375 antisense oligonucleotides	miR-375/PTPN4/ STAT3	PCa	PCa progression↓	[25]
None reported	None reported	IUAs	Endometrial regeneration↑, fertility↑	[344]
circBRCA1	miR-642a-5p/FOXO1	POI	Oxidative stress↓, GC apoptosis↓	[345]
miR-21	LATS1/LOXL2/YAP	POI	Estrogen production↑	[346]
None reported	PI3K/AKT	Ovarian damage	Angiogenesis↑, follicular development↑	[347]
None reported	NF-κB	PCOS	GC inflammation↓, progesterone synthesis↑	[348]
None reported	PI3K/mTOR	Ovarian aging	Follicular quality and yield↑, fertility↑	[349]
None reported	NF-κB	Tubal inflammatory infertility	M2 polarization↑, inflammation↓	[350]
miR-146a	LAMC2, PI3K/Akt	OC	OC cell proliferation↓, chemoresistance↓	[26]

(*Continued*)

Table 9 (Continued).

HucMSCs-EVs Cargo	Target/signaling	Conditions/ diseases	Action[a]	Reference
miR-26a-5p, miR-222-3p, let-7i-5p	caspase	POI	GC apoptosis↓, ovarian atrophy↓	[27]
None reported	None reported	Cervical inflammation	Inflammation↓, emt↓	[352]
miR-370-3p	DHCR24	Cervical precancerous	Malignant transformation↓	[355]
Jagged1	NOTCH	Cervical cancer	Cancer cell proliferation and migration↓	[356]

Notes: [a] ↑ indicates promotion or upregulation; ↓ indicates inhibition or downregulation.

In diabetic nephropathy (DN), hucMSCs-EVs alleviate renal injury by targeting fibrosis, inflammation, and oxidative stress. They transfer miR-23a-3p and miR-146a-5p to renal cells, suppressing KLF3/STAT3 and TRAF6/STAT1 signaling to drive M2 macrophage polarization, thereby reducing inflammatory cytokine production (eg, IL-1β, TNF-α) and attenuating fibrosis.[324,359] Additionally, miR-22-3p in EVs inhibits NLRP3 activation in podocytes, reducing glomerular damage and proteinuria. Meanwhile, engineered EVs loaded with Exendin-4 further enhance renal protection by promoting the induction of gut microbiota-mediated $CD4^+$ Treg cell.[325,360] These effects collectively restore renal function and reduce collagen deposition in diabetic kidneys.[361,362]

For diabetic wound healing, hucMSCs-EVs accelerate tissue repair through multifaceted mechanisms. Encapsulated in biomaterials such as GelMA hydrogels or gallium/chitosan/silk scaffolds, they activate the miR-17-5p-dependent PTEN/AKT pathway, upregulate VEGF, bFGF, and HIF-1α to promote angiogenesis.[363–365] EVs pretreated with Nocardia rubra cell wall skeleton promotes angiogenesis through circIARS1/miR-4782-5p/VEGFA signaling. Coenzyme Q10 (Q10)-stimulated EVs inhibit ferroptosis by downregulating ACSL4. EVs pretreated with quercetin also modulate gut microbiota to enrich *Faecalibacterium*, thus promoting a regenerative microenvironment.[366–368] These effects lead to rapid re-epithelialization, reduced bacterial load, and improved vascularization in chronic wounds.[369,370]

In diabetic retinopathy (DR), hucMSCs-EVs protect retinal neurons and vessels by delivering miR-126, miR-30c-5p, and miR-17-3p. These miRNAs inhibit HMGB1, PLCG1/PKC/NF-κB, and STAT1 pathways respectively, reducing VEGF overexpression, retinal inflammation, and ganglion cell apoptosis.[371–373] They also restore the levels of glutamine synthetase, alleviate oxidative injury, and protect retinal structure and function.[374,375]

For diabetic cardiomyopathy, hucMSCs-EVs regulate excessive autophagy through AMPK-ULK1 signaling, reversing mitochondrial dysfunction and improving cardiac output by modulating LC3-II, Beclin1, and p62 expression.[376]

Beyond tissue-specific repair, hucMSCs-EVs enhance systemic metabolic homeostasis. They improve insulin sensitivity by restoring IRS-1 phosphorylation and GLUT4 translocation in skeletal muscle and adipocytes. Meanwhile, miR-21-rich EVs protect pancreatic β-cells from hypoxia-induced apoptosis by inhibiting endoplasmic reticulum stress.[377–379] In islet transplantation, alginate-encapsulated EVs inhibit foreign body responses by inhibiting T-cell proliferation and cytokine secretion (eg, IL-2, IL-6), thereby prolonging graft survival.[380]

By synergistically targeting inflammation, fibrosis, oxidative stress, and metabolic dysregulation, hucMSCs-EVs offer a multifunctional, cell-free therapeutic strategy for diabetes and its complications. It is gratifying to know that besides the support of these animal data, clinical trial data may also be presented for the efficacy of hucMSCs-EVs on diabetes and its complications, because the treatment of hucMSCs-EVs on diabetic foot has entered clinical trial (Tables 1 and 2).

Anti-Tumor Effects

Papillary Thyroid Carcinoma

HucMSCs-EVs exhibit anti-tumor effects in papillary thyroid carcinoma (PTC) through delivering miRNA and regulating oncogenic pathway. Zheng et al identified miR-30c-5p as a key tumor-suppressive miRNA downregulated in PTC, which directly inhibits the oncogenic E3 ubiquitin ligase PELI1, a driver of PI3K/AKT pathway activation. Engineered hucMSCs-EVs loaded with miR-30c-5p effectively silenced PELI1, suppressing AKT phosphorylation and downstream markers of proliferation (Ki-67) and metastasis (MMP-2). In vitro, miR-30c-5p-EVs reduced PTC cell growth and migration, while in vivo intra-tumoral administration halved tumor volume in xenograft models. These EVs offer a cell-free strategy to

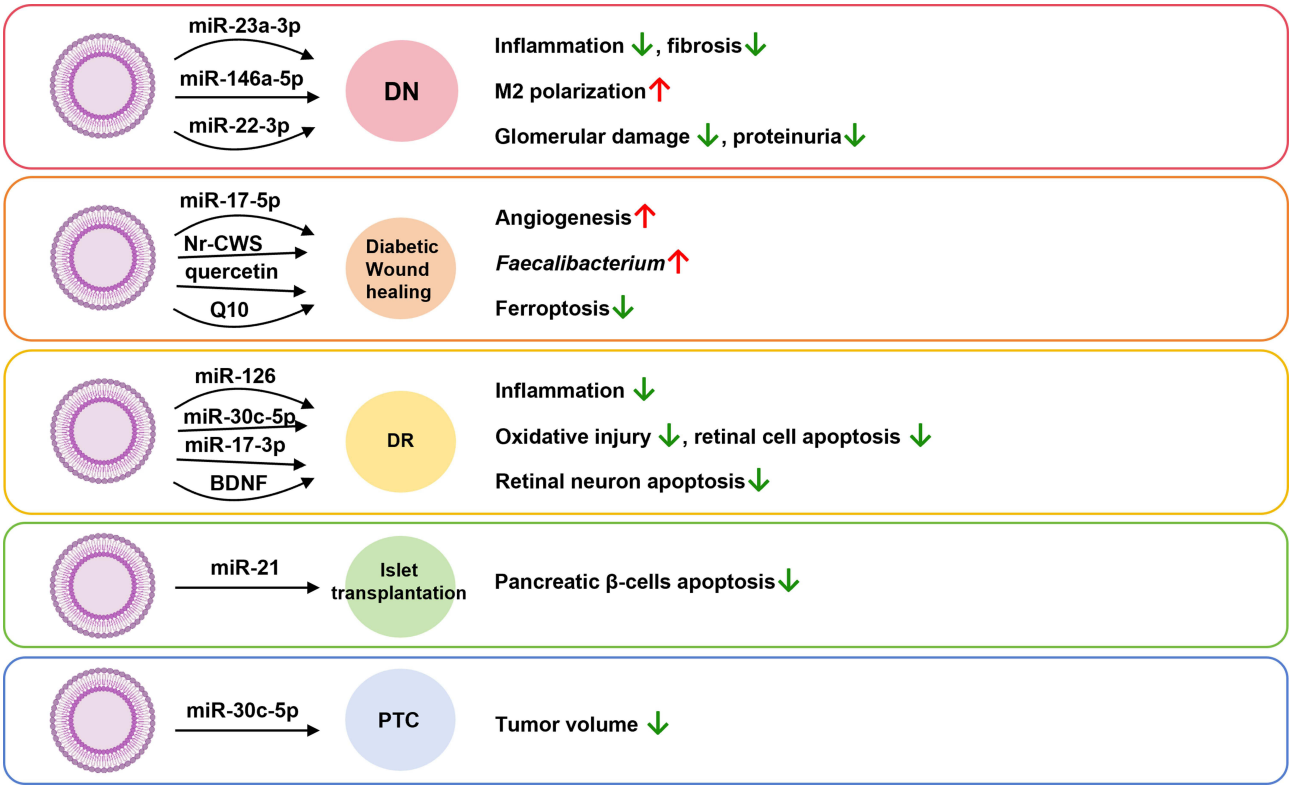


Figure 11 The effects of hucMSCs-EVs carrying different cargoes on different hormonal system diseases. The red colored upward arrows indicate promotion or upregulation, while the green colored downward arrows indicate inhibition or downregulation.

counteract PTC progression by restoring miR-30c-5p/PELI1 balance and blocking PI3K/AKT signaling.[381] Their biocompatibility and targeted delivery make hucMSCs-EVs a promising therapeutic pathway for PTC, even better if supported by clinical data. HucMSCs-EVs intervene in endocrine diseases through metabolic regulation, oxidative stress inhibition, and targeted signaling pathways, as summarized in Figure 11 and Table 10.

Table 10 Molecular Mechanism of hucMSCs-EVs in Treating Different Diseases in the Hormonal System

HucMSCs-EVs Cargo	Target/Signaling	Conditions/ Diseases	Action[a]	Reference
miR-23a-3p	KLF3/STAT3	DN	Inflammation↓, fibrosis↓	[324]
miR-146a-5p	TRAF6/STAT1	DN	M2 polarization↑, inflammation↓	[359]
miR-22-3p	NLRP3	DN	Glomerular damage↓, proteinuria↓	[325]
None reported	ERK1/2	Diabetic wound healing	Angiogenesis↑	[363]
None reported	None reported	Diabetic wound healing	Angiogenesis↑, antibacteria↑	[364]
miR-17-5p	PTEN/AKT	Diabetic wound healing	Angiogenesis↑	[365]
Nr-CWS	circIARS1/miR-4782-5p/ VEGFA	Diabetic wound healing	Angiogenesis↑	[366]
quercetin	None reported	Diabetic wound healing	*Faecalibacterium*↑	[367]
Q10	ACSL4	Diabetic wound healing	Ferroptosis↓	[368]
miR-126	HMGB1	DR	Inflammation↓	[371]
miR-30c-5p	PLCG1/PKC/NF-κB	DR	Inflammation↓	[372]
miR-17-3p	STAT1	DR	Inflammation↓, oxidative injury↓, retinal cell apoptosis↓	[373]

(*Continued*)

Table 10 (Continued).

HucMSCs-EVs Cargo	Target/Signaling	Conditions/ Diseases	Action[a]	Reference
BDNF	TrkB	DR	Retinal neuron apoptosis↓	[374]
None reported	p38 MAPK	DR	Protect retinal structure and function	[375]
None reported	AMPK-ULK1	Diabetic cardiomyopathy	Autophagy↓	[376]
miR-21	p38 MAPK3	Islet transplantation	Pancreatic β-cells apoptosis↓	[377]
None reported	None reported	Islet transplantation	Foreign body responses↓, graft survival↑	[380]
miR-30c-5p	PELI1, PI3K/AKT	PTC	tumor volume↓	[381]

Notes: [a] ↑ indicates promotion or upregulation; ↓ indicates inhibition or downregulation.

Translational Challenges

While hucMSCs-EVs offer a promising cell-free alternative to whole MSC therapy, it is crucial to recognize that they are not a panacea and face their own set of translational hurdles.

Production and Standardization

Due to insufficient understanding of the mechanisms of endogenous biogenesis and cargo sorting, we are currently unable to develop a production process that can precisely control the composition of hucMSCs-EVs cargo, and can only passively obtain heterogeneous mixtures. This fundamental limitation severely hinders the clinical translation of hucMSCs-EVs into therapeutic applications, primarily due to challenges in achieving production and standardization that comply with Good Manufacturing Practice (GMP). A main obstacle lies in the isolation and purification of EVs. Traditional methods such as ultracentrifugation, although widely used, have the disadvantages of low throughput, potential damage to the vesicles, and co-isolation of contaminants, which compromise the purity and scalability.[183,382–384] Emerging alternatives like tangential flow filtration (TFF) and size exclusion chromatography (SEC) offer improved yield and integrity. However, their transition to industrial-scale production requires optimization of reproducibility and cost-effectiveness.[183,382,385] Equally important is the establishment of strict quality control (QC) protocols to define critical quality attributes (CQAs), such as particle size, molecular composition, and bioactivity. Techniques like nanoparticle tracking analysis (NTA), Western blotting, and RNA sequencing are essential for characterizing EVs. But the lack of standardized markers and heterogeneity in EVs populations leads to variability among studies.[16,183,386–389] Recent initiatives by organizations like the International Society for Extracellular Vesicles (ISEV) aim to harmonize characterization criteria, emphasizing lipid-membrane integrity, cellular origin, and functional potency assays.[16] Storage stability further complicates clinical readiness, as EVs are sensitive to environmental conditions. Studies advocate the use of cryoprotectants such as mannitol or sucrose to optimize cryopreservation protocols, so as to maintain the bioactivity during long-term storage.[183,382,384,387,390]

Pharmacokinetics and Delivery

The administration route is a primary determinant of the biodistribution and therapeutic efficacy of hucMSCs-EVs, as it directly influences their bioavailability, tissue orientation, and eventual biological function. Therefore, choosing the optimal delivery strategy is crucial for targeting specific diseases. As the most common route, intravenous injection leads to a systemic distribution but results in rapid clearance by the mononuclear phagocyte system, with predominant accumulation in the liver, spleen, and lungs.[391] This limits the fraction of EVs that reach target sites. However, for treating systemic conditions, intravenous delivery may be necessary to achieve widespread distribution. Direct injection into the target tissue, such as intra-articular for OA,[180] or intrathecal for SCI,[129] maximizes local EVs concentration, minimizes systemic exposure and off-target effects, and bypasses first-pass clearance. This approach is highly effective for localized diseases but may be invasive for some applications. Intranasal administration is non-invasive route that bypasses the BBB and delivers EVs directly to the CNS.[392,393] However, dose consistency and deep lung deposition can be variable. Inhalation represents a paradigm-shifting route for treating respiratory pathologies. Nebulized hucMSCs-EVs

are delivered directly to the alveolar epithelium, achieving high local bioavailability and greatly reducing the required therapeutic dose compared to systemic administration. For example, in COVID-19 pneumonia, nebulized hucMSCs-EVs significantly accelerated the absorption of lung lesions and shortened hospitalization time by directly suppressing the cytokine storm and promoting alveolar repair.[213] The major challenges for this route include standardizing nebulization protocols to prevent EVs aggregation and ensuring consistent dosing throughout the respiratory system. Therefore, the choice of administration route is a key trade-off between achieving sufficient target tissue concentration and minimizing non-specific distribution, which directly affects the therapeutic biological function of hucMSCs-EVs.

The clinical translation of hucMSCs-EVs faces significant challenges in achieving precise biodistribution, effective targeting, and reliable delivery, despite their demonstrated therapeutic potential. A primary barrier lies in the rapid systemic clearance and non-specific biodistribution of EVs after administration. Intravenous injection resulting in predominant accumulation in reticuloendothelial organs such as the liver, spleen, and lungs. Coupled with an exceptionally short plasma half-life of 10–30 minutes, it severely limits their availability at pathological sites.[391,394–398] This non-specific capture is exacerbated by the inherent "eat me" signals on EVs surfaces, such as phosphatidylserine, which promote phagocytic clearance and reduce circulation time.[396] While alternative delivery routes like intranasal administration show promise for bypassing biological barriers such as the BBB,[392,393] there are still challenges in optimizing these methods for large-scale clinical use, particularly in terms of dose consistency and tissue penetration depth.[399] The intrinsic heterogeneity of EVs further complicates biodistribution predictability, because different isolation methods generate populations with different surface compositions, which unpredictably influence cellular uptake and organ targeting.[397,400] Although engineering strategies, including genetic modification, chemical conjugation of targeting ligands, and membrane fusion, have been explored to enhance specificity, these approaches face translational barriers. Genetic engineering, while enabling surface display of tumor-homing peptides or BBB-crossing antibodies, is affected by labor-intensive protocols, variable transfection efficiencies, and potential disruption of EVs cargo during biogenesis.[394,398,401] Chemical modifications using click chemistry or lipid insertion may damage the membrane integrity and biological function, while physical methods like magnetic nanoparticle loading raise concerns about cytotoxicity and long-term stability.[394,402] Even if successfully engineered, modified EVs must deal with receptor saturation, non-specific binding in complex physiological environments, and immune recognition—these factors will disrupt the targeting precision in heterogeneous patient populations.[393,394,403] The therapeutic payload itself presents additional hurdles, as current drug-loading techniques—whether endogenous (eg, parental cell transfection) or exogenous (eg, electroporation, sonication)—face problems of low efficiency, cargo leakage, and batch-to-batch variability.[399,402] Complicating these issues is the lack of standardized protocols for EVs isolation, characterization, and quality control. Traditional RNA analysis methods proving inadequate for EVs-specific cargo and surface marker profiling.[400,404] Emerging solutions, such as gold nanoparticle labeling and molecular imaging-guided delivery, demonstrate the potential for real-time tracking and enhanced tumor accumulation,[405,406] but scalability and regulatory acceptance remain uncertain. Ultimately, advancing hucMSCs-EVs into clinical practice demands comprehensive innovations in EVs engineering, biodistribution modulation, and delivery route optimization, supplemented by strong standardization efforts to ensure reproducible treatments across diverse diseases.[391,399,400]

Safety and Regulatory Hurdles

The clinical translation of hucMSCs-EVs also faces various safety and regulatory challenges that must be addressed to ensure therapeutic efficacy and patient safety. A major safety concern is the heterogeneity of EVs production processes, which significantly impacts product consistency and reliability. As highlighted by Krishnan et al (2024), proteomic analyses of hucMSCs-EVs remain in their infancy. There are significant differences in isolation techniques, culture conditions (eg, media composition, cell passage number), and enrichment methods, leading to unpredictable differences in EVs composition and bioactivity.[407] This variability complicates the assessment of therapeutic outcomes and raises questions about batch-to-batch reproducibility. Furthermore, although EVs are generally considered safer than whole-cell therapies due to their lower risk of tumorigenicity and autoimmune reactions, emerging risks such as immunogenicity, oncogenic potential, and off-target effects require rigorous evaluation, particularly in patients with comorbidities who may show a higher susceptibility to adverse events.[408,409] These risks are amplified when gene-editing tools like

CRISPR/Cas9 are employed to engineer EVs for enhanced therapeutic properties, as unexpected genetic modifications or off-target effects could inadvertently promote oncogenesis or disrupt immune homeostasis.[410]

Regulatory hurdles further impede clinical progress due to the absence of unified global frameworks for EVs-based therapies. Current regulatory classifications vary regionally: in Europe, EVs products may fall under advanced therapy medicinal products (ATMPs) or biological medicinal products, whereas the US FDA applies distinct criteria, creating a fragmented compliance landscape.[411] Compounding this issue is the lack of standardized protocols for clinical-grade EV manufacturing, storage, and characterization. Chen et al (2024) emphasized that undefined production parameters and insufficient quality control measures hinder the establishment of processes that comply with current good manufacturing practice (cGMP), which are critical for ensuring product safety, consistency, and scalability.[412] Although organizations like the ISEV have proposed preliminary guidelines for clinical translation, these remain insufficiently detailed to address the complexities of EVs-based therapeutics, particularly in areas such as sterilization, stability testing, and long-term safety monitoring.[409] To bridge these gaps, concerted efforts are needed to develop universally accepted standards for EVs isolation, characterization, and preclinical safety analysis, while formulating adaptable regulatory policies that strike a balance between innovation and strict risk control. Only through such interdisciplinary collaboration can the transformative potential of hucMSCs-EVs be safely and effectively realized in clinical practice (Figure 12).

