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REVIEW

Therapeutic applications of mesenchymal stem cell-derived extracellular vesicles in pain management: A narrative review of emerging evidence and future directions

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Abstract

Pain remains a major clinical challenge because current therapies often have limited efficacy and substantial adverse effects. Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) are emerging as promising candidates with anti-inflammatory, immunomodulatory, and neuroprotective actions. Preclinical studies show that MSC-EVs alleviate inflammatory, neuropathic, and cancer-related pain by modulating immune responses and promoting neural repair, thereby reducing nociceptor sensitization. MSC-EVs also hold potential as drug-delivery vehicles and as biomarkers for pain diagnosis due to their stability and bioactive cargo (*e.g.*, microRNAs and proteins). This narrative review summarizes terminology, mechanisms, therapeutic applications, and translational challenges of MSC-EVs in pain management, emphasizing their capacity to reshape the treatment landscape. Despite hurdles in scalable manufacturing, dosing, and regulation, ongoing clinical investigations support their promise as a biologically driven strategy for pain therapy.

Key Words: Mesenchymal stem cell-derived extracellular vesicles; Pain management; Drug delivery; Biomarkers; Immunomodulation; Nociceptor sensitization

Core Tip: This review summarizes the mechanistic and translational evidence on how mesenchymal stem cell-derived extracellular vesicles (EVs) coordinately regulate inflammation, immunity and nociceptor sensitization to reduce pain. However, clinical advances are impeded by various factors like non-standardized EV isolation, indistinct dosing and regulatory constraints, hindering therapeutic validation process. Next generation EV engineering techniques, targeted cargo loading and scalable production approaches offer promise for future mesenchymal stem cell-derived EV therapies targeting chronic and refractory pain conditions.

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INTRODUCTION

Pain is a complex, subjective experience and a leading cause of disability worldwide[1]. According to the International Association for the Study of Pain, pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage[2]. Nociceptive input from dorsal root ganglion neurons, *via* peripheral nociceptor terminals, axons, and presynaptic terminals, converges on the central nervous system (CNS), where it is encoded and perceived as pain[3-5]. Acute pain serves as a protective signal, alerting the brain to potentially harmful stimuli such as injury, heat, or pressure. However, when pain persists beyond tissue healing, it becomes maladaptive and may progress to chronic pain[6]. Inflammatory pain, arising from tissue injury and the ensuing immune response, is often reversible and promotes protective behaviors that facilitate healing[7]. Pain is frequently categorized on the basis of: (1) Severity - acute pain, chronic pain, and cancer or malignant pain; (2) Tissue type - neuropathic pain, inflammatory pain, and nociceptive pain; and (3) Site - central neuropathic pain, and peripheral neuropathic pain. Acute pain arises from a specific injury and is limited to days to weeks, whereas chronic pain persists beyond normal healing, typically > 3-6 months. Cancer pain can be described as sharp, throbbing, achy or stabbing in nature. Neuropathic pain is caused by any damage occurred to peripheral nervous system or the CNS, evoked by stimuli or spontaneous. Inflammatory pain occurs in the setting of tissue injury or active inflammation, whereas nociceptive pain can be somatic or visceral and arises from mechanical, thermal or chemical injury to tissue. This injury stimulates pain receptors, which transmit signals to the CNS, leading to the perception of pain. As the name suggests, central neuropathic pain occurs in the CNS, while peripheral neuropathic pain is related to the peripheral nervous system[8-15]. Supplementary Figure 1 summarizes pain classifications.

Despite advances in medical science, effective pain control remains a global challenge. More than 30% of the world's population experiences some form of pain[16]. Moreover, pain and opioid analgesic misuse, suicide, depression, and related conditions significantly impair quality of life and create substantial personal and economic burdens[17]. Traditional therapies - nonsteroidal anti-inflammatory drugs, opioids, and adjuvant medications - often provide only

partial relief and are associated with adverse effects (*e.g.*, gastrointestinal toxicity, organ injury), dependence, and limited long-term efficacy[18-20]. This therapeutic gap underscores the need for novel, safe, and targeted approaches to pain management.

Stem cell-based therapies offer a promising alternative[21]. Mesenchymal stem cells (MSCs) - adult mesoderm-derived stem cells - modulate immune responses, attenuate inflammation, and promote tissue repair, while retaining proliferative and multipotent capacity[22-24]. MSCs may reduce pain by dampening neuroinflammation and limiting glial and neuronal overactivation[25-27]. To date, MSCs have demonstrated efficacy in preclinical models and in clinical studies across multiple indications[28,29]. Their immunomodulatory properties are well established in preclinical research[30-32], and clinical data supports benefits in immune regulation among transplant recipients[33,34]. The low immunogenicity of MSCs supports allogeneic use and broadens clinical applicability in pain therapy. MSCs can be administered *via* local injection at the injury site or by intrathecal or intravenous (IV) routes. MSC homing is the process by which cells are recruited to injured tissues by cytokines, chemokines, adhesion molecules, and growth factors released from the local microenvironment[35-38].

Given the functional properties of MSCs, MSC-derived analgesic therapies have the potential to become a new approach to pain management with strong translational prospects. Notably, MSCs release extracellular vesicles (EVs) that are considered primary mediators of the therapeutic effects of MSCs[39-41]. These extracellular, membrane-bound vesicles, including exosomes and microvesicles (MVs), carry bioactive cargo such as proteins, lipids, and nucleic acids that influence recipient cells and modulate pathologic mechanisms. They also express MSC-associated markers, including CD117, CD105, CD90, CD73, CD44, and CD29[42]. Furthermore, the role of MSC-derived EVs (MSC-EVs) in pain management, particularly regarding biodistribution to dorsal root ganglia (DRG) and crossing of the blood brain barrier (BBB), is attracting a lot of attention in recent research. Studies have shown that MSC-EVs can accumulate in DRGs, where they modulate inflammatory responses and promote an anti-inflammatory microenvironment, and hence, reduce pain signaling[43]. In addition, the presence of the bioactive molecules in MSC-EVs facilitates communication with sensory neurons, potentially altering pain transmission pathways[44]. MSC-EVs have also demonstrated potential in improving blood spinal-cord barrier integrity, which is similar in structure to the BBB. MSC-EVs can contribute to restoring barrier function by improving endothelial cell functions and mitigating inflammation, hence allowing for better therapeutic delivery to CNS targets[45]. Mechanistically, EV trafficking across vascular barriers is mediated by transcytosis and endocytic pathways like clathrin-dependent internalization[46,47]. Additionally, altered mitochondrial function in DRGs by MSC-EVs suggests a mechanism through which EVs can exert neuroprotective effects, potentially influencing BBB permeability[48]. Compared with MSCs, EVs poses better safety due to their inability to proliferate, differentiate or form ectopic tissue, while offering more predictable biodistribution and stability of therapeutic cargo[49, 50].

Given their inherent anti-inflammatory, neuromodulatory, and neuroprotective properties, MSC-EVs are emerging as potential therapeutics for pain management. By modulating nociceptors, supporting neural and tissue repair, and transporting therapeutic cargo, they offer a cell-free alternative to conventional medicines. The purpose of this review is to summarize recent data, mechanisms, and therapeutic uses of MSC-EVs in pain, emphasizing their possible use as biomarkers and drug delivery systems. Additionally, we highlight current challenges, translational barriers, and emerging opportunities for the safe and efficient use of MSC-EVs in pain management.

