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REVIEW

The New Approach to Treating Erectile Dysfunction: Stem Cell-Derived Extracellular Vesicles

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Abstract: Erectile dysfunction refers to the inability of men to achieve or maintain sufficient erection during sexual activity, which significantly impacts their quality of life and mental health. The causes of erectile dysfunction are complex, involving multiple systems such as vascular, neural, endocrine, and psychological factors. Current treatment methods for erectile dysfunction have significant limitations in addressing organic lesions, particularly penile fibrosis and hypoxic microenvironments. However, the latest stem cell-derived nanovesicle technology has been found to significantly reverse cellular fibrosis and alter the cellular microenvironment, potentially offering a new therapeutic approach for erectile dysfunction. Additionally, extracellular vesicles derived from stem cells can exert stem cell-like regenerative effects while overcoming challenges associated with cell therapy, making them excellent tools for regenerative repair. Therefore, this paper summarizes the potential of extracellular vesicles from different stem cell sources in the treatment of erectile dysfunction and analyzes their engineered preclinical studies to facilitate their translation from the laboratory to clinical applications.

Keywords: erectile dysfunction, stem cells, stem cell-derived extracellular vesicles, regenerative medicine, nanomedicine

Introduction

Background

Erectile dysfunction (ED) has been documented since ancient times, with descriptions found in medical literature dating back over 5000 years.[1] ED, also known as penile erectile dysfunction, refers to the inability of men to achieve or maintain an erection sufficient for sexual intercourse under sexual stimulation.[2] According to the latest report from the International Consultation Committee for Sexual Medicine on Definitions/Epidemiology/Risk Factors for Sexual Dysfunction, ED is widespread among men over 40, with its prevalence gradually increasing with age.[3,4] In particular, among men over 70, the prevalence of ED ranges from 50% to 100%.[5–9] It is estimated that by 2025, the global number of ED patients will rise to 322 million.[10,11] The high incidence of ED makes it an increasingly prominent health issue in aging societies.

Although current treatment methods such as lifestyle adjustments, psychotherapy, and pharmacological interventions have achieved certain effects, ED treatment still faces many challenges. Studies have shown that broad improvements in lifestyle, such as dietary changes and increased physical activity, can effectively alleviate ED symptoms in some patients.[12–17] Psychotherapy can help reduce anxiety and stress, especially for those with psychological ED.[18] However, for many patients with comorbid chronic diseases such as diabetes or cardiovascular disease, the effect of lifestyle adjustments is limited.[19–21] While dietary regulation or the use of statins to lower blood lipid levels and cholesterol concentrations may improve symptoms in some patients,[22] these approaches do not fundamentally address ED caused by organic factors. In terms of pharmacological treatment, selective phosphodiesterase type 5 inhibitors (PDE5i), such as sildenafil, are currently the most commonly used drugs in clinical practice.[23–27] These drugs improve

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erectile function by enhancing the relaxation effect of nitric oxide (NO) on penile smooth muscle[19,28–30] with their effectiveness depending on the integrity of the patient's own neurological and vascular functions. Therefore, for patients with severe vascular or neurological damage, such as those with vascular complications from diabetes or nerve injury after prostate surgery, the efficacy of PDE5i is limited. Moreover, although PDE5i shows significant short-term effects, the issue of drug resistance and dependence with long-term treatment limits its effectiveness, and it is not suitable for some patients with cardiovascular diseases.[31,32]

With the in-depth study of the pathophysiological mechanisms of ED, SCs-EVs have emerged as a novel biological therapeutic approach, showing significant potential for treating ED. SCs-EVs possess multiple biological functions, including anti-inflammatory, pro-angiogenic, and tissue repair properties,[33–36] which specifically target the core causes of organic ED, such as nerve damage and vascular lesions. Particularly in neurogenic and vascular ED, SCs-EVs can promote the regeneration and functional recovery of damaged tissues, filling the gap left by existing therapeutic methods. Furthermore, as natural intercellular communication vehicles, EVs can circumvent common issues such as immune rejection and ethical concerns in cell-based therapies, demonstrating good safety and feasibility.[37] Therefore, although current lifestyle interventions and pharmacological treatments can improve ED to some extent, the efficacy remains unsatisfactory, especially for patients with complex, organic ED.[38,39] SCs-EVs, as a promising therapeutic approach, offer new possibilities, particularly due to their unique advantages in repairing nerve and vascular damage, suggesting their potential in future clinical applications.

Etiology and Pathogenesis of ED

Sexual activity is an indispensable part of many men's lives, with sexual function often closely tied to self-esteem and male identity. ED not only undermines self-esteem and confidence but also significantly affects overall quality of life.[40,41] The causes of ED can be broadly classified into psychological and organic categories. Psychological factors include anxiety, depression, low self-esteem, psychological stress, and relationship issues with a partner,[38,42–46] while organic causes encompass abnormalities in the neurological, endocrine, vascular, and anatomical systems. Specifically, organic ED can be further subdivided into neurogenic, endocrine, arterial, cavernous, and drug-induced types.[19,38]

The specific causes of organic ED are extensive. Neurogenic causes include multiple sclerosis, Parkinson's disease, spinal cord injuries, and prostate surgery,[19,47–51] while endocrine factors primarily involve low testosterone and hyperprolactinemia.[22,52] Vascular issues, such as diabetes, hypertension, hyperlipidemia, and metabolic syndrome, are also common causes of ED, as these conditions negatively impact vascular function, obstructing normal blood flow.[53–61] Additionally, conditions like obstructive sleep apnea and lower urinary tract symptoms are closely associated with ED.[53–61] It is important to note that ED is not only a reproductive system disorder but has also been identified as an early warning sign or associated symptom of cardiovascular diseases,[58,60,62] with independent associations to coronary heart disease, stroke, and all-cause mortality.[63,64] Besides organic factors, environmental and lifestyle factors also play a significant role in ED. Smoking, obesity, and lack of physical activity have been confirmed as risk factors for ED.[63,65,66] Moreover, certain medications, particularly antihypertensive and antidepressant drugs, may trigger or worsen ED symptoms.[67]

Normal sexual function is a complex physiological process coordinated by the psychological, endocrine, vascular, and nervous systems.[68] During this process, penile erection is regulated by multiple mechanisms, with smooth muscle relaxation and contraction playing a key role (Figure 1). Adrenergic nerves, endogenous muscle factors, and endothelial factors together regulate smooth muscle contraction.[69–71] Upon sexual stimulation, non-adrenergic, non-cholinergic nerve fibers release NO, while parasympathetic cholinergic nerve fibers release acetylcholine, promoting smooth muscle relaxation.[71,72] This process is achieved by increasing cyclic guanosine monophosphate (cGMP) levels and reducing intracellular calcium ion concentration.[71,72] After smooth muscle relaxation, blood fills the cavernous bodies, compressing the veins and preventing blood from flowing back, thus achieving an erection. When phosphodiesterase type 5 (PDE5) breaks down cGMP, the erection process is reversed[71,72] (Figure 2). Therefore, any disruption in these mechanisms can lead to the occurrence of ED.

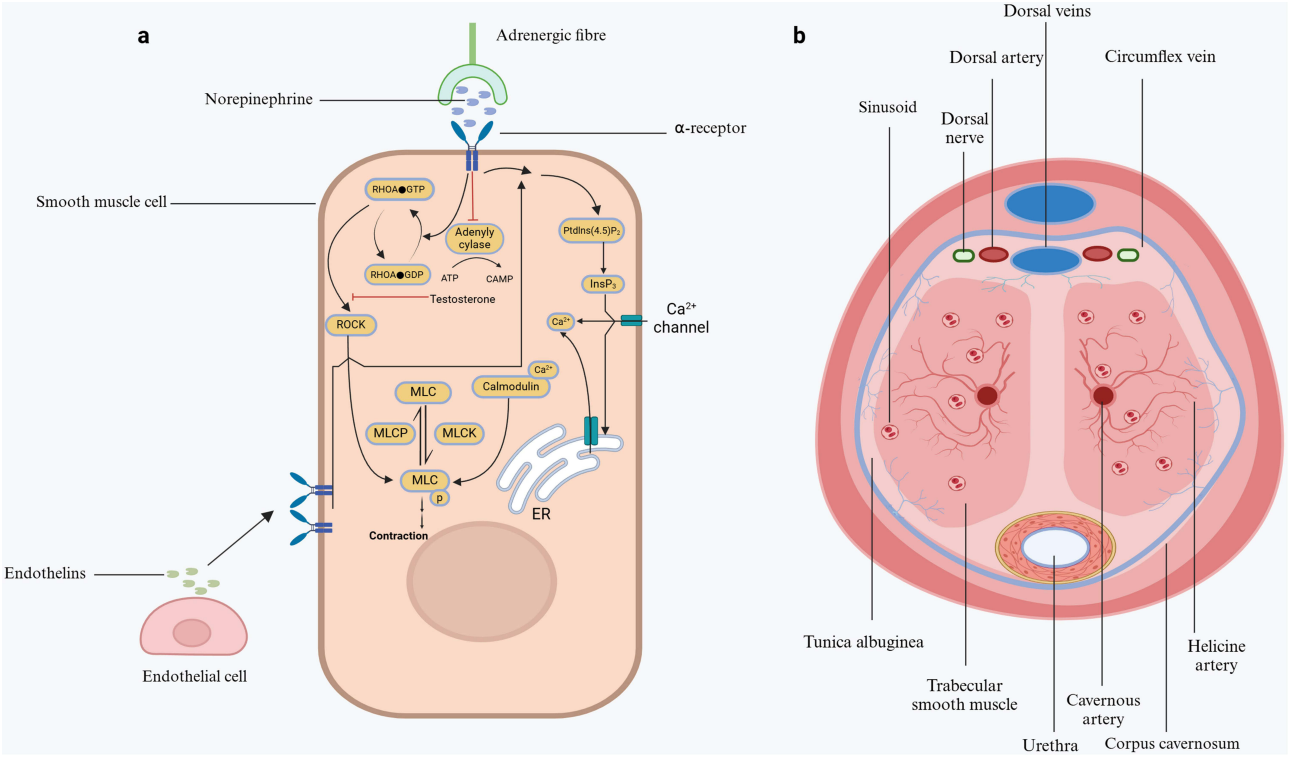

Figure 1 Flaccidity State. a. Intracellular Ca^{2+} influx is regulated by norepinephrine signaling and the level of inositol-1,4,5-trisphosphate ($Ins(1,4,5)P_3$), which is generated by phospholipase C (PLC) from phosphatidylinositol-4,5-bisphosphate ($PtdIns(4,5)P_2$). Elevated intracellular Ca^{2+} binds to calmodulin, facilitating the formation of the calmodulin-myosin light-chain kinase (MLCK) complex. This results in phosphorylation of myosin light chains (MLC), leading to smooth muscle contraction and penile flaccidity. Norepinephrine signaling also inhibits adenylate cyclase and modulates the Rho-associated protein kinase (ROCK) pathway, thereby increasing MLC sensitivity to Ca^{2+}. Testosterone negatively regulates this process. Additionally, endothelin and prostaglandins from the endothelium further elevate intracellular Ca^{2+}, promoting smooth muscle contraction. (**b**) During smooth muscle contraction, minimal blood enters through the cavernosal artery, allowing free outflow via the subtunical venous plexus. ⊣ inhibitory effect; ⟶ promoting effect.

Abbreviations: ER, endoplasmic reticulum; MLCP, myosin light-chain phosphatase.

