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The Role of Extracellular Vesicles in Musculoskeletal Diseases

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ABSTRACT

Extracellular Vesicles (EVs), nanoscale membrane-bound cell-released structures, are vital for intercellular communication and material transport. Their role in musculoskeletal health and diseases has recently drawn significant attention. This review focuses on the latest EV research in musculoskeletal diseases, including their roles in disease progression and potential as biomarkers and therapies. Musculoskeletal disorders are the third-leading cause of global disability-adjusted life-years among adolescents and young adults. Current treatments face issues like limited tissue regeneration and poor drug targeting. With their natural messenger function and low immunogenicity, EVs have become a research focus. However, their action mechanisms in the musculoskeletal system remain un-systematically understood. This paper reviews EVs' role in musculoskeletal diseases. It covers classification, biogenesis, release, internalization, cargo and their involvement in muscle cell processes, joint diseases, bone metabolism and disc degeneration. It also explores EVs' role in musculoskeletal crosstalk and their potential as therapeutic agents and drug carriers through engineering with biomaterials. Future research should delve deeper into EV action mechanisms for better treatments. Overall, while EVs offer new treatment strategies for musculoskeletal diseases, more research is needed to overcome technical and clinical barriers.

1 | Introduction

The musculoskeletal system is primarily composed of bones, muscles and joints, along with cartilage, tendons and ligaments. Both bones and skeletal muscles function as multifunctional organs that interact mechanically and biochemically, thereby maintaining musculoskeletal homeostasis and overall health (Bonewald 2019). Globally, the burden of musculoskeletal disorders is gradually worsening, with low back pain, neck pain and osteoarthritis (OA) being particularly burdensome among older female population (Safiri et al. 2021). From 1990 to 2021, the age-standardized prevalence rate and disability-adjusted life years rate of musculoskeletal disorders in postmenopausal women increased significantly, among which OA and low back pain were the main contributors to this burden. Projections indicate that the global burden of musculoskeletal disorders may double by 2045 (Tan et al. 2025). Additionally, Musculoskeletal disorders have emerged as the third leading cause of global

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disability-adjusted life-years among adolescents and young adults (Guan et al. 2023). Currently, treatment options for musculoskeletal disorders are relatively limited, for instance, drug therapy can to some extent alleviate the symptoms of rheumatoid arthritis (RA); however, these drugs may not achieve ideal results for all patients, and some may experience adverse drug reactions or treatment resistance (Smolen et al. 2018). In contrast, OA currently lacks effective treatment methods. Most existing treatments can only relieve symptoms, such as using non-steroidal anti-inflammatory drugs to reduce pain and physical therapy to improve joint function, but they cannot reverse the damage to articular cartilage or the progression of the disease (Martel-Pelletier et al. 2016). Surgical interventions are not only associated with the risk of complications, such as osteolysis induced by wear particles, which can subsequently trigger periprosthetic inflammation and pain, but may also fail to attain the intended therapeutic outcomes (Werner et al. 2018; Aabedi et al. 2025). Regarding bone repair, commonly utilized autologous bone grafts present challenges related to donor site morbidity and volume limitations (Dawson et al. 2014).

Extracellular vesicles (EVs) play an important role in the musculoskeletal system, especially in the production and repair of muscles, osteocartilage, and degenerative joint diseases such as OA and RA. These small membrane-enclosed particle are secreted by a variety of cell types, including mesenchymal stem cells (MSCs), osteoblasts, osteoclasts, skeletal muscle cells and chondrocytes. They facilitate intercellular communication by transferring multiple bioactive molecules such as proteins, lipids and nucleic acids (Murphy et al. 2018). One of the primary functions of EVs in the musculoskeletal system is their involvement in bone remodelling and homeostasis. For instance, studies have shown that MSC-derived EVs (MSC-EVs) can regulate osteoblast activity and differentiation through specific microRNAs, such as miR-196a, which have been implicated in promoting osteogenic processes (Lee et al. 2021). Additionally, EVs derived from osteoclasts can inhibit osteogenic activity, highlighting the complex interplay between different cell types in bone metabolism (Lee et al. 2021). This paracrine signalling is crucial for maintaining the balance between bone formation and resorption. EVs secreted by articular chondrocytes are involved in non-classical protein secretion and intercellular communication, contributing to the maintenance of cartilage homeostasis and the repair of the extracellular matrix (ECM) (Casanova et al. 2021). In addition to the effects on bone and cartilage, miR-494 and miR-29c in EVs derived from bone marrow mesenchymal stromal cells (BMSCs) can promote the proliferation and differentiation of myoblasts, providing a new perspective for understanding the intercellular communication mechanisms underlying skeletal muscle development and regeneration (Yue et al. 2020). Notably, pathological EVs have also attracted attention in musculoskeletal diseases. EVs derived from inflammatory fibroblast-like synoviocytes (FLSs) of patients with OA can exacerbate cartilage damage and the progression of disease (Liu, Xian, et al. 2024). In addition, EVs are also pivotal players in the pathological progression of a range of musculoskeletal disorders, including RA (Bakinowska et al. 2023), sarcopenia (Shao et al. 2022) and intervertebral disc degeneration (IVDD) (Fan, Wang, et al. 2024), as well as others.

The therapeutic potential of EVs is also being explored, particularly in drug delivery and vaccine development. Their inherent biocompatibility and the capacity to traverse biological barriers render them appealing options for the delivery of therapeutic substances, including proteins, RNA and small molecules, to target cells (Tian et al. 2020; Park et al. 2022). EVs have been shown to enhance the retention and therapeutic efficacy of MSCs in musculoskeletal tissue repair. For instance, collagen-binding EVs have been engineered to improve their in situ retention within the ECM, thereby enhancing their therapeutic effects in various musculoskeletal disorders (Hao et al. 2022). This approach addresses a significant limitation of traditional EVs therapies, which often suffer from rapid degradation and diffusion after administration. Overall, the multifaceted roles of EVs in the musculoskeletal system underscore their potential as therapeutic agents for various conditions, including osteoporosis, OA, muscle atrophy, and other degenerative diseases (Chen, Yuan, et al. 2022). A novel production system for EVs has been developed that enhances their yield and therapeutic properties, particularly through the modulation of macrophage polarization and the activation of anabolic pathways in cartilage (Wang, Zhao, et al. 2024). A recent study has completed the first-in-human intra-articular injection validation of clinical-grade EVs derived from umbilical cord mesenchymal stromal cells (UCMSC-EVs). Currently, the Phase I clinical trial (NCT06431152) is underway, confirming its biological effects and clinical translational potential in the treatment of OA. The ability of EVs to facilitate communication between cells, modulate immune responses, and enhance tissue regeneration positions them as promising candidates for future clinical applications in musculoskeletal health and disease management.

Although the role and therapeutic potential of EVs in musculoskeletal disorders are increasingly recognized, translating these research findings into clinical applications still faces several challenges, including large-scale production and isolation, long-term storage, stability, and tissue-specific targeting and delivery strategies (Youssef El Baradie and Hamrick 2021). Therefore, this review will comprehensively analyse the mechanisms of EVs in musculoskeletal disorders, explore their potential as biomarkers and therapeutic tools, and discuss current challenges and future research directions.

2 | Methodology

2.1 | Search Strategy

For this review, we used the following keywords to search for literature published before October 2025 in the PubMed, Web of Science, and Scopus databases, in order to secure comprehensive coverage of major research studies. We searched for clinical trials on clinicaltrials.gov and trialsearch.who.int, and conducted an analysis of them.

A combination of keywords was used for the search, including “Extracellular Vesicles” “Exosome” “Microvesicles” “Muscle” “Bone” “joint” “Cartilage” “Rheumatoid Arthritis” “Osteoarthritis” “Repair” “Intervertebral disc” “Biomarker” “Diagnosis” “Mesenchymal stem cells”“cargo” “Treatment” “Therapy” “Crosstalk” “Communication” “Musculoskeletal disease”. To ensure no significant research in this field is overlooked, the aforementioned keywords are frequently used

either in paired combinations or even individually when conducting searches. Detailed descriptions of the specific search strategies are omitted herein.