Therapeutic Restrictions

Despite convincing preclinical results, the therapeutic application of hucMSCs-EVs still face significant limitations, which must be acknowledged in order to ensure clinical translation. These limitations underscore that their efficacy is not universal but is governed by specific biological and practical factors.

The functionality of hucMSCs-EVs is not absolute but is profoundly influenced by the pathological microenvironment of the target disease. Their efficacy is depended on a complex interplay between the EVs cargo and the recipient

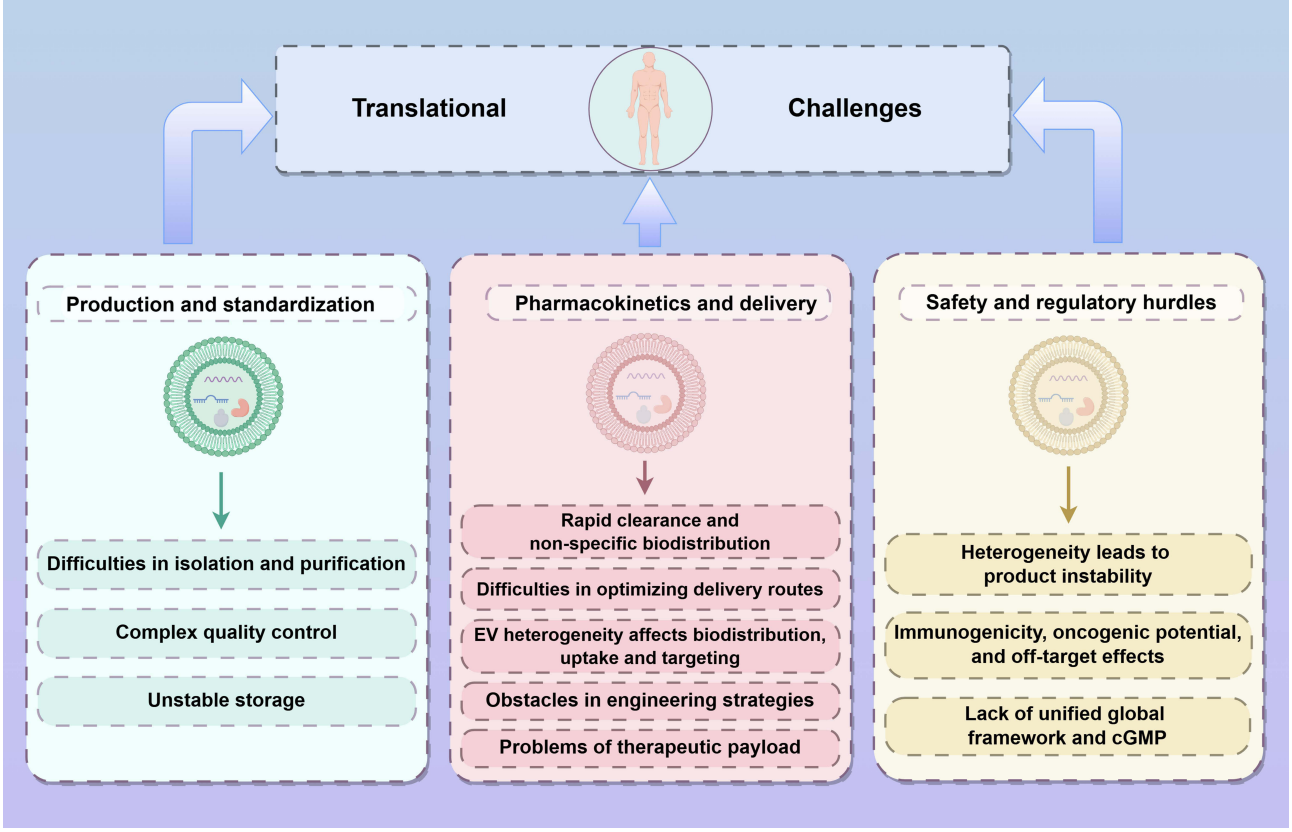


Figure 12 The barriers to hucMSCs-EVs translation into the clinical. The clinical translation of hucMSCs-EVs face three major challenges: production and standardization, pharmacokinetics and delivery, and safety and regulatory hurdles. (Figure created with Figdraw).

https://doi.org/10.2147/IJN.S550390

cells' state. In addition, critical questions regarding the optimal dosage, frequency of administration, route of delivery, and treatment initiation window remain largely unanswered. Preclinical studies show efficacy across a wide range of doses, making it difficult to infer human equivalents. The inherent homing properties of MSCs towards inflammatory and tumor sites can be a double-edged sword. Although beneficial for targeted drug delivery, natural hucMSCs-EVs may unintentionally promote tumor growth under specific conditions. Therefore, detailed safety studies must be conducted, especially in oncology applications, to ensure that the treatment does not exacerbate disease progression in a subset of patients. In short, it is necessary to have a clear understanding of these limitations in order to pave the way for hucMSCs-EVs.

Conclusion and Future Perspectives

HucMSCs-EVs represent a groundbreaking cell-free therapeutic platform in regenerative and oncological medicine, offering multifaceted advantages such as low immunogenicity, non-invasive sourcing, and the ability to modulate diverse pathological processes. Numerous studies have demonstrated their remarkable efficacy in various diseases through mechanisms such as immunomodulation, anti-apoptosis, angiogenesis, and tissue repair. The bioactive cargo of hucMSCs-EVs is rich in miRNAs, proteins, and signaling molecules, which can precisely regulate cellular pathways and restore the homeostasis of damaged tissues. Moreover, advancements in engineering strategies, such as cargo modification, surface functionalization, and biomaterial integration, have further enhanced their therapeutic precision and delivery efficiency. However, critical translational challenges still remain. Standardized protocols for EVs isolation, characterization, and large-scale production under GMP are still difficult to achieve. Pharmacokinetic hurdles, including rapid clearance, biodistribution heterogeneity, and insufficient targeting, require innovative solutions. Safety concerns, such as batch-to-batch variability and the risks of environment-dependent oncogenic signaling, need rigorous preclinical validation. Regulatory frameworks must be continuously improved to address the unique complexities of EVs-based therapies and ensure the efficacy and patient safety in clinical trials.

Encouragingly, there are currently multiple registered clinical trials evaluating hucMSCs-EVs in different therapeutic fields (Tables 1 and 2), which reflect the growing confidence in their clinical viability. Early-phase trials have reported preliminary safety and tolerability, with emerging evidence of functional improvement in diseases such as AD, PD, Arthritis, COVID-19, Female Infertility, and diabetic complications. These studies highlight the potential of hucMSCs-EVs to bridge regenerative and oncological therapies, offering hope for chronic and refractory diseases.

Future research should prioritize optimizing EVs engineering, developing real-time tracking systems, and conducting large-scale, randomized clinical trials to validate long-term outcomes. In particular, the development of personalized EVs engineering have significant prospects. By customizing EVs based on individual patient conditions, such as loading specific miRNAs or therapeutic proteins according to disease subtypes, genetic backgrounds, or metabolic states, treatment efficacy can be greatly improved while minimizing off target effects. Personalized EVs may be designed to respond to the unique tumor microenvironment in cancer patients, or to complement specific deficits in regenerative environment, effectively supporting precision medicine. Additionally, the use of patient-derived MSC-EVs could further reduce immunogenic risks and improve biocompatibility. However, this approach also presents challenges including manufacturing complexity, cost-effectiveness, and the need for companion diagnostics. Interdisciplinary collaboration among researchers, clinicians, and regulators is crucial for overcoming production standardization and challenges. By coordinating technological innovation with robust regulatory standards, hucMSCs-EVs have the potential to revolutionize regenerative and oncological medicine, bringing hope to millions of people suffering from chronic and refractory diseases.

Abbreviations

EVs, Extracellular vesicles; HucMSCs-EVs, Human umbilical cord-derived MSCs-EVs; ESCRT, Endosomal sorting complex required for transport; TME, Tumor microenvironments; ARRDC1, Arrestin domain-containing protein 1; TSG101, Tumor susceptibility gene 101; Vps4, Vacuolar protein sorting-associated protein 4; MVBs, Multivesicular bodies; ECM, Extracellular matrix; IGF, Insulin-like growth factor; TBI, Traumatic brain injury; BBB, Blood-brain barrier; rt-PA, Recombinant tissue plasminogen activator; AAK1, Adaptor-associated kinase 1; AD, Alzheimer's disease; Aβ, B-amyloid; PD, Parkinson's disease; BDNF, Brain-derived neurotrophic factor; MS, Multiple sclerosis; CNS,

Central nervous system; DMTs, Disease-modifying therapies; Treg, Regulatory T cell; SCI, Spinal cord injury; PNI, Peripheral nerve injury; SC, Schwann cell; dECM, Decellularized ECM; OA, Osteoarthritis; RA, Rheumatoid arthritis; ALI/ARDS, Acute lung injury/acute respiratory distress syndrome; COPD, Chronic obstructive pulmonary disease; EMT, Epithelial-mesenchymal transition; GC, Gastric cancer; HCC, Hepatocellular carcinoma; IBD, Inflammatory bowel disease; CRC, Colorectal cancer; SAP, Severe acute pancreatitis; PDAC, Pancreatic ductal adenocarcinoma; DKD, Diabetic kidney disease; AKI, Acute kidney injury; NOA, Nonobstructive azoospermia; PCa, Prostate cancer; IUAs, Intrauterine adhesions; POI, Premature ovarian insufficiency; OC, Ovarian cancer; MI, Myocardial infarction; PH, Pulmonary hypertension; EndMT, Endothelial-mesenchymal transition; AAA, Abdominal aortic aneurysm; DN, Diabetic nephropathy; DR, Diabetic retinopathy; PTC, Papillary thyroid carcinoma; GMP, Good manufacturing practice; TFF, Tangential flow filtration; SEC, Size exclusion chromatography; QC, Quality control; CQAs, Critical quality attributes; NTA, Nanoparticle tracking analysis; ISEV International Society for Extracellular Vesicles.

Data Sharing Statement

Data sharing not applicable – no new data generated.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (82301567); the China Postdoctoral Science Foundation (2024M761195); the Zhenjiang Key Laboratory of High Technology Research on Exosomes Foundation and Transformation Application (SS2018003); the Priority Academic Program Development of Jiangsu Higher Education Institutions (Phase IV, Clinical Medicine); the General Project of Jiangsu Provincial Health Commission (H2023112).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982–3021. doi:10.1016/j.jacc.2020.11.010
2. Li X, Sun X, Feng X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. *Front Aging Neurosci*. 2022;14:937486. doi:10.3389/fnagi.2022.937486
3. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: a lancet commission. *Lancet*. 2020;396(10264):1711–1712. doi:10.1016/S0140-6736(20)32230-3
4. Dong Y, Yang Y, Wang H, et al. Single-cell chromatin profiling reveals genetic programs activating proregenerative states in nonmyocyte cells. *Sci Adv*. 2024;10(8):eadk4694. doi:10.1126/sciadv.adk4694
5. Xu P, Kankala RK, Wang S, Chen A. Decellularized extracellular matrix-based composite scaffolds for tissue engineering and regenerative medicine. *Regen Biomater*. 2024;11:rbad107. doi:10.1093/rb/rbad107
6. Chauhan G, Wang X, Yousry C, Gupta V. Scalable production and in vitro efficacy of inhaled erlotinib nanoemulsion for enhanced efficacy in non-small cell lung cancer (NSCLC). *Pharmaceutics*. 2023;15(3). doi:10.3390/pharmaceutics15030996
7. Zabaleta ME, Forbes-Hernandez TY, Simal-Gandara J, et al. Effect of polyphenols on HER2-positive breast cancer and related miRNAs: epigenomic regulation. *Food Res Int*. 2020;137:109623. doi:10.1016/j.foodres.2020.109623
8. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;8(4):315–317. doi:10.1080/14653240600855905
9. Wei M, Yang Z, Li S, Le W. Nanotherapeutic and stem cell therapeutic strategies in neurodegenerative diseases: a promising therapeutic approach. *Int J Nanomed*. 2023;18:611–626. doi:10.2147/IJN.S395010
10. Ljubic A, Dinic M, Svraka D, Vujovic S. Dual-double stem cell ovarian therapy: a comprehensive approach in regenerative medicine. *Int J Mol Sci*. 2024;26(1). doi:10.3390/ijms26010069