Stem Cells-Derived Extracellular Vesicles

Since Ernst Haeckel first proposed the concept of "stem cells" in 1868, the exploration of stem cells in scientific research and clinical applications has become one of the key fields of study.[73] In fact, stem cells have significant therapeutic potential for various diseases and have greatly advanced the development of regenerative medicine.[74] Stem cells not only possess self-renewal ability but can also differentiate both in vitro and in vivo into tissues derived from the mesoderm and non-mesodermal layers, ultimately differentiating into mature cells.[75] Based on their differentiation potential, stem cells can be classified into totipotent stem cells (eg, zygotes), pluripotent stem cells (eg, embryonic stem cells), multipotent stem cells (eg, mesenchymal stem cells), oligopotent stem cells, and unipotent stem cells.[76,77] Among them, mesenchymal stem cells (MSCs) are the most commonly used and easily accessible type, considered multipotent adult stem cells. They are nearly non-tumorigenic and free from ethical concerns.[78]

Extracellular particles (EPs) is the preferred overarching term for cell-derived multimolecular assemblies in the nanometre to micron size range, including both EVs and Non-vesicular extracellular particles (NVEPs).[79] EVs is the term for particles that are delimited by a lipid bilayer and cannot replicate on their own (vesicular component of extracellular particles). In addition to naturally released EVs, there are also EV mimetics, artificial cell-derived vesicles (ACDVs), and synthetic vesicles.[79] Other terms, such as exosomes, ectosomes, and microvesicles, are generally used in specific contexts as the research on EVs is finer grained.[79] EVs contain various molecules from within the cell and act as a novel tool for intercellular communication. Based on their size and biological origin, EVs are derived from a wide range of sources, with nearly all living cells capable of releasing EVs. These EVs are rich in RNA, bioactive lipids, and proteins associated with various biological processes.[80–82] Through membrane fusion or endocytosis, they transfer soluble factors, such as growth factors, cytokines, and genetic material, to target cells,[83–86] thereby regulating their biological activity.[87,88] Moreover, EVs can regulate gene

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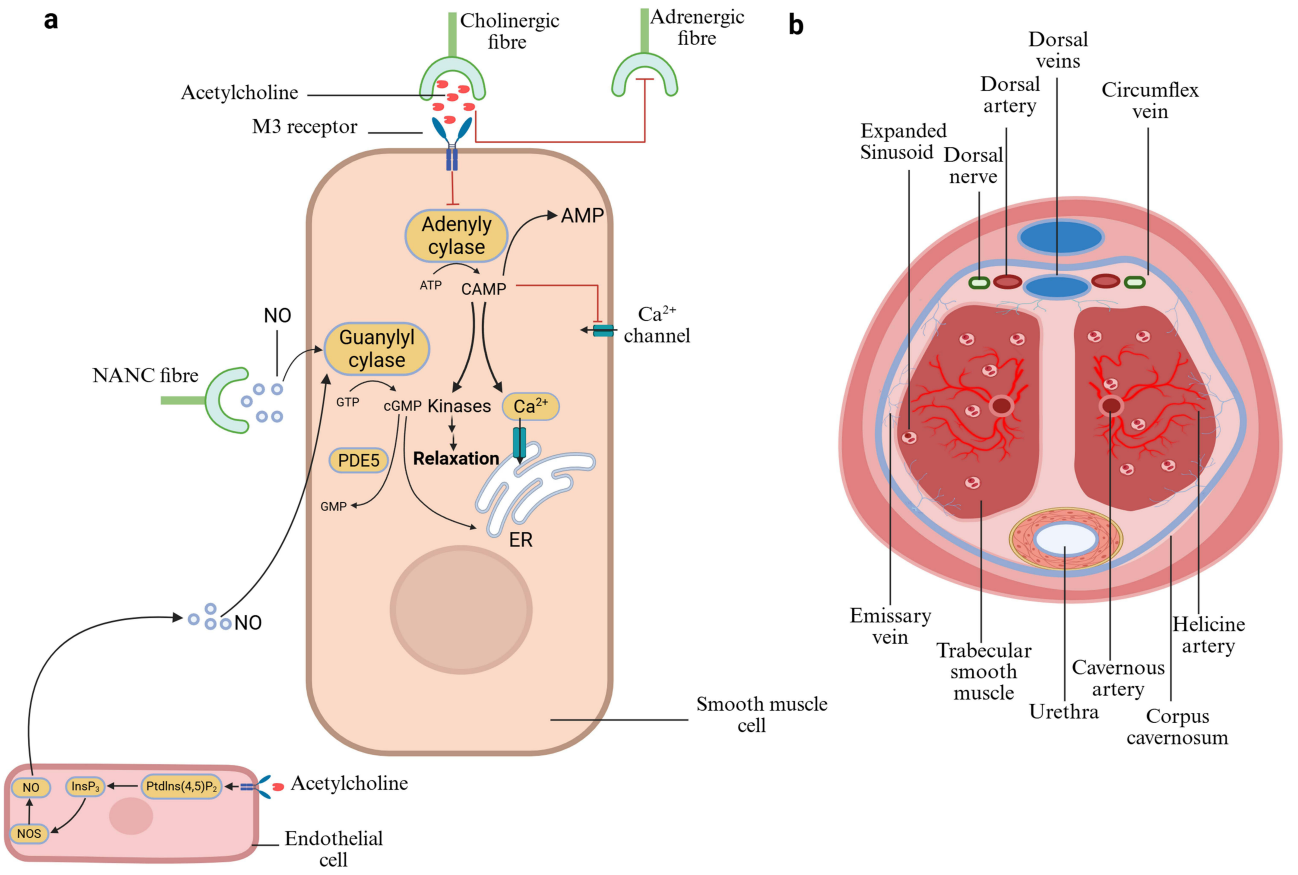

Figure 2 Erection State. (**a**) Upon sexual stimulation, nitric oxide (NO) released from non-adrenergic non-cholinergic (NANC) nerve fibers activates guanylate cyclase, increasing cyclic guanosine monophosphate (cGMP) levels. Concurrently, acetylcholine released from parasympathetic cholinergic nerve fibers activates adenylate cyclase, elevating cyclic adenosine monophosphate (cAMP) levels. (**b**) Smooth muscle relaxation enables blood to fill the cavernosal sinusoids, compressing the subtunical veins and blocking venous outflow. This process reverses when phosphodiesterase type 5 (PDE5) hydrolyzes cGMP. ⊣ inhibitory effect; → promoting effect.
Abbreviations: ER, endoplasmic reticulum; $InsP_3$, inositol trisphosphate; NOS, nitric oxide synthase; $PtdIns(4,5)P_2$, phosphatidylinositol-4,5-bisphosphate.

expression by transporting miRNAs and can program the function of cells involved in tissue repair,[89,90] playing roles in physiological and pathological processes within the body. Due to their broad biological effects, EVs play a key role in regulating the tissue microenvironment, promoting the repair and regeneration of damaged or diseased tissues, and helping to clear unnecessary proteins and toxic substances.[85,91,92] These unique properties make EVs particularly important in the study of the pathophysiological mechanisms of various diseases, including cancer, cardiovascular diseases, infectious diseases, tissue repair and regeneration, and neurodegenerative diseases.[33,85,92–94]

EVs play a significant synergistic role with stem cells in activating immune and inflammatory pathways.[33,34,95] After immune cells reach the site of tissue damage, SCs-EVs regulate the immune process by reducing inflammation and enhancing the local immune response.[82] Specifically, EVs can modulate both innate and adaptive immune responses.[33,34] Broadly, SCs-EVs have been found to perform the following functions: (i) promote the survival of hematopoietic stem cells; (ii) activate monocytes, macrophages, and B cells; (iii) enhance the function of CD4+ regulatory T cells; (iv) inhibit the activity of natural killer cells and CD8+ cytotoxic T cells. Furthermore, studies have reported that EVs can recruit various stem cells from the microenvironment to the site of tissue damage, coordinate their functions, and promote tissue repair.[90,92] Once mobilized, stem cells reach the damaged tissue, where they secrete growth factors and cytokines through paracrine signaling, promoting tissue repair and wound healing.[35,36] Evidence suggests that stem cells can migrate to the injury site via chemotactic gradients and form connections with damaged cells, generating replacement and supporting cells to facilitate tissue regeneration.[96,97] Studies also show that SCs-EVs have broad biological functions, such as promoting the self-renewal of bone marrow cells,[98,99] aiding the repair and regeneration of nerve damage,[100,101]

accelerating skin regeneration after burns,[102,103] inducing angiogenesis in quiescent endothelial cells,[104,105] and influencing the phenotypic differentiation of downstream recruited stem cells.

Since the discovery of the immune-regulating and regenerative properties of EVs, numerous animal models have demonstrated the important role of stem cells and their derived EVs in treating various diseases, including but not limited to skin injury, cardiac injury, spinal cord nerve injury, kidney damage, retinal diseases, arthritis, skeletal deformities, muscle degeneration, liver injury, brain injury, and cancer immunotherapy.[106,107] Importantly, increasing research shows that SCs-EVs can effectively increase smooth muscle content, promote angiogenesis, reduce fibrosis, and thereby restore tissue function.[108–110] Additionally, EVs can inhibit cell apoptosis, reduce neuronal damage, and promote the recovery of neurological functions.[111–113] These findings highlight the tremendous potential of SCs-EVs in restoring the function of tissues and organs.

Given the role of EVs in stem cell recruitment, inflammatory response modulation, and tissue repair, EVs are regarded as a promising new therapeutic tool. They not only serve as carriers for therapeutic molecules but also act as adjunctive drugs to enhance the effects of stem cell transplantation therapy at injury sites (Table 1).[103]

Exploration of Stem Cells-Derived EVs in the Treatment of ED

Stem cells applications in the treatment of ED began relatively late, with relevant studies only emerging in the 21st century.[114] However, significant progress has been made in Stem cells therapy (SCT) for treating ED.[115,116] A wealth of basic research and clinical trials have demonstrated that SCT can partially restore erectile dysfunction caused by various factors and significantly improve patients' quality of life.[117–119] More importantly, stem cells not only alleviate symptoms but also exert therapeutic effects by repairing the underlying pathological mechanisms. These mechanisms include differentiation into specific functional cells, secretion of a large number of growth factors and extracellular vesicles (Table 2), thereby improving the local pathological environment and promoting tissue repair and regeneration (Figure 3).[114,120–122]

Table 1 The Comparison Between Stem Cell Therapy and Stem Cell-Derived Exosome Therapy

Treatment Modality	Advantages	Limitations
Stem cells therapy	Multilineage differentiation potential	Short survival time after injection, low transplantation rate
	Suitable for the treatment of various diseases	Strict storage and transportation requirements
	Accumulation of extensive laboratory and clinical data	Potential tumorigenicity
	Easy to isolate, suitable for large-scale production	Infusion toxicity
	Less pain and fewer complications	Immunogenicity
	Well-established regulatory guidelines	Some stem cells may have ethical issues (eg, embryonic stem cells)
		Preparation process needs improvement
		Variability in therapeutic outcomes
Stem cells-derived extracellular vesicles therapy	Comparable therapeutic effects to stem cells but with a smaller size	Batch-to-batch inconsistency
	More concentrated functional carriers (eg, cytokines)	Lack of standardized purification and storage protocols
	Can be modified on their surface and within the carriers	Relatively low yield in large-scale production
	Various delivery methods	Higher costs
	Long-term storage and high transport efficiency	No industry-standard quality specifications
	EVs derived from non-tumorigenic cells pose minimal tumorigenic risk.	Insufficient regulatory oversight
	Lack of ethical issues	

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Table 2 Summary of Key Studies on Stem Cell-Derived EVs for ED Treatment and Their Mechanisms

Stem Cell EV Source	ED Model	Key Findings	Study Reference
BM-MSC-EVs	Rat (Cavernous nerve injury)	↑ Smooth muscle content, ↑ nNOS; ↓ Caspase-3; Improved erectile function.	[123]
MSC-EVs	Rat (Iliac artery injury)	↑ Endothelialization, ↓ Oxidative stress; Comparable efficacy to whole MSCs.	[124]
CCSMC-EXOs	Rat (Diabetic ED)	Superior uptake and retention; ↑ NO/cGMP pathway; ↓ Fibrosis.	[125]
MSC-EXOs	Rat (Aged ED)	Regulated PTEN/PI3K/AKT via miR-296-5p/miR-337-3p; ↓ Apoptosis.	[126]
ADSC-EVs	Rat (Diabetic ED)	Restored erectile function via ↑ Angiogenesis, ↓ Fibrosis.	[127]
ADSC-EXOs	Rat (Diabetic ED)	↑ Corin gene activity; Improved neurovascular parameters.	[128]
ADSC-EVs	Rat (Type 2 Diabetic ED)	↑ ICP/MAP ratio; ↑ Bcl-2, ↓ Caspase-3; ↓ Endothelial apoptosis.	[129]
ADSC-EVs vs BMSC-EVs	Rat (Bilateral nerve injury)	Both ↑ Cavernous pressure; Enhanced endothelial internalization.	[130]
ADSC-EVs (miR-301a-3p)	Rat (OSA-related ED)	Targeted PTEN/TLR4; ↑ Autophagy, ↓ Apoptosis in smooth muscle.	[131]
Engineered ADSC-Exos (circPIP5K1C)	Rat (CIH-induced ED)	miR-153-3p/SMURF1 axis ↓ Glycolysis; Restored erectile function.	[132]
USC-EVs	Rat (Peyronie's disease)	↓ Fibroblast transformation; Balanced MMP/TIMP; ↓ Tunica albuginea fibrosis.	[133]
USC-EVs	Rat (Diabetic ED)	Pro-angiogenic miRNAs (miR-21-5p, let-7); ↑ CD31/eNOS; ↑ ICP/MAP ratio.	[134]
ESC-NVs	Mouse (Diabetic ED)	↑ Angiogenesis (HGF, Angiopoietin-1) and neuroregeneration (NGF); 96% functional recovery.	[135]
PC-NVs	Mouse (Nerve injury)	Activated Akt/eNOS; ↑ Endothelial tube formation and neuronal sprouting.	[136]
MCP-EVs (miR-148a-3p)	Mouse (Diabetic ED)	↓ PDK4; ↑ Endothelial migration/proliferation; ↓ Apoptosis.	[137]

MSCs-EVs

Mesenchymal stem cells-derived extracellular vesicles (MSCs-EVs) are vesicles secreted by mesenchymal stem cells, rich in a variety of bioactive molecules, including microRNAs, proteins, and lipids. They play an important role in promoting tissue repair, reducing inflammation, and regulating immune responses, and have been widely applied in the treatment of cardiovascular diseases, nerve injuries, and other conditions.