The literature search focused on the most up-to-date research results in this field over the last 5 years, while additionally integrating classic earlier researches that hold great significance for the discipline. Only English-language publications were included to guarantee both readability and global academic relevance.

2.2 | Inclusion and Exclusion Criteria

The inclusion criteria specifically cover original research (including both experimental and clinical studies) as well as high-quality review articles, along with studies that focus on the relevant cells and mechanisms underlying the role of EVs in musculoskeletal diseases; the exclusion criteria include studies unrelated to EVs or musculoskeletal diseases, and publications that lack complete data or an adequate experimental design.

2.3 | Literature Screening Process

First, for the initial screening, researchers screened relevant literature based on titles and abstracts, excluding articles that were clearly irrelevant; secondly, for the full text review, articles that potentially met the inclusion criteria underwent further evaluation to verify their compliance with the criteria; and for dispute resolution, in cases of disagreements arising during the screening process, two researchers engaged in joint discussion to ensure the objectivity of literature selection.

3 | Overview of EVs

EVs are membrane-bound structures released by various cell types, playing a crucial role in intercellular communication and influencing numerous physiological and pathological processes. The sizes of these vesicles are heterogeneous, typically ranging from 30 nanometres to several micrometres. According to MISEV 2018 and MISEV 2023, EVs can be classified into medium/large EVs (m/lEVs, >200 nm) and small EVs (sEVs, <200 nm) (Théry et al. 2018; Welsh et al. 2024). EVs can also be classified into three types according to their sources: exosomes (30–150 nm, average~100 nm), microvesicles (MVs, 100–1000 nm) and apoptotic bodies (ABs, 1–5 μm) (Colombo et al. 2014; Yáñez-Mó et al. 2015). Exosomes are formed within multivesicular bodies and are released when these bodies fuse with the plasma membrane. In contrast, microvesicles bud directly from the plasma membrane. Microvesicles are produced by the inward protrusion and fragmentation of the cell membrane. Apoptotic bodies represent membrane fragments of apoptotic cells and are composed of encapsulated organelles or DNA (Cho et al. 2021; Yong, Li, et al. 2020). However, in many literatures, exosome is often used to refer to small-sized EVs that can pass through a filter with a pore size of 220 nm, or are obtained based on the experience of differential centrifugation rather than on a biogenetic definition. It is worth noting that MISEV 2023 states that "sEVs" and "exosome" are not synonymous: the small EVs population includes small ectosomes and exosomes (Welsh et al. 2024). Therefore, except for the part "Biogenesis, release, and internalization of EVs", in the subsequent sections of this article, exosomes will be termed as sEVs (Gould and Raposo 2013; Kowal et al. 2016).

The composition of EVs is diverse, containing proteins, lipids, nucleic acids (such as mRNA and microRNA) and other bioactive molecules. This cargo reflects the physiological state of the parent cell and can influence recipient cells by transferring molecular signals that modulate various cellular functions, including proliferation, differentiation and immune response (Ilahibaks et al. 2023; Yong, Wang, et al. 2020). Techniques such as nanoparticle tracking analysis (NTA), dynamic light scattering and super-resolution microscopy have been employed to study EVs at the single-particle level, revealing their heterogeneity and the presence of specific surface markers, such as tetraspanins (CD9, CD63, and CD81) (Cocozza et al. 2020; Mehanny et al. 2021). In addition, Golgi apparatus, endoplasmic reticulum, mitochondria, or nuclear components may also be loaded into EVs. The larger the EVs, the greater the likelihood of passive loading of any randomly selected molecular or organelle entities in the cell (Théry et al. 2018). Under oxidative stress, human MSCs expel partially depolarized mitochondria into microvesicles. The mitochondria within these microvesicles are internalized and repurposed by human macrophages, thereby boosting their bioenergetic capacity (Phinney et al. 2015).

3.1 | Methods for Isolation and Identification of EVs

Given the multiple functions and clinical translation potential of EVs, it is of great significance to obtain EVs with high yield and quality. Currently, a variety of EV isolation techniques have been developed, which rely on the biophysical and/or biochemical properties of EVs. Different EV isolation methods significantly affect their purity, yield, as well as structural integrity and functional activity. The most commonly used and cutting-edge EV isolation techniques are summarized in the following table (Table 1). A more comprehensive account of the details has been provided in previous reviews (Jia et al. 2022; Ma et al. 2025). In practical applications, due to the heterogeneity of EVs and the differences in their content and characteristics across different samples, a single isolation technique often fails to meet the requirements (Cosenza et al. 2017). Therefore, it is necessary to combine multiple techniques to optimize the isolation efficiency of EVs. For instance, the combination of ultracentrifugation with size exclusion chromatography (SEC), as well as the combination of SEC with immunoaffinity capture technology, can both improve the isolation efficiency and the functional integrity of the isolated EVs (Visan et al. 2022; Zhang, Yin, et al. 2022).

3.2 | Biogenesis, Release and Internalization of EVs

Exosomes originate from the endosomal system and are released into the extracellular environment via a tightly regulated process. Exosome biogenesis and release are mediated through two primary mechanisms: endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent

TABLE 1 | Comparison of different EVs isolation method.

EVs-based features	Isolation techniques	Equipment requirements	Time	Advantage	Disadvantage	References
Density	Density gradient centrifugation	Normal	Long (>16 h)	High purity and resolution, suitable for large sample volumes	Cumbersome procedures and susceptibility of samples to damage	(Allelein et al. 2021)
	Isopycnic density gradient centrifugation	High	Long (>16 h)	Higher purity compared to differential ultracentrifugation	Complex operation	(Li et al. 2017)
	Differential ultracentrifugation	Normal	Long (>4 h)	Standard gold method and low cost	Low purity and low sample utilization	(Huang et al. 2021)
Size	Size exclusion chromatography	High	Short (0.3 h)	High purity, good integrity, and excellent functional preservation	Low yield and low sample utilization	(Sidhom et al. 2020)
	Rate zone ultracentrifugation	High	Long (>16 h)	Higher purity compared to differential ultracentrifugation	Strict time control is needed	(Yang, Zhang, et al. 2020)
	Circulating tangential flow filtration (TFF) system	Normal	—	High purity than single cycle TFF and good bioactivity protection	Adaptability to various types of biological fluids is unclear	(Kim et al. 2021)
	Asymmetric flow field flow fractionation (AF4)	High	Normal (4–5 h)	High purity and good integrity can separate EVs subtypes	High-standard experimental conditions and not suitable for large samples	(Zhang et al. 2018; Zhang and Lyden 2019)
	Ultrafiltration	Low	Short (<4 h)	Timesaving and labor-saving, as a supplement to the centrifugation	Low purity and yield, shear stress may damage EVs integrity	(Yang, Zhang, et al. 2020)
Surface proteins	Immunoaffinity capture	Low	Normal (4–20 h)	High purity and specific separation of EVs	Dependence on antibodies, the need for pretreatment, expensive and low yield	(Sidhom et al. 2020)

(Continues)

TABLE 1 | (Continued)

EVs-based features	Isolation techniques	Equipment requirements	Time	Advantage	Disadvantage	References
IAC-AsFlFFF system	High	Normal (4–6 h)	Highly reproducible and automated	Complex setup and operation and unclear applicability for samples other than plasma	(Multia et al. 2020)	
Microfluidics isolation	High	Short	High efficiency, high purity, integrated and multifunctional	Limited sample volume for separation	(Wang et al. 2021)	
Synthetic peptide (Vn96) based isolation	High	—	High efficiency, high output, low cost, high versatility	Limited sample volume for separation	(Ghosh et al. 2014)	
Dispersibility and solubility	Precipitation	Low	Normal (0.3–12 h)	High yield, simple operation, suitable for large samples and excellent functional preservation	Low purity, contaminated with co-precipitated substances	(Morani et al. 2022)

pathways (Figure 1). The specific mechanisms of the pathways have been elaborated in detail in previous reviews (Teng and Fussenegger 2020; Rädler et al. 2023). Exosome formation begins with the inward budding of the endosomal membrane to form intraluminal vesicles (ILVs) within multivesicular bodies (MVBs), MVBs come into existence in the course of endosomal maturation (Rink et al. 2005; Poteryaev et al. 2010). MVBs can follow one of two fates: lysosomal degradation or fusion with the plasma membrane to release their ILV contents as exosomes (Rädler et al. 2023). Recent studies have also identified direct exosome budding from the plasma membrane as an alternative release mechanism. This unconventional pathway bypasses the MVBs stage, further expanding the understanding of exosome release dynamics (Krylova and Feng 2023). MVs are primarily formed by budding from the plasma membrane, and their biogenesis has attracted considerable attention, although the precise mechanisms remain incompletely understood (Clancy et al. 2021). Various studies have shown that the ESCRT machinery traditionally associated with exosome biogenesis may also play a key role in the formation of MVs, promoting membrane invagination and vesicle cleavage from the plasma membrane (Mathieu et al. 2019).