BIOLOGY AND BIOGENESIS OF MSC-EVs

EVs are categorized into three major types based on size and biogenesis: (1) Exosomes (30-150 nm), which originate from endosomes; (2) MVs, also called ectosomes, 100-1000 nm, which are derived from the plasma membrane; and (3) Apoptotic bodies (1000-5000 nm), which form *via* blebbing of apoptotic cells[51-53]. Within cells, multivesicular bodies (MVBs) form small vesicles called exosomes. Endocytosis produces early endosomes that mature into late endosomes, and ultimately, MVBs. MVBs contain small molecules and metabolites. Two principal fates exist for MVBs: (1) Fusion with lysosomes followed by degradation of their contents without exosome release; and (2) Fusion with the plasma membrane, resulting in exocytosis of intraluminal vesicles as exosomes[54,55]. MVs (ectosomes) originate from the plasma membrane through outward budding driven by increased protein degradation and cytosolic calcium. These changes disassemble the cytoskeleton, producing a membrane bud. Activation of lipid translocases further alters the bilayer, facilitating ectosome release from the plasma membrane[56]. Apoptotic bodies are cellular fragments generated during apoptosis. Their size and composition vary by cell type and disassembly mechanisms. Some cells shed protective structures from membrane protrusions, whereas others undergo complex, coordinated morphological steps[57].

MSC-EVs include at least 730 distinct proteins, identified *via* liquid chromatography-tandem mass spectrometry analysis[58,59], and display characteristics of both MSCs and EVs. For example, 25 proteins in MSC-EVs are associated with MSC differentiation genes, whereas 53 are linked to MSC self-renewal genes. One study showed that MSC-EV proteins include MSC surface markers and MSC-specific signaling proteins. Proteins in MSC-EVs also participate in EV biogenesis, trafficking, docking, and fusion. Modulation of MSC therapeutic potential has been attributed to EV proteins, including the surface receptors platelet-derived growth factor receptor-beta (PDGFR-β) and epidermal growth factor receptor (EGFR); signaling molecules from the RAS-mitogen-activated protein kinase, CDC42, and RHO pathways; cell-adhesion molecules; and other MSC antigens. These proteins may promote tissue regeneration and repair. Additionally, 171 microRNAs (miRNAs) have been identified in MSC-EVs, 23 of which target 5481 genes that regulate specific pathways. For example, miR-199a and miR-130a-3p are involved in preventing apoptosis, stimulating angiogenesis, and enhancing cellular proliferation. Furthermore, the proteome of purified MSC-derived exosomes has 938 distinct gene

products encompassing diverse biochemical and cellular processes[58,59].

MSC-EVs also contribute to intercellular communication by delivering proteins, mRNAs, and miRNAs. Similar to MSCs, they play vital roles in both pathological and physiological processes, such as tissue repair and angiogenesis. MSC-EVs exhibit low immunogenicity and high stability, making them suitable for treating autoimmune diseases[60-62]. They can reprogram target cells, improving viability and migration, and have been reported to possess greater regenerative potential than intact stem cells[63]. Their molecular cargo supports disease monitoring, enabling MSC-EVs to serve as biomarkers. Multiple studies indicate that MSC-EVs show promise for treating rheumatoid arthritis and myocardial infarction, offering cell-free therapeutic approaches[60,64]. Additional advantages include targeted delivery, prevention of long-term maldifferentiation, and lower toxicity[65]. Further research focusing on process optimization is needed to unlock the full benefits of MSC-EVs in regenerative medicine[66].

PAIN MODULATION MECHANISMS BY MSC-EVs

Immunomodulatory activities and anti-inflammatory effects

The immunomodulatory and anti-inflammatory actions of MSC-EVs are tightly interconnected and are central to pain modulation. MSC-EVs are rich in bioactive cargo that can recalibrate immune responses, thereby reducing inflammation and associated pain. As potent mediators of immune regulation, MSC-EVs carry miRNAs, proteins, and lipids that modulate immune pathways affecting T cells, B cells, and macrophages implicated in pain and inflammation[67]. These immunomodulatory effects establish a pro-regenerative microenvironment that allows subsequent neural repair processes. A simplified overview of the anti-inflammatory and immunomodulatory pathways is provided in Figures 1 and 2, respectively.

The anti-inflammatory effects of MSC-EVs depend on the transfer of immunoregulatory miRNAs and immunomodulatory proteins to inflammatory cells, including M1 macrophages, dendritic cells, CD4+ T cells, T helper 1 cells, and T helper 17 cells, thereby promoting transformation to immunosuppressive M2 macrophages, tolerogenic dendritic cells, and T regulatory cells. This, in turn, enhances immunosuppressive functions and decreases inflammation[68,69]. Furthermore, MSC-EVs inhibit the Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) pathway and NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome activation in models of neuroinflammation, thereby reducing glial activation and proinflammatory cytokines and decreasing pain sensitivity and mechanical allodynia in conditions such as interstitial cystitis[70,71]. Moreover, miR-124-enriched MSC-EVs decrease proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, and IL-1β, while increasing anti-inflammatory cytokines, including IL-10 and transforming growth factor-β (TGF-β). These changes help balance immune responses, inhibit macrophage activation, reduce apoptosis and oxidative stress *via* delivered noncoding RNAs, mRNAs, and miRNAs, modulate pain pathways, and promote regeneration and pain relief in inflammation-related conditions such as rheumatoid arthritis and osteoarthritis (OA)[68,69,72,73].

Other studies have also shown the potential of MSC-EVs to reduce proinflammatory cytokine release, thereby promoting an anti-inflammatory milieu and expansion of T regulatory cells that can alleviate pain associated with autoimmune and other conditions[74-76]. By enhancing tissue regeneration and homeostasis, MSC-EVs further contribute to pain relief in degenerative conditions, such as intervertebral disc degeneration[77].

Despite consistent results of anti-inflammatory effects, findings across MSC-EVs remain difficult to compare, as EV isolation protocols are inconsistent and variable across studies, making it more challenging to even compare the immunomodulatory effects. Heterogeneity in EV cargo across MSC sources, and MSC culture conditions are also responsible for inconsistent anti-inflammatory outcomes. Moreover, studies examining the neuroprotection properties often rely on small sample sizes or single model validation. Additionally, transient receptor potential V1/voltage-gated sodium channel regulation is not consistently replicated, and many studies use basic immune cell assays but fail to validate their results in more complex inflammatory conditions, thereby restricting reproducibility across various laboratories[78].

Neural repair and neuroprotection

MSC-EVs have demonstrated the potential to mitigate pain and support recovery in conditions such as spinal cord injury and related disorders. Therapeutic effects are primarily attributed to EV cargo - particularly miRNAs - that regulate inflammation, oxidative stress, and neuronal excitability. Owing to their anti-inflammatory and regenerative properties, MSC-EVs support neuronal repair, neuroprotection (Figure 3), and homeostasis (Figure 4). Restoration of neural structure and synaptic function ultimately contributes to reduced nociceptor signaling (Figure 5). They reduce inflammation and modulate oxidative stress, thereby influencing apoptosis through exosomal miRNAs, which in spinal cord injury models decreases inflammation linked with pain and recovery processes[79]. MSC-EVs also enhance neuroprotection by modulating pathways such as phosphoinositide 3-kinase/protein kinase B, helping prevent neuronal death during ischemia. Studies further indicate that EV-mediated neuroprotection involves diverse paracrine factors and pathways[80,81].

Furthermore, MSC-EVs have been shown to normalize hyperexcitability in sensory neurons, suggesting direct action on peripheral sensory neurons to modulate pain-related behaviors in OA models[82]. These EVs have also shown utility for chronic pain, including chemotherapy-induced and degenerative-disease-related pain[48]. They also protect against intracerebral hemorrhage-induced neuronal damage by modulating ferroptosis, further suggesting therapeutic potential in brain disorders[83].

