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REVIEW

Bone marrow mesenchymal stromal cell-derived exosomes in knee osteoarthritis: Bridging mechanistic understanding to clinical applications

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Abstract

Knee osteoarthritis is recognised as a whole-joint disorder involving cartilage, synovium, subchondral bone and nociceptive pathways. Conventional therapies provide symptomatic relief but rarely alter structural progression. Mesenchymal stromal cell (MSC) injections improve pain and function, yet structural benefits remain modest and variable. Increasing evidence indicates that much of the MSC effect is mediated by secreted extracellular vesicles (EVs), particularly those derived from bone marrow MSCs. These vesicles deliver proteins, lipids, microRNAs and long noncoding RNAs that regulate catabolic enzymes, inflammatory mediators and survival pathways, thereby influencing chondrocyte apoptosis, matrix turnover, macrophage polarisation, osteoclast activity and nociceptive signalling. This review uniquely synthesises mechanistic insights into extracellular vesicles derived from bone marrow MSCs cargo, compares their performance with other MSC sources, and highlights translational priorities including Minimal Information for Studies of EVs 2023-compliant characterisation, dose-finding, and adequately powered trials with structural and biomarker endpoints.

Key Words: Knee osteoarthritis; Bone marrow; Mesenchymal stromal cells; Extracellular vesicles; Exosomes; Hydrogels

Core Tip: Bone marrow mesenchymal stromal cell exosomes show promise as cell-free therapeutics for knee osteoarthritis by delivering microRNAs and long noncoding RNAs that modulate nuclear factor kappa B, Wnt/β-catenin, phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin and mitogen-activated protein kinases pathways. They suppress chondrocyte apoptosis, enhance matrix synthesis, polarise macrophages, and reduce pain behaviours. Delivery innovations like hydrogels improve retention, but rigorous Minimal Information for Studies of Extracellular Vesicles 2023-compliant characterisation and adequately powered randomised trials remain essential before clinical translation as disease-modifying therapy.

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INTRODUCTION

Knee osteoarthritis (KOA) is a leading cause of chronic pain and disability worldwide. It is now recognised as a complex joint organ disease rather than a simple problem of "wear and tear"[1,2]. Cartilage loss, osteophyte formation, subchondral bone remodelling, synovitis, meniscal degeneration and periarticular muscle changes all contribute to the clinical phenotype[3].

Conservative management centres on education, weight reduction, exercise, analgesics, non-steroidal anti-inflammatory drugs and intra-articular injections of corticosteroids or hyaluronic acid. These approaches relieve symptoms but rarely alter long-term structural progression. Total knee arthroplasty is highly effective for end-stage disease, but many patients are too young, too comorbid or unwilling to accept prosthetic joint replacement[4].

Intra-articular mesenchymal stromal cell (MSC) injections have been promoted as disease-modifying options. Recent meta-analyses in the usage of intra-articular MSC show significant improvements in pain and function compared with placebo or hyaluronic acid[5-7]. While intra-articular MSC injections consistently demonstrate symptomatic improvements in pain and function, structural benefits observed on magnetic resonance imaging (MRI) or radiographic imaging remain modest and inconsistent, with subgroup analyses often showing stronger clinical responses for adipose- or umbilical-derived MSCs compared to bone marrow MSCs (BM-MSCs)[8]. Direct MSC therapy is further constrained by limited engraftment in the hostile osteoarthritic milieu, donor-to-donor variability in potency, theoretical risks of ectopic tissue formation and the logistical burden of cell manufacturing[9].

These observations have shifted attention toward the MSC secretome and, specifically, extracellular vesicles (EVs). EVs can recapitulate many immunomodulatory and regenerative effects of the parent cells while sidestepping some of the safety and regulatory issues associated with live-cell products[10]. Within this broader field, BM-MSC exosomes (BM-MSC-Exos) deserve particular scrutiny because BM-MSCs have historically been central to cartilage repair research and possess strong chondrogenic capacity[11].

The goal of this review is to provide a deeper and more critical synthesis of the literature on BM-MSC-Exos in KOA, moving beyond descriptive summaries. We focus on the biology and characterisation of BM-MSC-Exos, their proteomic and RNA cargo, molecular mechanisms in joint tissues, engineering strategies, comparative performance *vs* other MSC sources, preclinical *in vivo* evidence, emerging clinical data, regulatory considerations and priorities for future translational work.

BIOLOGY, BIOGENESIS AND CHARACTERISATION

EVs comprise a heterogeneous spectrum of lipid-bilayer particles released by cells. Classical exosomes arise from inward budding of late endosomal membranes to form intraluminal vesicles[12]. These accumulate within multivesicular bodies that can fuse with the plasma membrane and release their contents into the extracellular space. Endosomal Sorting Complex Required for Transport complexes, ceramide-dependent Endosomal Sorting Complex Required for Transport-independent pathways and Rab GTPases all contribute to exosome biogenesis[13]. Microvesicles bud directly from the plasma membrane and apoptotic bodies are shed from dying cells, and the size ranges of these populations overlap extensively[14] (Figures 1 and 2).

Traditionally, "exosomes" have been defined by size and marker expression. Small vesicles of roughly 30-150 nm enriched for tetraspanins (CD9, CD63, CD81) and endosomal proteins such as ALIX and TSG101 are often labelled as exosomes[15]. It is increasingly accepted, however, that most available separation techniques produce mixtures of small EVs and non-vesicular particles rather than pure exosome subsets[16].