After being released from source cells, EVs can directly adhere to the ECM and neighbouring cells, or be transferred to distant organs via body fluid pathways. After interacting with recipient cells, EVs mediate intercellular signalling through two main mechanisms: ligand-receptor interactions and internalization of EVs contents into target cells (Mathieu et al. 2019; Zheng et al. 2019) (Figure 1). Two models of EVs internalization are widely accepted: direct membrane fusion and endocytosis (Abels and Breakefield 2016). The most common mechanism for the internalization of EVs is endocytosis, through which cells engulf EVs via multiple pathways, including receptor-mediated endocytosis, macropinocytosis and phagocytosis (Mulcahy et al. 2014; Doherty and McMahon 2009).

3.3 | EV Cargo

Cargo sorting is critical for determining EVs' composition and functionality, influenced by subtype of EVs, physiological state of the parent cell and sorting machinery. EVs carry diverse cargo: proteins, lipids, DNA, RNA and other biomolecules, with composition shaped by biogenesis-associated sorting mechanisms (von Lersner et al. 2024; Chen et al. 2021) (Figure 1).

3.3.1 | Protein Cargo

EVs carry a broad spectrum of proteins, including transmembrane proteins, membrane-associated proteins and soluble luminal proteins. Although most EV proteomes share a core set of proteins linked to vesicle biogenesis, a distinct subset of proteins reflects the unique identity and functional state of the cell that produced the EVs (Kugeratski et al. 2021; Hoshino et al. 2020). A significant feature of EVs is the enrichment of tetraspanins such as CD81, CD63, CD9, CD82 and CD37 (Escola et al. 1998). Other membrane-associated proteins such as flotillin (Phuyal et al. 2014), EGFR (Adamczyk et al. 2011), IL-6R (Arnold et al. 2020), TGF-β (Shelke et al. 2019), ADAM proteases (Keller et al.

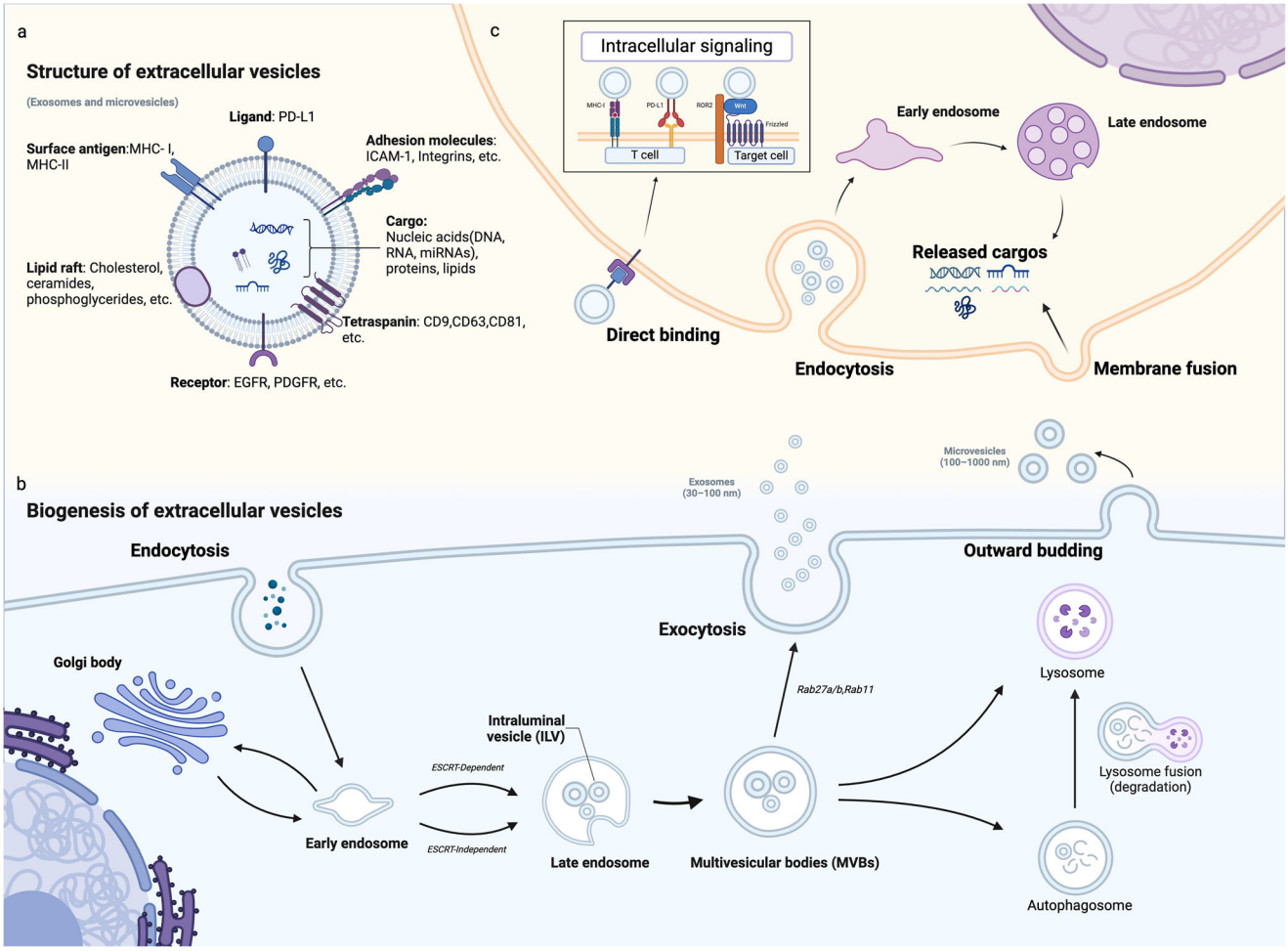

FIGURE 1 | Overview of EVs. (a) Composition and structure of EVs. EVs contain many components, including proteins, lipids, DNA and RNA. (**b**) Biogenesis and release of EVs. The process of releasing exosomes into the extracellular environment involves three distinct steps: exosome biogenesis, the intracellular transport of MVBs, and the fusion of MVBs with the plasma membrane. MVs are primarily formed by budding from the plasma membrane. (**c**) The interaction process between EVs and target cells includes: exosomes can directly bind to receptors on the surface of target cell membranes, activating intercellular signal transduction pathways; they can also enter the interior of target cells through endocytosis or membrane fusion, releasing the bioactive molecules they carry.

2020), T cell receptor (Blanchard et al. 2002), chimeric antigen receptor (Fu et al. 2019), Notch receptors (Sheldon et al. 2010), GPCR receptors and PD-L1 (Chen et al. 2018), as well as cytosolic proteins like actin and tubulin, have also been identified in EVs (Hurwitz et al. 2016).