Ouyang et al isolated MSCs-EVs from rat bone marrow and applied them to corpus cavernosum smooth muscle cells (CCSMCs). The study found that treatment with MSCs-EVs significantly increased the smooth muscle content in the corpus cavernosum and the level of neuronal nitric oxide synthase, improved the ratio of smooth muscle to collagen, enhanced CCSMCs viability, and reduced caspase-3, effectively improving erectile dysfunction in a rat model of cavernous nerve injury.[123] Similarly, Liu et al injected MSCs-EVs into the corpus cavernosum of a rat model of ED induced by iliac artery injury. The results indicated that MSCs-EVs could promote endothelial formation in the cavernous sinus, alleviate oxidative stress damage, and increase nitric oxide synthase and smooth muscle content in the corpus cavernosum. Compared with MSCs treatment alone, MSCs-EVs showed similar therapeutic effects but also provided unique advantages, making them an effective means of treating erectile dysfunction caused by arterial injury.[124]

However, the experiments by Ouyang and Song did not further investigate the composition and mechanisms of MSCs-EVs, which is an important aspect for future applications of MSCs-EVs in ED treatment. As research continued, Song et al further validated the effects of MSCs-EVs in a diabetic rat model, confirming that MSCs-EVs could improve erectile function in diabetic erectile dysfunction (DMED) rats. Interestingly, they compared the effects of corpus cavernosum smooth muscle cell-derived exosomes (CCSMCs-EXOs) and MSC-derived exosomes (MSCs-EXOs). The results showed that CCSMCs-EXOs were more readily absorbed by CCSMCs and had a higher peak concentration and longer retention time in the corpus cavernosum. By inhibiting fibrosis and regulating the NO/cGMP signaling pathway (including increasing smooth muscle content, reducing collagen deposition, and elevating NO and cGMP levels), CCSMCs-EXOs significantly improved erectile function in DMED rats.[125] Additionally, Li et al found that injecting MSCs-EXOs into elderly rats improved age-related erectile dysfunction (AED). These EVs regulated the PTEN/PI3K/AKT signaling pathway through miR-296-5p and miR-337-3p, improving the histological structure of the corpus cavernosum and inhibiting cell apoptosis.[126]

MSCs-EVs have effectively alleviated ED caused by nerve injury, diabetes, and arterial injury by improving smooth muscle content in the corpus cavernosum, reducing fibrosis, and influencing key signaling pathways.

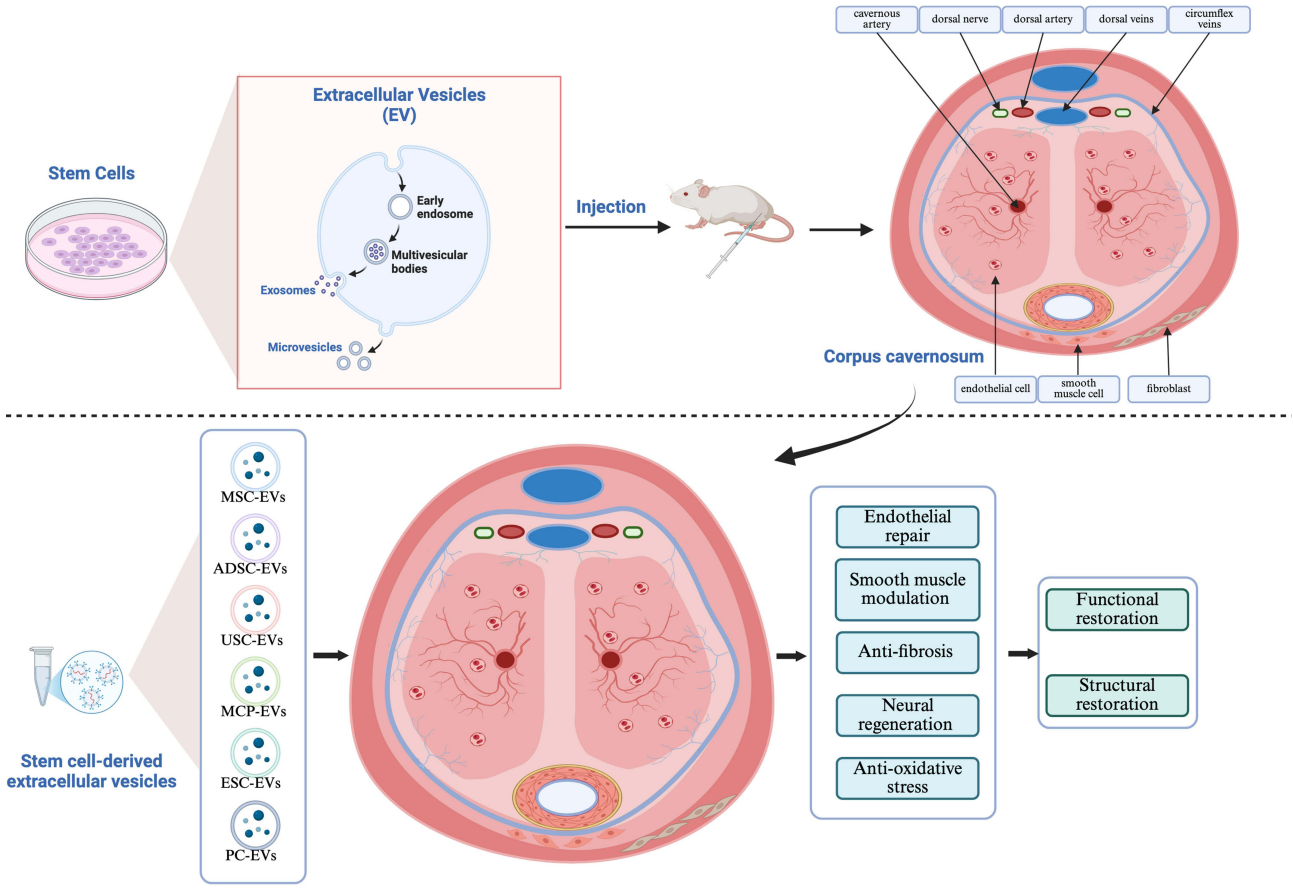

Figure 3 SC-EVs ameliorate ED through comprehensive multi-target mechanisms involving endothelial repair, smooth muscle modulation, antifibrotic processes, and neural regeneration. In endothelial repair, MSC-EVs enhance NO production by upregulating eNOS/nNOS expression and activating the PTEN/PI3K/AKT pathway via miR-296-5p, while USC-EVs promote CD31+/eNOS+ endothelial proliferation and improve erectile function (ICP/MAP ratio) through miR-21-5p and let-7 family-mediated mechanisms. For smooth muscle regulation, MSC-EVs restore contractile function by increasing α-SMA expression and inhibiting caspase-3-dependent apoptosis, whereas ADSC-EVs counteract fibrosis and metabolic dysfunction via miR-301a-3p-mediated PTEN/TLR4 suppression and the circPIP5K1C-miR-153-3p-SMURF1 axis. In antifibrotic processes, USC-EVs reduce collagen deposition by modulating MMP/TIMP balance, while ADSC-EVs enhance endothelial function through corin gene activity. Neural regeneration is facilitated by ESC/PC-EVs, which promote axonal growth through neurotrophin-3 and Schwann cell migration via Akt/eNOS signaling. Additionally, MSC-EVs mitigate oxidative stress by suppressing NOX4 through miR-337-3p, and ADSC-EVs exert antiapoptotic effects by upregulating Bcl-2 and reducing caspase-3 activity, collectively restoring erectile function through synergistic pathways..

ADSCs-EVs

Adipose-derived mesenchymal stem cells-derived extracellular vesicles (ADSCs-EVs) are vesicles secreted by ADSCs that are rich in angiogenic and anti-fibrotic components. These extracellular vesicles show promising potential in improving wound healing, promoting angiogenesis, and alleviating fibrosis, especially in the context of diabetes and ED.

Zhu et al utilized ADSCs-EVs to treat diabetic ED in rats and found that these EVs, containing angiogenic and anti-fibrotic microRNAs, could induce endothelial cell proliferation, restore erectile function, and reduce cavernous fibrosis.[127] Wang et al also applied ADSCs-EXOs to a rat model of diabetic ED. Their results showed that ADSCs-EXOs could restore erectile function in diabetic rats, enhance neurovascular function, and inhibit the expression of inflammatory factors. Furthermore, they identified that the content of the corin gene in EVs was a critical factor in their therapeutic effect.[128] Additionally, Chen et al found that ADSCs-EVs injection significantly improved the ratio of cavernous pressure to mean arterial pressure, increased the smooth muscle to collagen ratio, and promoted the expression of the anti-apoptotic protein Bcl-2 while reducing the apoptotic protein caspase-3, leading to reduced apoptosis of endothelial and smooth muscle cells.[129]

In a bilateral cavernous nerve injury (BCNI) model, Li et al compared ADSCs-EVs with bone marrow mesenchymal stem cells-derived extracellular vesicles (BMSCs-EVs) and found that both types of EVs could effectively internalize into human umbilical vein endothelial cells and improve cavernous function. After treatment, the BCNI rats showed a significant increase in the cavernous pressure/mean arterial pressure ratio, with noticeable improvement in erectile

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function.[130] To further elucidate the specific components of ADSCs-EVs involved in improving ED, Li et al extracted ADSCs-EVs and used them to treat obstructive sleep apnea (OSA)-related ED in rats. The study revealed that ADSCs-EVs, enriched with miR-301a-3p, targeted phosphatase and tensin homolog (PTEN) and Toll-like receptor 4 (TLR4), promoting autophagy and inhibiting apoptosis, which successfully restored erectile function in corpus cavernosum smooth muscle cells. Treatment also significantly elevated α-smooth muscle actin (α-SMA) levels.[131]

Furthermore, Gu et al injected ADSCs-Exos-circ (ADSCs-derived exosomes overexpressing circPIP5K1C) into the corpus cavernosum of OSA-related ED rats. Their findings indicated that ADSCs-Exos-circ improved erectile function induced by chronic intermittent hypoxia (CIH) exposure. The mechanism involved the adsorption of miR-153-3p in the corpus cavernosum, which promoted the expression of the downstream target gene SMURF1, leading to the binding and ubiquitination of SMURF1 and PFKFB3, inhibiting smooth muscle glycolysis, and ultimately restoring smooth muscle function.[132]

ADSCs-EVs show significant therapeutic effects in treating ED associated with diabetes, OSA, and aging by regulating key signaling pathways, reducing fibrosis, and promoting angiogenesis. These findings suggest that ADSCs-derived EVs hold great potential as a therapeutic modality in ED treatment.

USCs-EVs

Urine-derived stem cells-derived extracellular vesicles (USCs-EVs) are extracellular vesicles extracted from urine, rich in various biomolecules such as microRNAs and proteins. These EVs have shown potential in the study of renal diseases, urinary tract infections, and other urological disorders due to their non-invasive nature, serving as biomarkers and therapeutic carriers.