BM-MSC-Exos for osteoarthritis research are usually obtained from conditioned media using differential ultracentrifugation, polymer precipitation, size-exclusion chromatography, ultrafiltration or combinations of these[17]. Differential ultracentrifugation yields relatively clean small-particle fractions but is labour-intensive and can induce vesicle aggregation at high g-forces[18]. Polymer precipitation increases yield and convenience but often co-isolates lipoproteins and protein aggregates that may confound mechanistic work[19]. Size-exclusion chromatography coupled with tangential flow filtration is more amenable to clinical-scale manufacture and tends to preserve vesicle integrity, though it may discard a proportion of very small particles and still requires careful assessment of contaminants[20].

Minimal Information for Studies of EVs 2023 (MISEV2023) has formalised minimal criteria for EV studies. It recommends transparent reporting of the cell source and culture conditions, separation and concentration methods, at least three positive protein markers and one or more negative markers, orthogonal size and concentration measurements and critical assessment of co-isolated proteins and lipoproteins[21]. Many preclinical KOA studies with BM-MSC-Exos predate these guidelines or only partially comply. Exosome identity is often inferred from particle size and CD63/CD81 expression, without negative markers or detailed contaminant profiling. This undercuts reproducibility and complicates cross-study comparisons[22].

The membrane lipid composition of BM-MSC-Exos, including high proportions of cholesterol, sphingomyelin and ceramide, contributes to vesicle stability in the synovial environment and may influence uptake pathways such as endocytosis or direct fusion[23]. This lipid biology remains comparatively underexplored in the OA setting but is likely to be relevant for joint retention and biodistribution[24].

MISEV2023-COMPLIANT RESEARCH OPERATION GUIDELINES

Despite promising preclinical evidence, many BM-MSC-derived EV (BM-MSC-EV) studies predate or only partially comply with MISEV2023 standards, limiting reproducibility and comparability. To address this, future research should adopt the following operational guidelines: (1) Source documentation: Clearly report MSC tissue origin, donor age, comorbidities, and culture conditions; (2) Isolation methods: Specify separation techniques (*e.g.*, ultracentrifugation, size-exclusion chromatography) and provide orthogonal validation of vesicle identity; (3) Characterisation: Include at least three positive protein markers (CD9, CD63, CD81, ALIX, TSG101) and one or more negative markers (*e.g.*, calnexin, albumin) to exclude contaminants; (4) Quantification: Report EV dose using particle counts (nanoparticle tracking analysis) or functional units, rather than protein mass alone; (5) Contaminant profiling: Assess and disclose co-isolated proteins, lipoproteins, or aggregates that may confound mechanistic interpretation; (6) Functional assays: Complement molecular profiling with assays that confirm biological activity (*e.g.*, chondrocyte apoptosis suppression, macrophage polarisation); and (7) Transparent reporting: Provide detailed methodological appendices to facilitate replication across laboratories. Adopting these MISEV2023-compliant practices will enhance reproducibility, enable meaningful cross-study comparisons, and accelerate clinical translation of BM-MSC-EVs in KOA.

Cargo of BM-MSC EVs

Proteomic studies have catalogued several hundred proteins in BM-MSC-Exos, spanning cytoskeletal regulators, metabolic enzymes, extracellular matrix components and immunomodulatory molecules[25-27]. Proteomic profiling of BM-MSC-EVs has consistently identified gelsolin as one of the more abundant cytoskeletal regulators, with relative enrichment compared to other actin-binding proteins[28]. Experimental studies using mass spectrometry confirmed that gelsolin levels are markedly higher in BM-MSC-EVs than in parental cell lysates, suggesting selective packaging. Functionally, gelsolin has been linked to enhanced migration and cytoskeletal reorganisation in articular chondrocytes, and its localisation to cartilage after intra-articular delivery supports the concept that EVs can deliver bioactive proteins directly to joint tissues. Macrophage migration inhibitory factor (MIF), traditionally considered pro-inflammatory, has been directly identified in proteomic analyses of BM-MSC-EVs[29]. Recent experimental studies demonstrate that MIF-containing EVs can modulate osteoclastogenesis and bone remodelling, suggesting a homeostatic role in subchondral bone. Physiological MIF signalling appears to restrain excessive osteoclast activity, and BM-MSC-EVs may exploit this pathway to stabilise bone architecture in osteoarthritic joints[30].

BM-MSC-Exos also carry extracellular matrix proteins such as collagen VI and biglycan, along with enzymes involved in collagen crosslinking such as PLOD1[31,32]. This suggests that exosomes may not only modulate the behaviour of resident cells but also contribute structural components and matrix-organising signals directly to the osteoarthritic