3.3.2 | RNA Cargo

The RNA content within EVs is highly diverse, encompassing both coding and non-coding RNAs (ncRNAs) species, including mRNAs, microRNAs (miRNAs), transfer RNAs (tRNAs), small nucleolar RNAs (snoRNAs), long non-coding RNAs (lncRNAs), mitochondrial RNAs (mtRNAs) and piwi-interacting RNAs (piRNAs) (Dixson et al. 2023). A key mechanism underlying the selective loading of RNA into EVs involves RNA-binding proteins (RBPs), which serve as adapters between the RNA cargo and the vesicle biogenesis machinery (Statello et al. 2018). These RBPs contain sequence-specific RNA-binding domains (RBDs), enabling them to recognize and bind specific RNA sequences, thereby facilitating their incorporation into EVs (Villarroya-Beltri et al. 2013).

3.3.3 | DNA Cargo

Although RNA has been the primary focus of research in EVs cargo, multiple DNA species identified in EVs preparations. These include both single-stranded DNA (ssDNA) (Balaj et al. 2011) and double-stranded DNA (dsDNA) (Kahlert et al. 2014), as well as mitochondrial DNA (mtDNA) (Sansone et al. 2017). Interestingly, larger EVs are more likely to harbour DNA than their smaller counterparts (Vagner et al. 2018). Research has indicated that DNA is often associated with specific cellular processes. In tumour cells, for example, cytoplasmic micronuclei are thought to interact with tetraspanins, which facilitate the sorting of DNA into EVs (Yokoi et al. 2019). Additionally, the interaction between mitochondria and MVBs can result in the transfer of mitochondrial DNA to EVs, allowing it to be released into the extracellular space (Rabas et al. 2021).

3.4 | Newly Discovered EVs

Over the past decade, researchers have continuously identified new types of vesicles involved in specific cellular processes. Migrasomes are a newly discovered type of EVs, whose formation depends on cell migration. In 2015, Ma et al. first identified these special vesicles at the tips of retraction fibres (Ma et al. 2015). Migrasomes differ from other EVs not only in size (500–3000 nm) but also in their cargo content and release mechanisms (Ozkocak et al. 2022). They also play crucial roles in maintaining cellular homeostasis, intercellular communication, and material exchange between cells and the ECM (Jiao et al. 2021). For instance, migrasomes can mediate mitochondrial quality control in cells (Mehra and Pernas 2021) and improve outcomes of chronic inflammatory musculoskeletal diseases through mitochondrial transfer (Wu, Shieh, et al. 2024). The therapeutic potential of migrasomes in bone regeneration has also been confirmed (Yan et al. 2025), migrasomes derived from BMSCs can recruit regenerative cells and directly promote osteogenesis, emerging as novel therapeutic EVs in bone tissue engineering (Li, Zhang, et al. 2025). Jeppesen et al. recently reported their discovery of blebbisomes, the largest EVs identified to date (with diameters up to 20 μm) (Jeppesen et al. 2025). Blebbisomes differ in their formation from oncosomes and microvesicles—these latter vesicles bud outward from plasma membrane areas exhibiting high blebbing activity (Di Vizio et al. 2009; Sedgwick et al. 2015). Their formation also stands apart from that of migrasomes, which originate from membrane ballooning on retraction fibres located at the trailing edge of cells (Ma et al. 2015). Blebbisomes possess cytoskeletal structures, and researchers speculate that components of the cytokinetic machinery may contribute to their formation (Jeppesen et al. 2025). Notably, the newly discovered migrasomes and blebbisomes have not been clearly classified in the latest EV-related guidelines. Although migrasomes detached from cells qualify as EVs, they perform numerous functions as part of the cell before shedding to become EVs. In the original study, researchers preferred to classify migrasomes as a new type of organelle (Ma et al. 2015). Blebbisomes can move independently of cells, secrete exosomes and microvesicles, and internalize EVs from the extracellular environment. Furthermore, the presence of abundant organelles within blebbisomes endows them with cell-like characteristics (Jeppesen et al. 2025).

3.5 | Cargo of MSC-EVs

Associated with the prominent immunomodulatory and tissue repair functions of MSCs, MSC-EVs exhibit excellent therapeutic efficacy in the field of tissue repair and regeneration, and are a highly promising cell-free therapeutic approach for musculoskeletal system diseases (Wu, Wu, Liu, et al. 2024). Currently, MSC-EVs have demonstrated favourable therapeutic effects in preclinical studies, and relevant clinical trials are at the forefront of EVs-based clinical translational therapy (You et al. 2023; Mizenko et al. 2024). Meanwhile, their carried cargo profile plays a crucial role in the process of exerting therapeutic efficacy. The concept of cell-free therapy using MSC-EVs continues to gain momentum, it is necessary to describe the unique cargo of MSC-EVs (Pincela Lins et al. 2023). In common with the majority of EVs, MSC-EVs are capable of carrying RNA cargo as a key component. The RNA in MSC-EVs is relatively short, with most RNA fragments being less than 300 nucleotides in length (Chen et al. 2010). The therapeutic effects of MSC-EVs are increasingly attributed to the intercellular transfer of miRNAs (Valadi et al. 2007; Skog et al. 2008). Deep sequencing studies on RNA in MSC-EVs have revealed a significant increase in miRNA content within EVs (Pritchard et al. 2012). Compared with MSCs themselves, miR-183, miR-378, miR-140-3p and miR-222 are more abundantly expressed in EVs (Eirin et al. 2017). An analysis of the miRNA content in EVs derived from human bone marrow mesenchymal stem cells (hBMSCs) cultured with xenogen-free supplements (XFS) showed that miRNAs with chondroprotective functions (e.g., let-7b-5p, miR-17, miR-145, miR-21-5p, miR-214-3p, miR-30b-5p and miR-30c-5p) were upregulated. Among these, miR-145 and miR-214 can protect chondrocytes from IL-1α-induced inflammatory damage (Palamà et al. 2023). In addition, miR-3960 in MSC-EVs can improve cartilage morphology, reduce chondrocyte apoptosis, and thereby alleviate OA-related pain (Ye et al. 2022). It should be noted that due to the influence of multiple factors such as MSC source and culture conditions, there is a lack of a consistent miRNA profile among different MSC-EVs (Ferguson et al. 2018; Ragni et al. 2022). The synergistic effects of different miRNA combinations are the key to ensuring that MSC-EVs exert stable biological functions. Circular RNA (circRNA) profiles in MSC-EVs have also gained increasing attention, and they are recognized as potential novel players in the field of functional ncRNAs (Barilani et al. 2024). A recent study further identified EV-circRNA_0001236 as an important participant in alleviating cartilage degradation in OA (Mao et al. 2021). More than 1000 proteins have been identified in MSC-EVs (Anderson et al. 2016). Among these proteins, four major categories are considered therapeutically relevant to EVs: surface receptors (e.g., PDGFRB and EGFR); signalling molecules (e.g., RRAS/NRAS and MAPK1); cell adhesion molecules (e.g., FN1, EZR and IQGAP1) and MSC-associated antigens (e.g., CD9, CD63, CD81 and CD109) (Kim et al. 2012). Like miRNAs in MSC-EVs, proteomic analysis and other approaches have revealed that multiple types of proteins in MSC-EVs exhibit the potential to regulate numerous biological processes in the musculoskeletal system. For instance, one study has demonstrated that UCMSC-EVs can act as a key regulator of bone metabolism by delivering CLEC11A (Hu et al. 2020). In addition, recent studies have also found that MSC-EVs can carry mtDNA to alleviate mitochondrial damage and inflammatory responses, which demonstrates the potential of MSC-EVs in treating mitochondrial damage-related diseases (Zhao et al. 2021; Cao et al. 2020).