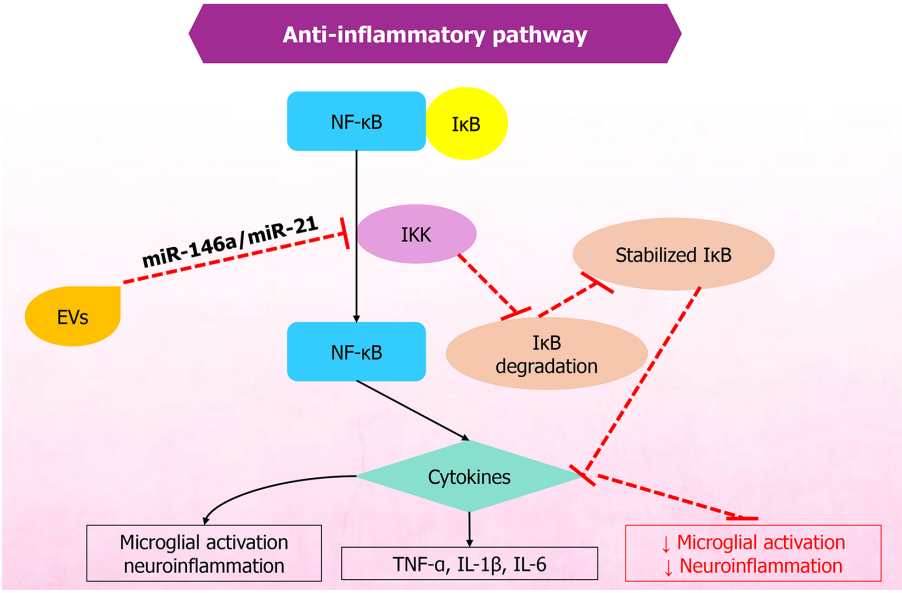

Figure 1 Schematic representation of extracellular vesicle-mediated modulation of nuclear factor kappa B-light chain enhancer of activated B cells signaling pathway. Under inflammatory stimulation, receptor activation triggers the inhibitor of kappa B (IκB) kinase complex, leading to IκB phosphorylation and degradation, allowing nuclear factor kappa B to translocate into the nucleus and induce the expression of pro-inflammatory cytokines. Extracellular vesicle-derived microRNAs inhibit IκB kinase activity, thus stabilizing IκB and suppressing nuclear factor kappa B activation and downstream cytokine release. This mechanism helps reduce microglial activation and mitigate neuroinflammation. NF-κB: Nuclear factor kappa B; IκB: Inhibitor of kappa B; IKK: Inhibitor of kappa B kinase; EVs: Extracellular vesicles; TNF: Tumor necrosis factor; IL: Interleukin.

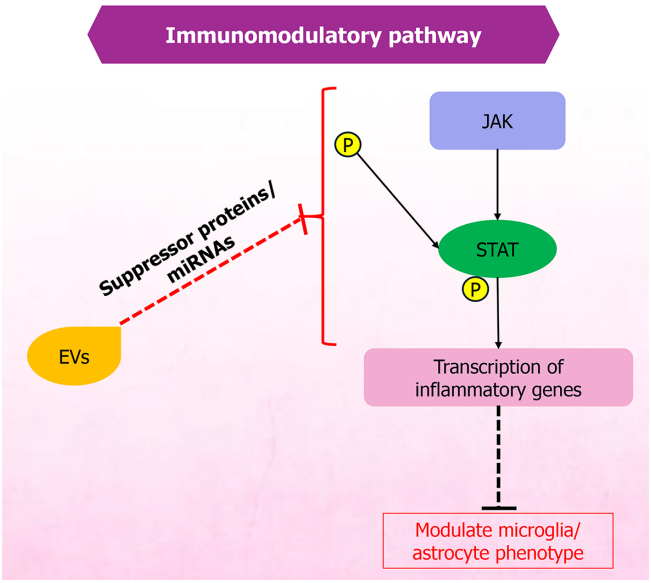

Figure 2 Extracellular vesicle-mediated regulation of Janus kinases/signal transducer and activator of transcription signaling pathway in glial immunomodulation. Cytokine-receptor binding activates Janus kinases, leading to signal transducer and activator of transcription phosphorylation and nuclear translocation, which drives transcription of proinflammatory genes. Extracellular vesicle-derived cargo - including suppressor proteins and specific microRNAs - can inhibit Janus kinases/signal transducer and activator of transcription activation, modulating microglial and astrocytic phenotypes toward anti-inflammatory, neuroprotective states. EVs: Extracellular vesicles; miRNAs: MicroRNAs; JAK: Janus kinases; STAT: Signal transducer and activator of transcription.

Although MSC-EVs have shown neuroprotective effects, most evidence is based on early treatment rodent models and high EV doses that may not be translationally realistic. Studies often fail to differentiate whether improvement arises from direct neuronal repair or secondary immune modulation process[84]. Additionally, bulk EV preparations restrict the potential to identify which EV subtypes or cargo components play roles in neuroprotection.

Regulation of nociceptor sensitization

Nociceptors are sensory nerve endings in the skin, joints, muscles, and viscera that respond to noxious or potentially damaging stimuli. Nociceptors undergo sensitization, which increases their excitability. Sensitization typically follows

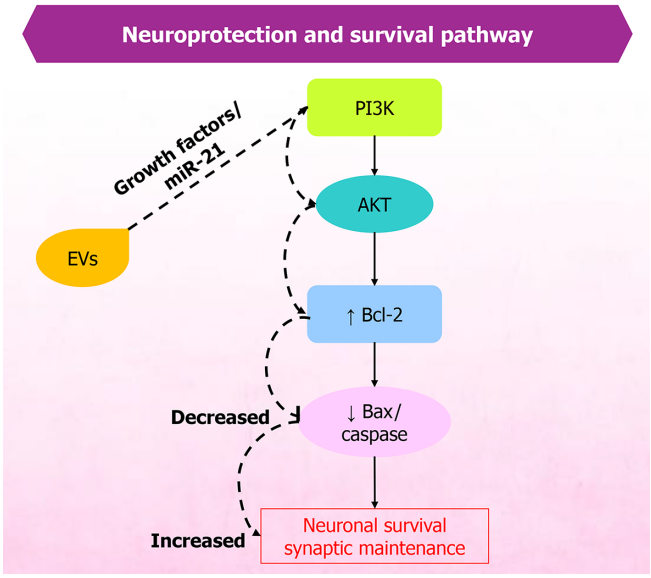

Figure 3 Extracellular vesicle-mediated activation of phosphoinositide 3-kinase/protein kinase B signaling pathway promotes neuronal survival and neuroprotection. Ligand binding to surface receptors activates phosphoinositide 3-kinase, leading to protein kinase B phosphorylation, upregulation of antiapoptotic proteins, and downregulation of proapoptotic factors. Extracellular vesicle cargo enhances protein kinase B phosphorylation, supporting neuronal survival, synaptic maintenance, and resistance to neurodegenerative stress. EVs: Extracellular vesicles; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B.