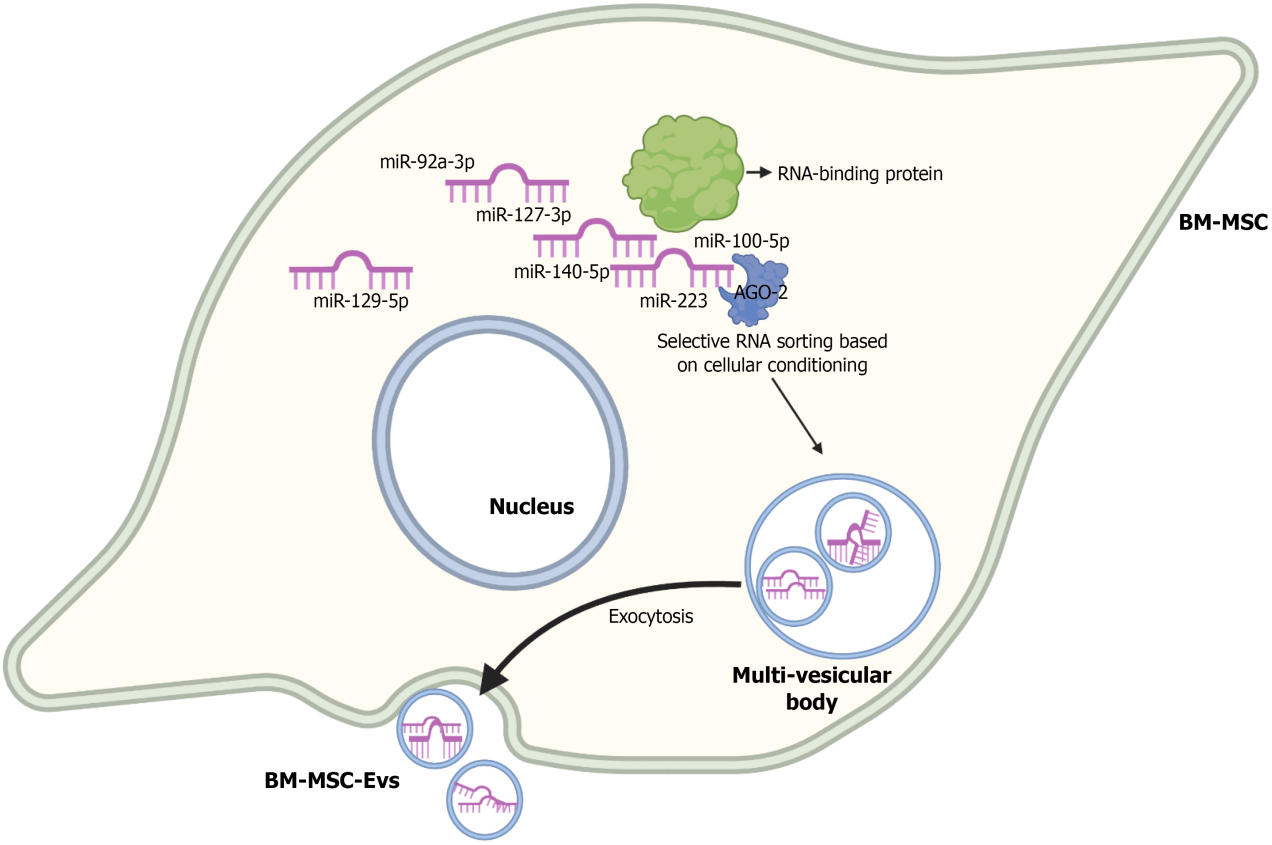

Figure 1 Biogenesis of bone marrow mesenchymal stromal cell derived exosomes. Created in BioRender (Supplementary material). BM-MSC: Bone marrow mesenchymal stromal cell; BM-MSC-EVs: Bone marrow mesenchymal stromal cell derived exosomes.

cartilage microenvironment[33].

On the RNA side, a relatively consistent set of microRNAs (miRNAs) emerges across independent profiles of BM-MSC-Exos in KOA models. miR-140-5p, miR-127-3p, miR-92a-3p, miR-129-5p, miR-223 and miR-100-5p recur in studies that demonstrate chondroprotection, reduced catabolism and enhanced autophagy[34]. These miRNAs target key OA-related genes including a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5), matrix metalloproteinase-13 (MMP-13), WNT ligands, high mobility group B1, nod-like receptor protein 3 and mechanistic target of rapamycin (mTOR)[35]. Long noncoding RNAs (lncRNAs) such as MEG3, KLF3-AS1, SNHG7 and LYRM4-AS1 act as competing endogenous RNAs, binding specific miRNAs and thereby regulating ferroptosis suppressor protein 1, G protein-coupled receptor kinase-interactor 1 and other chondroprotective targets[36].

Crucially, the cargo of BM-MSC-Exos is not fixed. Inflammatory priming of parental BM-MSCs with interleukin (IL)-1β or tumor necrosis factor (TNF)-α, hypoxic culture and three-dimensional scaffolds all alter exosomal profiles[37]. In several reports, such conditioning enhances anti-inflammatory and regenerative properties, but it also introduces further complexity for product standardisation[38]. Table 1 summarises selected miRNAs and lncRNAs identified in BM-MSC-EVs that are repeatedly implicated in KOA models.

Molecular mechanisms in osteoarthritic joints

BM-MSC-Exos act on several cell populations within the knee joint. In articular chondrocytes exposed to IL-1β or TNF-α, BM-MSC-Exos consistently reduce markers of apoptosis such as BAX and cleaved caspase-3 and increase expression of BCL-2[39]. These changes are accompanied by recovery of mitochondrial membrane potential, increased collagen type II alpha 1 and aggrecan expression and suppression of MMP-13 and ADAMTS5. In combination, these effects shift the balance from catabolic degradation to anabolic matrix synthesis[40].

Nuclear factor kappa B is a central inflammatory pathway in KOA. BM-MSC-Exos deliver miR-129-5p and related miRNAs that target high mobility group B1 and upstream components of the Toll-like receptor 4 pathway[41]. As a result, IκBα phosphorylation and p65 nuclear translocation are reduced and the transcription of IL-1β, TNF-α and matrix-degrading enzymes falls[42]. This mechanism is supported by both *in vitro* chondrocyte work and *in vivo* reductions in synovial and serum cytokine levels after exosome treatment[43].

Aberrant Wnt/β-catenin signalling drives chondrocyte hypertrophy and cartilage calcification[44]. miR-127-3p and miR-376c-3p within BM-MSC-Exos inhibit cadherin-11 and certain Wnt ligands, limiting β-catenin accumulation in the nucleus and preserving the non-hypertrophic articular phenotype[45]. Separate studies implicate exosomal miR-92a-3p in enhancement of hyaline cartilage markers and suppression of catabolic enzymes, further corroborating a Wnt-modulating role[46].