4 | Regulatory Roles of EVs in Physiological Processes and Pathological Mechanisms of the Musculoskeletal System

4.1 | Regulation and Function of EVs in Skeletal Muscle

Skeletal muscle accounts for approximately 30%–40% of the total body mass. It is one of the largest organs in the body and has important functions. Skeletal muscle not only responds to external stimuli through changes in muscle fibre size and structure

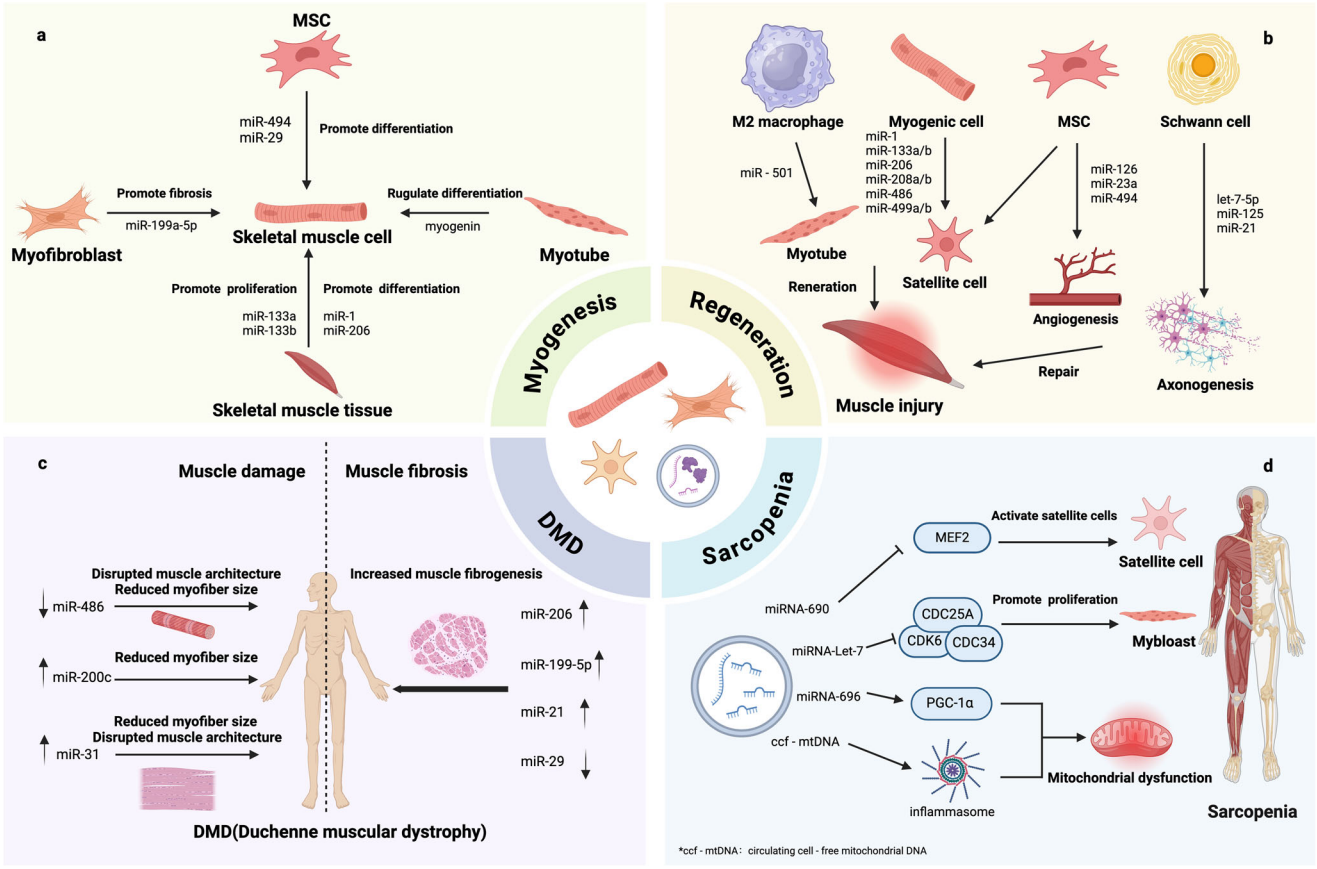

FIGURE 2 | Regulation and function of EVs in skeletal muscle. (**a**) EVs in skeletal muscle cell generation. (**b**) The functions of EVs in muscle injury repair. (**c**) The association between EVs and muscle damage and fibrosis in Duchenne muscular dystrophy (DMD). (**d**) The mechanism of action of EVs in the pathological process of sarcopenia.

but also responds adaptively to the external environment by secreting signalling molecules (myokine) (Whitham and Febbraio 2016). These signalling molecules affect different organs in the body (e.g., pancreas, adipose tissue, bone) through EVs, and regulate the physiology of peripheral tissues through autocrine, paracrine or endocrine pathways. And pathological processes (Schnyder and Handschin 2015). For example, IL-6, a known myokine, can be encapsulated in sEVs and regulate glucose uptake and fatty acid oxidation by activating AMP-Activated Protein Kinase (AMPK) (Carey et al. 2006). The development and regeneration process of skeletal muscle also involves complex processes of cell division and fusion. The source of skeletal muscle is mainly derived from the somites of the paraxial mesoderm (Guo et al. 2015). During embryonic development, postnatal growth, and muscle regeneration, myogenic cells increase their number through proliferation, fuse to form multinucleated myotubes, and further differentiate into mature muscle fibres. Myogenesis is regulated by a series of transcription factors, especially the precise coordination of myogenic regulatory factors (MRFs) and myocyte enhancer factor 2 (MEF2) family members (Buckingham 2006). EVs play a vital role in regulating myogenesis, muscle homeostasis and regeneration. Muscle cells, including myoblasts and myotubes, actively secrete EVs that contain various signalling molecules, such as miRNAs, growth factors and proteins, which are crucial for muscle differentiation, function and repair (Figure 2).

4.1.1 | EVs and Myogenesis

During myogenic differentiation, the miRNA content in muscle-derived EVs (Mu-EVs) undergoes significant change. Muscle-specific miRNAs, known as myomiRs, include miR-1, miR-133a, miR-133b and miR-206, regulate muscle cell proliferation, differentiation and function (Mytidou et al. 2021). The miRNA-1 and miRNA-206 inhibit myoblast proliferation and promote differentiation by targeting specific proteins like (paired box 7) PAX7 and (histone deacetylase 4) HDAC4 (Chen et al. 2006; Dai et al. 2016). These miRNAs are regulated by muscle-specific transcription factors, forming complex feedback loops that control myoblast proliferation and differentiation (Chal and Pourquié 2017). MSCs are multipotent stem cells derived from the mesoderm and can be divided into adipogenic, myogenic, and osteogenic lineages (Toh et al. 2018). Recent studies have shown that hBMSCs derived sEVs promote the proliferation and differentiation of C2C12 cells, in part through miR-494 (Nakamura et al. 2015). Another study found that MSCs from the placenta released miR-29-enriched sEVs, which enhanced human muscle cell differentiation through miR-29c transfer (Bier et al. 2018).

4.1.2 | EVs and Muscle Regeneration

Muscle regeneration requires the sequential expression of various factors, including growth factors, inflammatory cytokines, and

membrane lipids, to repair muscle fibres and promote satellite cell activation (Lombardo et al. 2024). EVs not only carry critical myomiRNAs but also secrete key growth factors such as bFGF, IGF-1, TGF-β1, TGF-β3, VEGF, and FGF2 (Domenis et al. 2017; Guescini et al. 2010). Studies have shown that myoblast-derived EVs, particularly those released during myotube formation, have distinct proteomic profiles, with higher levels of myogenin and other differentiation markers, suggesting their role in promoting muscle regeneration (Jalabert et al. 2021). Additionally, evidence from studies on C2C12 myoblasts and primary human myoblasts indicates that EVs secretion increases during differentiation, suggesting that EVs are active participants in the regeneration process (Matsuzaka et al. 2016). Qin et al. discovered that miR-146a-5p in adipose-derived sEVs targets insulin-like growth factor 1 receptor (IGF1R), regulates the PI3K/AKT/mTOR and FoxO3 signalling pathways, promotes muscle protein synthesis, inhibits protein breakdown, ameliorates skeletal muscle atrophy, and may also be involved in the regulation of fat metabolism (Qin et al. 2024). Hu et al. found in their research that Follistatin carried in the sEVs derived from umbilical cord mesenchymal stem cells can inhibit muscle fibrosis and promote muscle regeneration in mice by regulating the Smad2 and AKT signalling pathways (Hu et al. 2025).