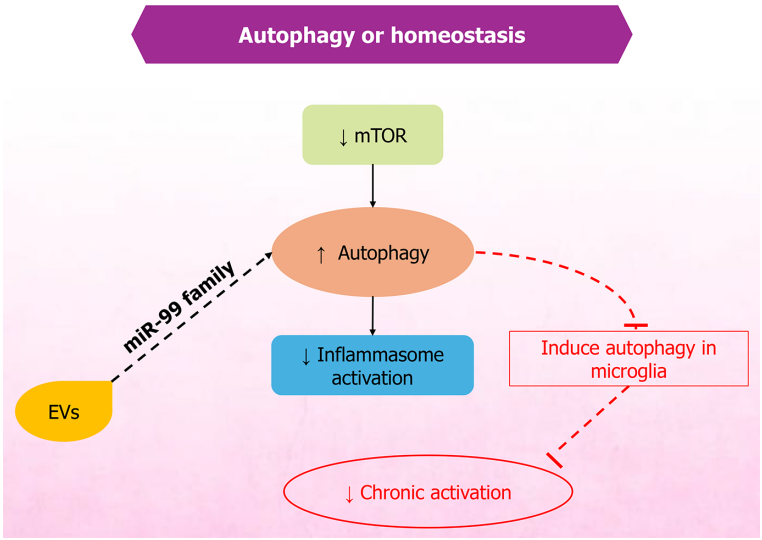

Figure 4 Extracellular vesicle-mediated modulation of mammalian target of rapamycin-autophagy pathway maintains cellular homeostasis. Inhibition of mammalian target of rapamycin enhances autophagic activity, promoting cellular clearance and reducing inflammasome activation. Extracellular vesicle cargo, particularly microRNAs (miR-99 family), can downregulate mammalian target of rapamycin signaling in microglia, inducing autophagy and mitigating chronic microglial activation and neuroinflammatory responses. mTOR: Mammalian target of rapamycin; EVs: Extracellular vesicles.

tissue injury and inflammation, lowering activation thresholds and increasing response magnitude to a noxious stimulus, thereby rendering previously ineffective stimuli painful and promoting spontaneous activity[85,86].

Nociceptor sensitization is regulated by reciprocal signaling between immune cells and sensory neurons. Inflammatory mediators lower nociceptor thresholds during inflammation, driving peripheral sensitization. Mast cells release cytokines such as IL-5, IL-6, TNF-α, and IL-1β, as well as histamine and nerve growth factor, which activate transient receptor potential and voltage-gated sodium channels. This activation induces hyperalgesia[48,87,88]. Macrophages and monocytes sustain pain *via* cytokines, growth factors, and prostaglandins[89]. Activated microglia, astrocytes, and oligodendrocytes further amplify nociceptive signaling through TNF-α, IL-1β, IL-33, and other mediators, producing central sensitization[90-93]. Beyond well-characterized pathways, MSC-EVs may also modulate intracellular signaling cascades and ion channels involved in nociceptor sensitization (Figure 5). Together, all the pathways describe a continuum of MSC-EV action from immune modulation to neural repair, culminating in analgesia.

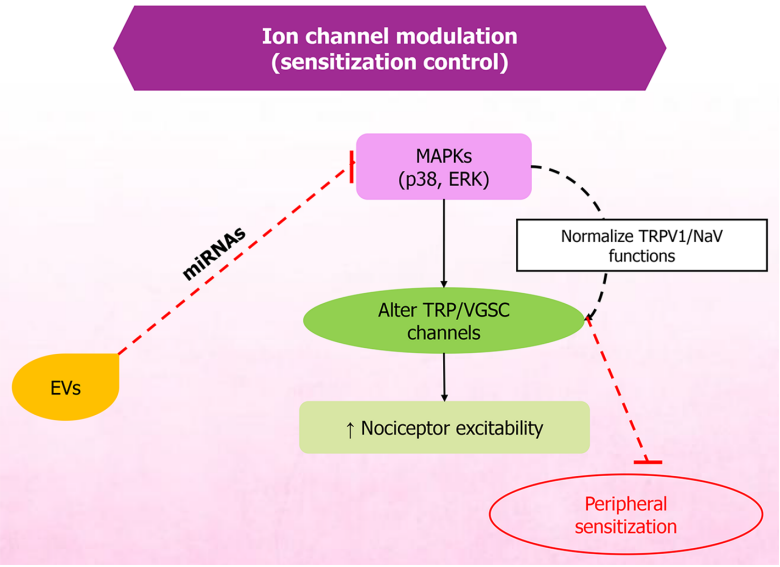

Figure 5 Extracellular vesicle-mediated modulation of mitogen-activated protein kinase and ion channel signaling in peripheral sensitization. Activation of mitogen-activated protein kinase (p38 and extracellular signal regulated kinase) increases transient receptor potential and voltage-gated sodium channel activity, leading to greater nociceptor excitability and pain sensitization. Extracellular vesicle-derived proteins and microRNAs can suppress p38/extracellular signal regulated kinase activation, normalizing transient receptor potential V1 and voltage-gated sodium channel function. This mechanism reduces peripheral sensitization and neuroinflammatory pain responses. EVs: Extracellular vesicles; miRNAs: MicroRNAs; MAPKs: Mitogen-activated protein kinases; ERK: Extracellular signal regulated kinase; TRP: Transient receptor potential; VGSC: Voltage-gated sodium channel; TRPV1: Transient receptor potential V1; NaV: Voltage-gated sodium.

Nociceptors release neuropeptides such as substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide, which mediate neurogenic inflammation through vasodilation and plasma extravasation, while simultaneously regulating immune cell functions and thereby shaping immune responses. For example, calcitonin gene-related peptide upregulates IL-10 and downregulates TNF-α in macrophages[94-99]. Together, this bidirectional neuroimmune process regulates the initiation, persistence, and resolution of pain and guides its management. Research on MSC-EV regulatory management of nociceptor sensitization is still preliminary. Differences in EV cargo and neuronal culture systems often yield conflicting data, whereas others show minimal effects. A few studies include neuroimmune interactions and hence limit the interpretation of how these results translate to chronic pain conditions.

PRECLINICAL AND CLINICAL EVIDENCE

Preclinical studies

Preclinical *in vitro* models have become key tools for advancing diverse research. In this context, they are essential for studying the therapeutic potential of EVs across pain conditions. These systems enable mechanism-based studies showing how EVs - especially exosomes - modulate pain by targeting key signaling pathways, thereby informing novel treatment approaches.

As described earlier, exosomes target inflammation and neuronal excitability through their molecular constituents, and thus, benefit chronic pain conditions like OA and neuropathic pain[100]. *In vitro* neuronal models assess the effects of exosomes on neuronal cells, providing insight into pain modulation and aiding phenotypic screening to identify pain-mitigating compounds[101]. EVs have also been investigated as potential alternatives to conventional cell-based therapies by modulating inflammatory responses and promoting tissue regeneration. Studies have shown that MSC-EVs effectively modulate pain pathways in animal models, indicating potential clinical applicability[76,102]. Moreover, MSC-EVs have produced significant analgesia in neuropathic pain models, including rat chronic constriction injury and mouse partial sciatic nerve ligation[103,104]. Their pain-modulating and regenerative properties also suggest applicability to cancer pain management[105]. Despite this promise, challenges in EV isolation, optimization, and characterization, as well as in elucidating mechanisms of action and therapeutic outcomes, necessitate further research to enable clinical translation[105,106]. Some preclinical studies were described earlier; a summary of recent work is presented in Table 1[48,82,103,104,107-111].

Preclinical MSC-EV studies often lack blinding, use small cohort sizes and apply inconsistent behavioral endpoints leading concerns for replication or reproducibility. Many neuropathic pain models vary widely, thereby limiting comparability. Moreover, *in vivo* biodistribution is rarely rigorously characterized, and the same is true for pharmacokinetic data. Dosing metrics vary widely, and most of the studies rely on single pain models, thus limiting generalizability. Publication bias is very likely, as only a few studies report negative results.