Table 1 Selected bone marrow mesenchymal stromal cell-exosomal microRNAs and long noncoding RNAs relevant to knee osteoarthritis

Cargo species	Principal targets/pathways (examples)	Main joint-level effects (preclinical)	Ref.
miR-140-5p	ADAMTS5, MMP-13, IGFBP5, Notch and Wnt components	Promotes chondrogenesis and matrix synthesis; suppresses catabolic enzymes and hypertrophic signalling	[34,35]
miR-127-3p	Cadherin-11 and Wnt/β-catenin signalling	Inhibits chondrocyte hypertrophy and cartilage calcification	[34,45]
miR-92a-3p	WNT5A and associated kinases	Increases COL2A1 and aggrecan; reduces MMP expression	[34,46]
miR-129-5p	HMGB1 and TLR4/NF-κB axis	Dampens synovial inflammation and chondrocyte apoptosis	[35,41]
miR-223	NLRP3 inflammasome components	Inhibits pyroptosis in chondrocytes and macrophages	[35,43]
miR-100-5p	mTOR	Enhances autophagy and survival in stressed chondrocytes	[35,47]
lncRNA KLF3-AS1	Sponges miR-206, maintains GIT1	Supports PI3K/Akt signalling; promotes chondrocyte proliferation and survival	[47]
lncRNA SNHG7	miR-485-5p/FSP1 axis	Anti-ferroptotic and anti-senescent effects in cartilage	[36]

ADAMTS5: A disintegrin and metalloproteinase with thrombospondin motifs 5; MMP-13: Matrix metalloproteinase-13; IGFBP5: Insulin-like growth factor-binding protein 5; COL2A1: Collagen type II alpha 1; HMGB1: High mobility group B1; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor kappa B; NLRP3: Nod-like receptor protein 3; mTOR: Mechanistic target of rapamycin; GIT1: G protein-coupled receptor kinase-interactor 1; PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; FSP1: Ferroptosis suppressor protein 1.

PI3K/Akt/mTOR and mitogen-activated protein kinases cascades integrate growth, stress and survival signals. lncRNA KLF3-AS1 within BM-MSC-Exos acts as a sponge for miR-206, preserving G protein-coupled receptor kinase-interactor 1 expression and thereby supporting PI3K/Akt signalling in chondrocytes[47]. In parallel, miR-100-5p-mediated regulation of mTOR restores autophagic flux, which is often impaired in OA cartilage. BM-MSC-Exos also reduce phosphorylation of p38 and extracellular signal-related kinases 1 and 2 in response to inflammatory stimuli, leading to lower inducible nitric oxide synthase and COX-2 expression and reduced prostaglandin E2 production[48].

In synovium, BM-MSC-Exos reduce macrophage infiltration and favour a shift from pro-inflammatory M1 to anti-inflammatory M2 phenotypes. Synovial fluid levels of IL-1β, TNF-α and IL-6 fall while IL-10 rises in several rodent studies[49]. These changes are consistent with the broader MSC-EV literature in which M2 polarisation is necessary for cartilage protection[50].

Subchondral bone responses are less extensively mapped, but BM-MSC-Exos appear to modulate osteoclastogenesis through RANKL/OPG signalling and MIF-associated pathways. In KOA models, exosome treatment reduces subchondral bone loss and osteophyte formation, suggesting that bone effects are not merely secondary to cartilage changes[51].

From a pain perspective, intra-articular BM-MSC-Exos increase paw-withdrawal thresholds, restore weight-bearing symmetry and improve spontaneous activity in rodents[52]. These behavioural changes co-localise with reduced inflammatory mediators in the joint and decreased expression of nociceptive markers such as calcitonin gene-related peptide and inducible nitric oxide synthase in dorsal root ganglia. In humans, these findings suggest a plausible mechanism by which BM-MSC-EVs could attenuate peripheral nociceptive input and thereby reduce central sensitisation, a key driver of chronic pain in KOA. However, direct evidence of central modulation remains lacking, and future trials should incorporate neurophysiological endpoints or pain biomarkers to clarify translation[53].

Engineered cargo and "designer" exosomes

The capacity to manipulate parental MSCs has been used to generate exosomes with enriched therapeutic cargo. BM-MSCs or synovial MSCs engineered to overexpress miR-140-5p produce exosomes with superior chondroprotective effects in rat KOA models, including more complete preservation of cartilage thickness, reduced osteophytes and better histological scores than unmodified exosomes[54]. Enrichment for miR-127-3p or miR-92a-3p yields stronger suppression of Wnt signalling and matrix degradation, further supporting the causal role of these miRNAs[55].

lncRNA-based engineering is another approach. Overexpression of SNHG7 in MSCs leads to exosomes that modulate the miR-485-5p/ferroptosis suppressor protein 1 axis, reduce ferroptosis markers and attenuate cartilage degeneration in experimental OA. Other lncRNAs have been targeted to reinforce anti-senescent and antioxidant pathways[56]. These studies provide convincing proof of concept that specific exosomal RNAs drive key aspects of chondroprotection. However, they also push the resulting products closer to gene therapy in regulatory terms[57]. Engineered exosomes may be judged as genetically modified advanced therapies, with stricter expectations for vector characterisation, off-target risk assessment and long-term follow up. For practical clinical translation in KOA, there remains a tension between maximising mechanistic precision and preserving manufacturing simplicity[58].