11. Cooper LF, Ravindran S, Huang CC, Kang M. A role for exosomes in craniofacial tissue engineering and regeneration. *Front Physiol*. 2019;10:1569. doi:10.3389/fphys.2019.01569
12. Zou Y, Liao L, Dai J, et al. Mesenchymal stem cell-derived extracellular vesicles/exosome: a promising therapeutic strategy for intracerebral hemorrhage. *Regen Ther*. 2023;22:181–190. doi:10.1016/j.reth.2023.01.006
13. Dixson AC, Dawson TR, Di Vizio D, Weaver AM. Context-specific regulation of extracellular vesicle biogenesis and cargo selection. *Nat Rev Mol Cell Biol*. 2023;24(7):454–476. doi:10.1038/s41580-023-00576-0
14. Yang S, Sun Y, Yan C. Recent advances in the use of extracellular vesicles from adipose-derived stem cells for regenerative medical therapeutics. *J Nanobiotechnol*. 2024;22(1):316. doi:10.1186/s12951-024-02603-4
15. Wang YK, Zhao YP, Ye MZ, et al. Chimeric CNS-targeting-peptide engineered exosomes for experimental autoimmune encephalomyelitis therapy. *Int Immunopharmacol*. 2023;124(Pt B):110835. doi:10.1016/j.intimp.2023.110835
16. Welsh JA, Goberdhan DCI, O'Driscoll L, et al. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. *J Extracell Vesicles*. 2024;13(2):e12404. doi:10.1002/jev2.12404
17. Wu M, Chen L, Qi Y, et al. Human umbilical cord mesenchymal stem cell promotes angiogenesis via integrin beta1/ERK1/2/HIF-1alpha/VEGF-A signaling pathway for off-the-shelf breast tissue engineering. *Stem Cell Res Ther*. 2022;13(1):99. doi:10.1186/s13287-022-02770-x
18. Cui L, Luo W, Jiang W, et al. Human umbilical cord mesenchymal stem cell-derived exosomes promote neurological function recovery in rat after traumatic brain injury by inhibiting the activation of microglia and astrocyte. *Regen Ther*. 2022;21:282–287. doi:10.1016/j.reth.2022.07.005
19. Huang JH, Yin XM, Xu Y, et al. Systemic administration of exosomes released from mesenchymal stromal cells attenuates apoptosis, inflammation, and promotes angiogenesis after spinal cord injury in rats. *J Neurotrauma*. 2017;34(24):3388–3396. doi:10.1089/neu.2017.5063
20. Liu W, Liu A, Li X, et al. Dual-engineered cartilage-targeting extracellular vesicles derived from mesenchymal stem cells enhance osteoarthritis treatment via miR-223/NLRP3/pyroptosis axis: toward a precision therapy. *Bioact Mater*. 2023;30:169–183. doi:10.1016/j.bioactmat.2023.06.012
21. Zhou H, Shen X, Yan C, et al. Extracellular vesicles derived from human umbilical cord mesenchymal stem cells alleviate osteoarthritis of the knee in mice model by interacting with METTL3 to reduce m6A of NLRP3 in macrophage. *Stem Cell Res Ther*. 2022;13(1):322. doi:10.1186/s13287-022-03005-9
22. Khanh VC, Fukushige M, Chang YH, et al. Wharton's jelly mesenchymal stem cell-derived extracellular vesicles reduce SARS-CoV2-induced inflammatory cytokines under high glucose and uremic toxin conditions. *Stem Cells Dev*. 2021;30(15):758–772. doi:10.1089/scd.2021.0065
23. Wu P, Wang M, Jin C, et al. Highly efficient delivery of novel MiR-13896 by human umbilical cord mesenchymal stem cell-derived small extracellular vesicles inhibits gastric cancer progression by targeting ATG2A-mediated autophagy. *Biomater Res*. 2024;28:119. doi:10.34133/bmr.0119
24. Dolatshahi M, Bahrami AR, Sheikh QI, Ghanbari M, Matin MM. Gastric cancer and mesenchymal stem cell-derived exosomes: from pro-tumorigenic effects to anti-cancer vehicles. *Arch Pharm Res*. 2024;47(1):1–19. doi:10.1007/s12272-023-01477-8
25. Gan J, Liu S, Zhang Y, et al. MicroRNA-375 is a therapeutic target for castration-resistant prostate cancer through the PTPN4/STAT3 axis. *Exp Mol Med*. 2022;54(8):1290–1305. doi:10.1038/s12276-022-00837-6
26. Qiu L, Wang J, Chen M, Chen F, Tu W. Exosomal microRNA-146a derived from mesenchymal stem cells increases the sensitivity of ovarian cancer cells to docetaxel and taxane via a LAMC2-mediated PI3K/Akt axis. *Int J Mol Med*. 2020;46(2):609–620. doi:10.3892/ijmm.2020.4634
27. Tang W, Yan H, Chen X, et al. hUCMSC-derived extracellular vesicles relieve cisplatin-induced granulosa cell apoptosis in mice by transferring anti-apoptotic miRNAs. *J Biomed Res*. 2024;39(1):36–49. doi:10.7555/JBR.37.20230310
28. Wu P, Zhang B, Ocansey DKW, Xu W, Qian H. Extracellular vesicles: a bright star of nanomedicine. *Biomaterials*. 2021;269:120467. doi:10.1016/j.biomaterials.2020.120467
29. Lin R, Zhang T, Gao J. Apoptotic vesicles of MSCs: the natural therapeutic agents and bio-vehicles for targeting drug delivery. *Small*. 2023;19(47):e2301671. doi:10.1002/smll.202301671
30. Zou X, Lei Q, Luo X, et al. Advances in biological functions and applications of apoptotic vesicles. *Cell Commun Signal*. 2023;21(1):260. doi:10.1186/s12964-023-01251-9
31. Dharan R, Huang Y, Cheppali SK, et al. Tetraspanin 4 stabilizes membrane swellings and facilitates their maturation into migrasomes. *Nat Commun*. 2023;14(1):1037. doi:10.1038/s41467-023-36596-9
32. Ding T, Ji J, Zhang W, et al. The phosphatidylinositol (4,5)-bisphosphate-Rab35 axis regulates migrasome formation. *Cell Res*. 2023;33(8):617–627. doi:10.1038/s41422-023-00811-5
33. Jr B, Singh KK, Aquilano K, et al. Recommendations for mitochondria transfer and transplantation nomenclature and characterization. *Nat Metab*. 2025;7(1):53–67. doi:10.1038/s42255-024-01200-x
34. Li F, Wu J, Li D, et al. Engineering stem cells to produce exosomes with enhanced bone regeneration effects: an alternative strategy for gene therapy. *J Nanobiotechnol*. 2022;20(1):135. doi:10.1186/s12951-022-01347-3
35. Urzi O, Olofsson Bagge R, Crescitelli R. The dark side of foetal bovine serum in extracellular vesicle studies. *J Extracell Vesicles*. 2022;11(10):e12271. doi:10.1002/jev2.12271
36. Sharma V, Nikolajeff F, Kumar S. Employing nanoparticle tracking analysis of salivary neuronal exosomes for early detection of neurodegenerative diseases. *Transl Neurodegener*. 2023;12(1):7. doi:10.1186/s40035-023-00339-z
37. Zhu J, Huang J, Sun Y, Xu W, Qian H. Emerging role of extracellular vesicles in diabetic retinopathy. *Theranostics*. 2024;14(4):1631–1646. doi:10.7150/thno.92463
38. Rosu A, Ghaemi B, Bulte JWM, Shakeri-Zadeh A. Tumor-tropic Trojan horses: using mesenchymal stem cells as cellular nanotheranostics. *Theranostics*. 2024;14(2):571–591. doi:10.7150/thno.90187
39. Qiu G, Zheng G, Ge M, et al. Functional proteins of mesenchymal stem cell-derived extracellular vesicles. *Stem Cell Res Ther*. 2019;10(1):359. doi:10.1186/s13287-019-1484-6
40. Ding Z, Greenberg ZF, Serafim MF, et al. Understanding molecular characteristics of extracellular vesicles derived from different types of mesenchymal stem cells for therapeutic translation. *Extracell Vesicle*. 2024;3. doi:10.1016/j.vesic.2024.100034
41. Tao H, Chen X, Cao H, et al. Mesenchymal stem cell-derived extracellular vesicles for corneal wound repair. *Stem Cells Int*. 2019;2019:5738510. doi:10.1155/2019/5738510
42. Fuloria S, Subramaniyan V, Dahiya R, et al. Mesenchymal stem cell-derived extracellular vesicles: regenerative potential and challenges. *Biology*. 2021;10(3). doi:10.3390/biology10030172

43. Zhu L, Wang Q, Guo M, et al. Mesenchymal stem cell-derived exosomes in various chronic liver diseases: hype or hope? *J Inflamm Res*. 2024;17:171–189. doi:10.2147/JIR.S439974
44. Shin S, Lee J, Kwon Y, et al. Comparative proteomic analysis of the mesenchymal stem cells secretome from adipose, bone marrow, placenta and Wharton's jelly. *Int J Mol Sci*. 2021;22(2). doi:10.3390/ijms22020845
45. Gao J, Zhu D, Fan Y, Liu H, Shen Z. Human umbilical cord mesenchymal stem cells-derived extracellular vesicles for rat jawbone regeneration in periapical periodontitis. *ACS Biomater Sci Eng*. 2024;10(9):5784–5795. doi:10.1021/acsbiomaterials.4c00622
46. Zhang ZW, Wei P, Zhang GJ, et al. Intravenous infusion of the exosomes derived from human umbilical cord mesenchymal stem cells enhance neurological recovery after traumatic brain injury via suppressing the NF-kappaB pathway. *Open Life Sci*. 2022;17(1):189–201. doi:10.1515/biol-2022-0022
47. Zhang Z, Zou X, Zhang R, et al. Human umbilical cord mesenchymal stem cell-derived exosomal miR-146a-5p reduces microglial-mediated neuroinflammation via suppression of the IRAK1/TRAF6 signaling pathway after ischemic stroke. *Aging*. 2021;13(2):3060–3079. doi:10.18632/aging.202466
48. Abdi SMY, Al-Bakri SSM, Nordin N. Insights on the characteristics and therapeutic potential of mesenchymal stem cell-derived exosomes for mitigation of alzheimer's disease's pathogenicity: a systematic review. *Cell Biochem Biophys*. 2024. doi:10.1007/s12013-024-01598-x
49. Li X, Hu Y, Wu Y, Yang Z, Liu Y, Liu H. Exosomal let-7a-5p derived from human umbilical cord mesenchymal stem cells alleviates coxsackievirus B3-induced cardiomyocyte ferroptosis via the SMAD2/ZFP36 signal axis. *J Zhejiang Univ Sci B*. 2024;25(5):422–437. doi:10.1631/jzus.B2300077
50. Lilova RL, Hernandez M, Kelliher C, Lafrenaye A. Increased incidence of weight-loss-associated humane endpoints in rats administered buprenorphine slow-release LAB formulation following traumatic brain injury: a retrospective study. *Front Neurol*. 2024;15:1467419. doi:10.3389/fneur.2024.1467419
51. Zhang SL, Yuan JY, Meng N, et al. A meta-analysis of cognitive and functional outcomes in severe brain trauma cases. *Front Behav Neurosci*. 2024;18. doi:10.3389/fnbeh.2024.1349672
52. Kapapa T, Jesuthasan S, Schiller F, et al. Outcome after decompressive craniectomy in older adults after traumatic brain injury. *Front Med*. 2024;11:1422040. doi:10.3389/fmed.2024.1422040
53. Molstrom S, Nielsen TH, Nordstrom CH, et al. A randomized, double-blind trial comparing the effect of two blood pressure targets on global brain metabolism after out-of-hospital cardiac arrest. *Crit Care*. 2023;27(1):73. doi:10.1186/s13054-023-04376-y
54. Gouvea Bogossian E, Battaglini D, Fratino S, et al. The role of brain tissue oxygenation monitoring in the management of subarachnoid hemorrhage: a scoping review. *Neurocrit Care*. 2023;39(1):229–240. doi:10.1007/s12028-023-01680-x
55. Falcone JA, Chen JW. Technical notes on the placement of cerebral microdialysis: a single center experience. *Front Neurol*. 2022;13:1041952. doi:10.3389/fneur.2022.1041952
56. Ramos-Zaldivar HM, Polakovicova I, Salas-Huenuleo E, et al. Extracellular vesicles through the blood-brain barrier: a review. *Fluids Barriers CNS*. 2022;19(1):60. doi:10.1186/s12987-022-00359-3
57. Ruan J, Miao X, Schluter D, Lin L, Wang X. Extracellular vesicles in neuroinflammation: pathogenesis, diagnosis, and therapy. *Mol Ther*. 2021;29(6):1946–1957. doi:10.1016/j.ymthe.2021.04.020
58. Cui L, Li D, Xu J, et al. Exosomal miRNA-21 derived from umbilical cord mesenchymal stem cells inhibits microglial overactivation to counteract nerve damage. *Mol Biol Rep*. 2024;51(1):941. doi:10.1007/s11033-024-09878-8
59. Lai X, Wang Y, Wang X, Liu B, Rong L. miR-146a-5p-modified hUCMSC-derived exosomes facilitate spinal cord function recovery by targeting neurotoxic astrocytes. *Stem Cell Res Ther*. 2022;13(1):487. doi:10.1186/s13287-022-03116-3
60. Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541(7638):481–487. doi:10.1038/nature21029
61. Zhang L, Lin Y, Bai W, Sun L, Tian M. Human umbilical cord mesenchymal stem cell-derived exosome suppresses programmed cell death in traumatic brain injury via PINK1/Parkin-mediated mitophagy. *CNS Neurosci Ther*. 2023;29(8):2236–2258. doi:10.1111/cns.14159
62. Collaborators GBDSRF. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the global burden of disease study 2021. *Lancet Neurol*. 2024;23(10):973–1003. doi:10.1016/S1474-4422(24)00369-7.
63. Li B, Li J, Meng X, et al. The association of blood urea nitrogen-to-creatinine ratio and in-hospital mortality in acute ischemic stroke patients with atrial fibrillation: data from the MIMIC-IV database. *Front Neurol*. 2024;15:1331626. doi:10.3389/fneur.2024.1331626
64. Guo F, Qin Y, Fu H, Xu F. The impact of COVID-19 on Emergency Department length of stay for urgent and life-threatening patients. *BMC Health Serv Res*. 2022;22(1):696. doi:10.1186/s12913-022-08084-1
65. Bhatti AA, Mahajan NP, Vyas DD, Shah MM, Huded V. Rescue strategies in anterior circulation stroke with failed mechanical Thrombectomy-A retrospective observational study (RAFT). *Ann Indian Acad Neurol*. 2021;24(6):885–890. doi:10.4103/aian.AIAN_87_21
66. Ni H, Yang T, Jia Z, Shi H, Liu S, Zhao L. Outcomes in acute ischemic stroke patients undergoing endovascular thrombectomy: cervical internal carotid artery pseudo-occlusion vs. true occlusion. *Front Neurol*. 2022;13:1106358. doi:10.3389/fneur.2022.1106358
67. Kuang Y, Zhang L, Ye K, Jiang Z, Shi C, Luo L. Clinical and imaging predictors for hemorrhagic transformation of acute ischemic stroke after endovascular thrombectomy. *J Neuroimaging*. 2024;34(3):339–347. doi:10.1111/jon.13191
68. Ayub T, Barwari A, Finsterer J. Frequency, severity, risk factors, and outcome of hemorrhagic transformation in anterior and posterior stroke. *J Clin Med*. 2024;13(7). doi:10.3390/jcm13072010
69. Lin Y, Luo Y, Li Y, Han J. Development and validation of an explainable machine learning prediction model of hemorrhagic transformation after intravenous thrombolysis in stroke. *Front Neurol*. 2024;15:1446250. doi:10.3389/fneur.2024.1446250
70. Pluta R, Januszewski S, Czuczwar SJ. Neuroinflammation in post-ischemic neurodegeneration of the brain: friend, foe, or both? *Int J Mol Sci*. 2021;22(9). doi:10.3390/ijms22094405
71. Yang Y, Gao L, Xi J, et al. Mesenchymal stem cell-derived extracellular vesicles mitigate neuronal damage from intracerebral hemorrhage by modulating ferroptosis. *Stem Cell Res Ther*. 2024;15(1):255. doi:10.1186/s13287-024-03879-x
72. Shen B, Liu N, Dai Y. Exosomes derived from umbilical cord mesenchymal stem cells ameliorate ischemic brain injury in mice by regulating AAK1 via miR-664a-5p. *Int J Neurosci*. 2024;1–15. doi:10.1080/00207454.2024.2441120
73. Xu K, Zhao X, He Y, Guo H, Zhang Y. Stem cell-derived exosomes for ischemic stroke: a conventional and network meta-analysis based on animal models. *Front Pharmacol*. 2024;15:1481617. doi:10.3389/fphar.2024.1481617

74. Zheng X, Hermann DM, Bahr M, Doeppner TR. The role of small extracellular vesicles in cerebral and myocardial ischemia-Molecular signals, treatment targets, and future clinical translation. *Stem Cells*. 2021;39(4):403–413. doi:10.1002/stem.3329
75. Alzheimer's Association. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):3708–3821. doi:10.1002/alz.13809
76. Shukla D, Suryavanshi A, Bharti SK, Asati V, Mahapatra DK. Recent advances in the treatment and management of alzheimer's disease: a precision medicine perspective. *Curr Top Med Chem*. 2024;24(19):1699–1737. doi:10.2174/0115680266299847240328045737
77. Kumar A, Kim F, Song DK, Choung JJ. Polypharmacological potential of phosphodiesterase 5 inhibitors for the treatment of neurocognitive disorders. *Aging Dis*. 2024;15(5):2008–2014. doi:10.14336/AD.2023.1129
78. Lu CH, Chang HT, Hsu LF, et al. In silico and in vitro screening of serine racemase agonist and in vivo efficacy on alzheimer's disease drosophila melanogaster. *Pharmaceuticals*. 2023;16(2). doi:10.3390/ph16020280
79. Amano A, Sanjo N, Araki W, et al. Peripheral administration of nanomicelle-encapsulated anti-Abeta oligomer fragment antibody reduces various toxic Abeta species in the brain. *J Nanobiotechnol*. 2023;21(1):36. doi:10.1186/s12951-023-01772-y
80. Savva K, Zachariou M, Bourdakou MM, Dietis N, Spyrou GM. Network-based stage-specific drug repurposing for Alzheimer's disease. *Comput Struct Biotechnol J*. 2022;20:1427–1438. doi:10.1016/j.csbj.2022.03.013
81. Ding M, Shen Y, Wang P, et al. Exosomes isolated from human umbilical cord mesenchymal stem cells alleviate neuroinflammation and reduce amyloid-beta deposition by modulating microglial activation in alzheimer's disease. *Neurochem Res*. 2018;43(11):2165–2177. doi:10.1007/s11064-018-2641-5
82. Yang L, Zhai Y, Hao Y, Zhu Z, Cheng G. The regulatory functionality of exosomes derived from hUMSCs in 3D culture for alzheimer's disease therapy. *Small*. 2020;16(3):e1906273. doi:10.1002/smll.201906273
83. Zhang Z, Sheng H, Liao L, et al. Mesenchymal stem cell-conditioned medium improves mitochondrial dysfunction and suppresses apoptosis in okadaic acid-treated sh-sy5y cells by extracellular vesicle mitochondrial transfer. *J Alzheimers Dis*. 2020;78(3):1161–1176. doi:10.3233/JAD-200686
84. Chen H, Huang Z, Lei A, Yu X, Shen M. Wu D: miRNA-211-5p inhibition enhances the protective effect of hucMSC-derived exosome in Abeta (1-40) -induced SH-SY5Y cells by increasing NEP expression. *J Biochem Mol Toxicol*. 2024;38(1):e23624. doi:10.1002/jbt.23624
85. Zhdanova DY, Poltavtseva RA, Svirshchevskaya EV, Bobkova NV. Effect of intranasal administration of multipotent mesenchymal stromal cell exosomes on memory of mice in alzheimer's disease model. *Bull Exp Biol Med*. 2021;170(4):575–582. doi:10.1007/s10517-021-05109-3
86. Luo Y, Qiao L, Li M, Wen X, Zhang W, Li X. Global, regional, national epidemiology and trends of Parkinson's disease from 1990 to 2021: findings from the Global Burden of Disease Study 2021. *Front Aging Neurosci*. 2024;16:1498756. doi:10.3389/fnagi.2024.1498756
87. Yuan J, Liu Y, Liao H, et al. Alterations in cortical volume and complexity in Parkinson's disease with depression. *CNS Neurosci Ther*. 2024;30(2):e14582. doi:10.1111/cns.14582
88. Yin W, Zhu W, Gao H, et al. Gait analysis in the early stage of Parkinson's disease with a machine learning approach. *Front Neurol*. 2024;15:1472956. doi:10.3389/fneur.2024.1472956
89. Masood N, Jimenez-Shahed J. Effective management of "OFF" episodes in parkinson's disease: emerging treatment strategies and unmet clinical needs. *Neuropsychiatr Dis Treat*. 2023;19:247–266. doi:10.2147/NDT.S273121
90. Ahn JH, Kang MC, Lee D, Cho JW, Park KA, Youn J. Central retinal microvasculature damage is associated with orthostatic hypotension in Parkinson's disease. *NPJ Parkinsons Dis*. 2023;9(1):36. doi:10.1038/s41531-023-00480-6
91. De Carolis L, Galli S, Bianchini E, et al. Age at onset influences progression of motor and non-motor symptoms during the early stage of parkinson's disease: a monocentric retrospective study. *Brain Sci*. 2023;13(2). doi:10.3390/brainsci13020157
92. Malaguti MC, Di Fonzo A, Longo C, et al. Monfrini E: a novel pathogenic PSEN1 variant in a patient with dystonia-parkinsonism without dementia. *J Mov Disord*. 2024;17(1):102–105. doi:10.14802/jmd.23125
93. Woitalla D, Buhmann C, Hilker-Roggendorf R, et al. Role of dopamine agonists in Parkinson's disease therapy. *J Neural Transm*. 2023;130(6):863–873. doi:10.1007/s00702-023-02647-0
94. Macerollo A, Zrinzo L, Akram H, Foltynie T, Limousin P. Subthalamic nucleus deep brain stimulation for Parkinson's disease: current trends and future directions. *Expert Rev Med Devices*. 2020;17(10):1063–1074. doi:10.1080/17434440.2020.1747433
95. Huang W, Zhang T, Li X, et al. Intranasal administration of umbilical cord mesenchymal stem cell exosomes alleviates parkinson's disease. *Neuroscience*. 2024;549:1–12. doi:10.1016/j.neuroscience.2024.04.010
96. He Y, Li R, Yu Y, et al. HucMSC extracellular vesicles increasing SATB 1 to activate the Wnt/beta-catenin pathway in 6-OHDA-induced Parkinson's disease model. *IUBMB Life*. 2024;76(12):1154–1174. doi:10.1002/iub.2893
97. Zhang ZX, Zhou YJ, Gu P, et al. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate Parkinson's disease and neuronal damage through inhibition of microglia. *Neural Regen Res*. 2023;18(10):2291–2300. doi:10.4103/1673-5374.368300
98. Chen HX, Liang FC, Gu P, et al. Exosomes derived from mesenchymal stem cells repair a Parkinson's disease model by inducing autophagy. *Cell Death Dis*. 2020;11(4):288. doi:10.1038/s41419-020-2473-5
99. Aliakbari F, Marzookian K, Parsafar S, et al. The impact of hUC MSC-derived exosome-nanoliposome hybrids on alpha-synuclein fibrillation and neurotoxicity. *Sci Adv*. 2024;10(14):eadl3406. doi:10.1126/sciadv.adl3406
100. Wang CC, Hu XM, Long YF, et al. Treatment of Parkinson's disease model with human umbilical cord mesenchymal stem cell-derived exosomes loaded with BDNF. *Life Sci*. 2024;356:123014. doi:10.1016/j.lfs.2024.123014
101. Vatsa P, Negi R, Ansari UA, Khanna VK, Pant AB. Insights of extracellular vesicles of mesenchymal stem cells: a prospective cell-free regenerative medicine for neurodegenerative disorders. *Mol Neurobiol*. 2022;59(1):459–474. doi:10.1007/s12035-021-02603-7
102. Ridley B, Nonino F, Baldin E, Casetta I, Iuliano G, Filippini G. Azathioprine for people with multiple sclerosis. *Cochrane Database Syst Rev*. 2024;12(12):CD015005. doi:10.1002/14651858.CD015005.pub2
103. Wiendl H, Gold R, Berger T, et al. Multiple sclerosis therapy consensus group (MSTCG): position statement on disease-modifying therapies for multiple sclerosis (white paper). *Ther Adv Neurol Disord*. 2021;14:17562864211039648. doi:10.1177/17562864211039648
104. Saleh SR, Ghareeb DA, Masoud AA, et al. Phoenix dactilyfera L. Pits extract restored bone homeostasis in glucocorticoid-induced osteoporotic animal model through the antioxidant effect and Wnt5a non-canonical signaling. *Antioxidants*. 2022;11(3). doi:10.3390/antiox11030508
105. Noto A, Cassin R, Mattiello V, Reda G. The role of novel agents in treating CLL-associated autoimmune hemolytic anemia. *J Clin Med*. 2021;10(10). doi:10.3390/jcm10102064
106. McGinley MP, Goldschmidt CH, Rae-Grant AD. Incorrect data in table. *JAMA*. 2021;325(21):2211. doi:10.1001/jama.2021.7928