4.1.3 | EVs-Mediated Communication and Muscle Homeostasis

EVs from differentiating myotubes can reduce myoblast proliferation while inducing differentiation, demonstrating their importance in cell-to-cell communication during muscle development (Forterre et al. 2014). Furthermore, myomiRNAs like miR-1, miR-206 and miR-133a experience a notable reduction during the proliferation of myoblasts. These findings imply that sEVs secreted by skeletal muscle might carry particular biochemical signals relevant to skeletal muscle myogenesis, thus suggesting the involvement of sEVs in the communication between mature muscle and myoblasts (Aswad et al. 2016). Further research by Guescini et al. revealed that sEVs secreted by C2C12 cells contain mtDNA and proteins that can be delivered to recipient cells, influencing muscle cell signalling and mitochondrial function (Guescini et al. 2010). Similarly, high-fat diet-induced sEVs release in mice alters gene expression related to muscle cell cycle regulation and differentiation, highlighting the paracrine signalling capabilities of Mu-EVs (Aswad et al. 2014).

4.1.4 | EVs and Muscle Diseases

Adipose tissue-derived exosomal miRNAs, such as miR-27a, can influence skeletal muscle function by modulating pathways like PPARγ, which is involved in glucose homeostasis (Li et al. 2015). This highlights the broader role of sEVs in muscle tissue regulation, even in pathological conditions like obesity and muscular dystrophy. For example, sEVs from myofibroblasts in Duchenne muscular dystrophy (DMD) patients carry miR-199a-5p, which targets caveolin-1 in normal muscle, affecting its expression and function (Zanotti et al. 2018). In DMD, EVs derived from skeletal muscle may have an anti-myogenic effect. For example, miR-206 is upregulated in dystrophic mice, which may lead to fibrosis. Under conditions of oxidative stress, skeletal muscle EVs may induce more oxidative stress (Yedigaryan et al. 2022; Yedigaryan and Sampaolesi 2023). EVs from DMD fibroblasts contain high levels of miR-199a-5p, which can induce the phenotypic conversion of normal fibroblasts to myofibroblasts (Zanotti et al. 2018). This conversion leads to increased collagen production and deposition, exacerbating muscle fibrosis. Fibrosis is also a common feature in sarcopenia, contributing to muscle stiffness and impaired function.

Sarcopenia, characterized by age-related muscle mass and strength decline, is a significant global health concern. EVs have emerged as crucial players in muscle biology and the development of sarcopenia (Lombardo et al. 2024). Sarcopenia is characterized by mitochondrial inflammation and dysfunction. Elevated levels of proinflammatory cytokines are commonly observed in sarcopenic patients. The inflammatory process triggers the release of damage-associated molecular pattern molecules (DAMPs). Furthermore, the mitochondrial quality control machinery is disrupted in sarcopenia, which impairs the regenerative capacity of skeletal muscle (Kapetanovic et al. 2015). Muscle satellite cells are essential for muscle growth, repair, and regeneration. Their function is severely compromised in sarcopenia. Shao et al. demonstrated that miRNA-690, which is discharged from Mu-EVs in atrophied muscles, suppresses the myogenic activity of satellite cells through targeting MEF2 (Shao et al. 2022). Some miRNAs carried by EVs may have a positive impact on muscle regeneration. For example, miR-1 and miR-206 are inversely correlated with the expression of PAX7, which maintains satellite cells in a quiescent state. Their levels are downregulated in damaged or sarcopenic muscles. Studies have shown that direct infusion of miR-1, miR-133 and miR-206 can stimulate the expression of MRFs and promote muscle recovery in rats with muscle damage (Dai et al. 2023). In addition, mitochondrial dysfunction is one of the important characteristics of sarcopenia. Mitochondrial components such as ATP5A (Complex V), NDUFS3 (Complex I), SDHB (Complex II) and mtDNA have been detected in the muscle EVs of sarcopenia patients. These mitochondrial components can activate multiple receptors/systems, including TLRs, NLRP3 inflammasome and cGAS-STING DNA sensing system, triggering an inflammatory response and leading to impaired muscle function (Byappanahalli et al. 2023). In skeletal muscle cells, miR-696 levels increase during metabolic stress, inhibiting PGC-1α expression and reducing mitochondrial function (Queiroz et al. 2021). During the muscle atrophy associated with sarcopenia, protein degradation increases while protein synthesis decreases. miRNA-23a, miRNA-27a and miRNA-351 can regulate the two E3 ubiquitin ligases, MuRF1 and MAFbx, which play important roles in protein degradation during muscle atrophy (Silva et al. 2019).

4.2 | EVs in Joint System

EVs affect the pathogenesis of OA through various mechanisms, such as inflammation, cartilage degradation, cartilage calcification, cell death, and senescence, and play an important role in the diagnosis and treatment of OA (Liu et al. 2023). One of the

most significant roles of EVs in the pathological changes of OA is to exacerbate the development of inflammation. Synovitis is a common feature of OA, characterized by prominent synovial cell proliferation, tissue enlargement, and vascular hyperplasia. EVs cause the spread of synovial inflammation by activating macrophages in the synovial fluid (Scanzello and Goldring 2012). Studies have shown that sEVs derived from synovial fibroblasts stimulated by IL-1β promote TNFα expression in chondrocytes (Kato et al. 2014). Meanwhile, chondrocytes derived from IL-1β can stimulate the production of IL-1β in macrophages by releasing EVs, which can inhibit (Autophagy related 4B) ATG4B expression through miR-449a-5p, resulting in LPS-induced autophagy of macrophages inhibition (Ni, Kuang, et al. 2019).

Secondly, EVs originating from diverse cells in the joint microenvironment have an impact on chondrocyte catabolism and facilitate cartilage damage. Multiple investigations have indicated that EVs serve as a crucial medium for cell-to-cell communication within articular cartilage tissues and play a role in the development of OA (Asghar et al. 2020; Wu et al. 2022). EVs derived from IL-1β-stimulated synovial fibroblasts can promote MMP-13 and inhibit ACAN expression. LncRNA-PCGEM1 present in sEVs from OA-FLSs promote chondrocyte apoptosis. In addition, it can also promote MMP-13 and inhibit COL2A1 and Aggrecan expression in chondrocytes. Currently, MMP-13 is considered the main mediator of the destruction of ECM, leading to most of the pathology in OA. It is induced mainly by the inflammatory cytokines IL-1β and TNF-α in the articular space (Liacini et al. 2003). EVs secreted by inflammatory FLSs can also promote M1 polarization of macrophages through the HIF1A-mediated glycolytic pathway, thereby exacerbating joint inflammation and cartilage degeneration (Liu, Xian, et al. 2024). In addition, IL-1β-stimulated chondrocyte secretion sEVs have elevated Circ-BrWD1 and Circ_0001846 expressions, which are involved in cartilage degradation (Guo et al. 2021). Circ_0001846 expression increases mediate chondrocyte damage through miR-149-5p/Wnt5b (Zhu et al. 2021).