Yang et al injected EVs derived from human urine-derived stem cells (USCs-EVs) into the testes of a Peyronie's disease (PD) rat model. Their findings revealed that USCs-EVs could inhibit the transformation of fibroblasts into myofibroblasts, reduce the expression of tissue inhibitors of metalloproteinases (TIMPs) (−1, −2, and −3), and enhance the activity of matrix metalloproteinases (MMPs) (−1, −3, and −9). These effects significantly improved testicular tunica fibrosis and enhanced erectile function in the rats.[133]

To explore the specific components in USCs-EVs that improve ED, Ouyang et al extracted USCs-EVs and applied them to diabetic ED rat models. The USCs-EVs were found to be rich in angiogenesis-promoting microRNAs (miR-21-5p, let-7 family, miR-10 family, miR-30 family, and miR-148a-3p), which improved the intracavernous pressure (ICP) and the ICP/mean arterial pressure (MAP) ratio. The study demonstrated that USCs-EVs significantly improved the cavernous pressure/mean arterial pressure ratio in rats, increased the expression of CD31, eNOS, phospho-eNOS, and nNOS in the corpus cavernosum, significantly enhanced the smooth muscle to collagen ratio, and improved erectile function in diabetic rats.[134]

These findings highlight the significant role of USCs-EVs in promoting angiogenesis, improving erectile function, and reducing testicular fibrosis induced by diabetes and Peyronie's disease. USCs-EVs hold promise as a potential therapeutic approach for ED, offering non-invasive treatment options with beneficial effects on vascular regeneration and tissue repair.

ESCs-EVs

ESCs-EVs (Embryonic stem cells-derived EVs) are vesicles secreted by embryonic stem cells, which have the ability to promote cell proliferation and differentiation. These EVs hold significant value in regenerative medicine, particularly due to their potential to modulate immune responses and promote tissue repair. They are especially promising in the fields of tissue engineering and regenerative therapies.

Kwon et al extracted embryonic stem cells-derived nanovesicles (ESCs-NVs) and applied them to diabetic ED mice models. The study found that ESC-NVs enhanced the expression of angiogenic factors and neurotrophic factors, such as hepatocyte growth factor (HGF), angiopoietin-1, nerve growth factor (NGF), and neurotrophin-3. Additionally, ESCs-NVs activated cell survival and proliferation pathways, including the Akt and ERK pathways. In high glucose conditions, ESCs-NVs promoted the formation of endothelial and pericyte tubes in primary cultures of mouse cavernous endothelial cells and pericytes, and accelerated the sprouting of microvessels and neurons in the aortic ring and major pelvic ganglia. By enhancing angiogenesis and nerve regeneration in vivo, ESC-NVs completely restored erectile function to

approximately 96% of control values, while ESC treatment alone only partially restored erectile function to about 77% of control values.[135]

These results highlight the potential of ESCs-NVs in significantly improving erectile dysfunction caused by diabetes and nerve damage by enhancing vascular regeneration and nerve repair. ESCs-NVs, through their regenerative properties, could provide a promising therapeutic strategy for ED treatment, particularly in cases where both vascular and neural damage contribute to the dysfunction.

PC-EVs and MCP-EVs

Pericyte-derived EVs (PC-EVs) are vesicles secreted by pericytes, which play crucial roles in regulating vascular function, supporting cell survival, and promoting tissue repair. These EVs show potential therapeutic applications in cardiovascular diseases, neurodegenerative disorders, and the tumor microenvironment.

Yin et al demonstrated the positive effects of PC-NVs (pericyte-derived nanovesicles) in a mouse model of cavernous nerve injury. Their research showed that PC-NVs promoted endothelial cell tube formation, Schwann cell migration, and neuronal sprouting. Additionally, PC-NVs significantly enhanced cell survival signaling pathways (such as Akt and eNOS) and induced the expression of neurotrophic factors, ultimately improving erectile function.[136]

Mouse corpus cavernous pericyte-derived extracellular vesicle (MCP-EVs) also reflect the physiological state and functional characteristics of the originating cells. These EVs contain various bioactive molecules and play a key role in studying intercellular interactions, disease mechanisms, and potential therapeutic approaches. Ock et al injected MCP-EVs into diabetic ED mice, and the study revealed that miR-148a-3p in MCP-EVs inhibited PDK4 expression, promoting the migration, proliferation, and tube formation of mouse cavernous endothelial cells (MCECs). Additionally, MCP-EVs reduced MCECs apoptosis under high-glucose conditions, thereby improving erectile function in diabetic mice.[137] PC-NVs and MCP-EVs can effectively improve erectile function in diabetic ED mice by enhancing angiogenesis, promoting nerve regeneration, and reducing cell apoptosis.

The therapeutic potential of stem cell-derived EVs (MSCs-EVs, ADSCs-EVs, USCs-EVs, ESCs-EVs, etc) has been demonstrated across different types of ED, not limited to neurogenic or age-related ED, but also extending to diabetes and other endocrine-related ED.[125,138,139] These EVs improve cavernous body function through mechanisms such as promoting angiogenesis, inhibiting fibrosis, and enhancing cell survival. EVs-based therapies present a promising supplement to standard ED treatments, particularly in cases where conventional methods are less effective or not applicable.

However, there remains a lack of detailed research into the content and specific mechanisms of EVs, which limits our understanding of their mode of action. Future studies should focus on identifying specific biomarkers and functional components in EVs derived from different sources of stem cells, to better elucidate their roles in promoting angiogenesis, antifibrosis, and cell protection.

Engineered SCs-EVs: Strategies and Applications in ED

Tissue engineering approaches that integrate biotechnology, materials science, and engineering methodologies have provided innovative solutions for ED treatment. These therapeutic strategies offer distinct advantages including precise targeting capability, minimal immunogenicity, and significant tissue regenerative potential. Engineered stem cells, through genetic editing and bioengineering techniques, enable precise modulation of cellular functions to substantially enhance tissue repair capacity. Engineered EVs, serving as biomimetic nanocarriers derived from natural EVs, demonstrate tremendous promise in precision medicine following genetic or molecular modifications.[140,141] Research has shown that EVs exhibit excellent tissue tropism in various disease models. Local administration in myocardial infarction,[142] ischemic limb,[143] or murine wound healing models[144] results in rapid accumulation within target tissues within hours, providing a rationale for sustained-release strategies to optimize tissue regeneration.

Current engineering strategies for EVs primarily fall into two categories: First, parental cell modification through vectors that induce progenitor cells to express specific proteins or non-coding RNAs,[145] enabling packaging of these therapeutic molecules into EVs for release in specific microenvironments.[146] Second, direct EV modification approaches including genetic engineering, metabolic engineering, and surface molecular engineering.[147,148] For instance, membrane

permeabilization techniques allow small molecule drug loading into EVs, while biochemical modifications enable covalent conjugation of chemotherapeutic agents or siRNA to EVs surfaces for tissue-specific targeted therapy.[147,149]

In the field of ED treatment, engineered stem cells and EVs have achieved remarkable progress. For example, Liu et al generated OE-miR-145-BMSCs by transfecting bone marrow mesenchymal stem cells (BMSCs) with lentivirus overexpressing miR-145, which significantly increased smooth muscle content and elevated expression of α-SMA, desmin, and SM-MHC in penile tissues of ED rats.[150] Kim's team seeded mesenchymal stem cells onto nanofiber scaffolds and transplanted them around injured cavernous nerves, successfully promoting regeneration of neurons, endothelial cells, and smooth muscle.[151] Fu et al developed a black phosphorus nanosheet-SDF1α complex (BP@SDF1-α) that effectively recruits endogenous/exogenous stem cells, markedly improving ED caused by nerve injury.[152] Chen et al discovered that melatonin-pretreated MSC-EVs (MT-EVs) improved corpus cavernosum smooth muscle function via the miR-10a-3p/PKIA/RhoA/ROCK pathway.[153] Zhang's team demonstrated that MSC-EVs enriched with miR-200a-3p alleviated oxidative stress damage in diabetic ED through the Keap1/Nrf2 pathway.[154] Huo et al transfected miR-21-5p into MSCs and isolated modified exosomes (miR-21-5p-MSC-Exos) that reduced apoptosis and increased proliferation of corpus cavernosum smooth muscle cells (CCSMCs), improving diabetes-induced ED and smooth muscle density.[155] Additionally, miR-126-modified muscle-derived stem cell EVs targeted IRS1/KLF10 to promote cavernosal repair,[156] while MCP-derived EVs delivering Hebp1 enhanced neurovascular regeneration.[157]

However, direct injection of exosomes into injured areas may yield suboptimal results, as free exosomes in aqueous solutions struggle to remain localized in target regions, leading to washout or rapid clearance that prevents full biological functionality.[158] Therefore, effective tissue repair requires an exosome delivery vehicle with dose- and time-dependent controlled release properties, minimal adverse effects on exosome internalization, and appropriate degradation rates.[159] The combination of exosomes with biomaterials has partially addressed these challenges, with hydrogels being the most widely utilized. Materials such as hyaluronic acid,[144,160,161] alginate,[162,163] chitosan,[164,165] and collagen[166,167] can form stable delivery carriers through physical or chemical conjugation with EVs, significantly prolonging EV retention in target tissues.[144,161,163,165,167,168] These biomaterial-based EV delivery systems have markedly enhanced their potential for tissue repair applications.

The development of intelligent delivery systems has further improved therapeutic outcomes. Liu et al's injectable thermosensitive hydroxyethyl chitosan hydrogel (HG@Exo) substantially extended ADSC-Exos retention time and improved ED following nerve injury.[169] Zhuang's team combined USC-EVs with hyaluronic acid (USC-EVs-HA) to effectively enhance endothelial cell function.[170] Liang et al designed a polydopamine nanoparticle composite hydrogel (PDNPs-PELA) that combines photoacoustic navigation with controlled release capabilities, promoting endothelial cell and neuronal regeneration while increasing intracavernosal pressure to restore erectile function.[171]

SC-EVs play a crucial role in promoting tissue regeneration, while engineered EVs strategies offer additional advantages including diversified administration routes, enhanced drug-loading capacity, reduced side effects, improved targeting precision, controllable release mechanisms, and fewer ethical concerns, demonstrating excellent clinical translation potential. Future research should further explore combinatorial applications of multiple engineered EVs platforms or their integration with other therapeutic modalities such as pharmacotherapy, physical therapy, or biomaterials to optimize treatment efficacy.

Prospects and Challenges

SC-EVs demonstrate unique therapeutic potential for ED, particularly in addressing the multifactorial pathogenesis involving vascular insufficiency, neural damage, and smooth muscle dysfunction. The primary bottleneck lies in EVs heterogeneity, where variations in cellular sources and isolation methods lead to divergent biological properties, compromising treatment predictability.[140,172] Scaling up production remains problematic, with clinical-grade EVs requiring optimization in both yield and purity.[141,148] The primary challenge lies in penile tissue-specific delivery, as the unique anatomical structure of corporal tissue presents distinct barriers for EVs homing. Current studies show only partial accumulation of intravenously administered EVs in the penile tissue, with significant off-target distribution to other organs.[173–175] The lack of definitive surface markers for corpus cavernosum endothelial cells and smooth muscle cells hampers targeted delivery design.[176,177] Moreover, current research predominantly focuses on final therapeutic

outcomes, with most studies examining single-factor triggers or isolated biomarkers, failing to replicate the intricate penile microenvironment.[178] In addition, the unique hemodynamic environment during erection affects EVs retention, requiring specially engineered formulations.[178]

Production challenges are particularly acute for ED applications, where clinical-grade EVs demand: Advanced biomanufacturing platforms including microfluidic systems and bioreactors show promise for scaling up clinical-grade EVs production while maintaining quality standards, higher purity standardsto avoid pro-inflammatory responses in sensitive penile tissue, specialized cryopreservation protocols to maintain bioactivity after intracavernosal injection, scalable manufacturing for chronic administration needs in ED patients.[179–181] Nanotechnology and novel biomaterials are being leveraged to improve targeted delivery precision, ensuring focused action on damaged penile tissues.[182–184] Furthermore, by optimizing electroporation, membrane fusion, 3D printing and other technical means, the loading efficiency of therapeutic molecules can be improved, immune response can be reduced and safety can be enhanced, thus enhancing the overall therapeutic efficacy and safety for ED.[185–187] Ethical considerations are being addressed through stringent review frameworks ensuring compliant cell sourcing, transparent informed consent protocols, and multi-stakeholder engagement involving scientists, ethicists, and public representatives to balance scientific progress with social responsibility.