107. Baharlooi H, Nouraei Z, Azimi M, et al. Umbilical cord mesenchymal stem cells as well as their released exosomes suppress proliferation of activated PBMCs in multiple sclerosis. *Scand J Immunol*. 2021;93(6):e13013. doi:10.1111/sji.13013
108. Baharlooi H, Salehi Z, Minbashi Moeini M, Rezaei N, Azimi M. Immunomodulatory potential of human mesenchymal stem cells and their exosomes on multiple sclerosis. *Adv Pharm Bull*. 2022;12(2):389–397. doi:10.34172/apb.2022.038
109. Jafarinia M, Farrokhi MR, Vakili S, et al. Harnessing the therapeutic potential of mesenchymal stem/stromal cell-derived extracellular vesicles as a novel cell-free therapy for animal models of multiple sclerosis. *Exp Neurol*. 2024;373:114674. doi:10.1016/j.expneurol.2023.114674
110. Qin D, Wang C, Li D, Guo S. Exosomal miR-23a-3p derived from human umbilical cord mesenchymal stem cells promotes remyelination in central nervous system demyelinating diseases by targeting Tbr1/Wnt pathway. *J Biol Chem*. 2024;300(1):105487. doi:10.1016/j.jbc.2023.105487
111. Mohammadzadeh A, Lahouty M, Charkhian H, et al. Human umbilical cord mesenchymal stem cell-derived exosomes alleviate the severity of experimental autoimmune encephalomyelitis and enhance lag-3 expression on foxp3 + CD4 + T cells. *Mol Biol Rep*. 2024;51(1):522. doi:10.1007/s11033-024-09433-5
112. Guan B, Anderson DB, Chen L, Feng S, Zhou H. Global, regional and national burden of traumatic brain injury and spinal cord injury, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *BMJ Open*. 2023;13(10):e075049. doi:10.1136/bmjopen-2023-075049
113. He W, Li ZQ, Gu HY, Pan QL, Lin FX. Targeted therapy of spinal cord injury: inhibition of apoptosis is a promising therapeutic strategy. *Mol Neurobiol*. 2024;61(7):4222–4239. doi:10.1007/s12035-023-03814-w
114. Clifford T, Finkel Z, Rodriguez B, Joseph A, Cai L. Current advancements in spinal cord injury research-glial scar formation and neural regeneration. *Cells*. 2023;12(6). doi:10.3390/cells12060853
115. Rai B, Singh V, Sutar R, Agrawal A. Prevalence and interventions for behavioral pathology in spinal cord injury. *Ind J Neurotrauma*. 2024. doi:10.1055/s-0044-1779429
116. Ahuja CS, Wilson JR, Nori S, et al. Traumatic spinal cord injury. *Nat Rev Dis Primers*. 2017;3:17018. doi:10.1038/nrdp.2017.18
117. Zkib J, Sattout R, Faour S, et al. Corticosteroid-induced bradycardia following high-dose methylprednisolone administration: a case report. *Ann Med Surg Lond*. 2024;86(10):6300–6302. doi:10.1097/MS9.0000000000002530
118. Assinck P, Duncan GJ, Hilton BJ, Plemel JR. Tetzlaff W: cell transplantation therapy for spinal cord injury. *Nat Neurosci*. 2017;20(5):637–647. doi:10.1038/nn.4541
119. Sun G, Li G, Li D, et al. hucMSC derived exosomes promote functional recovery in spinal cord injury mice via attenuating inflammation. *Mater Sci Eng C Mater Biol Appl*. 2018;89:194–204. doi:10.1016/j.msec.2018.04.006
120. Zhai X, Chen K, Yang H, et al. Extracellular vesicles derived from CD73 modified human umbilical cord mesenchymal stem cells ameliorate inflammation after spinal cord injury. *J Nanobiotechnol*. 2021;19(1):274. doi:10.1186/s12951-021-01022-z
121. Wang J, Wei Q, Yang Y, et al. Small extracellular vesicles derived from four dimensional-culture of mesenchymal stem cells induce alternatively activated macrophages by upregulating IGFBP2/EGFR to attenuate inflammation in the spinal cord injury of rats. *Front Bioeng Biotechnol*. 2023;11:1146981. doi:10.3389/fbioe.2023.1146981
122. Li M, Zhang T, Li P, et al. IL-4-primed human umbilical cord mesenchymal stem cells-derived extracellular vesicles facilitate recovery in spinal cord injury via the miR-21-5p/PDCD4-mediated shifting of macrophage M1/M2 polarization. *Life Sci*. 2025;364:123441. doi:10.1016/j.lfs.2025.123441
123. Yang C, Xu T, Lu Y, et al. Quercetin-loaded human umbilical cord mesenchymal stem cell-derived sEVs for spinal cord injury recovery. *Neuroscience*. 2024;552:14–28. doi:10.1016/j.neuroscience.2024.05.028
124. Kang J, Guo Y. Human Umbilical cord mesenchymal stem cells derived exosomes promote neurological function recovery in a rat spinal cord injury model. *Neurochem Res*. 2022;47(6):1532–1540. doi:10.1007/s11064-022-03545-9
125. Sun Y, Zhao J, Liu Q, et al. Intranasal delivery of small extracellular vesicles from specific subpopulation of mesenchymal stem cells mitigates traumatic spinal cord injury. *J Control Release*. 2024;369:335–350. doi:10.1016/j.jconrel.2024.03.037
126. Li L, Mu J, Zhang Y, et al. Stimulation by exosomes from hypoxia preconditioned human umbilical vein endothelial cells facilitates mesenchymal stem cells angiogenic function for spinal cord repair. *ACS Nano*. 2022;16(7):10811–10823. doi:10.1021/acsnano.2c02898
127. Poongodi R, Yang TH, Huang YH, et al. Stem cell exosome-loaded Gelfoam improves locomotor dysfunction and neuropathic pain in a rat model of spinal cord injury. *Stem Cell Res Ther*. 2024;15(1):143. doi:10.1186/s13287-024-03758-5
128. Hu X, Liu Z, Zhou X, et al. Small extracellular vesicles derived from mesenchymal stem cell facilitate functional recovery in spinal cord injury by activating neural stem cells via the ERK1/2 pathway. *Front Cell Neurosci*. 2022;16:954597. doi:10.3389/fncel.2022.954597
129. Akhlaghpasand M, Tavanaei R, Hosseinpoor M, et al. Safety and potential effects of intrathecal injection of allogeneic human umbilical cord mesenchymal stem cell-derived exosomes in complete subacute spinal cord injury: a first-in-human, single-arm, open-label, phase I clinical trial. *Stem Cell Res Ther*. 2024;15(1):264. doi:10.1186/s13287-024-03868-0
130. Ju Y, Hu Y, Yang P, Xie X, Fang B. Extracellular vesicle-loaded hydrogels for tissue repair and regeneration. *Mater Today Bio*. 2023;18:100522. doi:10.1016/j.mtbio.2022.100522
131. Huang JH, Xu Y, Yin XM, Lin FY. Exosomes derived from miR-126-modified MSCs promote angiogenesis and neurogenesis and attenuate apoptosis after spinal cord injury in rats. *Neuroscience*. 2020;424:133–145. doi:10.1016/j.neuroscience.2019.10.043
132. Xiao X, Li W, Rong D, et al. Human umbilical cord mesenchymal stem cells-derived extracellular vesicles facilitate the repair of spinal cord injury via the miR-29b-3p/PTEN/Akt/mTOR axis. *Cell Death Discov*. 2021;7(1):212. doi:10.1038/s41420-021-00572-3
133. Zhang L, Fan C, Hao W, et al. NSCs migration promoted and drug delivered exosomes-collagen scaffold via a bio-specific peptide for one-step spinal cord injury repair. *Adv Healthc Mater*. 2021;10(8):e2001896. doi:10.1002/adhm.202001896
134. Li K, Liu Z, Wu P, et al. Micro electrical fields induced MSC-sEVs attenuate neuronal cell apoptosis by activating autophagy via lncRNA MALAT1/miR-22-3p/SIRT1/AMPK axis in spinal cord injury. *J Nanobiotechnol*. 2023;21(1):451. doi:10.1186/s12951-023-02217-2
135. Xue C, Ma X, Guan X, Feng H, Zheng M, Yang X. Small extracellular vesicles derived from umbilical cord mesenchymal stem cells repair blood-spinal cord barrier disruption after spinal cord injury through down-regulation of Endothelin-1 in rats. *PeerJ*. 2023;11:e16311. doi:10.7717/peerj.16311
136. Xie Y, Sun Y, Liu Y, et al. Targeted delivery of RGD-CD146(+)CD271(+) Human umbilical cord mesenchymal stem cell-derived exosomes promotes blood-spinal cord barrier repair after spinal cord injury. *ACS Nano*. 2023;17(18):18008–18024. doi:10.1021/acsnano.3c04423
137. Xiao Y, Hu X, Jiang P, Qi Z. Thermos-responsive hydrogel system encapsulated engineered exosomes attenuate inflammation and oxidative damage in acute spinal cord injury. *Front Bioeng Biotechnol*. 2023;11:1216878. doi:10.3389/fbioe.2023.1216878

138. Wang X, Li W, Hao M, Yang Y, Xu Y. Hypoxia-treated umbilical mesenchymal stem cell alleviates spinal cord ischemia-reperfusion injury in SCI by circular RNA circOXNAD1/ miR-29a-3p/ FOXO3a axis. *Biochem Biophys Rep*. 2023;34:101458. doi:10.1016/j.bbrep.2023.101458
139. Li L, Chu Z, Li S, et al. BDNF-loaded chitosan-based mimetic mussel polymer conduits for repair of peripheral nerve injury. *Front Cell Dev Biol*. 2024;12:1431558. doi:10.3389/fcell.2024.1431558
140. Yu C, Wang X, Qin J. Effect of necrostatin-1 on sciatic nerve crush injury in rat models. *J Orthop Surg Res*. 2023;18(1):74. doi:10.1186/s13018-023-03565-3
141. Lk L, Huang WC, Hsueh YY, et al. Intramuscular delivery of neural crest stem cell spheroids enhances neuromuscular regeneration after denervation injury. *Stem Cell Res Ther*. 2022;13(1):205. doi:10.1186/s13287-022-02877-1
142. Zhang X, Xiu X, Wang P, Han Y, Chang W, Zhao J. Intraoperative electrical stimulation promotes the short-term recovery of patients with cubital tunnel syndrome after surgery. *J Orthop Surg Res*. 2023;18(1):270. doi:10.1186/s13018-023-03668-x
143. Liu Z, Wang H, Yu T, et al. A review on the mechanism of tuina promoting the recovery of peripheral nerve injury. *Evid Based Complement Alternat Med*. 2021;2021:6652099. doi:10.1155/2021/6652099
144. Yi-Zhen L, Run-Pei M, Tian-Yuan Y, et al. Mild mechanic stimulate on acupoints regulation of CGRP-positive cells and microglia morphology in spinal cord of sciatic nerve injured rats. *Front Integr Neurosci*. 2019;13:58. doi:10.3389/fnint.2019.00058
145. Fan N, Song D, Ding H, et al. E-jet 3D printed aligned nerve guidance conduits incorporated with decellularized extracellular matrix hydrogel encapsulating extracellular vesicles for peripheral nerve repair. *Acta Biomater*. 2025;194:122–139. doi:10.1016/j.actbio.2025.01.025
146. Ma Y, Zhou D, Zhang H, Tang L, Qian F, Su J. Human Umbilical cord mesenchymal stem cell-derived extracellular vesicles promote the proliferation of schwann cells by regulating the PI3K/AKT signaling pathway via transferring miR-21. *Stem Cells Int*. 2021;2021:1496101. doi:10.1155/2021/1496101
147. Zhu Z, Zhang Y, Huang Z, Hao H, Yan M. Hypoxic culture of umbilical cord mesenchymal stem cell-derived sEVs prompts peripheral nerve injury repair. *Front Cell Neurosci*. 2022;16:897224. doi:10.3389/fncel.2022.897224
148. Zhang Y, Wang WT, Gong CR, Li C, Shi M. Combination of olfactory ensheathing cells and human umbilical cord mesenchymal stem cell-derived exosomes promotes sciatic nerve regeneration. *Neural Regen Res*. 2020;15(10):1903–1911. doi:10.4103/1673-5374.280330
149. Ma Y, Dong L, Zhou D, et al. Extracellular vesicles from human umbilical cord mesenchymal stem cells improve nerve regeneration after sciatic nerve transection in rats. *J Cell Mol Med*. 2019;23(4):2822–2835. doi:10.1111/jcmm.14190
150. Tang H, Li J, Wang H, et al. Human umbilical cord mesenchymal stem cell-derived exosomes loaded into a composite conduit promote functional recovery after peripheral nerve injury in rats. *Neural Regen Res*. 2024;19(4):900–907. doi:10.4103/1673-5374.380911
151. Chen J, Zhu Y, Gao H, et al. HucMSCs delay muscle atrophy after peripheral nerve injury through exosomes by repressing muscle-specific ubiquitin ligases. *Stem Cells*. 2024;42(5):460–474. doi:10.1093/stmcls/sxae017
152. Bu Z, Jing J, Liu W, et al. Treatment of denervated muscle atrophy by injectable dual-responsive hydrogels loaded with extracellular vesicles. *Adv Sci*. 2025:e2412248. doi:10.1002/advs.202412248.
153. Yueh PF, Chiang IT, Weng YS, et al. Innovative dual-gene delivery platform using miR-124 and PD-1 via umbilical cord mesenchymal stem cells and exosome for glioblastoma therapy. *J Exp Clin Cancer Res*. 2025;44(1):107. doi:10.1186/s13046-025-03336-4
154. Pavon LF, Sibov TT, de Souza AV, et al. Tropism of mesenchymal stem cell toward CD133(+) stem cell of glioblastoma in vitro and promote tumor proliferation in vivo. *Stem Cell Res Ther*. 2018;9(1):310. doi:10.1186/s13287-018-1049-0
155. Tibensky M, Jakubechova J, Altanerova U, et al. Gene-directed enzyme/prodrug therapy of rat brain tumor mediated by human mesenchymal stem cell suicide gene extracellular vesicles in vitro and in vivo. *Cancers*. 2022;14(3). doi:10.3390/cancers14030735
156. Del Fattore A, Luciano R, Saracino R, et al. Differential effects of extracellular vesicles secreted by mesenchymal stem cells from different sources on glioblastoma cells. *Expert Opin Biol Ther*. 2015;15(4):495–504. doi:10.1517/14712598.2015.997706
157. Stover DA, Housman G, Stone AC, Rosenberg MS, Verrelli BC. Evolutionary genetic signatures of selection on bone-related variation within human and chimpanzee populations. *Genes*. 2022;13(2). doi:10.3390/genes13020183
158. Zhang W, Zhang W, Huo L, et al. Rosavin suppresses osteoclastogenesis in vivo and in vitro by blocking the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) and mitogen-activated protein kinase (MAPK) signaling pathways. *Ann Transl Med*. 2021;9(5):383. doi:10.21037/atm-20-4255
159. Wang T, He C. Pro-inflammatory cytokines: the link between obesity and osteoarthritis. *Cytokine Growth Factor Rev*. 2018;44:38–50. doi:10.1016/j.cytogfr.2018.10.002
160. Ma Y, Lin Y, Zhang Y, Ding X, Zhang Y. Effects of osteogenic growth peptide C-terminal pentapeptide and its analogue on bone remodeling in an osteoporosis rat model. *Open Med*. 2023;18(1):20230656. doi:10.1515/med-2023-0656
161. Guo S, Zhao G, Chen XM, et al. Effect of transcutaneous electrical acupoint stimulation on bone metabolism in patients with immobilisation after foot and ankle fracture surgery: a randomised controlled trial study protocol. *BMJ Open*. 2022;12(9):e056691. doi:10.1136/bmjopen-2021-056691
162. Liu P, Qiao YJ, Lou JP, Cao G, Chang Y, Zhou SH. Cementless total Hip arthroplasty for treatment of acetabular protrusion secondary to rheumatoid arthritis. *J Orthop Surg Res*. 2023;18(1):282. doi:10.1186/s13018-023-03764-y
163. Chen R, Hao Z, Wang Y, et al. Mesenchymal stem cell-immune cell interaction and related modulations for bone tissue engineering. *Stem Cells Int*. 2022;2022:7153584. doi:10.1155/2022/7153584
164. Dimitriou R, Mataliotakis GI, Angoules AG, Kanakaris NK, Giannoudis PV. Complications following autologous bone graft harvesting from the iliac crest and using the RIA: a systematic review. *Injury*. 2011;42 Suppl 2:S3–15. doi:10.1016/j.injury.2011.06.015
165. Yang BC, Kuang MJ, Kang JY, Zhao J, Ma JX, Ma XL. Human umbilical cord mesenchymal stem cell-derived exosomes act via the miR-1263/ Mob1/Hippo signaling pathway to prevent apoptosis in disuse osteoporosis. *Biochem Biophys Res Commun*. 2020;524(4):883–889. doi:10.1016/j.bbrc.2020.02.001
166. Yahao G, Xinjia W. The role and mechanism of exosomes from umbilical cord mesenchymal stem cells in inducing osteogenesis and preventing osteoporosis. *Cell Transplant*. 2021;30:9636897211057465. doi:10.1177/09636897211057465
167. Hu Y, Zhang Y, Cy N, et al. Human umbilical cord mesenchymal stromal cells-derived extracellular vesicles exert potent bone protective effects by CLEC11A-mediated regulation of bone metabolism. *Theranostics*. 2020;10(5):2293–2308. doi:10.7150/thno.39238
168. Wang L, Wang J, Zhou X, et al. A New self-healing hydrogel containing hucMSC-derived exosomes promotes bone regeneration. *Front Bioeng Biotechnol*. 2020;8:564731. doi:10.3389/fbioe.2020.564731