In addition, studies have found that EVs mediate the observed calcification process of cartilage in the pathogenesis of OA (Liu et al. 2022). Senescence and apoptosis of chondrocytes are also closely related to EVs (Jeon et al. 2019), and sEVs derived from OA-FLSs promote iron apoptosis in IL-1β-stimulated chondrocytes (Kong et al. 2023). EVs secreted by macrophages stimulated with LPS can trigger noncanonical pyroptosis in chondrocytes by activating the caspase 11-gasdermin D axis, leading to cartilage catabolism (Ebata et al. 2023). Furthermore, EVs are closely related to the destruction and remodelling processes of the subchondral bone. Sympathetic innervation prompts osteoarthritic chondrocytes to secrete sEVs containing miR-125, disrupting subchondral bone homeostasis and aggravating cartilage damage. This provides a new perspective for understanding the pathogenesis of OA (Guan et al. 2025). Osteoclasts secrete sEVs that encapsulate miR-214-3p. These sEVs are taken up by osteoblasts, and as a result, they have an impact on the activity of osteoblasts and the process of bone formation. sEVs derived from osteoblasts in the sclerotic subchondral bone of OA carry miR-210-5p, regulate the energy metabolism and gene expression of chondrocytes, and promote cartilage degeneration (Wu, Crawford, et al. 2021). Osteoclast-derived exosomal miR-212-3p inhibits the anabolism and promotes the catabolism of chondrocytes through the TGF-β1/Smad2 signalling pathway (Dai et al. 2024). The infrapatellar fat pad (IPFP) is also considered to be associated with the development of OA. IPFP-derived sEVs from OA patients inhibit the expression of lamin B receptor (LBR) by transferring let-7b-5p and let-7c-5p, impair cartilage metabolism, induce chondrocyte senescence, and accelerate the progression of OA. Inhibiting let-7b-5p and let-7c-5p may be an effective strategy for the treatment of OA (Cao et al. 2024) (Figure 3).

Similarly, EVs play an extremely critical role in the pathological process of RA, mainly including the formation of immune complexes, antigen presentation, inflammatory response, miRNA delivery, bone destruction and cell-to-cell communication (Withrow et al. 2016). In the process of RA disease, the formation of autoantibodies is a key link. EVs can not only carry autoantigens such as citrulline proteins but also participate in the formation of immune complexes (Ucci et al. 2023; Villar-Vesga et al. 2019). EVs secreted by synovial cells after being stimulated by inflammation contain specific ncRNAs, such as miR-155-5p, miR-1307-3p, miR-323a-5p and miR-146a-5p (Takamura et al. 2018). These ncRNAs will further regulate the inflammatory response and can also promote macrophage migration and T-cell differentiation. In addition, bone destruction is a common pathological phenomenon in RA. EVs affect bone metabolism by regulating the balance between osteoclasts and osteoblasts. Specifically, sEVs secreted by FLSs in RA contain miR-221-3p which inhibits osteoblast differentiation while promoting osteoclast production (Maeda et al. 2017). Microvesicles secreted by FLSs contain enzymes that degrade the ECM, which also aggravates the process of bone destruction (Lo Cicero et al. 2012). EVs secreted by RA-FLSs also contain substances with proangiogenic properties, such as inhibitory DNA binding protein 1 (id1) and miR-1972. These substances can promote the migration of vascular endothelial cells and the formation of the lumen, which is conducive to the infiltration of immune cells (Edhayan et al. 2016; Chen, Dang, et al. 2022).

In contrast, the therapeutic potential of EVs on RA has also been emphasized, especially the therapeutic effect of MSC-EVs, which inhibit the proliferation, migration and invasion of RA-FLS and promote cartilage repair and osteogenesis (Pistoia and Raffaghello 2017). For example, miR-451a carried by hUCMSC-EVs can inhibit the proliferation, migration, and invasion of RA synovial fibroblasts (Mi et al. 2024). MiR-34a in BMSC-EVs can reduce RA inflammation by targeting related signalling pathways. Engineered modified MSC-EVs can improve therapeutic effects, such as MSC-EVs co-incubated with curcumin can effectively regulate the proliferation and inflammatory response of RA-FLS (Wu, Zhou, et al. 2021). In addition, EVs can also inhibit the inflammatory process. For example, EVs derived from M2 macrophages can promote the polarization of M1 to M2 and reduce inflammation (Zhang, Lai, et al. 2023). The NF-κB inhibitor srIkB carried by EVs can reduce the production of inflammatory cytokines, and reduce arthritis and cartilage degradation (Lee et al. 2024). EVs derived from human gingival mesenchymal stem cells (GMSC-EVs) can effectively treat RA by regulating he Treg/Th17 balance and the IKKB/NF-κB signalling pathway (Chen, Shi, et al. 2024) (Table 2).

TABLE 2 | Summary of cells secreting extracellular vesicles in various musculoskeletal tissues, their miRNA cargo, and proposed role in joint.

Tissue/cell source	cargo	Target cell	Function	Reference	OA/RA
Subchondral bone osteoblasts	miR-210-5p	Chondrocytes	Promote cartilage degeneration	(Wu, Crawford, et al. 2021)	OA
Infrapatellar fat pad	let-7b-5p, let-7c-5p	Chondrocytes	Induce chondrocyte senescence	(Cao et al. 2024)	OA
M1-polarized macrophages	miR-1246	Chondrocytes	Promote the expression of inflammatory factors and MMPs	(Peng et al. 2021)	OA
Chondrocytes	*LC*3	Chondrocytes	Initiate pathological cartilage calcification	(Yan et al. 2022)	OA
Fibroblast-like synoviocytes	LncRNA PCGEM1	Chondrocytes	Accelerate IL-1β-induced apoptosis and cartilage matrix degradation	(Zeng et al. 2022)	OA
IL-1β-induced chondrocyte	circ-BRWD1	Chondrocytes	Promote IL-1β-induced cell progression	(Guo et al. 2021)	OA
IL-1β-induced chondrocyte	circ_0001846	Chondrocytes	Modulate IL-1β-induced chondrocyte cell damage	(Zhu et al. 2021)	OA
Osteoarthritic subchondral bone osteoblasts	miR-210-5p	Chondrocytes	Promote cartilage degeneration	(Wu, Crawford, et al. 2021)	OA
Mesenchymal stem cells	circHIPK3, miR-124-3p	Chondrocytes	Promote chondrocyte proliferation and migration	(Li et al. 2021b)	OA
Chondrocyte	circ-BRWD1, miR-1277	Chondrocytes	Promotes IL-1β-induced chondrocyte injury	(Guo et al. 2021)	OA
Osteoclasts	let-7a-5p	Chondrocytes	Promote hypertrophic differentiation of chondrocytes	(Dai et al. 2020)	OA
Fibroblast-like synoviocytes	lncRNA H19, miR-106b-5p	Chondrocytes	Promote chondrocyte proliferation and migration	(Tan et al. 2020)	OA
Synovial fibroblasts	miR-126-3p	Chondrocytes	Suppress chondrocyte inflammation and apoptosis	(Zhou et al. 2021)	OA
Synovial mesenchymal stem cells	miR-129-5p	Chondrocytes	Reduce inflammatory response and apoptosis of chondrocytes	(Qiu et al. 2021)	OA
Bone marrow mesenchymal stem cells	miR-136-5p	Chondrocytes	Inhibit chondrocyte degeneration in traumatic osteoarthritis	(Chen, Shi, et al. 2020)	OA
Dental pulp stem cells	miR-140-5p	Chondrocytes	Inhibit IL-1β-induced chondrocyte apoptosis	(Lin et al. 2021)	OA

(Continues)

TABLE 2 | (Continued)

Tissue/cell source	cargo	Target cell	Function	Reference	OA/RA
Bone marrow mesenchymal stem cells	miR-9-5p	Chondrocytes	Reduce inflammation and oxidative stress injury	(Jin et al. 2020)	OA
Bone marrow mesenchymal stem cells	circRNA_0001236	Chondrocytes	Promote chondrogenesis, suppress cartilage degradation	(Mao et al. 2021)	OA
Osteoclasts	miR-212-3p	Chondrocytes	Promote catabolism in chondrocytes	(Dai et al. 2024)	OA
Osteoarthritic chondrocytes	miR-125	Osteoblasts in subchondral bone	Disrupt subchondral bone homeostasis and aggravate cartilage damage	(Guan et al. 2025)	OA
Synovial fibroblasts	miR-574-5p	Monocytes, M2-like macrophages	Induce osteoclast differentiation and promote bone resorption	(Hegewald et al. 2020)	RA
Synovial fibroblasts	miR-221-3p	Osteoblasts	Suppress osteoblast differentiation and mineralization	(Maeda et al. 2017)	RA
Synovial fibroblasts	miR-106b	Chondrocytes	Suppress chondrocyte proliferation and migration	(Liu, Fang, et al. 2020)	RA
Synovial fibroblasts	miR-424	T cells	Induce T cell differentiation, increase Th17 cells and decrease Treg cells	(Ding et al. 2020)	RA
Synovial fibroblasts	miR-124-3p	Macrophages	Suppress macrophage this migration	(Nakamachi et al. 2023)	RA
Fibroblast-like synoviocytes	miR-486-5p	Osteoblasts	Promote osteoblast differentiation	(Chen, Liu, et al. 2020)	RA