The transition from animal models to human clinical trials represents a pivotal phase in EVs therapeutics development. While translational pathways are becoming clearer.[188] The clinical trial, which starts on September 18, 2024, focuses on evaluating the role of SC-EVs in ED. Participants will receive an injection directly into the penis and blood flow will be checked through a specific scoring system and ultrasound testing. Participants will undergo multiple assessments at the start and then be followed up at 3, 6, 9 and 12 months to track their progress and any side effects (ClinicalTrials.gov identifier (NCT number): NCT06605508). Large-scale clinical validation remains essential for determining optimal treatment parameters including dosage, administration routes, and long-term efficacy. These systematic investigations will facilitate the translation of SC-EVs therapies from bench to bedside, ultimately providing ED patients with safer and more effective treatment options. Future directions should emphasize standardized production protocols, comprehensive safety profiling, and development of combinatorial approaches to address ED's multifactorial pathophysiology.

Summary

SC-EVs have demonstrated remarkable potential in the treatment of ED, particularly as an effective alternative to stem cell therapy in the fields of regenerative medicine, anti-inflammation, anti-apoptosis, and immunomodulation. By modulating multiple signaling pathways (eg, NO/cGMP, miR-10a-3p/PKIA/RhoA/ROCK, and PTEN/PI3K/Akt), SC-EVs can ameliorate various ED-related pathophysiological conditions, including cavernous nerve injury, oxidative stress-induced tissue fibrosis, and vascular endothelial dysfunction. Notably, engineered extracellular vesicles with enhanced targeting capabilities have shown improved therapeutic efficacy.

It is important to recognize that the therapeutic effects of SC-EVs vary depending on the etiology of ED. For diabetic ED, MSC-EVs and ADSC-EVs primarily exert their benefits by improving endothelial dysfunction and exerting antifibrotic effects, thereby restoring the smooth muscle/collagen ratio and NO signaling. Among these, CCSMC-EVs exhibit superior cellular uptake and longer-lasting therapeutic effects. In contrast, neurogenic ED benefits more significantly from ESC-EVs and MSC-EVs, which promote neural repair through neurotrophic factor delivery and vascular-nerve crosstalk. These differences highlight the importance of selecting EV subtypes based on the underlying pathology—antifibrotic EVs for diabetic ED and proneurogenic EVs for nerve injury-related ED—to optimize treatment outcomes. This tailored approach underscores the potential of SC-EVs as a precision medicine strategy for ED subtypes.

Despite these advances, specific challenges related to ED remain. First, the consequences of penile fibrosis often indicate that cells are processing chronic inflammatory states, and the high inflammatory state of the extracellular environment may prematurely disrupt the phospholipid bilayer of extracellular vesicles, leading to their premature lysis. Second, a hypoxic microenvironment can lead to excessive lactic acid secretion, and the extracellular environment is often acidic, which may also damage extracellular vesicles. This is similar to the limited efficacy of many oral extracellular vesicle therapies. Third, the targeting of extracellular vesicles remains inadequate. Even engineered

extracellular vesicles require specific targeting molecules, but current research on penile cell surface-specific molecules is insufficient. In summary, these specificity challenges limit the biodistribution and targeted therapeutic efficacy of extracellular vesicles. Therefore, innovative technological development is needed, such as considering collagenase-activated extracellular vesicles resistant to external interference or hypoxia-targeted delivery systems, especially appropriate administration methods such as local injection or topical application. Future research should prioritize extracellular vesicles customized according to the etiology of ED, as well as multimodal treatment regimens combining extracellular vesicles with existing therapies. The focus should be on integrating engineered innovations with the complex pathophysiology of ED to redefine the treatment standards for this debilitating condition using stem cell-derived extracellular vesicles (SCs-EVs).

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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.

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References

1. Shah J. Erectile dysfunction through the ages. *BJU Int*. 2002;90(4):433–441. doi:10.1046/j.1464-410X.2002.02911.x
2. Consensus development conference statement. National institutes of health. impotence. December 7-9, 1992. *Int J Impot Res*. 1993;5(4):181–284.
3. Lewis RW, Fugl-Meyer KS, Corona G, et al. Definitions/epidemiology/risk factors for sexual dysfunction. *J Sex Med*. 2010;7(4 Pt 2):1598–1607. doi:10.1111/j.1743-6109.2010.01778.x
4. Corona G, Dm L, Forti G, et al. Age-related changes in general and sexual health in middle-aged and older men: results from the European Male Ageing Study (EMAS). *J Sex Med*. 2010;7(4 Pt 1):1362–1380. doi:10.1111/j.1743-6109.2009.01601.x
5. Béjin A. Epidémiologie de l'éjaculation prématurée et de son cumul avec la dysfunction érectile. *Andrologie*. 1999;9(2):211–225. doi:10.1007/BF03035234
6. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res*. 2000;12(6):305–311. doi:10.1038/sj.ijir.3900622
7. Pinnock CB, Stapleton AM, Marshall VR. Erectile dysfunction in the community: a prevalence study. *Med J Aust*. 1999;171(7):353–357. doi:10.5694/j.1326-5377.1999.tb123691.x
8. Nicolosi A, Glasser DB, Kim SC, Marumo K, Laumann EO. Sexual behaviour and dysfunction and help-seeking patterns in adults aged 40-80 years in the urban population of Asian countries. *BJU Int*. 2005;95(4):609–614. doi:10.1111/j.1464-410X.2005.05348.x
9. Nicolosi A, Moreira ED Jr, Shirai M, Bin Mohd Tambi MI, Glasser DB. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. *Urology*. 2003;61(1):201–206. doi:10.1016/S0090-4295(02)02102-7
10. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. *Ann Intern Med*. 2003;139(3):161–168. doi:10.7326/0003-4819-139-3-200308050-00005
11. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int*. 1999;84(1):50–56. doi:10.1046/j.1464-410x.1999.00142.x
12. Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA*. 2004;291(24):2978–2984. doi:10.1001/jama.291.24.2978
13. Esposito K, Ciotola M, Giugliano F, et al. Effects of intensive lifestyle changes on erectile dysfunction in men. *J Sex Med*. 2009;6(1):243–250. doi:10.1111/j.1743-6109.2008.01030.x
14. Esposito K, Giugliano D. Lifestyle/dietary recommendations for erectile dysfunction and female sexual dysfunction. *Urol Clin North Am*. 2011;38(3):293–301. doi:10.1016/j.ucl.2011.04.006
15. Esposito K, Giugliano F, De Sio M, et al. Dietary factors in erectile dysfunction. *Int J Impot Res*. 2006;18(4):370–374. doi:10.1038/sj.ijir.3901438

16. Esposito K, Ciotola M, Giugliano F, et al. Mediterranean diet improves erectile function in subjects with the metabolic syndrome. *Int J Impot Res*. 2006;18(4):405–410. doi:10.1038/sj.ijir.3901447
17. Dorey G, Speakman MJ, Feneley RC, Swinkels A, Dunn CD. Pelvic floor exercises for erectile dysfunction. *BJU Int*. 2005;96(4):595–597. doi:10.1111/j.1464-410X.2005.05690.x
18. Hedon F. Anxiety and erectile dysfunction: a global approach to ED enhances results and quality of life. *Int J Impot Res*. 2003;15 Suppl 2:S16–19. doi:10.1038/sj.ijir.3900994
19. Lue TF. Neurogenic erectile dysfunction. *Clin Auton Res*. 2001;11(5):285–294. doi:10.1007/BF02332973
20. Yang Z, Du G, Ma L, Lv Y, Zhao Y, Yau TO. Continuous positive airway pressure therapy in obstructive sleep apnoea patients with erectile dysfunction-A meta-analysis. *Clin Respir J*. 2021;15(2):163–168. doi:10.1111/crj.13280
21. Manolis A, Doumas M, Ferri C, Mancia G. Erectile dysfunction and adherence to antihypertensive therapy: focus on β-blockers. *Eur J Intern Med*. 2020;81:1–6. doi:10.1016/j.ejim.2020.07.009
22. Corona G, Rastrelli G, Monami M, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol*. 2011;165(5):687–701. doi:10.1530/EJE-11-0447
23. Guay AT, Perez JB, Jacobson J, Newton RA. Efficacy and safety of sildenafil citrate for treatment of erectile dysfunction in a population with associated organic risk factors. *J Androl*. 2001;22(5):793–797. doi:10.1002/j.1939-4640.2001.tb02582.x
24. Kouvelas D, Goulas A, Papazisis G, Sardeli C, Pourzitaki C. PDE5 inhibitors: in vitro and in vivo pharmacological profile. *Curr Pharm Des*. 2009;15(30):3464–3475. doi:10.2174/138161209789206971
25. Fisher WA, Rosen RC, Eardley I, et al. The multinational Men's Attitudes to Life Events and Sexuality (MALES) Study Phase II: understanding PDE5 inhibitor treatment seeking patterns, among men with erectile dysfunction. *J Sex Med*. 2004;1(2):150–160. doi:10.1111/j.1743-6109.2004.04023.x
26. Sairam K, Kulinskaya E, Hanbury D, Boustead G, McNicholas T. Oral sildenafil (Viagra) in male erectile dysfunction: use, efficacy and safety profile in an unselected cohort presenting to a British district general hospital. *BMC Urol*. 2002;2:4. doi:10.1186/1471-2490-2-4
27. Tomlinson J, Wright D. Impact of erectile dysfunction and its subsequent treatment with sildenafil: qualitative study. *BMJ*. 2004;328 (7447):1037. doi:10.1136/bmj.38044.662176.EE
28. Mehrotra N, Gupta M, Kovar A, Meibohm B. The role of pharmacokinetics and pharmacodynamics in phosphodiesterase-5 inhibitor therapy. *Int J Impot Res*. 2007;19(3):253–264. doi:10.1038/sj.ijir.3901522
29. Supuran CT, Mastrolorenzo A, Barbaro G, Scozzafava A. Phosphodiesterase 5 inhibitors–drug design and differentiation based on selectivity, pharmacokinetic and efficacy profiles. *Curr Pharm Des*. 2006;12(27):3459–3465. doi:10.2174/138161206778343118
30. Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. *BJU Int*. 2005;96(3):257–280. doi:10.1111/j.1464-410X.2005.05614.x
31. Defeudis G, Mazzilli R, Tenuta M, et al. Erectile dysfunction and diabetes: a melting pot of circumstances and treatments. *Diabetes Metab Res Rev*. 2022;38(2):e3494. doi:10.1002/dmrr.3494
32. Mirza M, Griebling TL, Kazer MW. Erectile dysfunction and urinary incontinence after prostate cancer treatment. *Semin Oncol Nurs*. 2011;27 (4):278–289. doi:10.1016/j.soncn.2011.07.006
33. Robbins PD, Morelli AE. Regulation of immune responses by extracellular vesicles. *Nat Rev Immunol*. 2014;14(3):195–208. doi:10.1038/nri3622
34. Holodick NE, Rothstein TL. B cells in the aging immune system: time to consider B-1 cells. *Ann N Y Acad Sci*. 2015;1362(1):176–187. doi:10.1111/nyas.12825
35. Ullah M, Sun Z. Stem cells and anti-aging genes: double-edged sword-do the same job of life extension. *Stem Cell Res Ther*. 2018;9(1):3. doi:10.1186/s13287-017-0746-4
36. Kanada M, Bachmann MH, Contag CH. Signaling by extracellular vesicles advances cancer hallmarks. *Trends Cancer*. 2016;2(2):84–94. doi:10.1016/j.trecan.2015.12.005
37. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol*. 2018;19(4):213–228. doi:10.1038/nrm.2017.125
38. Fa Y, Jenkins L, Albersen M, et al. Erectile dysfunction. *Nat Rev Dis Primers*. 2016;2:16003. doi:10.1038/nrdp.2016.3
39. Mobley DF, Khera M, Baum N. Recent advances in the treatment of erectile dysfunction. *Postgrad Med J*. 2017;93(1105):679–685. doi:10.1136/postgradmedj-2016-134073
40. Shamloul R. Management of honeymoon impotence. *J Sex Med*. 2006;3(2):361–366. doi:10.1111/j.1743-6109.2005.00092.x
41. Corona G, Mannucci E, Lotti F, et al. Impairment of couple relationship in male patients with sexual dysfunction is associated with overt hypogonadism. *J Sex Med*. 2009;6(9):2591–2600. doi:10.1111/j.1743-6109.2009.01352.x
42. Muneer A, Kalsi J, Nazareth I, Arya M. Erectile dysfunction. *BMJ*. 2014;348:g129. doi:10.1136/bmj.g129
43. Velurajah R, Brunckhorst O, Waqar M, McMullen I, Ahmed K. Erectile dysfunction in patients with anxiety disorders: a systematic review. *Int J Impot Res*. 2022;34(2):177–186. doi:10.1038/s41443-020-00405-4
44. Manalo TA, Biermann HD, Patil DH, Mehta A. The temporal association of depression and anxiety in young men with erectile dysfunction. *J Sex Med*. 2022;19(2):201–206. doi:10.1016/j.jsxm.2021.11.011
45. Seidman SN, Roose SP. The relationship between depression and erectile dysfunction. *Curr Psychiatry Rep*. 2000;2(3):201–205. doi:10.1007/s11920-996-0008-0
46. Seagraves RT. Depression and erectile dysfunction. *Postgrad Med*. 2000;107(6 Suppl Educational):24–27. doi:10.3810/pgm.5.15.2000.suppl5.29
47. Jaeger VK, Walker UA. Erectile Dysfunction in Systemic Sclerosis. *Curr Rheumatol Rep*. 2016;18(8):49. doi:10.1007/s11926-016-0597-5
48. Singer C, Weiner WJ, Sanchez-Ramos J, Ackerman M. Sexual function in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1991;54(10):942. doi:10.1136/jnnp.54.10.942
49. Zeiss AM, Davies HD, Wood M, Tinklenberg JR. The incidence and correlates of erectile problems in patients with Alzheimer's disease. *Arch Sex Behav*. 1990;19(4):325–331. doi:10.1007/BF01541927
50. Palmer JS, Kaplan WE, Firlit CF. Erectile dysfunction in spina bifida is treatable. *Lancet*. 1999;354(9173):125–126. doi:10.1016/S0140-6736(99)02480-0

51. Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. *J Urol*. 1982;128(3):492–497. doi:10.1016/S0022-5347(17)53012-8
52. Traish AM, Munarriz R, O'Connell L, et al. Effects of medical or surgical castration on erectile function in an animal model. *J Androl*. 2003;24(3):381–387. doi:10.1002/j.1939-4640.2003.tb02686.x
53. Kim H, Kim KT, Shin WC, Yang KI, Ha JY, Cho YW. Erectile dysfunction in patient with obstructive sleep apnea: effects of continuous positive airway pressure. *Aging Male*. 2024;27(1):2317165. doi:10.1080/13685538.2024.2317165
54. Rosen RC, Link CL, Mp O, Giuliano F, Aiyer LP, Mollon P. Lower urinary tract symptoms and sexual health: the role of gender, lifestyle and medical comorbidities. *BJU Int*. 2009;103 Suppl 3:42–47. doi:10.1111/j.1464-410X.2009.08370.x
55. Inman BA, Sauver JL, Jacobson DJ, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc*. 2009;84(2):108–113. doi:10.4065/84.2.108
56. Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. *JAMA*. 2005;294(23):2996–3002. doi:10.1001/jama.294.23.2996
57. Quek KF, Sallam AA, Ng CH, Chua CB. Prevalence of sexual problems and its association with social, psychological and physical factors among men in a Malaysian population: a cross-sectional study. *J Sex Med*. 2008;5(1):70–76. doi:10.1111/j.1743-6109.2006.00423.x
58. Clark NG, Fox KM, Grandy S. Symptoms of diabetes and their association with the risk and presence of diabetes: findings from the study to help improve early evaluation and management of risk factors leading to diabetes (SHIELD). *Diabetes Care*. 2007;30(11):2868–2873. doi:10.2337/dc07-0816
59. Ponholzer A, Gutjahr G, Temml C, Madersbacher S. Is erectile dysfunction a predictor of cardiovascular events or stroke? A prospective study using a validated questionnaire. *Int J Impot Res*. 2010;22(1):25–29. doi:10.1038/ijir.2009.40
60. Chung SD, Chen YK, Lin HC, Lin HC. Increased risk of stroke among men with erectile dysfunction: a nationwide population-based study. *J Sex Med*. 2011;8(1):240–246. doi:10.1111/j.1743-6109.2010.01973.x
61. Azadzoi KM, Saenz de Tejada I. Diabetes mellitus impairs neurogenic and endothelium-dependent relaxation of rabbit corpus cavernosum smooth muscle. *J Urol*. 1992;148(5):1587–1591. doi:10.1016/S0022-5347(17)36975-6
62. Baraghoush A, Phan A, Willix RD Jr, Schwarz ER. Erectile dysfunction as a complication of heart failure. *Curr Heart Fail Rep*. 2010;7(4):194–201. doi:10.1007/s11897-010-0023-7
63. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. *J Am Coll Cardiol*. 2011;58(13):1378–1385. doi:10.1016/j.jacc.2011.06.024
64. Shamloul R, Ghanem H. Erectile dysfunction. *Lancet*. 2013;381(9861):153–165. doi:10.1016/S0140-6736(12)60520-0
65. Cheng JY, Ng EM. Body mass index, physical activity and erectile dysfunction: an U-shaped relationship from population-based study. *Int J Obes*. 2007;31(10):1571–1578. doi:10.1038/sj.ijo.0803639
66. Rosen RC, Wing R, Schneider S, Gendrano N. Epidemiology of erectile dysfunction: the role of medical comorbidities and lifestyle factors. *Urol Clin North Am*. 2005;32(4):403–417,v. doi:10.1016/j.ucl.2005.08.004
67. Av S, Jm H, Ih DB, et al. Blood pressure, antihypertensive medication use, and risk of erectile dysfunction in men with type I diabetes. *J Hypertens*. 2019;37(5):1070–1076. doi:10.1097/HJH.0000000000001988
68. Prieto D. Physiological regulation of penile arteries and veins. *Int J Impot Res*. 2008;20(1):17–29. doi:10.1038/sj.ijir.3901581
69. Andersson KE, Wagner G. Physiology of penile erection. *Physiol Rev*. 1995;75(1):191–236. doi:10.1152/physrev.1995.75.1.191
70. Saenz de Tejada I, Kim N, Lagan I, Krane RJ, Goldstein I. Regulation of adrenergic activity in penile corpus cavernosum. *J Urol*. 1989;142(4):1117–1121. doi:10.1016/S0022-5347(17)39009-2
71. Lue TF. Erectile dysfunction. *N Engl J Med*. 2000;342(24):1802–1813. doi:10.1056/NEJM200006153422407
72. Lue TF, Tanagho EA. Physiology of erection and pharmacological management of impotence. *J Urol*. 1987;137(5):829–836. doi:10.1016/S0022-5347(17)44267-4
73. Vasuri F, Fittipaldi S, Pasquinelli G. Arterial calcification: finger-pointing at resident and circulating stem cells. *World J Stem Cells*. 2014;6(5):540–551. doi:10.4252/wjsc.v6.i5.540
74. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. *Stem Cell Res Ther*. 2019;10(1):68. doi:10.1186/s13287-019-1165-5
75. Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: cell biology to clinical progress. *NPJ Regen Med*. 2019;4:22. doi:10.1038/s41536-019-0083-6
76. Castiglione F, Cakir OO, Satchi M, Fallara G, Pang KH. The current role and implications of stem cell therapy in erectile dysfunction: a transformation from caterpillar to butterfly is required. *Eur Urol Focus*. 2023;9(1):28–31. doi:10.1016/j.euf.2022.11.009
77. Sarkar A, Saha S, Paul A, Maji A, Roy P, Maity TK. Understanding stem cells and its pivotal role in regenerative medicine. *Life Sci*. 2021;273:119270. doi:10.1016/j.lfs.2021.119270
78. Campbell JD, Milenkovic U, Usta MF, Albersen M, Bivalacqua TJ. The good, bad, and the ugly of regenerative therapies for erectile dysfunction. *Transl Androl Urol*. 2020;9(Suppl 2):S252–s261. doi:10.21037/tau.2019.10.06
79. Ja W, Dci G, 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
80. Couzin J. Cell biology: the ins and outs of exosomes. *Science*. 2005;308(5730):1862–1863. doi:10.1126/science.308.5730.1862
81. De Jong OG, Van Balkom BW, Schiffelers RM, Bouten CV, Verhaar MC. Extracellular vesicles: potential roles in regenerative medicine. *Front Immunol*. 2014;5:608. doi:10.3389/fimmu.2014.00608
82. Buzas EI, György B, Nagy G, Falus A, Gay S. Emerging role of extracellular vesicles in inflammatory diseases. *Nat Rev Rheumatol*. 2014;10(6):356–364. doi:10.1038/nrrheum.2014.19
83. Zhang B, Yeo RW, Tan KH, Lim SK. Focus on extracellular vesicles: therapeutic potential of stem cell-derived extracellular vesicles. *Int J Mol Sci*. 2016;17(2):174. doi:10.3390/ijms17020174
84. Tkach M, Théry C. Communication by extracellular vesicles: where we are and where we need to go. *Cell*. 2016;164(6):1226–1232. doi:10.1016/j.cell.2016.01.043