Table 1 Recent preclinical evidence (qualitative data) for pain management using mesenchymal stem cell-derived extracellular vesicles

MSC source	*In vitro* experimental model	*In vivo* experimental model	Pain type	Key findings (qualitative analysis)	Mechanistic outcomes	Ref.
Mouse bone marrow MSCs	-	Partial sciatic nerve ligation in male C57BL/6	Neuropathic pain	MSCs produced long-lasting anti-nociception	Decreased IL-1β, TNF-α, and IL-6	[103]
				Reduced thermal hyperalgesia and mechanical allodynia	Increased IL-10	
					Secretome factors (VEGF, HGF chemerin, angiopoietin-1) mediating neuroprotection and immune modulation	
Mouse bone marrow MSCs	-	Diabetic db/db mouse model	Neuropathic pain	Increased thermal and mechanical sensitivity	Suppressed inflammatory cytokines	[107]
				Increased motor and sensory nerve conduction velocities	Macrophage polarization from M1 to M2	
				Increased intraepidermal nerve fiber density, myelin thickness, and axonemal diameter	Exosomal miRNAs targeted the TLR4/NF-κB pathway, reducing inflammation	
				Reduced neuroinflammation and macrophage infiltration in the sciatic nerve		
Rat bone marrow MSCs	IL-1β-treated rat chondrocytes	Rat OA model induced by sodium iodoacetate	Osteoarthritis pain	BMSC exosomes prolonged paw-withdrawal latency in OA rats	Reduced nociceptor mediator CGRP, decreasing neuronal sensitization	[108]
				Reduced CGRP and iNOS protein levels in DRG tissue	Reduced iNOS and inflammation	
				Indicated relief of both inflammatory and neuropathic components of pain	Modulated anti-inflammatory cytokines	
				Protected cartilage, indirectly reducing pain drivers		
hPMSCs	-	Nerve injury mouse model	Neuropathic pain	An intrathecal dose reversed mechanical allodynia	miR-26a-5p targeted Wnt5a and downstream Wnt5a/Ryk/CaMKII/NFAT signaling	[109]
				Produced long-lasting analgesia	Reduced neuroinflammation	
				Labeled EVs localized to microglia and neurons in the dorsal horn	Decreased TNF-α, IL-1β, and IL-6	
				miR-26a-5p-rich hPMSC-EVs significantly reduced neuropathic pain and neuroinflammation	Inhibited microglial activation	
					Mediated anti-neuroinflammatory and analgesic effects	
hUC-MSCs	LPS and ATP-stimulated BV2 microglia	CFA-induced inflammatory pain in C57BL/6 mice	Inflammatory pain	hUC-MSC exosomes reduced mechanical allodynia and thermal hyperalgesia	Attenuated inflammation-driven pain *via* the miR-146a-5p/TRAF6/autophagy-pyroptosis axis	[110]
				Reduced microglial activation and neuroinflammation		

				Increased autophagy		
hUC-MSCs	LPS-stimulated BV2 microglia	CCI rat model	Neuropathic pain	MSC-EVs reduced pain	EV miR-99b-3p inhibited the PI3K/AKT/mTOR pathway	[104]
				Reduced microglial activation and inflammation	Increased autophagy	
				Restored autophagy *via* miR-99b-3p delivery	Reduced proinflammatory cytokines	
Human bone marrow MSCs	-	High-fat diet plus groove surgery in rats	Osteoarthritis pain	MSC-EVs reduced structural joint degeneration and inflammation more than MSCs	Lower immunogenicity; reduced inflammation and cartilage catabolism	[111]
				EV-treated rats showed less cartilage damage, osteophytosis, synovitis, and pain-associated behavior	Synovitis drove pain and osteophyte formation	
Human bone marrow MSCs	NGF-sensitized DRG neurons	DMM-induced OA in mice	Osteoarthritis pain	Prevented pain-related behaviors	Direct action of MSC-EVs on sensory neurons normalized hyperexcitability	[82]
				MSC-EVs prevented NGF-induced hyperexcitability in cultured DRG neurons *in vitro*	Reduced release of proinflammatory mediators in the joint environment	
hUC-MSCs	DRG primary culture from SD rats	Paclitaxel-induced peripheral neuropathy in C57BL/6J mice	Chemotherapy-induced peripheral neuropathy	Cannabidiol-loaded hUC-MSC-EVs reduced paclitaxel-induced mechanical allodynia and thermal hyperalgesia	AMPK pathway activation	[48]
				Normalized mitochondrial function in DRG and spinal cord of treated mice	Increased mitochondrial function and bioenergetics	
					Modulated oxidative stress and inflammation by upregulating Nrf2 and downregulating NF-κB	
					Provided additional regenerative support	

MSCs: Mesenchymal stem cells; IL: Interleukin; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; HGF: Hepatocyte growth factor; miRNAs: MicroRNAs; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor kappa B; OA: Osteoarthritis; BMSC: Bone mesenchymal stem cell; CGRP: Calcitonin gene-related peptide; iNOS: Inducible nitric oxide synthase; Wnt5a: Wingless type MMTV integration site family, member 5A; Ryk: Receptor like tyrosine kinase; CaMKII: Calmodulin dependent protein kinase 2; NFAT: Nuclear factor of activated T cells; hPMSCs: Human placental mesenchymal stem cells; EVs: Extracellular vesicles; hUC-MSCs: Human umbilical cord mesenchymal stem cells; LPS: Lipopolysaccharide; CFA: Complete Freund's adjuvant; TRAF6: Tumor necrosis factor receptor associated factor 6; CCI: Chronic constriction injury; DMM: Destabilization of the medial meniscus; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; NGF: Nerve growth factor; DRG: Dorsal root ganglia; AMPK: AMP-activated protein kinase; Nrf2: Nuclear factor erythroid 2-related factor 2.

Clinical studies

Clinical studies of MSC-EVs in the context of pain remain at an early stage and primarily focus on pain-related disorders or on safety and feasibility. Several phase I trials are evaluating intra-articular or local delivery of MSC-EV-based or exosome-based products for OA-related joint pain, whereas others are testing exosome injections for neuropathic pain, craniomaxillofacial neuralgia, and low back pain. Most of the translational studies are in their early phases with small sample sizes. The heterogeneity in EV preparations, doses, delivery routes and quality controls also plays a vital role in study success. There are no data for long term toxicity, safety or immunogenicity, making it difficult to properly carry out the trials. Additionally, there are no proper comparisons being made with existing pain treatments. Many studies lack robust control, and regulatory compliance differs, underscoring the requirement for larger, rigorously designed studies.

Current findings and limitations

To date, the clinical landscape for MSC-EV-based pain interventions remains in early phases. After repeated searches and with various keywords, we identified only seven studies that are interventional in nature, mostly phase I or pilot designs with small sample sizes. The most rigorous published study is a randomized, triple blind clinical trial assessing a single intra-articular dose of placental MSC-EVs in knee OA patients (IRCT20210423051054N1). One study demonstrated insightful yet short term improvements in Visual Analogue Scale pain scores and functional outcomes without any serious data on adverse events. However, the study lacked mechanistic biomarkers, dose optimization and long-term evaluation that restricts confidence regarding the durability of the benefit[112]. In contrast, most of the other studies

remain in recruitment or early safety-only phases. For example, a study on the intra-articular EV injections for OA (NCT06431152; NCT06466850; NCT05060107) have not yet reported clinical outcomes, suggesting the nascency of the field. Furthermore, the ExoFlo epidural pilot for lumbar/cervical radiculopathy includes only ten participants and is currently reported solely in conference proceedings without any peer reviewed outcome confirmation. Table 2 summarizes the reported clinical trials[112-114].

Routes of administration and their rationale

The heterogeneity in administration approaches suggests a lack of consensus on optimal biodistribution. IV infusion is being evaluated for craniofacial neuralgia (NCT04202783), hypothesized to reach injured trigeminal branches through the systemic circulation and immune neuroinflammatory alteration. This remains speculative, as IV delivery may suffer from pulmonary trapping and may not efficiently reach the nerves. Therefore, direct comparisons with methods like perineural and intra-ganglionic delivery are required. On the other hand, intradiscal or intra-articular approaches (NCT04849429 for discogenic pain) aim to maximize local tissue exposure but encounter various challenges, including mechanical leakage, rapid clearance and unknown retention. Table 2 summarizes the reported trials[112-114].