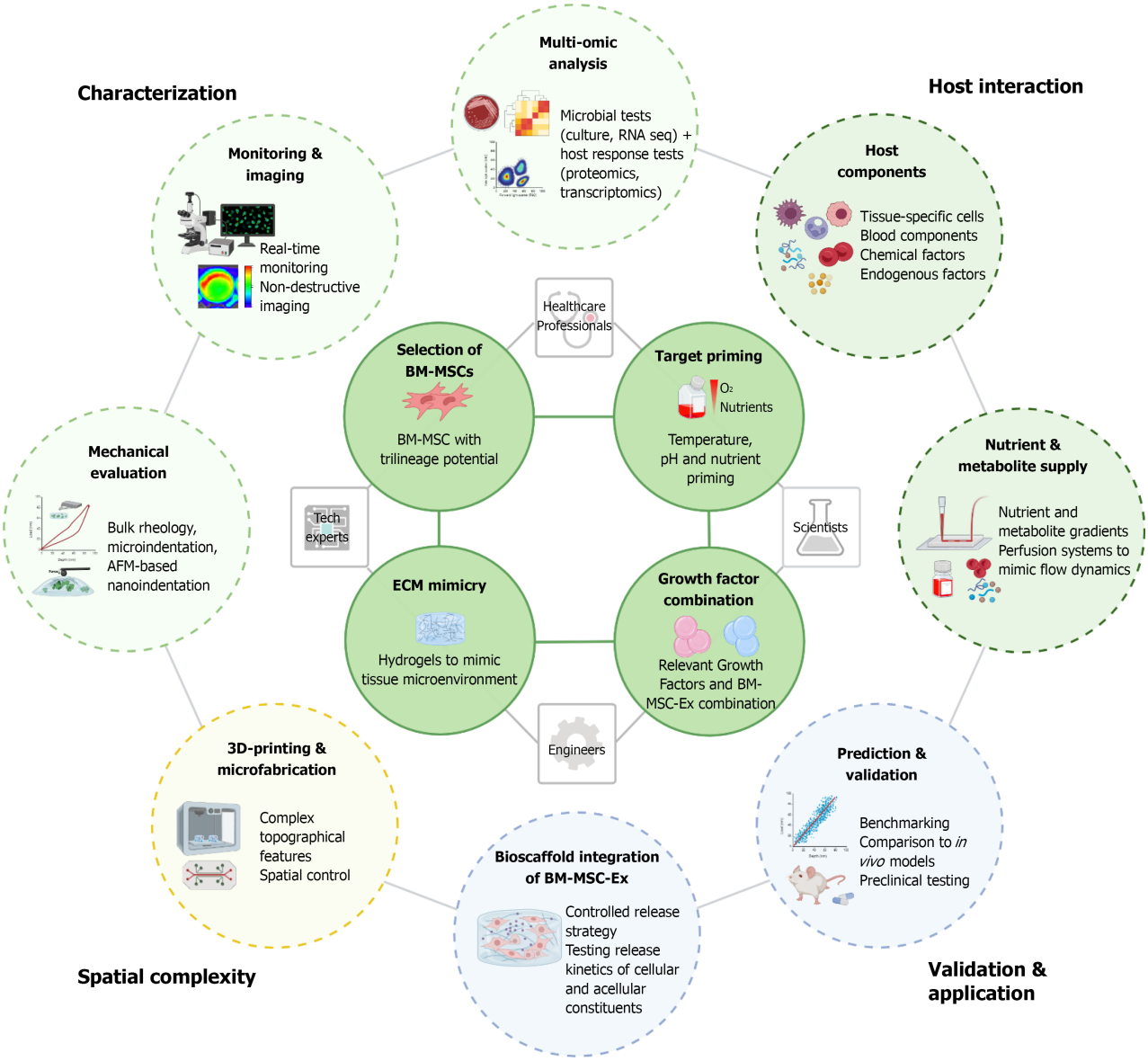

Figure 2 Facets of bone marrow mesenchymal stromal cell derived exosomes. Created in BioRender (Supplementary material). BM-MSC: Bone marrow mesenchymal stromal cell; ECM: Extracellular matrix; BM-MSC-Ex: Bone marrow mesenchymal stromal cell derived exosomes.

While engineered exosomes offer enhanced targeting and cargo specificity, their immunological safety profile remains incompletely characterised. Genetic modifications may alter surface protein expression, potentially increasing the risk of allograft rejection in allogeneic settings. Additionally, long-term immune activation may arise from repeated dosing or unintended interactions with antigen-presenting cells. Engineered EVs may also carry immunostimulatory nucleic acids or fusion proteins that trigger off-target effects. To mitigate these risks, future studies should incorporate immunogenicity assays, monitor cytokine profiles, and evaluate biodistribution in immune-competent models. Regulatory frameworks will likely require detailed immunological safety data before clinical translation of genetically modified EVs.

Comparative performance of BM-MSC-Exos and other MSC sources

Several tissues can serve as MSC and exosome sources, including bone marrow, adipose tissue, umbilical cord and synovium or synovial fluid. Source origin influences exosomal cargo composition and, in turn, functional potency[59].

A 2025 systematic review and network meta-analysis of rat KOA models pooled 28 studies that used exosomes from BM, adipose, umbilical cord and synovial fluid MSCs[60]. Across the network, MSC-derived exosomes significantly improved histological scores, cartilage thickness and gait measures compared with controls. Umbilical cord and synovial fluid exosomes ranked highest for structural repair, while BM-MSC-Exos showed intermediate performance[61]. The analysis also suggested that twice-weekly intra-articular dosing produced better cartilage outcomes than single or weekly injections[62].

Clinical network meta-analyses of intra-articular MSC cell therapies show a related pattern. Adipose-derived MSCs tend to rank best for pain relief, umbilical cord cells perform strongly for functional outcomes and BM-MSCs show more variable results, which may reflect donor age and comorbidity[63].