85. Koniusz S, Andrzejewska A, Muraca M, Srivastava AK, Janowski M, Lukomska B. Extracellular vesicles in physiology, pathology, and therapy of the immune and central nervous system, with focus on extracellular vesicles derived from mesenchymal stem cells as therapeutic tools. *Front Cell Neurosci*. 2016;10:109. doi:10.3389/fncel.2016.00109
86. Belov L, Matic KJ, Hallal S, Best OG, Mulligan SP, Christopherson RI. Extensive surface protein profiles of extracellular vesicles from cancer cells may provide diagnostic signatures from blood samples. *J Extracell Vesicles*. 2016;5:25355. doi:10.3402/jev.v5.25355
87. Raik S, Kumar A, Bhattacharyya S. Insights into cell-free therapeutic approach: role of stem cell "soup-ernatant". *Biotechnol Appl Biochem*. 2018;65(2):104–118. doi:10.1002/bab.1561
88. Sr B, Rooijers K, Koppers-Lalic D, et al. Human bone marrow- and adipose-mesenchymal stem cells secrete exosomes enriched in distinctive miRNA and tRNA species. *Stem Cell Res Ther*. 2015;6(1):127. doi:10.1186/s13287-015-0116-z
89. Riazifar M, Pone EJ, Lötvall J, Zhao W. Stem cell extracellular vesicles: extended messages of regeneration. *Annu Rev Pharmacol Toxicol*. 2017;57:125–154. doi:10.1146/annurev-pharmtox-061616-030146
90. Ullah M, Stich S, Notter M, Eucker J, Sittinger M, Ringe J. Transdifferentiation of mesenchymal stem cells-derived adipogenic-differentiated cells into osteogenic- or chondrogenic-differentiated cells proceeds via dedifferentiation and have a correlation with cell cycle arresting and driving genes. *Differentiation*. 2013;85(3):78–90. doi:10.1016/j.diff.2013.02.001
91. Haga H, Yan IK, Takahashi K, Matsuda A, Patel T. Extracellular vesicles from bone marrow-derived mesenchymal stem cells improve survival from lethal hepatic failure in mice. *Stem Cells Transl Med*. 2017;6(4):1262–1272. doi:10.1002/sctm.16-0226
92. Nawaz M, Fatima F, Kc V, et al. Extracellular vesicles: evolving factors in stem cell biology. *Stem Cells Int*. 2016;2016:1073140. doi:10.1155/2016/1073140
93. Smith JA, Leonardi T, Huang B, Iraci N, Vega B, Pluchino S. Extracellular vesicles and their synthetic analogues in aging and age-associated brain diseases. *Biogerontology*. 2015;16(2):147–185. doi:10.1007/s10522-014-9510-7
94. Ding JY, Chen MJ, Wu LF, et al. Mesenchymal stem cell-derived extracellular vesicles in skin wound healing: roles, opportunities and challenges. *Mil Med Res*. 2023;10(1):36. doi:10.1186/s40779-023-00472-w
95. Robbins PD, Dorronsoro A, Booker CN. Regulation of chronic inflammatory and immune processes by extracellular vesicles. *J Clin Invest*. 2016;126(4):1173–1180. doi:10.1172/JCI81131
96. Taverna S, Pucci M, Alessandro R. Extracellular vesicles: small bricks for tissue repair/regeneration. *Ann Transl Med*. 2017;5(4):83. doi:10.21037/atm.2017.01.53
97. Ullah M, Eucker J, Sittinger M, Ringe J. Mesenchymal stem cells and their chondrogenic differentiated and dedifferentiated progeny express chemokine receptor CCR9 and chemotactically migrate toward CCL25 or serum. *Stem Cell Res Ther*. 2013;4(4):99. doi:10.1186/scrt310
98. Di Rocco G, Baldari S, Toietta G. Towards therapeutic delivery of extracellular vesicles: strategies for in vivo tracking and biodistribution analysis. *Stem Cells Int*. 2016;2016:5029619. doi:10.1155/2016/5029619
99. Quesenberry PJ, Aliotta JM. Cellular phenotype switching and microvesicles. *Adv Drug Deliv Rev*. 2010;62(12):1141–1148. doi:10.1016/j.addr.2010.06.001
100. Se S, Ms S, Yi K, et al. Human epidural AD-MSC exosomes improve function recovery after spinal cord injury in rats. *Biomedicines*. 2022;10(3). doi:10.3390/biomedicines10030678.
101. Laloze J, Lacoste M, Marouf F, et al. Specific features of stromal cells isolated from the two layers of subcutaneous adipose tissue: roles of their secretion on angiogenesis and neurogenesis. *J Clin Med*. 2023;12(13):4214. doi:10.3390/jcm12134214
102. Armstrong JP, Holme MN, Stevens MM. Re-engineering extracellular vesicles as smart nanoscale therapeutics. *ACS Nano*. 2017;11(1):69–83. doi:10.1021/acsnano.6b07607
103. György B, Hung ME, Breakefield XO, Leonard JN. Therapeutic applications of extracellular vesicles: clinical promise and open questions. *Annu Rev Pharmacol Toxicol*. 2015;55:439–464. doi:10.1146/annurev-pharmtox-010814-124630
104. Shigemoto-Kuroda T, Jy O, Dk K, et al. MSC-derived extracellular vesicles attenuate immune responses in two autoimmune murine models: type 1 diabetes and uveoretinitis. *Stem Cell Rep*. 2017;8(5):1214–1225. doi:10.1016/j.stemcr.2017.04.008
105. Kørbling M, Estrov Z. Adult stem cells for tissue repair - a new therapeutic concept? *N Engl J Med*. 2003;349(6):570–582. doi:10.1056/NEJMra022361
106. Ullah M, Qiao Y, Concepcion W, Thakor AS. Stem cell-derived extracellular vesicles: role in oncogenic processes, bioengineering potential, and technical challenges. *Stem Cell Res Ther*. 2019;10(1):347. doi:10.1186/s13287-019-1468-6
107. Karnas E, Dudek P, Zuba-Surma EK. Stem cell- derived extracellular vesicles as new tools in regenerative medicine - Immunomodulatory role and future perspectives. *Front Immunol*. 2023;14:1120175. doi:10.3389/fimmu.2023.1120175
108. Li C, Wei S, Xu Q, Sun Y, Ning X, Wang Z. Application of ADSCs and their Exosomes in Scar Prevention. *Stem Cell Rev Rep*. 2022;18(3):952–967. doi:10.1007/s12015-021-10252-5
109. Zanzottera F, Lavezzari E, Trovato L, Icardi A, Graziano A. Adipose derived stem cells and growth factors applied on hair transplantation. follow-up of clinical outcome. *J Cosmet Dermatological Sci Appl*. 2014;04(04):268–274. doi:10.4236/jcdsa.2014.44036
110. Zhang W, Bai X, Zhao B, et al. Cell-free therapy based on adipose tissue stem cell-derived exosomes promotes wound healing via the PI3K/Akt signaling pathway. *Exp Cell Res*. 2018;370(2):333–342. doi:10.1016/j.yexcr.2018.06.035
111. Wang P, Zuo Y, Xue Y, et al. Exosome-encapsulated microRNA-140-5p alleviates neuronal injury following subarachnoid hemorrhage by regulating IGFBP5-mediated PI3K/AKT signaling pathway. *Mol Neurobiol*. 2022;59(12):7212–7228. doi:10.1007/s12035-022-03007-x
112. Liang Y, Wu JH, Zhu JH, Yang H. Exosomes secreted by hypoxia-pre-conditioned adipose-derived mesenchymal stem cells reduce neuronal apoptosis in rats with spinal cord injury. *J Neurotrauma*. 2022;39(9–10):701–714. doi:10.1089/neu.2021.0290
113. Rong Y, Liu W, Wang J, et al. Neural stem cell-derived small extracellular vesicles attenuate apoptosis and neuroinflammation after traumatic spinal cord injury by activating autophagy. *Cell Death Dis*. 2019;10(5):340. doi:10.1038/s41419-019-1571-8
114. Pakpahan C, Ibrahim R, William W, et al. Stem cell therapy and diabetic erectile dysfunction: a critical review. *World J Stem Cells*. 2021;13(10):1549–1563. doi:10.4252/wjsc.v13.i10.1549
115. Asker H, Sezen SF, Yilmaz-Oral D, et al. The beneficial effects of adipose-derived stem cell and hydrogen sulfide donor sodium hydrogen sulfide combination therapy on erectile dysfunction in a rat model of radical prostatectomy. *Eur J Pharmacol*. 2025;1001:177760. doi:10.1016/j.ejphar.2025.177760

116. Yilmaz-Oral D, Sf S, Turkcan D, et al. Dual strategy with adipose-derived stem cells and l-arginine recovered cavernosal functions in a rat model of radical prostatectomy. *Stem Cells Dev*. 2024;33(1–2):43–53. doi:10.1089/scd.2023.0178
117. Wang B, Gao W, Zheng MY, Lin G, Lue TF. Recent advances in stem cell therapy for erectile dysfunction: a narrative review. *Expert Opin Biol Ther*. 2023;23(6):565–573. doi:10.1080/14712598.2023.2203811
118. Gur S, Abdel-Mageed AB, Sikka SC, Hellstrom WJG. Advances in stem cell therapy for erectile dysfunction. *Expert Opin Biol Ther*. 2018;18 (11):1137–1150. doi:10.1080/14712598.2018.1534955
119. Kim SW, Zhu GQ, Bae WJ. Mesenchymal stem cells treatment for erectile dysfunction in diabetic rats. *Sex Med Rev*. 2020;8(1):114–121. doi:10.1016/j.sxmr.2019.09.003
120. Yang J, Zhang Y, Zang G, et al. Adipose-derived stem cells improve erectile function partially through the secretion of IGF-1, bFGF, and VEGF in aged rats. *Andrology*. 2018;6(3):498–509. doi:10.1111/andr.12483
121. Sun T, Xu W, Tu B, et al. Engineered adipose-derived stem cells overexpressing RXFP1 via CRISPR activation ameliorate erectile dysfunction in diabetic rats. *Antioxidants*. 2023;12(1). doi:10.3390/antiox12010171
122. Chen Z, Han X, Ouyang X, Fang J, Huang X, Wei H. Transplantation of induced pluripotent stem cell-derived mesenchymal stem cells improved erectile dysfunction induced by cavernous nerve injury. *Theranostics*. 2019;9(22):6354–6368. doi:10.7150/thno.34008
123. Ouyang X, Han X, Chen Z, Fang J, Huang X, Wei H. MSC-derived exosomes ameliorate erectile dysfunction by alleviation of corpus cavernosum smooth muscle apoptosis in a rat model of cavernous nerve injury. *Stem Cell Res Ther*. 2018;9(1):246. doi:10.1186/s13287-018-1003-1
124. Liu Y, Zhao S, Luo L, et al. Mesenchymal stem cell-derived exosomes ameliorate erection by reducing oxidative stress damage of corpus cavernosum in a rat model of artery injury. *J Cell Mol Med*. 2019;23(11):7462–7473. doi:10.1111/jcmm.14615
125. Song J, Sun T, Tang Z, et al. Exosomes derived from smooth muscle cells ameliorate diabetes-induced erectile dysfunction by inhibiting fibrosis and modulating the NO/cGMP pathway. *J Cell Mol Med*. 2020;24(22):13289–13302. doi:10.1111/jcmm.15946
126. Li K, Li R, Zhao Z, Feng C, Liu S, Fu Q. Therapeutic potential of mesenchymal stem cell-derived exosomal miR-296-5p and miR-337-3p in age-related erectile dysfunction via regulating PTEN/PI3K/AKT pathway. *Biomed Pharmacother*. 2023;167:115449. doi:10.1016/j.biopha.2023.115449
127. Zhu LL, Huang X, Yu W, Chen H, Chen Y, Dai YT. Transplantation of adipose tissue-derived stem cell-derived exosomes ameliorates erectile function in diabetic rats. *Andrologia*. 2018;50(2):e12871. doi:10.1111/and.12871
128. Wang J, Mi Y, Wu S, et al. Exosomes from adipose-derived stem cells protect against high glucose-induced erectile dysfunction by delivery of corin in a streptozotocin-induced diabetic rat model. *Regen Ther*. 2020;14:227–233. doi:10.1016/j.reth.2020.03.002
129. Chen F, Zhang H, Wang Z, et al. Adipose-derived stem cell-derived exosomes ameliorate erectile dysfunction in a rat model of type 2 diabetes. *J Sex Med*. 2017;14(9):1084–1094. doi:10.1016/j.jsxm.2017.07.005
130. Li M, Lei H, Xu Y, et al. Exosomes derived from mesenchymal stem cells exert therapeutic effect in a rat model of cavernous nerves injury. *Andrology*. 2018;6(6):927–935. doi:10.1111/andr.12519
131. Liang L, Zheng D, Lu C, et al. Exosomes derived from miR-301a-3p-overexpressing adipose-derived mesenchymal stem cells reverse hypoxia-induced erectile dysfunction in rat models. *Stem Cell Res Ther*. 2021;12(1):87. doi:10.1186/s13287-021-02161-8
132. Gu X, Liang L, Lu C, et al. Exosomes secreted by adipose mesenchymal stem cells overexpressing circPIP5K1C exert. *Biochim Biophys Acta Mol Basis Dis*. 2024;1870(6):167223. doi:10.1016/j.bbadis.2024.167223
133. Yang Q, Chen W, Han D, et al. Intratunical injection of human urine-derived stem cells derived exosomes prevents fibrosis and improves erectile function in a rat model of Peyronie's disease. *Andrologia*. 2020;52(11):e13831. doi:10.1111/and.13831
134. Ouyang B, Xie Y, Zhang C, et al. Extracellular vesicles from human urine-derived stem cells ameliorate erectile dysfunction in a diabetic rat model by delivering proangiogenic microRNA. *Sex Med*. 2019;7(2):241–250. doi:10.1016/j.esxm.2019.02.001
135. Mh K, Km S, Limanjaya A, et al. Embryonic stem cell-derived extracellular vesicle-mimetic nanovesicles rescue erectile function by enhancing penile neurovascular regeneration in the streptozotocin-induced diabetic mouse. *Sci Rep*. 2019;9(1):20072. doi:10.1038/s41598-019-54431-4
136. Gn Y, Sh P, Ock J, et al. Pericyte-derived extracellular vesicle-mimetic nanovesicles restore erectile function by enhancing neurovascular regeneration in a mouse model of cavernous nerve injury. *J Sex Med*. 2020;17(11):2118–2128. doi:10.1016/j.jsxm.2020.07.083
137. Ock J, Liu FY, Fridayana FR, et al. MicroRNA-148a-3p in pericyte-derived extracellular vesicles improves erectile function in diabetic mice by promoting cavernous neurovascular regeneration. *BMC Urol*. 2023;23(1):209. doi:10.1186/s12894-023-01378-4
138. El Assar M, La Fuente JM, Sosa P, et al. PKC inhibition improves human penile vascular function and the NO/cGMP pathway in diabetic erectile dysfunction: the role of NADPH oxidase. *Int J Mol Sci*. 2024;25(6):3111. doi:10.3390/ijms25063111
139. Engin S, Barut EN, Kaya Yaşar Y, et al. Niclosamide attenuates erectile dysfunction and corporal fibrosis via reversal of Smad signaling in diabetic rat model. *J Sex Med*. 2024;21(12):1111–1119. doi:10.1093/jsxmed/qdae129
140. Liu C, Su C. Design strategies and application progress of therapeutic exosomes. *Theranostics*. 2019;9(4):1015–1028. doi:10.7150/thno.30853
141. García-Manrique P, Matos M, Gutiérrez G, Pazos C, Blanco-López MC. Therapeutic biomaterials based on extracellular vesicles: classification of bio-engineering and mimetic preparation routes. *J Extracell Vesicles*. 2018;7(1):1422676. doi:10.1080/20013078.2017.1422676
142. Gallet R, Dawkins J, Valle J, et al. Exosomes secreted by cardiosphere-derived cells reduce scarring, attenuate adverse remodelling, and improve function in acute and chronic porcine myocardial infarction. *Eur Heart J*. 2017;38(3):201–211. doi:10.1093/eurheartj/ehw240
143. Mathiyalagan P, Liang Y, Kim D, et al. Angiogenic mechanisms of human CD34(+) stem cell exosomes in the repair of ischemic hindlimb. *Circ Res*. 2017;120(9):1466–1476. doi:10.1161/CIRCRESAHA.116.310557
144. Henriques-Antunes H, Rms C, Zonari A, et al. The kinetics of small extracellular vesicle delivery impacts skin tissue regeneration. *ACS Nano*. 2019;13(8):8694–8707. doi:10.1021/acsnano.9b00376
145. Ullah M, Kuroda Y, Bartosh TJ, et al. iPS-derived MSCs from an expandable bank to deliver a prodrug-converting enzyme that limits growth and metastases of human breast cancers. *Cell Death Discov*. 2017;3:16064. doi:10.1038/cddiscovery.2016.64
146. Yang B, Chen Y, Shi J. Exosome biochemistry and advanced nanotechnology for next-generation theranostic platforms. *Adv Mater*. 2019;31(2): e1802896. doi:10.1002/adma.201802896
147. Nasiri Kenari A, Kastaniegaard K, Greening DW, et al. Proteomic and post-translational modification profiling of exosome-mimetic nanovesicles compared to exosomes. *Proteomics*. 2019;19(8):e1800161. doi:10.1002/pmic.201800161
148. You B, Xu W, Zhang B. Engineering exosomes: a new direction for anticancer treatment. *Am J Cancer Res*. 2018;8(8):1332–1342.