169. Hu H, Zhang H, Bu Z, et al. Small extracellular vesicles released from bioglass/hydrogel scaffold promote vascularized bone regeneration by transferring miR-23a-3p. *Int J Nanomed*. 2022;17:6201–6220. doi:10.2147/IJN.S389471
170. Zhang Y, Hao Z, Wang P, et al. Exosomes from human umbilical cord mesenchymal stem cells enhance fracture healing through HIF-1alpha-mediated promotion of angiogenesis in a rat model of stabilized fracture. *Cell Prolif*. 2019;52(2):e12570. doi:10.1111/cpr.12570
171. Malekpour K, Hazrati A, Zahar M, et al. The potential use of mesenchymal stem cells and their derived exosomes for orthopedic diseases treatment. *Stem Cell Rev Rep*. 2022;18(3):933–951. doi:10.1007/s12015-021-10185-z
172. Deluca A, Wagner A, Heimel P, et al. Synergistic effect of umbilical cord extracellular vesicles and rhBMP-2 to enhance the regeneration of a metaphyseal femoral defect in osteoporotic rats. *Stem Cell Res Ther*. 2024;15(1):144. doi:10.1186/s13287-024-03755-8
173. Yang S, Zhu B, Yin P, et al. Integration of human umbilical cord mesenchymal stem cells-derived exosomes with hydroxyapatite-embedded hyaluronic acid-alginate hydrogel for bone regeneration. *ACS Biomater Sci Eng*. 2020;6(3):1590–1602. doi:10.1021/acsbiomaterials.9b01363
174. Zhang Y, Xie Y, Hao Z, et al. Umbilical mesenchymal stem cell-derived exosome-encapsulated hydrogels accelerate bone repair by enhancing angiogenesis. *ACS Appl Mater Interfaces*. 2021;13(16):18472–18487. doi:10.1021/acsami.0c22671
175. Collaborators GBDO. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the global burden of disease study 2021. *Lancet Rheumatol*. 2023;5(9):e508–e522. doi:10.1016/S2665-9913(23)00163-7.
176. Collaborators GBDRA. Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the global burden of disease study 2021. *Lancet Rheumatol*. 2023;5(10):e594–e610. doi:10.1016/S2665-9913(23)00211-4.
177. Zhang S, Ren Q, Qi H, Liu S, Liu Y. Adverse effects of fine-particle exposure on joints and their surrounding cells and microenvironment. *ACS Nano*. 2019;13(3):2729–2748. doi:10.1021/acsnano.8b08517
178. Iwaszko M, Wielinska J, Swierkot J, et al. IL-33 gene polymorphisms as potential biomarkers of disease susceptibility and response to TNF inhibitors in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis patients. *Front Immunol*. 2021;12:631603. doi:10.3389/fimmu.2021.631603
179. Lee YT, Mohd Yunus MH, Yazid MD, Ugusman A. Unraveling the path to osteoarthritis management: targeting chondrocyte apoptosis for therapeutic intervention. *Front Cell Dev Biol*. 2024;12:1347126. doi:10.3389/fcell.2024.1347126
180. Rodriguez-Merchan EC. Treatment of musculo-skeletal pain in haemophilia. *Blood Rev*. 2018;32(2):116–121. doi:10.1016/j.blre.2017.09.004
181. Baxter-Parker G, Roffe L, Cross S, Frampton C, Hooper GJ, Gieseg SP. Knee replacement surgery significantly elevates the urinary inflammatory biomarkers neopterin and 7,8-dihydroneopterin. *Clin Biochem*. 2019;63:39–45. doi:10.1016/j.clinbiochem.2018.11.002
182. Li K, Yan G, Huang H, et al. Anti-inflammatory and immunomodulatory effects of the extracellular vesicles derived from human umbilical cord mesenchymal stem cells on osteoarthritis via M2 macrophages. *J Nanobiotechnol*. 2022;20(1):38. doi:10.1186/s12951-021-01236-1
183. Figueroa-Valdes AI, Luz-Crawford P, Herrera-Luna Y, et al. Clinical-grade extracellular vesicles derived from umbilical cord mesenchymal stromal cells: preclinical development and first-in-human intra-articular validation as therapeutics for knee osteoarthritis. *J Nanobiotechnol*. 2025;23(1):13. doi:10.1186/s12951-024-03088-x
184. Nguyen TH, Dao HH, Duong CM, et al. Cytokine-primed umbilical cord mesenchymal stem cells enhanced therapeutic effects of extracellular vesicles on osteoarthritic chondrocytes. *Front Immunol*. 2022;13:1041592. doi:10.3389/fimmu.2022.1041592
185. Jenner F, Wagner A, Gerner I, et al. Evaluation of the potential of umbilical cord mesenchymal stromal cell-derived small extracellular vesicles to improve rotator cuff healing: a pilot ovine study. *Am J Sports Med*. 2023;51(2):331–342. doi:10.1177/03635465221145958
186. Li X, Wang Y, Cai Z, Zhou Q, Li L, Fu P. Exosomes from human umbilical cord mesenchymal stem cells inhibit ROS production and cell apoptosis in human articular chondrocytes via the miR-100-5p/NOX4 axis. *Cell Biol Int*. 2021;45(10):2096–2106. doi:10.1002/cbin.11657
187. Wu KC, Yang HI, Chang YH, Chiang RY, Ding DC. Extracellular vesicles derived from human umbilical mesenchymal stem cells transfected with miR-7704 improved damaged cartilage and reduced matrix metallopeptidase 13. *Cells*. 2025;14(2). doi:10.3390/cells14020082
188. Chen Z, Zhou T, Luo H, et al. HWJMSC-EVs promote cartilage regeneration and repair via the ITGB1/TGF-beta/Smad2/3 axis mediated by microfractures. *J Nanobiotechnol*. 2024;22(1):177. doi:10.1186/s12951-024-02451-2
189. Wang S, Jiang W, Lv S, et al. Human umbilical cord mesenchymal stem cells-derived exosomes exert anti-inflammatory effects on osteoarthritis chondrocytes. *Aging*. 2023;15(18):9544–9560. doi:10.18632/aging.205034
190. Tang S, Chen P, Zhang H, et al. Comparison of curative effect of human umbilical cord-derived mesenchymal stem cells and their small extracellular vesicles in treating osteoarthritis. *Int J Nanomed*. 2021;16:8185–8202. doi:10.2147/IJN.S336062
191. Zhang W, Li S, Peng Y, et al. Three-dimensional cell culture-derived extracellular vesicles loaded alginate/hyaluronic acid composite scaffold as an optimal therapy for cartilage defect regeneration. *Biomed Mater*. 2025;20(2). doi:10.1088/1748-605X/adb22e
192. Zhang Q, Cao L, Zou S, et al. Human umbilical cord mesenchymal stem cell-derived extracellular vesicles carrying MicroRNA-181c-5p Promote BMP2-induced repair of cartilage injury through inhibition of SMAD7 expression. *Stem Cells Int*. 2022;2022:1157498. doi:10.1155/2022/1157498
193. Hu H, Dong L, Bu Z, et al. Liu Z: miR-23a-3p-abundant small extracellular vesicles released from Gelma/nanoclay hydrogel for cartilage regeneration. *J Extracell Vesicles*. 2020;9(1):1778883. doi:10.1080/20013078.2020.1778883
194. Jy K, Sy L, Sg C, et al. Combinatory nanovesicle with siRNA-Loaded extracellular vesicle and IGF-1 for osteoarthritis treatments. *Int J Mol Sci*. 2024;25(10). doi:10.3390/ijms25105242
195. Cao H, Chen M, Cui X, et al. Cell-free osteoarthritis treatment with sustained-release of chondrocyte-targeting exosomes from umbilical cord-derived mesenchymal stem cells to rejuvenate aging chondrocytes. *ACS Nano*. 2023;17(14):13358–13376. doi:10.1021/acsnano.3c01612
196. Klyucherev TO, Peshkova MA, Revokatova DP, et al. The therapeutic potential of exosomes vs. matrix-bound nanovesicles from human umbilical cord mesenchymal stromal cells in osteoarthritis treatment. *Int J Mol Sci*. 2024;25(21). doi:10.3390/ijms252111564
197. Jiang S, Tian G, Yang Z, et al. Enhancement of acellular cartilage matrix scaffold by Wharton's jelly mesenchymal stem cell-derived exosomes to promote osteochondral regeneration. *Bioact Mater*. 2021;6(9):2711–2728. doi:10.1016/j.bioactmat.2021.01.031
198. Morente-Lopez M, Mato-Basalo R, Lucio-Gallego S, et al. Therapy free of cells vs human mesenchymal stem cells from umbilical cord stroma to treat the inflammation in OA. *Cell Mol Life Sci*. 2022;79(11):557. doi:10.1007/s00018-022-04580-z
199. Kang S, Shi X, Chen Y, et al. Injectable decellularized Wharton's jelly hydrogel containing CD56(+) umbilical cord mesenchymal stem cell-derived exosomes for meniscus tear healing and cartilage protection. *Mater Today Bio*. 2024;29:101258. doi:10.1016/j.mtbio.2024.101258
200. Ma D, Wu Z, Zhao X, et al. Immunomodulatory effects of umbilical mesenchymal stem cell-derived exosomes on CD4(+) T cells in patients with primary Sjogren's syndrome. *Inflammopharmacology*. 2023;31(4):1823–1838. doi:10.1007/s10787-023-01189-x

201. Fu Y, Li J, Zhang Z, et al. Umbilical cord mesenchymal stem cell-derived exosomes alleviate collagen-induced arthritis by balancing the population of Th17 and regulatory T cells. *FEBS Lett*. 2022;596(20):2668–2677. doi:10.1002/1873-3468.14460
202. Xu K, Ma D, Zhang G, et al. Human umbilical cord mesenchymal stem cell-derived small extracellular vesicles ameliorate collagen-induced arthritis via immunomodulatory T lymphocytes. *Mol Immunol*. 2021;135:36–44. doi:10.1016/j.molimm.2021.04.001
203. Zhou Z, Li Y, Wu S, Liu T, Jiang J. Host-microbiota interactions in collagen-induced arthritis rats treated with human umbilical cord mesenchymal stem cell exosome and ginsenoside Rh2. *Biomed Pharmacother*. 2024;174:116515. doi:10.1016/j.biopha.2024.116515
204. Mi L, Gao J, Li N, et al. Human umbilical cord mesenchymal stem cell-derived exosomes loaded miR-451a targets ATF2 to improve rheumatoid arthritis. *Int Immunopharmacol*. 2024;127:111365. doi:10.1016/j.intimp.2023.111365
205. Huang Y, Chen L, Chen D, Fan P, Yu H. Exosomal microRNA-140-3p from human umbilical cord mesenchymal stem cells attenuates joint injury of rats with rheumatoid arthritis by silencing SGK1. *Mol Med*. 2022;28(1):36. doi:10.1186/s10020-022-00451-2
206. Hyland M, Mennan C, Davies R, et al. Extracellular vesicles derived from umbilical cord mesenchymal stromal cells show enhanced anti-inflammatory properties via upregulation of miRNAs after pro-inflammatory priming. *Stem Cell Rev Rep*. 2023;19(7):2391–2406. doi:10.1007/s12015-023-10586-2
207. Ma H, Jing Y, Zeng J, et al. Human umbilical cord mesenchymal stem cell-derived exosomes ameliorate muscle atrophy via the miR-132-3p/FoxO3 axis. *J Orthop Translat*. 2024;49:23–36. doi:10.1016/j.jot.2024.08.005
208. Hu H, Yin Y, Zhou H, et al. Umbilical cord mesenchymal stem cell-derived exosomal Follistatin inhibits fibrosis and promotes muscle regeneration in mice by influencing Smad2 and AKT signaling. *Exp Cell Res*. 2025;444(2):114396. doi:10.1016/j.yexcr.2024.114396
209. Yao Z, Li J, Xiong H, et al. MicroRNA engineered umbilical cord stem cell-derived exosomes direct tendon regeneration by mTOR signaling. *J Nanobiotechnol*. 2021;19(1):169. doi:10.1186/s12951-021-00906-4
210. Kim H, Shim IK, Choi JH, et al. Extracellular vesicles delivered by injectable collagen promote bone-tendon interface healing and prevent fatty degeneration of rotator cuff muscle. *Arthroscopy*. 2022;38(7):2142–2153. doi:10.1016/j.arthro.2022.01.008
211. Chang X, Ma Z, Zhu G, Lu Y, Yang J. New perspective into mesenchymal stem cells: molecular mechanisms regulating osteosarcoma. *J Bone Oncol*. 2021;29:100372. doi:10.1016/j.jbo.2021.100372
212. Abello J, Nguyen TDT, Marasini R, Aryal S, Weiss ML. Biodistribution of gadolinium- and near infrared-labeled human umbilical cord mesenchymal stromal cell-derived exosomes in tumor bearing mice. *Theranostics*. 2019;9(8):2325–2345. doi:10.7150/thno.30030
213. Chu M, Wang H, Bian L, et al. Nebulization therapy with umbilical cord mesenchymal stem cell-derived exosomes for COVID-19 pneumonia. *Stem Cell Rev Rep*. 2022;18(6):2152–2163. doi:10.1007/s12015-022-10398-w
214. Oh SJ, Lee EN, Park JH, et al. Anti-viral activities of umbilical cord mesenchymal stem cell-derived small extracellular vesicles against human respiratory viruses. *Front Cell Infect Microbiol*. 2022;12:850744. doi:10.3389/fcimb.2022.850744
215. Warrier S, Sundaram mohana S, Varier L, Balasubramanian A. Stalling SARS-CoV2 infection with stem cells: can regenerating perinatal tissue mesenchymal stem cells offer a multi-tiered therapeutic approach to COVID-19? *Placenta*. 2022;117:161–168. doi:10.1016/j.placenta.2021.12.005
216. Schultz IC, Bertoni APS, Wink MR. Mesenchymal stem cell-derived extracellular vesicles carrying mirna as a potential multi target therapy to COVID-19: an in silico analysis. *Stem Cell Rev Rep*. 2021;17(2):341–356. doi:10.1007/s12015-021-10122-0
217. Pei Z, Cen J, Zhang X, et al. MiR-146a-5p delivered by hucMSC extracellular vesicles modulates the inflammatory response to sulfur mustard-induced acute lung injury. *Stem Cell Res Ther*. 2023;14(1):149. doi:10.1186/s13287-023-03375-8
218. Liu J, Xing F, Fu Q, et al. hUC-MSCs exosomal miR-451 alleviated acute lung injury by modulating macrophage M2 polarization via regulating MIF-PI3K-AKT signaling pathway. *Environ Toxicol*. 2022;37(12):2819–2831. doi:10.1002/tox.23639
219. Liu JS, Du J, Cheng X, Zhang XZ, Li Y, Chen XL. Exosomal miR-451 from human umbilical cord mesenchymal stem cells attenuates burn-induced acute lung injury. *J Chin Med Assoc*. 2019;82(12):895–901. doi:10.1097/JCMA.0000000000000189
220. Gong C, Gu Z, Zhang X, et al. HMSCs exosome-derived miR-199a-5p attenuates sulfur mustard-associated oxidative stress via the CAV1/NRF2 signalling pathway. *J Cell Mol Med*. 2023;27(15):2165–2182. doi:10.1111/jcmm.17803
221. Li L, Song QQ, Li SR, et al. Human umbilical cord mesenchymal stem cells-derived exosomes attenuate burn-induced acute lung injury via inhibiting ferroptosis. *Acta Histochem*. 2024;126(5–7):152189. doi:10.1016/j.acthis.2024.152189
222. Zhang WY, Wen L, Du L, et al. S-RBD-modified and miR-486-5p-engineered exosomes derived from mesenchymal stem cells suppress ferroptosis and alleviate radiation-induced lung injury and long-term pulmonary fibrosis. *J Nanobiotechnol*. 2024;22(1):662. doi:10.1186/s12951-024-02830-9
223. Stone ML, Zhao Y, Robert Smith J, et al. Mesenchymal stromal cell-derived extracellular vesicles attenuate lung ischemia-reperfusion injury and enhance reconditioning of donor lungs after circulatory death. *Respir Res*. 2017;18(1):212. doi:10.1186/s12931-017-0704-9
224. Gonzalez H, McCarthy S, Masterson C, et al. Nebulised mesenchymal stem cell derived extracellular vesicles ameliorate E. coli induced pneumonia in a rodent model. *Stem Cell Res Ther*. 2023;14(1):151. doi:10.1186/s13287-023-03385-6
225. Loy H, Kuok DIT, Hui KPY, et al. Therapeutic implications of human umbilical cord mesenchymal stromal cells in attenuating influenza A (H5N1) virus-associated acute lung injury. *J Infect Dis*. 2019;219(2):186–196. doi:10.1093/infdis/jiy478
226. Wang C, Yang Y, Jiang C, et al. Exosomes derived from hucMSCs primed with IFN-gamma Suppress the NF-kappaB signal pathway in LPS-induced ALI by modulating the miR-199b-5p/AFTPH axis. *Cell Biochem Biophys*. 2024;82(2):647–658. doi:10.1007/s12013-023-01208-2
227. Wei X, Yi X, Lv H, et al. MicroRNA-377-3p released by mesenchymal stem cell exosomes ameliorates lipopolysaccharide-induced acute lung injury by targeting RPTOR to induce autophagy. *Cell Death Dis*. 2020;11(8):657. doi:10.1038/s41419-020-02857-4
228. Jia ZG, Li L, Zhao P, et al. MicroRNA-451 from human umbilical cord-derived mesenchymal stem cell exosomes inhibits alveolar macrophage autophagy via tuberous sclerosis complex 1/mammalian target of rapamycin pathway to attenuate burn-induced acute lung injury in rats. *Biomed Environ Sci*. 2024;37(9):1030–1043. doi:10.3967/bes2024.128
229. Costa-Ferro ZSM, Rocha GV, da Silva KN, et al. GMP-compliant extracellular vesicles derived from umbilical cord mesenchymal stromal cells: manufacturing and pre-clinical evaluation in ARDS treatment. *Cytotherapy*. 2024;26(9):1013–1025. doi:10.1016/j.jcyt.2024.04.074
230. Wang C, Jiang C, Yang Y, et al. Therapeutic potential of HUC-MSC-exos primed with IFN-gamma against LPS-induced acute lung injury. *Iran J Basic Med Sci*. 2024;27(3):375–382. doi:10.22038/IJBMS.2023.74372.16156
231. Huang Y, Li G, Chen Z, et al. Exosomal drug delivery systems: a novel therapy targeting PD-1 in septic-ALI. *Stem Cell Rev Rep*. 2024;20(8):2253–2267. doi:10.1007/s12015-024-10784-6