In vitro comparisons indicate that BM-MSC-Exos favour hyaline-like cartilage formation and robust matrix synthesis, whereas adipose-derived exosomes may produce more fibrocartilaginous repair but display strong immunomodulatory activity[64]. Synovial MSC exosomes, especially when enriched for miR-140-5p, display very high chondrogenic potency that may relate to their developmental proximity to articular cartilage and preferential homing to joint surfaces[34]. Umbilical cord exosomes show broad anti-inflammatory and chondroprotective actions, and early translational work suggests a favourable safety profile[65]. Table 2 summarises the main advantages and limitations of exosomes from different MSC sources in the context of OA models.

BM-MSC-Exos therefore appear most attractive where structural cartilage and subchondral bone regeneration is the primary therapeutic goal and bone marrow donors are readily accessible[66]. Umbilical cord and synovial sources may be better suited for standardised off-the-shelf products that prioritise anti-inflammatory effects, while adipose-derived exosomes might fit symptom-focused strategies[67].

Preclinical in vivo evidence and delivery strategies

Rodent models provide the main functional evidence for BM-MSC-Exos in KOA. In destabilisation of the medial meniscus, anterior cruciate ligament transection and monosodium iodoacetate-induced models, repeated intra-articular injections of BM-MSC-Exos preserve cartilage structure, maintain proteoglycan staining, reduce osteophyte formation and lower Osteoarthritis Research Society International histological scores compared with saline or vehicle controls. Synovitis scores and local or systemic cytokine levels improve in an anti-inflammatory direction[68].

Pain-related behaviours improve in parallel. Exosome-treated animals typically show higher mechanical withdrawal thresholds, more symmetric weight-bearing and more normal spontaneous movement patterns[69]. In some studies, BM-MSC-EVs loaded with small molecules such as icariin or puerarin demonstrated enhanced cartilage protection and subchondral bone preservation, with improved histological scores and reduced osteophyte formation compared to unmodified EVs[70,71]. These findings suggest that BM-MSC-EVs provide a versatile platform for combination therapies [72].

A recurring constraint in these models is rapid clearance of exosomes from the joint cavity. Fluorescently labelled vesicles often disappear from the synovial space within hours to days, drained *via* lymphatics or taken up nonspecifically by synovial cells[73]. To overcome this, several delivery innovations have been developed. Hydrogels based on gelatin methacryloyl, chitosan or other cartilage-mimicking polymers are used as depots that entrap exosomes and release them slowly over one to three weeks[74]. In osteochondral defect and KOA models, hydrogel-delivered MSC exosomes yield smoother cartilage surfaces, more uniform collagen II staining and better mechanical properties than free vesicles or hydrogel alone[75].

Surface-engineered exosomes represent another strategy. Vesicle membranes have been modified with cartilage-affinity peptides or Lamp2b-fused targeting motifs that direct them toward cartilage matrix or endogenous MSCs within the joint[76]. In some cases, these targeted exosomes are co-loaded with chondrogenic small molecules such as kartogenin. Such designer vesicles show improved retention in cartilage and superior structural outcomes[77]. Magnetic nanoparticle loading with external magnetic guidance has also been explored, though this remains at a very early stage and has not yet been meaningfully evaluated in osteoarthritis models[78].

The overall preclinical message is consistent: BM-MSC-Exos are biologically active in KOA models and their effects can be amplified by optimised dosing schedules and delivery systems. At the same time, most studies use small animal cohorts, short follow up, incomplete randomisation or blinding and often report exosome doses as micrograms of protein rather than particle counts or functional units[79]. Publication bias is likely, as neutral or negative exosome studies seldom appear. These issues need to be recognised when extrapolating to human disease.

Clinical translation and emerging human data

Direct evidence for BM-MSC-Exos in KOA is limited. Much of the clinical experience relates either to intra-articular MSC injections, where exosomes are presumed mediators, or to exosome products derived from other tissues[80].

Multiple phase 1 and 2 trials of intra-articular MSCs, including BM-MSCs, report significant improvements in pain and function and acceptable short-term safety. Imaging outcomes are more variable, with small gains in cartilage thickness or delayed deterioration in some studies but neutral results in others[81]. These trials provide important reassurance about the safety of exposing osteoarthritic joints to MSC-derived paracrine products, but they do not by themselves prove that isolated exosomes will reproduce or exceed the same benefits[82].

For exosome products, the most robust KOA trial to date is a triple-blind randomised controlled study (NCT05012345) in which one knee of each participant with bilateral Kellgren-Lawrence grade 2 or 3 KOA received intra-articular placental MSC exosomes and the contralateral knee received saline[83]. The exosome-treated knees did not show clinically or statistically significant superiority over saline in pain, function or MRI cartilage metrics at short-term follow-up, although the treatment was safe[84]. Mechanistic explanations for this lack of efficacy may include insufficient EV dosage relative to the joint volume, rapid clearance from the synovial cavity, limited penetration into cartilage and subchondral bone, and absence of sustained release formulations. Furthermore, without biomarker-driven endpoints, subtle molecular effects may have been missed. Future trials should therefore optimise dose, delivery strategies (*e.g.*, hydrogels, scaffolds), and incorporate pharmacodynamic markers to better capture therapeutic activity. This negative result is a crucial counterpoint to preclinical enthusiasm and suggests that a single exosome injection of the type used in that study is insufficient for disease modification[85]. Further, current studies lack uniform standards for BM-MSC-EV dosage, with doses reported in terms of protein mass, particle counts, or volume equivalents. This heterogeneity limits comparability and reproducibility. Preclinical rodent studies typically employ intra-articular doses in the range of (1-10) × 10^9 particles per joint, corresponding to approximately 50-200 μg of EV protein. Scaled to human knee joint volumes (5-10 mL synovial fluid capacity), preliminary clinical dosage gradients may be explored at three levels: (1) Low-dose [(1-5) ×