149. Luan X, Sansanaphongpricha K, Myers I, Chen H, Yuan H, Sun D. Engineering exosomes as refined biological nanoplatforms for drug delivery. *Acta Pharmacol Sin*. 2017;38(6):754–763. doi:10.1038/aps.2017.12
150. Liu Q, Cui Y, Lin H, et al. MicroRNA-145 engineered bone marrow-derived mesenchymal stem cells alleviated erectile dysfunction in aged rats. *Stem Cell Res Ther*. 2019;10(1):398. doi:10.1186/s13287-019-1509-1
151. Kim JH, Yun JH, Song ES, Kim SU, Lee HJ, Song YS. Improvement of damaged cavernosa followed by neuron-like differentiation at injured cavernous nerve after transplantation of stem cells seeded on the PLA nanofiber in rats with cavernous nerve injury. *Mol Biol Rep*. 2021;48 (4):3549–3559. doi:10.1007/s11033-021-06332-x
152. Fu Q, Song L, Li J, et al. Biodegradable nano black phosphorus based SDF1-α delivery system ameliorates Erectile Dysfunction in a cavernous nerve injury rat model by recruiting endogenous stem/progenitor cells. *J Nanobiotechnol*. 2023;21(1):487. doi:10.1186/s12951-023-02238-x
153. Chen Z, Zhai J, Ma J, et al. Melatonin-primed mesenchymal stem cells-derived small extracellular vesicles alleviated neurogenic erectile dysfunction by reversing phenotypic modulation. *Adv Healthc Mater*. 2023;12(12):e2203087. doi:10.1002/adhm.202203087
154. Zhang J, Zhao D, Zang Z, Ruan Z, Fu Q, Zhang K. miR-200a-3p-enriched MSC-derived extracellular vesicles reverse erectile function in diabetic rats by targeting Keap1. *Biomed Pharmacother*. 2024;177:116964. doi:10.1016/j.biopha.2024.116964
155. Huo W, Zhang Y, Li Y, Li H. Mesenchymal stem cells-derived exosomal microRNA-21-5p downregulates PDCD4 and ameliorates erectile dysfunction in a rat model of diabetes mellitus. *FASEB j*. 2020;34(10):13345–13360. doi:10.1096/fj.202000102RR
156. Zou Z, Chai M, Guo F, et al. MicroRNA-126 engineered muscle-derived stem cells attenuates cavernosa injury-induced erectile dysfunction in rats. *Aging*. 2021;13(10):14399–14415. doi:10.18632/aging.203057
157. Ock J, Wu J, Fy L, et al. Heme-binding protein 1 delivered via pericyte-derived extracellular vesicles improves neurovascular regeneration in a mouse model of cavernous nerve injury. *Int J Biol Sci*. 2023;19(9):2663–2677. doi:10.7150/ijbs.81809
158. Imai T, Takahashi Y, Nishikawa M, et al. Macrophage-dependent clearance of systemically administered B16BL6-derived exosomes from the blood circulation in mice. *J Extracell Vesicles*. 2015;4:26238. doi:10.3402/jev.v4.26238
159. Yu H, Cheng J, Shi W, et al. Bone marrow mesenchymal stem cell-derived exosomes promote tendon regeneration by facilitating the proliferation and migration of endogenous tendon stem/progenitor cells. *Acta Biomater*. 2020;106:328–341. doi:10.1016/j.actbio.2020.01.051
160. Cw C, Ll W, Zaman S, et al. Sustained release of endothelial progenitor cell-derived extracellular vesicles from shear-thinning hydrogels improves angiogenesis and promotes function after myocardial infarction. *Cardiovasc Res*. 2018;114(7):1029–1040. doi:10.1093/cvr/cvy067
161. Jj C, Han J, Ll W, et al. Delayed delivery of endothelial progenitor cell-derived extracellular vesicles via shear thinning gel improves postinfarct hemodynamics. *J Thorac Cardiovasc Surg*. 2020;159(5):1825–1835.e1822. doi:10.1016/j.jtcvs.2019.06.017
162. Guo SC, Tao SC, Yin WJ, Qi X, Yuan T, Zhang CQ. Exosomes derived from platelet-rich plasma promote the re-epithelization of chronic cutaneous wounds via activation of YAP in a diabetic rat model. *Theranostics*. 2017;7(1):81–96. doi:10.7150/thno.16803
163. Lv K, Li Q, Zhang L, et al. Incorporation of small extracellular vesicles in sodium alginate hydrogel as a novel therapeutic strategy for myocardial infarction. *Theranostics*. 2019;9(24):7403–7416. doi:10.7150/thno.32637
164. Tao SC, Guo SC, Li M, Ke QF, Guo YP, Zhang CQ. Chitosan wound dressings incorporating exosomes derived from MicroRNA-126-overexpressing synovium mesenchymal stem cells provide sustained release of exosomes and heal full-thickness skin defects in a diabetic rat model. *Stem Cells Transl Med*. 2017;6(3):736–747. doi:10.5966/sctm.2016-0275
165. Zhang K, Zhao X, Chen X, et al. Enhanced therapeutic effects of mesenchymal stem cell-derived exosomes with an injectable hydrogel for hindlimb ischemia treatment. *ACS Appl Mater Interfaces*. 2018;10(36):30081–30091. doi:10.1021/acsami.8b08449
166. Liu B, Bw L, Nakanishi K, et al. Cardiac recovery via extended cell-free delivery of extracellular vesicles secreted by cardiomyocytes derived from induced pluripotent stem cells. *Nat Biomed Eng*. 2018;2(5):293–303. doi:10.1038/s41551-018-0229-7
167. Han C, Zhou J, Liang C, et al. Human umbilical cord mesenchymal stem cell derived exosomes encapsulated in functional peptide hydrogels promote cardiac repair. *Biomater Sci*. 2019;7(7):2920–2933. doi:10.1039/C9BM00101H
168. Xu N, Wang L, Guan J, et al. Wound healing effects of a Curcuma zedoaria polysaccharide with platelet-rich plasma exosomes assembled on chitosan/silk hydrogel sponge in a diabetic rat model. *Int J Biol Macromol*. 2018;117:102–107. doi:10.1016/j.ijbiomac.2018.05.066
169. Liu S, Li R, Dou K, Li K, Zhou Q, Fu Q. Injectable thermo-sensitive hydrogel containing ADSC-derived exosomes for the treatment of cavernous nerve injury. *Carbohydr Polym*. 2023;300:120226. doi:10.1016/j.carbpol.2022.120226
170. Zhuang J, Gao P, Chen H, et al. Extracellular vesicles from human urine-derived stem cells merged in hyaluronic acid ameliorate erectile dysfunction in type 2 diabetic rats by glans administration. *Andrology*. 2022;10(8):1673–1686. doi:10.1111/andr.13293
171. Liang L, Shen Y, Dong Z, Gu X. Photoacoustic image-guided corpus cavernosum intratunical injection of adipose stem cell-derived exosomes loaded polydopamine thermosensitive hydrogel for erectile dysfunction treatment. *Bioact Mater*. 2022;9:147–156. doi:10.1016/j.bioactmat.2021.07.024
172. Zhu Q, Heon M, Zhao Z, He M. Microfluidic engineering of exosomes: editing cellular messages for precision therapeutics. *Lab Chip*. 2018;18 (12):1690–1703. doi:10.1039/C8LC00246K
173. Liang Y, Duan L, Lu J, Xia J. Engineering exosomes for targeted drug delivery. *Theranostics*. 2021;11(7):3183–3195. doi:10.7150/thno.52570
174. Malekian F, Shamsian A, Kodam SP, Ullah M. Exosome engineering for efficient and targeted drug delivery: current status and future perspective. *J Physiol*. 2023;601(22):4853–4872. doi:10.1113/JP282799
175. Barile L, Vassalli G. Exosomes: therapy delivery tools and biomarkers of diseases. *Pharmacol Ther*. 2017;174:63–78. doi:10.1016/j.pharmthera.2017.02.020
176. Sadeghi S, Tehrani FR, Tahmasebi S, Shafiee A, Hashemi SM. Exosome engineering in cell therapy and drug delivery. *Inflammopharmacology*. 2023;31(1):145–169. doi:10.1007/s10787-022-01115-7
177. Yang M, Wu SY. The advances and challenges in utilizing exosomes for delivering cancer therapeutics. *Front Pharmacol*. 2018;9:735. doi:10.3389/fphar.2018.00735
178. Lyu S, Dong Z, Xu X, et al. Going below and beyond the surface: microneedle structure, materials, drugs, fabrication, and applications for wound healing and tissue regeneration. *Bioact Mater*. 2023;27:303–326. doi:10.1016/j.bioactmat.2023.04.003
179. Chen J, Jiao Z, Mo J, et al. Comparison of the variability of small extracellular vesicles derived from human liver cancer tissues and cultured from the tissue explants based on a simple enrichment method. *Stem Cell Rev Rep*. 2022;18(3):1067–1077. doi:10.1007/s12015-021-10264-1
180. Bordas M, Genard G, Ohl S, et al. Optimized protocol for isolation of small extracellular vesicles from human and murine lymphoid tissues. *Int J Mol Sci*. 2020;21(15):5586. doi:10.3390/ijms21155586

181. Ks V, Rj L, Ham S, et al. Comparative analysis of tangential flow filtration and ultracentrifugation, both combined with subsequent size exclusion chromatography, for the isolation of small extracellular vesicles. *J Extracell Vesicles*. 2022;11(9):e12266. doi:10.1002/jev2.12266
182. Shi J, Zhao YC, Niu ZF, et al. Mesenchymal stem cell-derived small extracellular vesicles in the treatment of human diseases: progress and prospect. *World J Stem Cells*. 2021;13(1):49–63. doi:10.4252/wjsc.v13.i1.49
183. Shi X, Cheng Q, Zhang Y. Reprogramming extracellular vesicles with engineered proteins. *Methods*. 2020;177:95–102. doi:10.1016/j.ymeth.2019.09.017
184. Zhang Y, Liu Y, Dou Y, et al. Advances in therapeutic applications of extracellular vesicles. *Int J Nanomed*. 2023;18:3285–3307. doi:10.2147/IJN.S409588
185. Zhang ZG, Buller B, Chopp M. Exosomes - beyond stem cells for restorative therapy in stroke and neurological injury. *Nat Rev Neurol*. 2019;15(4):193–203. doi:10.1038/s41582-018-0126-4
186. Cheng K, Kalluri R. Guidelines for clinical translation and commercialization of extracellular vesicles and exosomes based therapeutics. *Extracellular Vesicle*. 2023;2:100029. doi:10.1016/j.vesic.2023.100029
187. Zheng X, Ai H, Qian K, et al. Small extracellular vesicles purification and scale-up. *Front Immunol*. 2024;15:1344681. doi:10.3389/fimmu.2024.1344681
188. Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. *Signal Transduct Target Ther*. 2024;9(1):17. doi:10.1038/s41392-023-01704-0