232. Varkouhi AK, Jerkic M, Ormesher L, et al. Extracellular vesicles from interferon-gamma-primed human umbilical cord mesenchymal stromal cells reduce escherichia coli-induced acute lung injury in rats. *Anesthesiology*. 2019;130(5):778–790. doi:10.1097/ALN.0000000000002655
233. Ridzuan N, Zakaria N, Widera D, et al. Human umbilical cord mesenchymal stem cell-derived extracellular vesicles ameliorate airway inflammation in a rat model of chronic obstructive pulmonary disease (COPD). *Stem Cell Res Ther*. 2021;12(1):54. doi:10.1186/s13287-020-02088-6
234. Chen Q, Lin J, Deng Z, Qian W. Exosomes derived from human umbilical cord mesenchymal stem cells protect against papain-induced emphysema by preventing apoptosis through activating VEGF-VEGFR2-mediated AKT and MEK/ERK pathways in rats. *Regen Ther*. 2022;21:216–224. doi:10.1016/j.reth.2022.07.002
235. Dong B, Wang C, Zhang J, et al. Exosomes from human umbilical cord mesenchymal stem cells attenuate the inflammation of severe steroid-resistant asthma by reshaping macrophage polarization. *Stem Cell Res Ther*. 2021;12(1):204. doi:10.1186/s13287-021-02244-6
236. Fang SB, Zhang HY, Wang C, et al. Small extracellular vesicles derived from human mesenchymal stromal cells prevent group 2 innate lymphoid cell-dominant allergic airway inflammation through delivery of miR-146a-5p. *J Extracell Vesicles*. 2020;9(1):1723260. doi:10.1080/20013078.2020.1723260
237. Ma Y, Liu X, Long Y, Chen Y. Emerging therapeutic potential of mesenchymal stem cell-derived extracellular vesicles in chronic respiratory diseases: an overview of recent progress. *Front Bioeng Biotechnol*. 2022;10:845042. doi:10.3389/fbioe.2022.845042
238. Luo X, Wang Y, Mao Y, et al. Nebulization of hypoxic hUCMSC-EVs attenuates airway epithelial barrier defects in chronic asthma mice by transferring CAV-1. *Int J Nanomed*. 2024;19:10941–10959. doi:10.2147/IJN.S476151
239. Xu X, Wang Y, Luo X, et al. A non-invasive strategy for suppressing asthmatic airway inflammation and remodeling: inhalation of nebulized hypoxic hUCMSC-derived extracellular vesicles. *Front Immunol*. 2023;14:1150971. doi:10.3389/fimmu.2023.1150971
240. Liu J, Xu Z, Yu J, et al. MiR-146a-5p engineered hucMSC-derived extracellular vesicles attenuate Dermatophagoides farinae-induced allergic airway epithelial cell inflammation. *Front Immunol*. 2024;15:1443166. doi:10.3389/fimmu.2024.1443166
241. Jiang Q, Zhao J, Jia Q, et al. MiR-148a-3p within HucMSC-derived extracellular vesicles suppresses Hsp90b1 to prevent fibroblast collagen synthesis and secretion in silica-induced pulmonary fibrosis. *Int J Mol Sci*. 2023;24(19). doi:10.3390/ijms241914477
242. Xu C, Hou L, Zhao J, et al. Exosomal let-7i-5p from three-dimensional cultured human umbilical cord mesenchymal stem cells inhibits fibroblast activation in silicosis through targeting TGFBR1. *Ecotoxicol Environ Saf*. 2022;233:113302. doi:10.1016/j.ecoenv.2022.113302
243. Hou L, Zhu Z, Jiang F, et al. Human umbilical cord mesenchymal stem cell-derived extracellular vesicles alleviated silica induced lung inflammation and fibrosis in mice via circPWWP2A/miR-223-3p/NLRP3 axis. *Ecotoxicol Environ Saf*. 2023;251:114537. doi:10.1016/j.ecoenv.2023.114537
244. Zhao J, Jiang Q, Xu C, et al. MiR-26a-5p from HucMSC-derived extracellular vesicles inhibits epithelial mesenchymal transition by targeting Adam17 in silica-induced lung fibrosis. *Ecotoxicol Environ Saf*. 2023;257:114950. doi:10.1016/j.ecoenv.2023.114950
245. Xu C, Zhao J, Li Q, et al. Exosomes derived from three-dimensional cultured human umbilical cord mesenchymal stem cells ameliorate pulmonary fibrosis in a mouse silicosis model. *Stem Cell Res Ther*. 2020;11(1):503. doi:10.1186/s13287-020-02023-9
246. Arefnezhad R, Helfi M, Okhravijouybari R, et al. Umbilical cord mesenchymal stem cells and lung cancer: we should be hopeful or hopeless? *Tissue Cell*. 2024;88:102410. doi:10.1016/j.tice.2024.102410
247. Dong L, Pu Y, Zhang L, et al. Human umbilical cord mesenchymal stem cell-derived extracellular vesicles promote lung adenocarcinoma growth by transferring miR-410. *Cell Death Dis*. 2018;9(2):218. doi:10.1038/s41419-018-0323-5
248. Zhao X, Wu X, Qian M, Song Y, Wu D, Zhang W. Knockdown of TGF-beta1 expression in human umbilical cord mesenchymal stem cells reverts their exosome-mediated EMT promoting effect on lung cancer cells. *Cancer Lett*. 2018;428:34–44. doi:10.1016/j.canlet.2018.04.026
249. Xie H, Wang J. MicroRNA-320a-containing exosomes from human umbilical cord mesenchymal stem cells curtail proliferation and metastasis in lung cancer by binding to SOX4. *J Recept Signal Transduction Res*. 2022;42(3):268–278. doi:10.1080/10799893.2021.1918166
250. Liu G, Garcia Cenador MB, Si S, Wang H, Yang Q. Influences of umbilical cord mesenchymal stem cells and their exosomes on tumor cell phenotypes. *Am J Cancer Res*. 2023;13(12):6270–6279.
251. Patel AA, Mohamed AH, Rizaev J, et al. Application of mesenchymal stem cells derived from the umbilical cord or Wharton's jelly and their extracellular vesicles in the treatment of various diseases. *Tissue Cell*. 2024;89:102415. doi:10.1016/j.tice.2024.102415
252. Gu X, Li Y, Chen K, et al. Exosomes derived from umbilical cord mesenchymal stem cells alleviate viral myocarditis through activating AMPK/mTOR-mediated autophagy flux pathway. *J Cell Mol Med*. 2020;24(13):7515–7530. doi:10.1111/jcmm.15378
253. Gao T, Fan H, Wang J, Wang R. Extracellular vesicles derived from human umbilical cord mesenchymal stem cells stimulate angiogenesis in myocardial infarction via the microRNA-423-5p/EFNA3 axis. *Postepy Kardiol Interwencyjnej*. 2022;18(4):373–391. doi:10.5114/aic.2023.124797
254. Song Y, Wang B, Zhu X, et al. Human umbilical cord blood-derived MSCs exosome attenuate myocardial injury by inhibiting ferroptosis in acute myocardial infarction mice. *Cell Biol Toxicol*. 2021;37(1):51–64. doi:10.1007/s10565-020-09530-8
255. Zhu W, Sun L, Zhao P, et al. Macrophage migration inhibitory factor facilitates the therapeutic efficacy of mesenchymal stem cells derived exosomes in acute myocardial infarction through upregulating miR-133a-3p. *J Nanobiotechnol*. 2021;19(1):61. doi:10.1186/s12951-021-00808-5
256. Zhong Z, Tian Y, Luo X, Zou J, Wu L, Tian J. Extracellular Vesicles derived from human umbilical cord mesenchymal stem cells protect against DOX-induced heart failure through the miR-100-5p/NOX4 pathway. *Front Bioeng Biotechnol*. 2021;9:703241. doi:10.3389/fbioe.2021.703241
257. Zhang C, Wang H, Chan GCF, Zhou Y, Lai X, Lian M. Extracellular vesicles derived from human umbilical cord mesenchymal stromal cells protect cardiac cells against Hypoxia/Reoxygenation injury by inhibiting endoplasmic reticulum stress via activation of the PI3K/Akt pathway. *Cell Transplant*. 2020;29:963689720945677. doi:10.1177/0963689720945677
258. Zhou Q, Xie M, Zhu J, et al. PINK1 contained in huMSC-derived exosomes prevents cardiomyocyte mitochondrial calcium overload in sepsis via recovery of mitochondrial Ca(2+) efflux. *Stem Cell Res Ther*. 2021;12(1):269. doi:10.1186/s13287-021-02325-6
259. Yuan J, Yang H, Liu C, et al. Microneedle patch loaded with exosomes containing MicroRNA-29B prevents cardiac fibrosis after myocardial infarction. *Adv Healthc Mater*. 2023;12(13):e2202959. doi:10.1002/adhm.202202959
260. Wang XL, Zhao YY, Sun L, et al. Exosomes derived from human umbilical cord mesenchymal stem cells improve myocardial repair via upregulation of Smad7. *Int J Mol Med*. 2018;41(5):3063–3072. doi:10.3892/ijmm.2018.3496
261. Zhu B, Zhang L, Liang C, et al. Stem cell-derived exosomes prevent aging-induced cardiac dysfunction through a novel exosome/lncRNA MALAT1/NF-kappaB/TNF-alpha signaling pathway. *Oxid Med Cell Longev*. 2019;2019:9739258. doi:10.1155/2019/9739258

262. Ko KW, Yoo YI, Kim JY, et al. Attenuation of tumor necrosis factor-alpha induced inflammation by umbilical cord-mesenchymal stem cell derived exosome-mimetic nanovesicles in endothelial cells. *Tissue Eng Regen Med*. 2020;17(2):155–163. doi:10.1007/s13770-019-00234-7
263. Shi Y, Yang Y, Guo Q, et al. Exosomes derived from human umbilical cord mesenchymal stem cells promote fibroblast-to-myofibroblast differentiation in inflammatory environments and benefit cardioprotective effects. *Stem Cells Dev*. 2019;28(12):799–811. doi:10.1089/scd.2018.0242
264. Zou Y, Li L, Li Y, et al. Restoring cardiac functions after myocardial infarction-ischemia/reperfusion via an exosome anchoring conductive hydrogel. *ACS Appl Mater Interfaces*. 2021;13(48):56892–56908. doi:10.1021/acsami.1c16481
265. Zhang N, Zhu J, Ma Q, et al. Exosomes derived from human umbilical cord MSCs rejuvenate aged MSCs and enhance their functions for myocardial repair. *Stem Cell Res Ther*. 2020;11(1):273. doi:10.1186/s13287-020-01782-9
266. Zhang Z, Ji J, Pan X, et al. Normothermic ex vivo heart perfusion with exosomes from human umbilical cord mesenchymal stem cells improves graft function in donation after circulatory death hearts. *Transplantation*. 2024;108(11):2209–2221. doi:10.1097/TP.0000000000005040
267. Cao H, Yue L, Shao J, et al. Small extracellular vesicles derived from umbilical cord mesenchymal stem cells alleviate radiation-induced cardiac organoid injury. *Stem Cell Res Ther*. 2024;15(1):493. doi:10.1186/s13287-024-04115-2
268. Zhang S, Liu X, Ll G, et al. Mesenchymal stromal cell-derived exosomes improve pulmonary hypertension through inhibition of pulmonary vascular remodeling. *Respir Res*. 2020;21(1):71. doi:10.1186/s12931-020-1331-4
269. Ge L, Jiang W, Zhang S, et al. Mesenchymal stromal cell-derived exosomes attenuate experimental pulmonary arterial hypertension. *Curr Pharm Biotechnol*. 2021;22(12):1654–1662. doi:10.2174/1389201022666201231113127
270. Spinosa M, Lu G, Su G, et al. Human mesenchymal stromal cell-derived extracellular vesicles attenuate aortic aneurysm formation and macrophage activation via microRNA-147. *FASEB J*. 2018;32(11):fj201701138RR. doi:10.1096/fj.201701138RR
271. Qu Q, Pang Y, Zhang C, Liu L, Bi Y. Exosomes derived from human umbilical cord mesenchymal stem cells inhibit vein graft intimal hyperplasia and accelerate reendothelialization by enhancing endothelial function. *Stem Cell Res Ther*. 2020;11(1):133. doi:10.1186/s13287-020-01639-1
272. Qu Q, Wang L, Bing W, et al. miRNA-126-3p carried by human umbilical cord mesenchymal stem cell enhances endothelial function through exosome-mediated mechanisms in vitro and attenuates vein graft neointimal formation in vivo. *Stem Cell Res Ther*. 2020;11(1):464. doi:10.1186/s13287-020-01978-z
273. Zhang X, Zhou Y, Ye Y, et al. Human umbilical cord mesenchymal stem cell-derived exosomal microRNA-148a-3p inhibits neointimal hyperplasia by targeting Serpine1. *Arch Biochem Biophys*. 2022;719:109155. doi:10.1016/j.abb.2022.109155
274. Chen X, Chen Y, Zhang M, et al. HucMSC exosomes promoted imatinib-induced apoptosis in K562-R cells via a miR-145a-5p/USP6/GLS1 axis. *Cell Death Dis*. 2022;13(1):92. doi:10.1038/s41419-022-04531-3
275. Liu Y, Song B, Wei Y, et al. Exosomes from mesenchymal stromal cells enhance imatinib-induced apoptosis in human leukemia cells via activation of caspase signaling pathway. *Cytotherapy*. 2018;20(2):181–188. doi:10.1016/j.jcyt.2017.11.006
276. Yang A, Wang X, Jin L, et al. Human umbilical cord mesenchymal stem cell exosomes deliver potent oncolytic reovirus to acute myeloid leukemia cells. *Virology*. 2024;598:110171. doi:10.1016/j.virol.2024.110171
277. Li C, Wen Y, Wang J, et al. Human mesenchymal stem cell-derived exosomes as engineering vehicles of daunorubicin for targeted c-Mpl+ AML therapy. *Int J Nanomed*. 2025;20:5267–5289. doi:10.2147/IJN.S511713
278. Jiang L, Zhang S, Hu H, et al. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate acute liver failure by reducing the activity of the NLRP3 inflammasome in macrophages. *Biochem Biophys Res Commun*. 2019;508(3):735–741. doi:10.1016/j.bbrc.2018.11.189
279. Zhang S, Jiang L, Hu H, et al. Pretreatment of exosomes derived from hUCMSCs with TNF-alpha ameliorates acute liver failure by inhibiting the activation of NLRP3 in macrophage. *Life Sci*. 2020;246:117401. doi:10.1016/j.lfs.2020.117401
280. Pei L, Li R, Wang X, et al. MSCs-derived extracellular vesicles alleviate sepsis-associated liver dysfunction by inhibiting macrophage glycolysis-mediated inflammatory response. *Int Immunopharmacol*. 2024;128:111575. doi:10.1016/j.intimp.2024.111575
281. Wu HY, Zhang XC, Jia BB, et al. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate Acetaminophen-induced acute liver failure through activating ERK and IGF-1R/PI3K/AKT signaling pathway. *J Pharmacol Sci*. 2021;147(1):143–155. doi:10.1016/j.jphs.2021.06.008
282. Yan Y, Jiang W, Tan Y, et al. hucMSC exosome-derived GPX1 is required for the recovery of hepatic oxidant injury. *Mol Ther*. 2017;25(2):465–479. doi:10.1016/j.ymthe.2016.11.019
283. Cheng F, Yang F, Wang Y, Zhou J, Qian H, Yan Y. Mesenchymal stem cell-derived exosomal miR-27b-3p alleviates liver fibrosis via downregulating YAP/LOXL2 pathway. *J Nanobiotechnol*. 2023;21(1):195. doi:10.1186/s12951-023-01942-y
284. Yuan M, Yao L, Chen P, et al. Human umbilical cord mesenchymal stem cells inhibit liver fibrosis via the microRNA-148a-5p/SLIT3 axis. *Int Immunopharmacol*. 2023;125(Pt A):111134. doi:10.1016/j.intimp.2023.111134
285. Lin Y, Yan M, Bai Z, et al. Huc-MSC-derived exosomes modified with the targeting peptide of aHSCs for liver fibrosis therapy. *J Nanobiotechnol*. 2022;20(1):432. doi:10.1186/s12951-022-01636-x
286. Zhu D, Sun Z, Wei J, et al. BMP7-Loaded Human Umbilical Cord Mesenchymal Stem Cell-Derived Small Extracellular Vesicles Ameliorate Liver Fibrosis by Targeting Activated Hepatic Stellate Cells. *Int J Nanomed*. 2024;19:3475–3495. doi:10.2147/IJN.S450284
287. Tan Y, Huang Y, Mei R, et al. HucMSC-derived exosomes delivered BECN1 induces ferroptosis of hepatic stellate cells via regulating the xCT/GPX4 axis. *Cell Death Dis*. 2022;13(4):319. doi:10.1038/s41419-022-04764-2
288. Kang Y, Luo Y, Song Y, et al. Exosomes derived from human umbilical cord mesenchymal stem cells ameliorate experimental non-alcoholic steatohepatitis via Nrf2/NQO-1 pathway. *Free Radic Biol Med*. 2022;192:25–36. doi:10.1016/j.freeradbiomed.2022.08.037
289. Du X, Li H, Han X, Ma W. Mesenchymal stem cells-derived exosomal miR-24-3p ameliorates non-alcohol fatty liver disease by targeting Keap-1. *Biochem Biophys Res Commun*. 2022;637:331–340. doi:10.1016/j.bbrc.2022.11.012
290. Jiang W, Zeng Q, Ch L, et al. Huc-MSCs-derived exosomes alleviate non-alcoholic steatohepatitis by regulating macrophages polarization through miR-24-3p/STING axis. *Stem Cell Res Ther*. 2025;16(1):74. doi:10.1186/s13287-025-04197-6
291. Cheng L, Yu P, Li F, et al. Human umbilical cord-derived mesenchymal stem cell-exosomal miR-627-5p ameliorates non-alcoholic fatty liver disease by repressing FTO expression. *Hum Cell*. 2021;34(6):1697–1708. doi:10.1007/s13577-021-00593-1