Table 2 Comparative features of exosomes from mesenchymal stromal cell sources in osteoarthritis models

Source	Main advantages in osteoarthritis context	Principal limitations or concerns
Bone marrow[59-61]	Strong chondrogenic lineage; rich ECM-related proteome; extensive mechanistic data and historical use in cartilage repair	Donor age dependence; invasive harvest; intermediate performance in comparative exosome meta-analysis; variable outcomes in MSC trials
Adipose tissue[63,64]	Abundant, minimally invasive harvest; high cell yield; strong immunomodulatory profile; good pain relief in MSC trials	Some preparations favour fibrocartilage over hyaline repair; structural regeneration less consistent; potential influence of donor metabolic status
Umbilical cord[65]	Neonatal cells with high proliferative capacity; off-the-shelf allogeneic banking; robust anti-inflammatory and chondroprotective actions; early clinical data in KOA	Fewer long-term joint safety data; regulatory complexity of allogeneic products
Synovium/synovial fluid[34,60]	Joint-specific tissue origin; excellent targeting and regenerative potency, especially with miR-140-5p enrichment; top rankings in rodent network analyses	Arthroscopic retrieval for autologous use; scalability challenges; limited clinical-grade products

ECM: Extracellular matrix; MSC: Mesenchymal stromal cell; KOA: Knee osteoarthritis.

10^{10} particles]; (2) Mid-dose [(5-10) × 10^{10} particles]; and (3) High-dose (> 1 × 10^{11} particles). These ranges should be adjusted according to pharmacokinetic parameters such as clearance rates, biodistribution, and persistence within synovial fluid. Early-phase trials should incorporate dose-escalation designs, biomarker endpoints, and imaging correlates to define optimal therapeutic windows.

A more recent first-in-human open-label study (NCT05167890) administered small EVs derived from human umbilical cord MSCs into osteoarthritic knees. Participants showed symptomatic improvement and MRI evidence of cartilage regeneration together with favourable safety and signals of M2-like macrophage polarisation. However, the absence of a randomised control group means that placebo effects, regression to the mean and natural disease variability cannot be excluded[86].

BM-MSC-EV products such as ExoFlo have been used in small observational series for musculoskeletal indications, including osteoarthritis in combat-related injuries[87]. Reports describe improvements in pain and function and an absence of major acute toxicity after intra-articular injection. These studies are non-randomised, often industry-sponsored, and provide limited information on EV characterisation, dose metrics and long-term imaging[88].

Systemic trials of BM-MSC-derived exosomes in non-joint diseases, such as acute respiratory distress syndrome, suggest that intravenous administration is feasible and can be safe, with signals of efficacy in critically ill patients[89]. While reassuring, these findings do not directly address chronic intra-articular use in KOA or long-term joint-specific safety concerns such as ectopic calcification or accelerated osteophyte formation[90]. To frame the current evidence base, Table 3 outlines representative human studies of MSC-derived EVs that are relevant to KOA.

Differentiated clinical indications may be considered when selecting EV sources for KOA therapy. BM-MSC-EVs appear most suitable for patients with early-to-moderate KOA where structural cartilage and subchondral bone regeneration is a primary goal, particularly in younger or middle-aged individuals with high mechanical demands. In contrast, umbilical cord MSC-EVs may be better suited for older patients or those with advanced KOA, where anti-inflammatory and immunomodulatory effects are prioritised over structural regeneration. Synovial fluid MSC-EVs, enriched for chondrogenic miRNAs such as miR-140-5p, may be optimal for focal cartilage defects or early-stage KOA, given their strong regenerative potency and joint-specific origin. Adipose-derived EVs may be most appropriate for symptom-focused strategies, particularly in patients with metabolic comorbidities, where immunomodulation and pain relief are central. Refining target populations by age, disease stage, and therapeutic goals will be critical to designing future trials with meaningful clinical impact.

At present, there is no completed randomised trial demonstrating that BM-MSC-Exos are disease-modifying in KOA. The most rigorous KOA exosome trial, which used placental rather than bone marrow vesicles, did not show efficacy compared with saline. The positive umbilical cord small EV study is encouraging, but must be interpreted cautiously given its uncontrolled design[91].

Regulatory and manufacturing considerations

MISEV2023 and regulatory frameworks for biologics and advanced therapies together define the path that BM-MSC-Exos must follow to reach routine clinical use. Several points remain unresolved[21,92,93].

First, identity and potency assays need to be standardised. For BM-MSC-Exos, this implies a minimum marker set that distinguishes them from other EVs and from non-vesicular contaminants, together with potency assays that predict *in vivo* chondroprotective activity. Examples include suppression of IL-1β-induced MMP-13 and ADAMTS5 in human OA chondrocytes or inhibition of nod-like receptor protein 3 inflammasome activation in macrophages. These assays must be robust enough to serve as lot-release criteria[94].

Second, there is no consensus on the optimal dose metric. Studies variably report total protein mass, particle number or functional units in bioassays. Clinical EV trials to date have used a wide range of doses without clear justification. For BM-MSC-Exos in KOA, rational dose selection will require linking specific ranges of particle number and cargo content to reproducible *in vitro* potency and then to *in vivo* responses[95].