The translational "valley of death"

Despite strong biological plausibility, clinical translation barriers remain substantial. Table 3 provides a concise summary of current challenges and concerns associated with that challenge. Without addressing the mentioned gap (Table 3), efficacy effects will remain ambiguous even if early safety seems promising. Therefore, MSC-EV therapeutics should be regarded as investigational in some respects, with safety profiles currently outpacing true and clear evidence of translational benefits. Stronger trial designs using standardized potency metrics and longer follow-up are essential before the therapeutic positioning can be justified.

MSC-EVS AS DRUG DELIVERY SYSTEMS IN PAIN

MSC-EVs are increasingly recognized as a versatile drug-delivery platform for pain management. Their favorable size distribution, intrinsic biocompatibility, ability to traverse biological barriers, capacity to carry bioactive cargo, and low immunogenicity provide advantages over traditional nanocarriers. These EVs can be engineered to display specific ligands, such as streptavidin, which bind biotinylated drugs and enhance targeting to specific cells or tissues[115]. Other approaches, such as pH-sensitive fusogenic peptide modification, allow MSC-EVs to release cargo in inflamed tissues [115,116].

Engineering strategies for MSC-EVs generally fall into two categories: (1) Cargo-loading approaches (passive incubation, electroporation, sonication, or chemical permeabilization) that encapsulate small molecules, peptides, or small interfering RNAs (siRNAs); and (2) Surface-modification approaches that attach peptides, antibodies, or aptamers to EV membranes to improve tissue targeting and therapeutic specificity. For example, engineered EVs loaded with siRNAs or analgesic peptides have shown promise in preclinical models of neuropathic and inflammatory pain, where they suppress proinflammatory signaling and reduce neuronal excitability[117-119]. MSC-EVs can also deliver siRNAs for gene silencing, providing a means to treat pain by targeting specific molecular pathways involved in pain signaling[120].

Compared with synthetic nanoparticles, MSC-EVs provide several benefits in drug delivery systems like better biocompatibility, intrinsic target based on membrane proteins and reduced clearance by mononuclear phagocyte system, characteristic features that widen their translational potential in pain management. Their lipid bilayer membrane provides protection for the cargo against degradation, while the intrinsic proteins and miRNAs help in cellular uptake, enhancing therapeutic efficacy[121-124]. Also, MSC-EVs shows better stability and longer half-life compared to liposomes, which can be prone to degradation[125]. Unlike polymeric nanoparticles that require complex engineering for drug release, MSC-EVs naturally alter therapeutic effects through their cargo, thereby providing a more integrated approach to pain management[126]. In contrast to the polymeric nanoparticles or liposomes, MSC-EVs are much less likely to cause any adverse immune reactions; instead they can synergize their own endogenous cargo, which includes regenerative and anti-inflammatory molecules[49]. Additional advantages include low or no toxicity and improved tissue penetration across barriers such as the BBB. MSC-EVs can also be bioengineered to evade immune clearance, *e.g.*, by expressing CD47[127].

Despite various benefits, there are several limitations that create obstruction in clinical translation. Drug loading efficiency remains low and inconsistent, with active methods often causing EV membrane damage or even cargo leakage [128]. Heterogeneity in EV population and difficulty in large-scale, reproducible isolation complicates the standardized dose process. Additionally, ensuring stability during storage and transport as well as regulatory concerns regarding safety, identity and potency remail unsolved mystery[129]. Further, the efficient drug loading and long-term stability of MSC-EVs remain tough to achieve. Evidence of BBB/blood spinal-cord barrier crossing is mixed with disease state and EV source affecting transport[130]. In the context of pain management, available data remain relatively low compared with oncology or neurodegenerative research. While preclinical studies in models of neuropathic or inflammatory pain have shown promising analgesic results *via* MSC-EVs, evidence specific to chronic pain syndrome, cancer pain or clinical application in very much limited.

Emerging bioengineering and delivery innovations

Emerging bioengineering approaches that include synthetic EV mimetics, hybrid EV nanoparticles and 3D cell culture systems, hold promises to overcome the major limitations of EV therapy, particularly in regenerative medicine and pain

Table 2 Clinical trials evaluating mesenchymal stem cell-derived extracellular vesicle/exosome-based interventions for pain management

Study start year	Trial/study ID	Pain condition	Phase	Estimated enrollment	Intervention	Source
2024	NCT06431152	Knee osteoarthritis	Phase I	12	Intra-articular small EVs from umbilical cord MSCs	ClinicalTrials.gov
2024	NCT06466850	Osteoarthritis	N/A	20	Intra-articular MSC-derived exosomes	ClinicalTrials.gov
2021	NCT05060107	Knee osteoarthritis	Phase I	10	Single intra-articular MSC-derived exosome injection	ClinicalTrials.gov
2023	NCT04202783	Craniofacial neuralgia	Early phase (safety and efficacy)	100	Intravenous infusion of exosomes	ClinicalTrials.gov
2021	NCT04849429	Chronic low back pain (discogenic; intradiscal approach)	Phase I	30	Intradiscal injection of platelet-rich plasma with exosomes	[113]
2022 (approved year)	IRCT20210423051054N1	Knee osteoarthritis	Randomized, triple-blind clinical trial	31	Single intra-articular injection of placental MSC-EVs	[112]
-	ExoFlo interlaminar epidural safety study	Lumbar or cervical radiculopathy	Small open safety pilot study	10	Epidural injection of BM-MSC-EV isolate (ExoFlo); safety pilot	[114]

EVs: Extracellular vesicles; MSCs: Mesenchymal stem cells; N/A: Not applicable; MSC-EVs: Mesenchymal stem cell-derived extracellular vesicles; BM-MSC-EV: Bone marrow mesenchymal stem cell-derived extracellular vesicle.

Table 3 Translational barriers in clinical development of mesenchymal stem cell-derived extracellular vesicle therapies for pain

Challenges	Concerns
Study design	Lack of placebo/sham controls; open label designs dominate
	Limited inference of true clinical effect
Follow up duration	< 6 months endpoints
	Short for chronic pain assessment
Dosing and potency	No standardized unit of potency
	Prevents cross-trial comparison
Manufacturing	Heterogeneity in EV isolation protocols, and hence, unpredictable therapeutic consistency
	Inconsistent EV product quality
	Inconsistent therapeutic predictability
Regulatory	Unclear categorization (biologic *vs* cell-derived drug *vs* advanced therapy)
	Unclear oversight requirements

EVs: Extracellular vesicles.

management. Natural EV production is usually low and biodistribution non-specific, which hinders dosing and targeting in inflammatory, neuropathic or cancer pain models. To address this issue, EV mimetics like 'nanoghosts' or cell-membrane nanovesicles can be engineered at scale with EV-like contents. For example, sonication-derived MSC nanoghosts generated approximately twice as many vesicles per cell than native MSC-EVs, while retaining key bioactive proteins[131]. These mimetics can be loaded with analgesic cargo and targeting ligands to provide a place for injured nerves or inflamed tissue. Basically, synthetic EV mimetics can be produced using top-down approaches, improving yield while retaining biological properties like natural EVs[132]. Moreover, EV mimetics can be engineered to have better targeting abilities by incorporating specific peptides or antibodies, which can lead them to pain-affected tissues[133]. Likewise, hybrid nanoparticles that fuse EV membranes or surface proteins with synthetic cores/Liposomes combine EV tropism with tunable payloads and stability. One such example is the cartilage-targeted EV-liposome hybrids that have successfully achieved increased retention and sustained anti-inflammatory action in osteoarthritic joints[134,135].