292. Xu X, Peng J, Wang N, Ocansey DKW, Zhang X, Mao F. hucMSC-Ex alleviates inflammatory bowel disease in mice by enhancing M2-type macrophage polarization via the METTL3-Slc37a2-YTHDF1 axis. *Cell Biol Toxicol*. 2024;40(1):74. doi:10.1007/s10565-024-09921-1
293. Guo G, Tan Z, Liu Y, Shi F, She J. The therapeutic potential of stem cell-derived exosomes in the ulcerative colitis and colorectal cancer. *Stem Cell Res Ther*. 2022;13(1):138. doi:10.1186/s13287-022-02811-5
294. Mao F, Wu Y, Tang X, et al. Exosomes derived from human umbilical cord mesenchymal stem cells relieve inflammatory bowel disease in mice. *Biomed Res Int*. 2017;2017:5356760. doi:10.1155/2017/5356760
295. Cai X, Zhang ZY, Yuan JT, et al. hucMSC-derived exosomes attenuate colitis by regulating macrophage pyroptosis via the miR-378a-5p/NLRP3 axis. *Stem Cell Res Ther*. 2021;12(1):416. doi:10.1186/s13287-021-02492-6
296. Xu Y, Tang X, Fang A, et al. HucMSC-Ex carrying miR-203a-3p.2 ameliorates colitis through the suppression of caspase11/4-induced macrophage pyroptosis. *Int Immunopharmacol*. 2022;110:108925. doi:10.1016/j.intimp.2022.108925
297. Wei Z, Hang S, Wiredu Ocansey DK, et al. Human umbilical cord mesenchymal stem cells derived exosome shuttling mir-129-5p attenuates inflammatory bowel disease by inhibiting ferroptosis. *J Nanobiotechnol*. 2023;21(1):188. doi:10.1186/s12951-023-01951-x
298. Yang S, Liang X, Song J, et al. A novel therapeutic approach for inflammatory bowel disease by exosomes derived from human umbilical cord mesenchymal stem cells to repair intestinal barrier via TSG-6. *Stem Cell Res Ther*. 2021;12(1):315. doi:10.1186/s13287-021-02404-8
299. Liang X, Li C, Song J, et al. HucMSC-exo promote mucosal healing in experimental colitis by accelerating intestinal stem cells and epithelium regeneration via wnt signaling pathway. *Int J Nanomed*. 2023;18:2799–2818. doi:10.2147/IJN.S402179
300. Wang G, Yuan J, Cai X, et al. HucMSC-exosomes carrying miR-326 inhibit neddylation to relieve inflammatory bowel disease in mice. *Clin Transl Med*. 2020;10(2):e113. doi:10.1002/ctm2.113
301. Zhang L, Yuan J, Kofi Wiredu Ocansey D, et al. Exosomes derived from human umbilical cord mesenchymal stem cells regulate lymphangiogenesis via the miR-302d-3p/VEGFR3/AKT axis to ameliorate inflammatory bowel disease. *Int Immunopharmacol*. 2022;110:109066. doi:10.1016/j.intimp.2022.109066
302. Wang J, Pei B, Yan J, et al. hucMSC-derived exosomes alleviate the deterioration of colitis via the miR-146a/SUMO1 axis. *Mol Pharm*. 2022;19(2):484–493. doi:10.1021/acs.molpharmaceut.1c00450
303. Ma Z, Xie W, Luo T, et al. Exosomes from TNF-alpha preconditioned human umbilical cord mesenchymal stromal cells inhibit the autophagy of acinar cells of severe acute pancreatitis via shuttling bioactive metabolites. *Cell Mol Life Sci*. 2023;80(9):257. doi:10.1007/s00018-023-04861-1
304. Xie W, Luo T, Ma Z, et al. Tumor necrosis factor alpha preconditioned umbilical cord mesenchymal stem cell-derived extracellular vesicles enhance the inhibition of necroptosis of acinar cells in severe acute pancreatitis. *Tissue Eng Part A*. 2023;29(23–24):607–619. doi:10.1089/ten.TEA.2023.0139
305. Han L, Zhao Z, Chen X, et al. Human umbilical cord mesenchymal stem cells-derived exosomes for treating traumatic pancreatitis in rats. *Stem Cell Res Ther*. 2022;13(1):221. doi:10.1186/s13287-022-02893-1
306. Zhirong Z, Yiqun H, Chunyang H, et al. Enhancing or inhibiting apoptosis? The effects of ucMSC-Ex in the treatment of different degrees of traumatic pancreatitis. *Apoptosis*. 2022;27(7–8):521–530. doi:10.1007/s10495-022-01732-1
307. Zhao Z, Han L, Xin M, et al. Still water run deep: therapeutic TP effect of ucMSC-Ex via regulating mTOR to enhance autophagy. *J Cell Mol Med*. 2024;28(4):e18120. doi:10.1111/jcmm.18120
308. Yang WJ, Zhao HP, Yu Y, et al. Updates on global epidemiology, risk and prognostic factors of gastric cancer. *World J Gastroenterol*. 2023;29(16):2452–2468. doi:10.3748/wjg.v29.i16.2452
309. Liu F, Yang Z, Zheng L, et al. A tumor progression related 7-gene signature indicates prognosis and tumor immune characteristics of gastric cancer. *Front Oncol*. 2021;11:690129. doi:10.3389/fonc.2021.690129
310. Tang Z, Takahashi Y, Chen C, et al. Atg2A/B deficiency switches cytoprotective autophagy to non-canonical caspase-8 activation and apoptosis. *Cell Death Differ*. 2017;24(12):2127–2138. doi:10.1038/cdd.2017.133
311. Xu Y, Lai Y, Cao L, et al. Human umbilical cord mesenchymal stem cells-derived exosomal microRNA-451a represses epithelial-mesenchymal transition of hepatocellular carcinoma cells by inhibiting ADAM10. *RNA Biol*. 2021;18(10):1408–1423. doi:10.1080/15476286.2020.1851540
312. Xu G, Ban K, Mu H, Wang B. Human umbilical cord mesenchymal stem cells-derived exosomal lncRNA FAM99B represses hepatocellular carcinoma cell malignancy. *Mol Biotechnol*. 2024;66(6):1389–1401. doi:10.1007/s12033-023-00795-y
313. Cui F, Chen Y, Wu X, Zhao W. Mesenchymal stem cell-derived exosomes carrying miR-486-5p inhibit glycolysis and cell stemness in colorectal cancer by targeting NEK2. *BMC Cancer*. 2024;24(1):1356. doi:10.1186/s12885-024-13086-9
314. Qu M, Li J, Hong Z, Jia F, He Y, Yuan L. The role of human umbilical cord mesenchymal stem cells-derived exosomal microRNA-431-5p in survival and prognosis of colorectal cancer patients. *Mutagenesis*. 2022;37(2):164–171. doi:10.1093/mutage/geac007
315. Chen J, Li Z, Yue C, et al. Human umbilical cord mesenchymal stem cell-derived exosomes carrying miR-1827 downregulate SUCNR1 to inhibit macrophage M2 polarization and prevent colorectal liver metastasis. *Apoptosis*. 2023;28(3–4):549–565. doi:10.1007/s10495-022-01798-x
316. Wang Y, Zhang Y, Lu B, et al. hucMSC-Ex alleviates IBD-associated intestinal fibrosis by inhibiting ERK phosphorylation in intestinal fibroblasts. *Stem Cells Int*. 2023;2023:2828981. doi:10.1155/2023/2828981
317. Zhu L, He L, Duan W, Yang B, Li N. Umbilical cord mesenchymal stem cell exosomes alleviate necrotizing enterocolitis in neonatal mice by regulating intestinal epithelial cells autophagy. *World J Stem Cells*. 2024;16(6):728–738. doi:10.4252/wjsc.v16.i6.728
318. Lu Y, Huangfu S, Ma C, et al. Exosomes derived from umbilical cord mesenchymal stem cells promote healing of complex perianal fistulas in rats. *Stem Cell Res Ther*. 2024;15(1):414. doi:10.1186/s13287-024-04028-0
319. Zou Y, Xiao W, Liu D, et al. Human umbilical cord mesenchymal stem cells improve disease characterization of Sjogren's syndrome in NOD mice through regulation of gut microbiota and Treg/Th17 cellular immunity. *Immun Inflamm Dis*. 2024;12(1):e1139. doi:10.1002/iid3.1139
320. Heidari N, Abbasi-Kenarsari H, Namaki S, et al. Regulation of the Th17/Treg balance by human umbilical cord mesenchymal stem cell-derived exosomes protects against acute experimental colitis. *Exp Cell Res*. 2022;419(1):113296. doi:10.1016/j.yexcr.2022.113296
321. Ding Y, Cao F, Sun H, et al. Exosomes derived from human umbilical cord mesenchymal stromal cells deliver exogenous miR-145-5p to inhibit pancreatic ductal adenocarcinoma progression. *Cancer Lett*. 2019;442:351–361. doi:10.1016/j.canlet.2018.10.039
322. Xie X, Ji J, Chen X, et al. Human umbilical cord mesenchymal stem cell-derived exosomes carrying hsa-miRNA-128-3p suppress pancreatic ductal cell carcinoma by inhibiting Galectin-3. *Clin Transl Oncol*. 2022;24(3):517–531. doi:10.1007/s12094-021-02705-7
323. Ding Y, Mei W, Zheng Z, et al. Exosomes secreted from human umbilical cord mesenchymal stem cells promote pancreatic ductal adenocarcinoma growth by transferring miR-100-5p. *Tissue Cell*. 2021;73:101623. doi:10.1016/j.tice.2021.101623

324. Li Q, Liu J, Su R, Liu J, Liu G, Zhen J. Small extracellular vesicles-shuttled miR-23a-3p from mesenchymal stem cells alleviate renal fibrosis and inflammation by inhibiting KLF3/STAT3 axis in diabetic kidney disease. *Int Immunopharmacol*. 2024;139:112667. doi:10.1016/j.intimp.2024.112667
325. Wang Y, Liu J, Wang H, et al. Mesenchymal stem cell-derived exosomes ameliorate diabetic kidney disease through the NLRP3 signaling pathway. *Stem Cells*. 2023;41(4):368–383. doi:10.1093/stmcls/sxad010
326. Yu Y, Chen M, Guo Q, et al. Human umbilical cord mesenchymal stem cell exosome-derived miR-874-3p targeting RIPK1/PGAM5 attenuates kidney tubular epithelial cell damage. *Cell Mol Biol Lett*. 2023;28(1):12. doi:10.1186/s11658-023-00425-0
327. Chen G, Li X, Zhou X, et al. Extracellular vesicles secreted from mesenchymal stem cells ameliorate renal ischemia reperfusion injury by delivering miR-100-5p targeting FKBP5/AKT axis. *Sci Rep*. 2024;14(1):6720. doi:10.1038/s41598-024-56950-1
328. Wan Y, Yu Y, Yu C, et al. Human umbilical cord mesenchymal stem cell exosomes alleviate acute kidney injury by inhibiting pyroptosis in rats and NRK-52E cells. *Ren Fail*. 2023;45(1):2221138. doi:10.1080/0886022X.2023.2221138
329. Jin C, Wu P, Chen W, et al. Therapeutic role of hucMSC-sEV-enriched miR-13896 in cisplatin-induced acute kidney injury through M2 macrophage polarization. *Cell Biol Toxicol*. 2025;41(1):50. doi:10.1007/s10565-025-09998-2
330. Ji C, Zhang J, Zhu Y, et al. Exosomes derived from hucMSC attenuate renal fibrosis through CK1delta/beta-TRCP-mediated YAP degradation. *Cell Death Dis*. 2020;11(5):327. doi:10.1038/s41419-020-2510-4
331. Shi L, Hu Y, Zeng H, et al. Mesenchymal stem cell-derived extracellular vesicles ameliorate renal interstitial fibrosis via the miR-13474/ADAM17 axis. *Sci Rep*. 2024;14(1):17703. doi:10.1038/s41598-024-67339-5
332. Zhang R, Zhu Y, Li Y, et al. Human umbilical cord mesenchymal stem cell exosomes alleviate sepsis-associated acute kidney injury via regulating microRNA-146b expression. *Biotechnol Lett*. 2020;42(4):669–679. doi:10.1007/s10529-020-02831-2
333. Yuan F, Liu J, Zhong L, et al. Enhanced therapeutic effects of hypoxia-preconditioned mesenchymal stromal cell-derived extracellular vesicles in renal ischemic injury. *Stem Cell Res Ther*. 2025;16(1):39. doi:10.1186/s13287-025-04166-z
334. Shi W, Zhou X, Li X, et al. Human umbilical cord mesenchymal stem cells protect against renal ischemia-reperfusion injury by secreting extracellular vesicles loaded with mir-148b-3p that target pyruvate dehydrogenase kinase 4 to inhibit endoplasmic reticulum stress at the reperfusion stages. *Int J Mol Sci*. 2023;24(10). doi:10.3390/ijms24108899
335. Yu W, Jia X, Qiao H, et al. Phosphoproteomic analysis reveals the mechanisms of human umbilical cord mesenchymal stem cell-derived exosomes attenuate renal aging. *J Proteomics*. 2025;310:105335. doi:10.1016/j.jprot.2024.105335
336. Li C, Wu F, Mao J, et al. Mesenchymal stem cells-derived extracellular vesicles ameliorate lupus nephritis by regulating T and B cell responses. *Stem Cell Res Ther*. 2024;15(1):216. doi:10.1186/s13287-024-03834-w
337. Liu M, Chen X. Human umbilical cord-derived mesenchymal stem cells-exosomes-delivered miR-375 targets HDAC4 to promote autophagy and suppress T cell apoptosis in sepsis-associated acute kidney injury. *Appl Biochem Biotechnol*. 2024;196(11):7954–7973. doi:10.1007/s12010-024-04963-x
338. Wu P, Tang Y, Jin C, et al. Neutrophil membrane engineered HucMSC sEVs alleviate cisplatin-induced AKI by enhancing cellular uptake and targeting. *J Nanobiotechnol*. 2022;20(1):353. doi:10.1186/s12951-022-01574-8
339. Wang B, Jia H, Zhang B, et al. Pre-incubation with hucMSC-exosomes prevents cisplatin-induced nephrotoxicity by activating autophagy. *Stem Cell Res Ther*. 2017;8(1):75. doi:10.1186/s13287-016-0463-4
340. Cao J, Wang B, Tang T, et al. Three-dimensional culture of MSCs produces exosomes with improved yield and enhanced therapeutic efficacy for cisplatin-induced acute kidney injury. *Stem Cell Res Ther*. 2020;11(1):206. doi:10.1186/s13287-020-01719-2
341. Liang YC, Wu YP, Li XD, et al. TNF-alpha-induced exosomal miR-146a mediates mesenchymal stem cell-dependent suppression of urethral stricture. *J Cell Physiol*. 2019;234(12):23243–23255. doi:10.1002/jcp.28891
342. Huang H, Zhong P, Zhang J, et al. Human umbilical cord-mesenchymal stem cells-derived exosomes carrying microRNA-15a-5p possess therapeutic effects on Wilms tumor via regulating septin 2. *Bioengineered*. 2022;13(3):6136–6149. doi:10.1080/21655979.2022.2037379
343. Yue D, Wang F, Han Y, Xiong C, Yang R. Exosomes derived from umbilical cord mesenchymal stem cells ameliorate male infertility caused by busulfan in vivo and in vitro. *Ecotoxicol Environ Saf*. 2024;272:116063. doi:10.1016/j.ecoenv.2024.116063
344. Xin L, Lin X, Zhou F, et al. A scaffold laden with mesenchymal stem cell-derived exosomes for promoting endometrium regeneration and fertility restoration through macrophage immunomodulation. *Acta Biomater*. 2020;113:252–266. doi:10.1016/j.actbio.2020.06.029
345. Zhu X, Li W, Lu M, et al. M(6)A demethylase FTO-stabilized exosomal circBRCA1 alleviates oxidative stress-induced granulosa cell damage via the miR-642a-5p/FOXO1 axis. *J Nanobiotechnol*. 2024;22(1):367. doi:10.1186/s12951-024-02583-5
346. Cai JH, Sun YT, Bao S. HucMSCs-exosomes containing miR-21 promoted estrogen production in ovarian granulosa cells via LATS1-mediated phosphorylation of LOXL2 and YAP. *Gen Comp Endocrinol*. 2022;321-322:114015. doi:10.1016/j.ygcen.2022.114015
347. Yang Z, Du X, Wang C, et al. Therapeutic effects of human umbilical cord mesenchymal stem cell-derived microvesicles on premature ovarian insufficiency in mice. *Stem Cell Res Ther*. 2019;10(1):250. doi:10.1186/s13287-019-1327-5
348. Zhao Y, Pan S, Wu X. Human umbilical cord mesenchymal stem cell-derived exosomes inhibit ovarian granulosa cells inflammatory response through inhibition of NF-kappaB signaling in polycystic ovary syndrome. *J Reprod Immunol*. 2022;152:103638. doi:10.1016/j.jri.2022.103638
349. Yang W, Zhang J, Xu B, et al. HucMSC-derived exosomes mitigate the age-related retardation of fertility in female mice. *Mol Ther*. 2020;28(4):1200–1213. doi:10.1016/j.ymthe.2020.02.003
350. Zhang C, Liao W, Li W, et al. Human umbilical cord mesenchymal stem cells derived extracellular vesicles alleviate salpingitis by promoting M1-to-M2 transformation. *Front Physiol*. 2023;14:1131701. doi:10.3389/fphys.2023.1131701
351. Yu S, Zhang X, Li W, et al. Thermosensitive hydrogel as a sustained release carrier for mesenchymal stem cell-derived extracellular vesicles in the treatment of intrauterine adhesion. *J Nanobiotechnol*. 2024;22(1):570. doi:10.1186/s12951-024-02780-2
352. Yi C, Wang H, Din MAU, Xia Y, Akanyibah FA, Mao F. Human umbilical cord mesenchymal stem cells derived-exosomes alleviate LPS-induced cervical inflammation and epithelial-mesenchymal transition. *Am J Transl Res*. 2024;16(11):6903–6913. doi:10.62347/PKYU4876
353. Yuan H, Li S, Zhao Z, Wang Y. Regulation of interferon-beta-modified human umbilical cord mesenchymal stem cell-derived exosomes in proliferation and apoptosis of prostate cancer cells. *Organogenesis*. 2023;19(1):2285836. doi:10.1080/15476278.2023.2285836
354. Wu X, Zeng Z, Peng K, Ren D, Zhang L. Regulatory mechanism of DHRS2-modified human umbilical cord mesenchymal stem cells-derived exosomes in prostate cancer cell proliferation and apoptosis. *Tissue Cell*. 2023;82:102078. doi:10.1016/j.tice.2023.102078