Table 3 Human studies of mesenchymal stromal cell-derived extracellular vesicles relevant to knee osteoarthritis

EV source	Indication/design	Intervention and comparator	Main outcomes	Key limitations
Placental MSC exosomes[83-85]	Bilateral KOA, triple-blind randomised placebo-controlled trial	Single intra-articular exosome injection to one knee, saline to contralateral knee	Good short-term safety; no significant advantage over saline in pain, function or MRI cartilage metrics	Single-dose regimen; short follow up; partial EV characterisation; no dose-finding
Umbilical cord MSC small EVs [86]	KOA, first-in-human open-label phase I study	Intra-articular small EVs, single or repeated dosing, no control group	Acceptable 12-month safety; symptomatic improvement; MRI signs of cartilage regeneration; evidence of M2-like macrophage polarisation	Non-randomised; small sample; potential placebo and regression effects
BM-MSC-derived EV product (for example, ExoFlo) [87,88]	Osteoarthritis and joint injuries, observational cohorts	Intra-articular injection, no formal comparator	Symptomatic improvement reported; no major acute toxicity	Non-randomised; heterogeneous pathology; limited EV characterisation; lack of long-term imaging and independent replication

EV: Extracellular vesicle; MSC: Mesenchymal stromal cell; KOA: Knee osteoarthritis; MRI: Magnetic resonance imaging; BM-MSC: Bone marrow mesenchymal stromal cell.

Third, donor variability is a particular concern for BM-derived products. Donor age, metabolic status, medications and comorbidities can all influence MSC behaviour and EV cargo. Approaches such as pooled donors, stringent eligibility criteria, extensive screening and potency-based lot rejection will add cost and complexity[96].

Fourth, engineering strategies that overexpress selected miRNAs or lncRNAs shift BM-MSC-Exos closer to gene therapy[97-99]. Regulators may require vector-level safety data, off-target analyses and extended follow up. Combination products that pair BM-MSC-Exos with hydrogels, targeting peptides or small molecules will also be scrutinised as combination biologic-device or biologic-drug products, with the need to validate each component and their interactions [100].

Finally, long-term safety data specific to joints are lacking. For KOA, regulators and clinicians will want reassurance that repeated BM-MSC-Exo injections do not promote osteophyte formation, cartilage calcification, synovial hyperplasia or neoplasia over multi-year horizons. Existing data, largely limited to 6-12 months of follow up, are insufficient to answer these questions[101].

Critical appraisal and future directions

Although a relatively high proportion of the references cited are from 2025, these studies largely reinforce established findings rather than contradict them. Their conclusions align with the broader body of evidence accumulated over the past decade. Any outlier results were critically cross-checked against prior literature before inclusion, ensuring that they did not disproportionately influence the synthesis. This approach maintains consistency with existing knowledge while integrating the most up-to-date data available. Taken together, the available evidence paints a nuanced picture. BM-MSC-Exos have a strong mechanistic rationale in KOA. Their cargo targets multiple nodes of disease biology across cartilage, synovium, bone and nociceptive pathways. Preclinical models show coherent improvements in histology and pain-related behaviour, and delivery innovations can amplify these effects. In addition, exosomes avoid some of the risks inherent to live cell therapies, such as uncontrolled proliferation or ectopic tissue formation[102].

At the same time, there are important caveats. Much of the evidence is preclinical and based on small, short-term animal studies that do not fully reflect the age, comorbidity and chronicity of human KOA. Methodological limitations, including incomplete randomisation, lack of blinding, heterogeneous outcome measures and unclear dosing, are common. Direct human data for BM-MSC-Exos in KOA are scant, and the one rigorous KOA exosome trial conducted so far, which used placental exosomes, did not show superiority over saline. Early positive signals with umbilical cord MSC-derived small EVs are intriguing but remain preliminary, with open-label studies reporting symptomatic improvement and MRI evidence of cartilage regeneration[86,100,103]. However, these findings require confirmation in adequately powered randomised controlled trials before clinical translation can be considered robust.

Comparative data also challenge the assumption that bone marrow is the optimal exosome source. Synovial fluid and umbilical cord exosomes appear to outperform BM-MSC-Exos for structural repair in some rodent analyses, and adipose- or umbilical-derived cells fare better than BM-MSCs in several MSC meta-analyses for symptom relief. It is possible that BM-MSC-Exos will ultimately find a niche in particular patient subgroups or disease stages, for example younger individuals in whom structural regeneration is a realistic objective, but this remains to be proven[104].

Looking ahead, several priorities are clear. Product definition must be tightened, with BM-MSC-Exos intended for clinical use meeting or exceeding MISEV2023 criteria and incorporating robust potency assays. Dose-finding and scheduling studies should explicitly test different exosome doses and injection frequencies rather than extrapolating from cell therapy protocols. Head-to-head comparisons of BM-MSC-Exos with umbilical cord and synovial exosomes, conducted under harmonised isolation and dosing conditions, are needed to determine whether any source has a reproducible advantage[93].

Bioengineering advances in hydrogels, targeting peptides and small-molecule co-delivery should move from proof-of-concept studies toward manufacturable products suitable for regulatory evaluation, with careful attention to sterility, scalability and release kinetics. Translational trials ought to incorporate mechanistic biomarkers, such as synovial fluid EV profiling, serum and urine collagen turnover markers and imaging of bone marrow lesions and synovitis, to link exosome biology with patient-level outcomes and to distinguish genuine structural modification from symptomatic placebo effects[105].

CONCLUSION

BM-MSC-Exos offer a cell-free approach to KOA by modulating inflammatory, metabolic, and cell death pathways, showing benefits across cartilage, synovium, bone, and nociceptive circuits in preclinical models. Engineered cargo and delivery systems may enhance efficacy, but current evidence remains experimental, with small human studies and one rigorous trial showing no advantage over saline. MISEV2023 sets standards for future research, requiring compliant manufacturing, dose-controlled and source-comparative trials, robust imaging and biomarker endpoints, and long-term safety evaluation. Only through such rigor can BM-MSC-Exos be judged as potential disease-modifying alternatives to existing orthobiologic therapies.

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