Therefore, hybrid nanoparticles that integrate EV characteristics can achieve immune evasion and prolonged circulation, thus making them suitable for targeted drug delivery in various pain models. Therapeutic agents can be loaded into these nanoparticles, improving their efficacy in managing pain through the administration of drugs to the exact locations[136]. Furthermore, 3D culture platforms like spheroids, scaffold-based bioreactors and organoids significantly boost EV yield and function. This is because they provide a more physiologically relevant environment for pain mechanisms studies and testing EV-based therapies, and this will likely lead to a better result in preclinical models[137]. For example, dental-MSC spheroids grown in a 3D hydrogel produced approximately six times more exosomal protein than identical cells in 2D [135], and the EVs showed better regenerative effects. When combined with engineered EVs, the 3D systems can drive and enhance tissue regeneration while also alleviating pain by mimicking the natural extracellular matrix[133]. These systems have the potential to provide clinically relevant EV doses through any delivery route and allow for surface engineering (peptides or antibodies) to concentrate EVs at pain sites by enabling high-volume production. Above all, preliminary translational studies imply that EVs can relieve pain. In a clinical study in 2025 on the use of MSC-EVs in thumb joint OA, the intra-articular injection of MSC-EVs significantly decreased pain scores during the course of 1 year [135]. Hence, synthetic EV mimetic, hybrid carriers and 3D biomanufacturing together could provide better yield and generate targeted EV therapies for broader pain indications.

EV SIGNATURES IN PAIN DIAGNOSIS AND MSC-EV CHARACTERIZATION (ROLE AS BIOMARKERS)

The intersection of EVs and pain management encompasses two distinct but complementary areas: (1) The analysis of patient-derived circulating EVs as diagnostic biomarkers (liquid biopsy); and (2) The profiling of MSC-EVs to predict therapeutic potency. Liquid biopsy procedures using EVs have demonstrated better sensitivity and specificity compared with conventional diagnostic techniques, especially in terms of cancer that is now translating to pain medicine[138]. In the context of pain, circulating EVs, derived primarily from neurons, glial cells, and immune cells rather than MSCs, carry specific protein and miRNA signatures that reflect the pathological state. For example, circulating miRNAs exhibit altered expression in chronic pain conditions and offer stability that allows for retrospective studies by the utilization of archived samples[139]. These signatures assist in categorizing patients based on severity and identifying specific pain phenotypes, potentially acting as objective metrices for pain, a condition historically reliant on subjective self-reporting and monitoring[140]. Integration of machine learning further adds to diagnostic accuracy by combining multiple EV biomarker signals into composite profiles, thereby offering a robust approach to differentiate complex pain syndromes[138].

Unlike patient-derived EVs used for diagnosis, MSC-EVs are primarily used as therapeutic agents. However, the proper analysis of their molecular cargo *i.e.,* biomarker profiling, is crucial for predicting their therapeutic efficacy outcomes, often referred to as "potency marking". For example, MSC-EVs are rich in some specific miRNAs, such as miR124 and miR9, which have shown anti-inflammatory effects in pain models of arthritis and interstitial cystitis by the regulation of various inflammatory pathways[71,73].

Consequently, characterizing the levels of these miRNAs within MSC-EVs serves as a quality control biomarker to ensure the batch will be effective prior to its administration. While the detection of endogenous MSC-EVs in patient blood for diagnostics remains theoretical and technically challenging due to their low abundance relative to hematopoietic EVs, the profiling of exogenous or therapeutic MSC-EVs provides a "fingerprint" of their immunomodulatory potential[44, 141]. Furthermore, modified MSC-EVs are being explored in theragnostic, simultaneously delivering analgesia while carrying imaging agents to monitor or track retention in injured tissues[142,143].

Despite the promise of circulating EVs as diagnostic tools and MSC-EV cargo as potency markers, significant challenges remain. EV biomarker signatures differ considerably across individuals and are altered by comorbidities and physiological states. Most of the studies provide correlational evidence without any mechanistic validation and inconsistent EV isolation from biofluids residues reproducibly across cohorts. More standardized, longitudinal studies are required prior to transition from preclinical to clinical stage. Still, after so many advancements and promise of MSC-EVs functioning as biomarkers in pain management and diagnosis, there are still various challenges that require further research to validate their translational utility and further applications in pain management approaches.

CHALLENGES AND FUTURE PERSPECTIVES

Successful clinical translation of MSC-EVs for pain management requires rigorous study designs and compliant regulatory frameworks. Because pain is multifactorial, defining EV profiles that correspond to distinct pain states remains challenging[143]. Heterogeneity in production procedures and cargo complexity further undermine reproducibility, underscoring the need for standardized isolation and characterization protocols. Optimizing delivery systems to target sites of action also remains a major challenge[79,144]. Adherence to the Minimum Information for Studies of Extracellular Vesicles recommendations is essential to ensure transparent documentation of MSC-EV sources and isolation methods and to mandate physicochemical/biochemical analyses and appropriate functional controls[78,145]. Beyond standardization, validated impurity profiling and potency assays are required to develop safe MSC-EV-based therapeutics. Regulatory authorities increasingly require risk-based dossiers - including biodistribution, stability, batch-to-batch consistency, and nonclinical toxicology - rather than simple particle counts, to support investigational new drug applications. Agencies also emphasize Good Manufacturing Practice (GMP)-compliant manufacturing, robust potency assays, and precise stability testing tailored to the complexity of EV-based products[146-148]. Navigating the regulatory landscape for MSC-EV therapeutics is complex and demands rigorous testing and validation before clinical translation[144].

Manufacturing clinic grade MSC-EVs remains a major challenge, as it is very expensive. For example, one analysis estimated that producing a 5 × 10^{12} EV lot (approximately 125 human doses of about 4 × 10^{10} EVs) costs on the order of $1 million, equaling roughly $8000 per dose[149]. Purification using ultracentrifugation, tangential flow filtration, chromatography and extensive quality control with sterility, identity, purity, potency, *etc.* add substantially to the cost. Even the use of automated bioreactors only modestly reduces costs. One study found only approximately $1000 per dose savings using a 3D closed system[150], and consumables/Labor remains costly. Thus, the "cost of gold" per MSC-EV dose often runs into the tens of thousand dollars.

Scaling EV production poses additional technical and biological hurdles. Ultracentrifugation-based workflows are poorly suited for clinical manufacturing, whereas tangential-flow filtration coupled with size-exclusion chromatography can improve yield while limiting vesicle damage. Nonetheless, heterogeneity arising from source-cell selection, culture conditions, and suboptimal purification remains a major determinant of cost and reproducibility[147,151]. The scale-up is also limited by yield. Conventional 2D flask culture produces about 10^7-10^9 EVs per liter, only thereby forcing large cultures to obtain a therapeutic dose. Methods like bioreactor methods (hollow-fiber, microcarriers or stirred up tanks) can boost yield, as reports cite (5-140) × higher EV recovery *vs* flasks, and closed systems permit cGMP production. However, making ≥ 10^{11} EVs per batch still requires massive cell banks and large volumes. Every scale-up step must meet strict GMP standards, thereby adding complexity[152-155]. Downstream isolation is a bottleneck: Ultracentrifugation is not scalable, and while tangential flow filtration is more scalable, it requires expensive equipment and still yields limited concentration gains. Also, dosing is very important and in pain and injury models, as rodents are usually treated with approximately 10^9-10^{10} EVs/kg. Allometric scaling, meaning body-surface area scaling, implies a human equivalent dose on the order of 10^{11}-10^{12} EVs for a 70 kg patient[156-158]. Such large doses stretches manufacturing capacity and cost. Route of administration further influences dose; IV delivery helps achieve better EV distribution, necessitating high total doses, whereas localized routes can achieve therapeutic concentrations with far fewer EVs[159].