355. Li W, Zhang C, Gao T, et al. Human umbilical cord mesenchymal stem cells small extracellular vesicles-derived miR-370-3p inhibits cervical precancerous lesions by targeting DHCR24. *Stem Cells Transl Med*. 2025;14(1). doi:10.1093/stcltm/szae087
356. Li W, Zhang X, Gao T, et al. Jagged1 contained in MSC-derived small extracellular vesicles promotes squamous differentiation of cervical cancer by activating NOTCH pathway. *J Cancer Res Clin Oncol*. 2023;149(20):18093–18102. doi:10.1007/s00432-023-05495-3
357. Abas BI, Demirbolat GM, Cevik O. Wharton jelly-derived mesenchymal stem cell exosomes induce apoptosis and suppress EMT signaling in cervical cancer cells as an effective drug carrier system of paclitaxel. *PLoS One*. 2022;17(9):e0274607. doi:10.1371/journal.pone.0274607
358. Osuagwu UL, Langsi R, Ovenseri-Ogbomo G, et al. Analysis of perception, reasons, and motivations for COVID-19 vaccination in people with diabetes across sub-saharan africa: a mixed-method approach. *Int J Environ Res Public Health*. 2022;19(13). doi:10.3390/ijerph19137875
359. Zhang Y, Le X, Zheng S, et al. MicroRNA-146a-5p-modified human umbilical cord mesenchymal stem cells enhance protection against diabetic nephropathy in rats through facilitating M2 macrophage polarization. *Stem Cell Res Ther*. 2022;13(1):171. doi:10.1186/s13287-022-02855-7
360. Wang L, Liang A, Huang J. Exendin-4-enriched exosomes from hUCMSCs alleviate diabetic nephropathy via gut microbiota and immune modulation. *Front Microbiol*. 2024;15:1399632. doi:10.3389/fmicb.2024.1399632
361. Zhang K, Zheng S, Wu J, et al. Human umbilical cord mesenchymal stem cell-derived exosomes ameliorate renal fibrosis in diabetic nephropathy by targeting Hedgehog/SMO signaling. *FASEB J*. 2024;38(7):e23599. doi:10.1096/fj.202302324R
362. Li X, Chen M, Cao J, et al. Human umbilical cord mesenchymal stem cell-derived exosomes mitigate diabetic nephropathy via enhancing M2 macrophages polarization. *Heliyon*. 2024;10(17):e37002. doi:10.1016/j.heliyon.2024.e37002
363. Zhang Y, Zhang P, Gao X, Chang L, Chen Z, Mei X. Preparation of exosomes encapsulated nanohydrogel for accelerating wound healing of diabetic rats by promoting angiogenesis. *Mater Sci Eng C Mater Biol Appl*. 2021;120:111671. doi:10.1016/j.msec.2020.111671
364. Shi X, Li Y, Kang S, et al. Dual-functional gallium/chitosan/silk/umbilical cord mesenchymal stem cell exosome sponge scaffold for diabetic wound by angiogenesis and antibacteria. *Int J Biol Macromol*. 2024;274(Pt 2):133420. doi:10.1016/j.ijbiomac.2024.133420
365. Wei Q, Wang Y, Ma K, et al. Extracellular vesicles from human umbilical cord mesenchymal stem cells facilitate diabetic wound healing through MiR-17-5P-mediated enhancement of angiogenesis. *Stem Cell Rev Rep*. 2022;18(3):1025–1040. doi:10.1007/s12015-021-10176-0
366. Li Q, Guo L, Wang J, Tao S, Jin P. Exosomes derived from Nr-CWS pretreated MSCs facilitate diabetic wound healing by promoting angiogenesis via the circIARS1/miR-4782-5p/VEGFA axis. *Chin J Nat Med*. 2023;21(3):172–184. doi:10.1016/S1875-5364(23)60419-4
367. Wu S, Zhou Z, Li Y, Wu R, Jiang J. Pretreatment of human umbilical cord mesenchymal stem cell-derived exosomes with quercetin enhances the healing of diabetic skin wounds by modulating host-microbiota interactions. *Int J Nanomed*. 2024;19:12557–12581. doi:10.2147/IJN.S491471
368. Yang R, Zhou S, Huang J, et al. The role of Q10 engineering mesenchymal stem cell-derived exosomes in inhibiting ferroptosis for diabetic wound healing. *Burns Trauma*. 2024;12:tkae054. doi:10.1093/burnst/tkae054
369. Teng L, Maqsood M, Zhu M, et al. Exosomes Derived from human umbilical cord mesenchymal stem cells accelerate diabetic wound healing via promoting M2 macrophage polarization, angiogenesis, and collagen deposition. *Int J Mol Sci*. 2022;23(18). doi:10.3390/ijms231810421
370. Yang S, Chen S, Zhang C, et al. Enhanced therapeutic effects of mesenchymal stem cell-derived extracellular vesicles within chitosan hydrogel in the treatment of diabetic foot ulcers. *J Mater Sci Mater Med*. 2023;34(9):43. doi:10.1007/s10856-023-06746-y
371. Zhang W, Wang Y, Kong Y. Exosomes derived from mesenchymal stem cells modulate miR-126 to ameliorate hyperglycemia-induced retinal inflammation via targeting HMGB1. *Invest Ophthalmol Vis Sci*. 2019;60(1):294–303. doi:10.1167/iovs.18-25617
372. He Y, Zhang Z, Yao T, et al. Extracellular vesicles derived from human umbilical cord mesenchymal stem cells relieves diabetic retinopathy through a microRNA-30c-5p-dependent mechanism. *Diabet Res Clin Pract*. 2022;190:109861. doi:10.1016/j.diabres.2022.109861
373. Li W, Jin LY, Cui YB, Xie N. Human umbilical cord mesenchymal stem cells-derived exosomal microRNA-17-3p ameliorates inflammatory reaction and antioxidant injury of mice with diabetic retinopathy via targeting STAT1. *Int Immunopharmacol*. 2021;90:107010. doi:10.1016/j.intimp.2020.107010
374. Gao X, He GH, Zhang XT, Chen S. Protective effect of human umbilical cord mesenchymal stem cell-derived exosomes on rat retinal neurons in hyperglycemia through the brain-derived neurotrophic factor/TrkB pathway. *Int J Ophthalmol*. 2021;14(11):1683–1689. doi:10.18240/ijo.2021.11.06
375. Fu Y, Xie TH, Zhang YL, Gu ZH. The effect of human umbilical cord mesenchymal stem cell-derived exosomes on diabetic retinal neurodegeneration in a rat model. *J Chem Neuroanat*. 2022;126:102181. doi:10.1016/j.jchemneu.2022.102181
376. Zhang Z, Chen L, Chen X, et al. Exosomes derived from human umbilical cord mesenchymal stem cells (HUCMSC-EXO) regulate autophagy through AMPK-ULK1 signaling pathway to ameliorate diabetic cardiomyopathy. *Biochem Biophys Res Commun*. 2022;632:195–203. doi:10.1016/j.bbrc.2022.10.001
377. Chen J, Chen J, Cheng Y, et al. Mesenchymal stem cell-derived exosomes protect beta cells against hypoxia-induced apoptosis via miR-21 by alleviating ER stress and inhibiting p38 MAPK phosphorylation. *Stem Cell Res Ther*. 2020;11(1):97. doi:10.1186/s13287-020-01610-0
378. Yap SK, Tan KL, Abd Rahaman NY, et al. Human umbilical cord mesenchymal stem cell-derived small extracellular vesicles ameliorated insulin resistance in type 2 diabetes mellitus rats. *Pharmaceutics*. 2022;14(3). doi:10.3390/pharmaceutics14030649
379. Sun Y, Shi H, Yin S, et al. Human mesenchymal stem cell derived exosomes alleviate type 2 diabetes mellitus by reversing peripheral insulin resistance and relieving beta-cell destruction. *ACS Nano*. 2018;12(8):7613–7628. doi:10.1021/acsnano.7b07643
380. Mohammadi MR, Rodriguez SM, Luong JC, et al. Exosome loaded immunomodulatory biomaterials alleviate local immune response in immunocompetent diabetic mice post islet xenotransplantation. *Commun Biol*. 2021;4(1):685. doi:10.1038/s42003-021-02229-4
381. Zheng T, Zhou Y, Xu X, et al. MiR-30c-5p loss-induced PELI1 accumulation regulates cell proliferation and migration via activating PI3K/AKT pathway in papillary thyroid carcinoma. *J Transl Med*. 2022;20(1):20. doi:10.1186/s12967-021-03226-1
382. Giancaterino S, Boi C. Alternative biological sources for extracellular vesicles production and purification strategies for process scale-up. *Biotechnol Adv*. 2023;63:108092. doi:10.1016/j.biotechadv.2022.108092
383. Witwer KW, Van Balkom BWM, Bruno S, et al. Defining mesenchymal stromal cell (MSC)-derived small extracellular vesicles for therapeutic applications. *J Extracell Vesicles*. 2019;8(1):1609206. doi:10.1080/20013078.2019.1609206
384. Mendt M, Kamerkar S, Sugimoto H, et al. Generation and testing of clinical-grade exosomes for pancreatic cancer. *JCI Insight*. 2018;3(8). doi:10.1172/jci.insight.99263
385. Zhang F, Zhang L, Yu H. Potential druggability of mesenchymal stem/stromal cell-derived exosomes. *Curr Stem Cell Res Ther*. 2024;19(9):1195–1209. doi:10.2174/011574888X311270240319084835

386. Shekari F, Alibhai FJ, Baharvand H, et al. Cell culture-derived extracellular vesicles: considerations for reporting cell culturing parameters. *J Extracell Biol*. 2023;2(10):e115. doi:10.1002/jex2.115
387. Mocchi M, Bari E, Marrubini G, et al. Freeze-dried mesenchymal stem cell-secretome pharmaceuticalization: optimization of formulation and manufacturing process robustness. *Pharmaceutics*. 2021;13(8). doi:10.3390/pharmaceutics13081129
388. Gimona M, Pachler K, Laner-Plamberger S, Schallmoser K, Rohde E. Manufacturing of human extracellular vesicle-based therapeutics for clinical use. *Int J Mol Sci*. 2017;18(6). doi:10.3390/ijms18061190
389. Arjmand B, Alavi-Moghadam S, Rezaei-Tavirani M, et al. GMP-compliant mesenchymal stem cell-derived exosomes for cell-free therapy in cancer. *Methods Mol Biol*. 2024;2736:163–176. doi:10.1007/7651_2022_467
390. Lai JJ, Hill JJ, Huang CY, et al. Unveiling the complex world of extracellular vesicles: novel characterization techniques and manufacturing considerations. *Chonnam Med J*. 2024;60(1):1–12. doi:10.4068/cmj.2024.60.1.1
391. Zhao S, Di Y, Fan H, et al. Targeted delivery of extracellular vesicles: the mechanisms, techniques and therapeutic applications. *Mol Biomed*. 2024;5(1):60. doi:10.1186/s43556-024-00230-x
392. Pan WY, Weng PW, Wu SH, et al. Intranasal delivery of epigallocatechin gallate-laden platelet extracellular vesicles for mitigating retinal glaucoma. *J Control Release*. 2025;381:113596. doi:10.1016/j.jconrel.2025.113596
393. Guo Y, Hu D, Lian L, et al. Stem cell-derived extracellular vesicles: a promising nano delivery platform to the brain? *Stem Cell Rev Rep*. 2023;19(2):285–308. doi:10.1007/s12015-022-10455-4
394. Li J, Wang J, Chen Z. Emerging role of exosomes in cancer therapy: progress and challenges. *Mol Cancer*. 2025;24(1):13. doi:10.1186/s12943-024-02215-4
395. Jin Y, Xu C, Zhu Y, Gu Z. Extracellular vesicle as a next-generation drug delivery platform for rheumatoid arthritis therapy. *J Control Release*. 2025;381:113610. doi:10.1016/j.jconrel.2025.113610
396. Pirisinu M, Pham TC, Zhang DX, Hong TN, Nguyen LT, Le MT. Extracellular vesicles as natural therapeutic agents and innate drug delivery systems for cancer treatment: recent advances, current obstacles, and challenges for clinical translation. *Semin Cancer Biol*. 2022;80:340–355. doi:10.1016/j.semcancer.2020.08.007
397. Xing Y, Zhang F, Ji P, et al. Efficient delivery of GSDMD-N mRNA by engineered extracellular vesicles induces pyroptosis for enhanced immunotherapy. *Small*. 2023;19(20):e2204031. doi:10.1002/smll.202204031
398. Jayasinghe MK, Pirisinu M, Yang Y, et al. Surface-engineered extracellular vesicles for targeted delivery of therapeutic RNAs and peptides for cancer therapy. *Theranostics*. 2022;12(7):3288–3315. doi:10.7150/thno.68667
399. Koh HB, Kim HJ, Kang SW, Yoo TH. Exosome-based drug delivery: translation from bench to clinic. *Pharmaceutics*. 2023;15(8). doi:10.3390/pharmaceutics15082042
400. Greenberg ZF, Graim KS, He M. Towards artificial intelligence-enabled extracellular vesicle precision drug delivery. *Adv Drug Deliv Rev*. 2023;199:114974. doi:10.1016/j.addr.2023.114974
401. Yao C, Zhang H, Wang C. Recent advances in therapeutic engineered extracellular vesicles. *Nanoscale*. 2024;16(16):7825–7840. doi:10.1039/d3nr05470e
402. Tian J, Han Z, Song D, et al. Engineered exosome for drug delivery: recent development and clinical applications. *Int J Nanomed*. 2023;18:7923–7940. doi:10.2147/IJN.S444582
403. Sun Y, Sun F, Xu W, Qian H. Engineered extracellular vesicles as a targeted delivery platform for precision therapy. *Tissue Eng Regen Med*. 2023;20(2):157–175. doi:10.1007/s13770-022-00503-y
404. Miceli RT, Chen TY, Nose Y, et al. Extracellular vesicles, RNA sequencing, and bioinformatic analyses: challenges, solutions, and recommendations. *J Extracell Vesicles*. 2024;13(12):e70005. doi:10.1002/jev2.70005
405. Cheng Z, Shang J, Wang H, et al. Molecular imaging-guided extracellular vesicle-based drug delivery for precise cancer management: current status and future perspectives. *J Control Release*. 2023;362:97–120. doi:10.1016/j.jconrel.2023.08.040
406. Lara P, Palma-Florez S, Salas-Huenuleo E, et al. Gold nanoparticle based double-labeling of melanoma extracellular vesicles to determine the specificity of uptake by cells and preferential accumulation in small metastatic lung tumors. *J Nanobiotechnol*. 2020;18(1):20. doi:10.1186/s12951-020-0573-0
407. Krishnan I, Chan AML, Law JX, Ng MH, Jayapalan JJ, Lokanathan Y. Proteomic analysis of umbilical cord mesenchymal stem cell-derived extracellular vesicles: a systematic review. *Int J Mol Sci*. 2024;25(10). doi:10.3390/ijms25105340
408. Song J, Zhou D, Cui L, et al. Advancing stroke therapy: innovative approaches with stem cell-derived extracellular vesicles. *Cell Commun Signal*. 2024;22(1):369. doi:10.1186/s12964-024-01752-1
409. Lesage F, Thebaud B. Mesenchymal stromal cell-derived extracellular vesicles for neonatal lung disease: tiny particles, major promise, rigorous requirements for clinical translation. *Cells*. 2022;11(7). doi:10.3390/cells11071176
410. Shimizu Y, Ntege EH, Inoue Y, Matsuura N, Sunami H, Sowa Y. Optimizing mesenchymal stem cell extracellular vesicles for chronic wound healing: bioengineering, standardization, and safety. *Regen Ther*. 2024;26:260–274. doi:10.1016/j.reth.2024.06.001
411. Silva AKA, Morille M, Piffoux M, et al. Development of extracellular vesicle-based medicinal products: a position paper of the group "Extracellular Vesicle translatiOn to clinicaL perspectiVEs - EVOLVE France". *Adv Drug Deliv Rev*. 2021;179:114001. doi:10.1016/j.addr.2021.114001
412. Chen Q, Zheng Y, Jiang X, Wang Y, Chen Z, Wu D. Nature's carriers: leveraging extracellular vesicles for targeted drug delivery. *Drug Deliv*. 2024;31(1):2361165. doi:10.1080/10717544.2024.2361165