Additionally, safety concerns specific to pain indications also warrant scrutiny, including risks of protumorigenic or profibrotic signaling, unintended immunomodulation, and off-target distribution, necessitating long-term preclinical evaluation[148]. Moreover, factors underlying clinical failures with MSCs include poor quality control and variability in immunocompatibility, differentiation, and migratory capacity[160].

Future directions include synthetic EV mimetics, surface engineering, nucleic-acid loading, and designer EVs to enhance cargo loading and targeting, enabling delivery of analgesics, siRNAs, or neurotrophic factors[161,162]. However, these strategies introduce additional quality-control and regulatory challenges, such as immunogenicity and novel impurities, that require systematic head-to-head comparisons with natural EVs and early-phase clinical study designs. Identifying key therapeutic miRNAs within MSC-EVs and optimizing their production may further enhance efficacy[79,142]. Ultimately, coordinated efforts across academia, industry, and regulators - adhering to Minimum Information for Studies of Extracellular Vesicles-aligned standards, validated potency and safety assays, and GMP-compatible bioprocessing - are needed to transition MSC-EVs from promising preclinical candidates to reliable, approved pain therapies.

CONCLUSION

MSC-EVs have surfaced as a promising therapeutic approach for pain management in the preclinical setting due to their potential to modulate the critical molecular and cellular pathways underlying nociception, but they still require robust clinical validation. Preclinical evidence indicates that MSC-EVs downregulate proinflammatory mediators - particularly IL-1β and TNF-α - while upregulating anti-inflammatory cytokines such as TGF-β and IL-10. Their regenerative effects are also associated with reduced glial activation, thereby attenuating peripheral and central sensitization in models of neuropathic, inflammatory, and cancer pain. Furthermore, EV-borne miRNAs and proteins regulate apoptosis, oxidative stress, and synaptic plasticity, promoting neuronal survival, axonal regeneration, and functional recovery. MSC-EVs also facilitate tissue repair by delivering growth factors and regulatory RNAs that enhance cartilage regeneration and mitigate pain. MSC-EVs have not only shown potential in OA and neuropathic pain in the preclinical phase, but also in a variety of other pains like chronic pain, thereby suggesting avenues to reshape pain management paradigms (Figure 6). Also, further studies are required for the successful transition of the preclinical to clinical phase, and more importantly, to late clinical phases, as almost no studies have reached phase III.

MSC-EVs possess intrinsic therapeutic activity and can function as biocompatible nanocarriers for targeted drug delivery. Their lipid bilayer confers stability and helps evade immune surveillance. Engineering approaches enable drug loading and efficient delivery of analgesics, siRNAs, and peptides to target tissues, often with greater efficacy than synthetic nanoparticles. Meanwhile, different engineering approaches are utilized to allow the drug loading processes and effective delivery of analgesics, siRNAs and peptides to its target with greater efficacy. EV-linked molecular signatures - especially miRNAs and proteins - also hold promise as minimally invasive biomarkers for pain stratification and disease monitoring.

Despite substantial progress, significant challenges remain, including EV heterogeneity, limitations in isolation and evaluation methods, scalability, dosing reliability, and long-term safety. Furthermore, despite promising preclinical results, there is a lack of clinical studies validating these findings in human subjects, necessitating further research. Moreover, priority should be given to placebo-controlled phase II trials in diseases like OA with at least ≥ 1 year follow up. It is crucial to address all the related concerns for the translational application of EV based therapies. Moreover, despite promising preclinical results, clinical validation in humans is limited and warrants further study. Addressing these issues is crucial for the translational application of EV-based therapies. To realize clinical value, well-designed mechanistic studies, standardized manufacturing procedures, and carefully controlled clinical trials are needed. Thus,

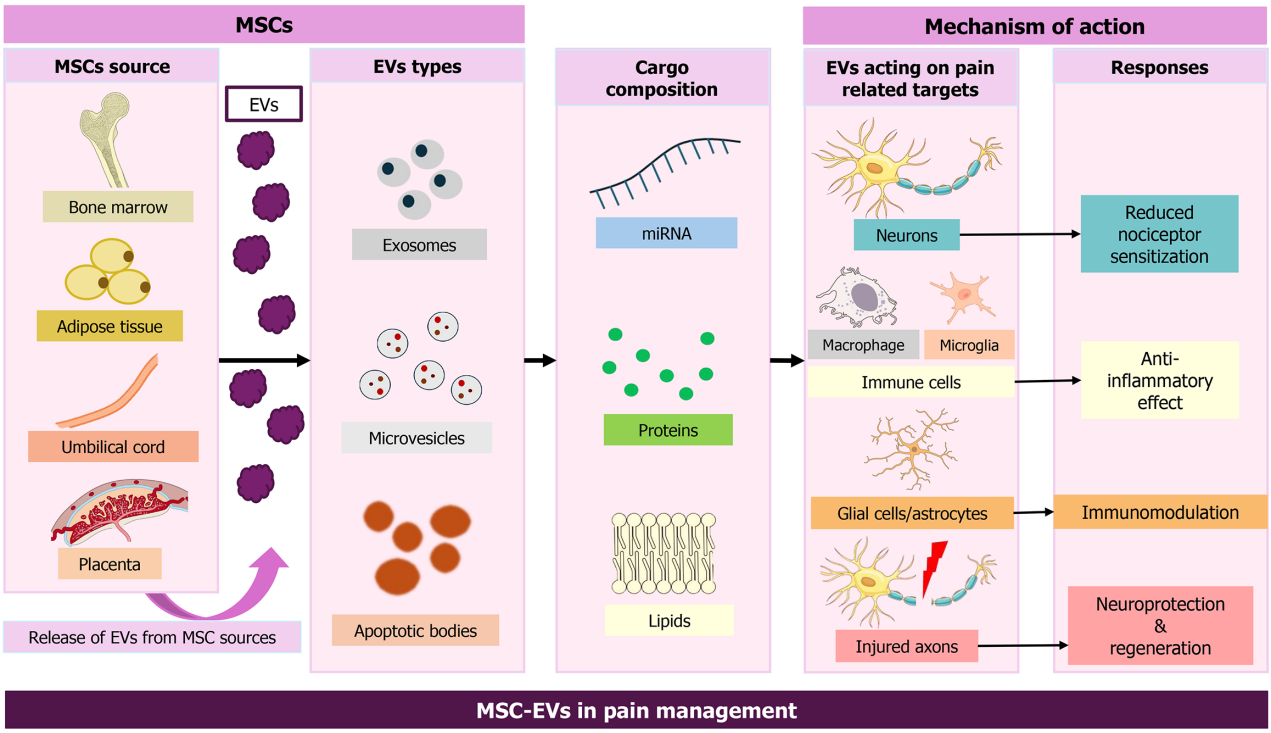

Figure 6 Summary of how mesenchymal stem cell-derived extracellular vesicles (from source to response) help in pain management. Mesenchymal stem cells from various tissue sources secrete various types of extracellular vesicles, which contain bioactive cargo such as microRNAs, proteins, and lipids. These mesenchymal stem cell-derived extracellular vesicles target major pain-associated cells that result in therapeutic outcomes encompassing anti-inflammatory effects, neuroprotection, immunomodulation, and neuroprotection, thereby demonstrating their multifaceted mechanisms in reducing pain. MSCs: Mesenchymal stem cells; EVs: Extracellular vesicles; miRNAs: MicroRNAs; MSC-EVs: Mesenchymal stem cell-derived extracellular vesicles.

MSC-EVs can be utilized as a versatile and multifunctional therapeutic platform and possess the potential to change the landscape of pain in future.

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