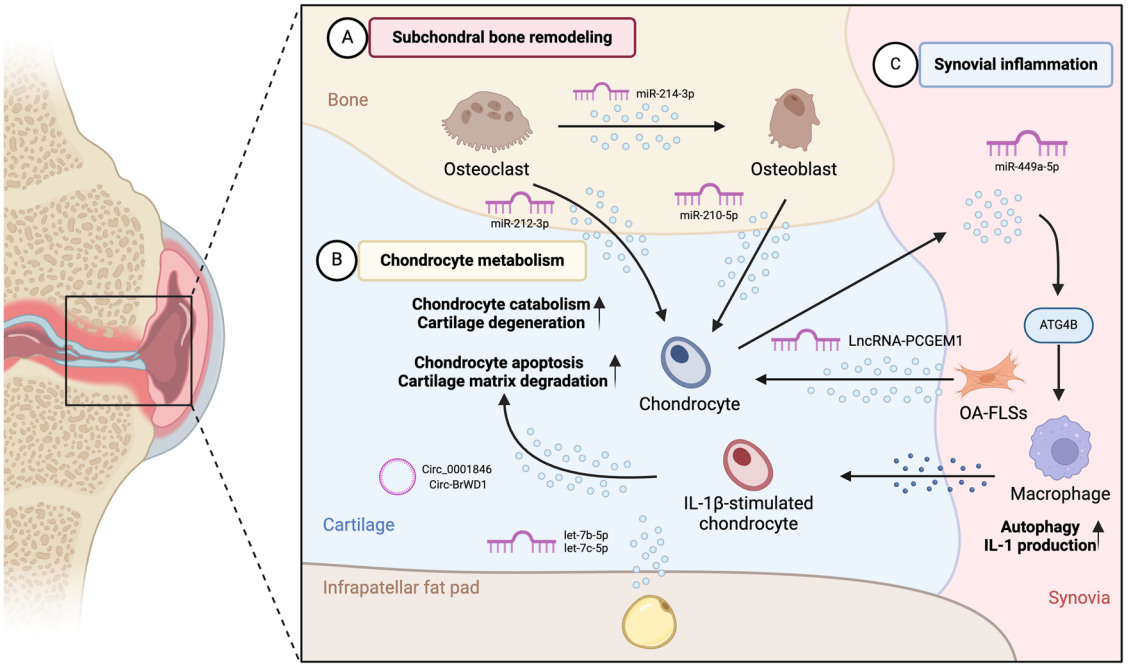

FIGURE 3 | The mechanisms of EVs in the pathological process of OA. One of the most important roles of EVs in the pathological changes of OA is to exacerbate the development of synovial inflammation. Secondly, EVs derived from different cells in the joint microenvironment affect chondrocyte catabolism and promote cartilage damage. In addition, EVs are closely associated with cartilage calcification, as well as the destruction and remodelling processes of subchondral bone in OA.

4.3 | EVs in Skeletal System

4.3.1 | EVs and Bone Metabolism

Cells in the bone microenvironment include osteoclasts, osteoblasts, osteocytes, BMSCs, myeloid and immune cells, platelets, hematopoietic and bone marrow endothelial cells. Osteoclasts and osteoblasts dominate the bone repair and remodelling process, maintaining the balance of bone metabolism (Hu, Chen, et al. 2021). Osteoclast-derived EVs regulate bone formation, it can inhibit osteoblast activity and stimulate osteoclast genesis transmitting miRNAs, such as the miR-214 family, thereby regulating bone formation (Zhao et al. 2015; Li et al. 2016). In addition, certain osteoclast-derived EVs can promote bone resorption through pathways such as receptor activator of nuclear factor-κB ligand (RANKL) reverse signalling (Ikebuchi et al. 2018). EVs released by mature osteoblasts contain miR-21a-5p, miR-148a-3p and miR-143. MiR-143 can regulate the expression of osteoblast differentiation-related transcription factors by targeting the core binding factor β (Cbfb) (Uenaka et al. 2022). EVs can also promote the osteogenic differentiation of bone marrow mesenchymal stem cells through the carried protein molecules, such as the membrane protein annexin (Uenaka et al. 2022). The regulatory role of osteoblast-derived EVs on osteoclast differentiation is controversial, studies have shown that RANKL-rich osteoblast-derived EVs promote osteoclast activity (Deng et al. 2015). In contrast, a different study reported that mineralized osteoblasts secrete EVs that contain miR-503-3p. These EVs impede the generation of osteoclasts through the inhibition of RANK expression (Chen et al. 2014). Osteocytes and BMSCs-derived EVs can promote bone formation. Osteocyte-derived EVs contain miR-218, which can promote osteoblast differentiation by negatively regulating the expression of osteoporotic factor sclerotic hormones (Qin et al. 2016), and BMSCs-derived EVs By upregulating the expression of TGF-β1 and BMP-9 (Narayanan et al. 2016), the differentiation of BMSCs into osteoblasts can be promoted, and EVs rich in miRNAs such as miR-27a, miR-196 and miR-206 can stimulate osteoblast differentiation (Qin et al. 2016). Moreover, MSC-EVs are capable of modulating the bone immune microenvironment. They can enhance the infiltration of M2 macrophages, decrease the expression of M1 macrophages and pro-inflammatory cytokines, and facilitate bone formation (Hu et al. 2022).

4.3.2 | EVs and Bone Diseases

Various studies have highlighted the therapeutic potential of EVs in osteoporosis. Studies have shown that electric vehicles from adipose tissue-derived stem cells (ASC-EVs) can inhibit osteocyte differentiation and promote the migration of BMSCs (Lee et al. 2021), and M2 macrophage-derived EVs (M2-EVs), can promote osteogenesis of MSCs differentiation, carrying miR-378a and miR-21a-5p (Kang et al. 2020). Recent studies have found that M2-EVs reshape the fate of osteoclast precursors (OCPs) by delivering glutamate, converting them into M2-like macrophages, thus alleviating osteoporosis through this new mechanism (Huang et al. 2024). In addition, the role of EVs in osteoporosis is not limited to their therapeutic potential but also plays a role in the pathogenesis of the disease. EVs derived from tumour mast cells have been associated with inhibition of osteoblast differentiation by specific miRNAs such as miR-23a and miR-30a. These miRNAs limit the critical transcriptional procedures necessary for osteoblast differentiation, resulting in bone loss observed under conditions such as systemic mastoid endocytosis (Kim et al. 2021), and M1 macrophage-derived EVs (M1-EVs) are

rich in miRNA-155, can inhibit the osteogenic differentiation of mesenchymal stem cells and aggravate osteoporosis (Kang et al. 2020) (Table 3).

MSC-EVs carry a variety of angiogenesis-related molecules, such as VEGF, lncRNA-H19 and miR-23a-3p. In bone injury and fracture repair models, MSC-EVs can accelerate angiogenesis, and promotes the regeneration and repair of bone tissue (Huang et al. 2020). Micro-CT analysis and histological examination showed that injection of BMSC-EV-miR-148a-3p can improve the bone structure of osteonecrosis of the femoral head (ONFH) rats, increase bone density and trabecular bone number, and enhance the osteogenic response of the femoral head (Huang et al. 2020). In addition, BMSC-EVs carrying miR-668-3p promote the proliferation and differentiation of osteoblasts by upregulating the expression of CD63 and CD9, thereby inhibiting the progression of osteonecrosis of the femoral head (Qiu et al. 2024). Exosomal miR-122 derived from M2 macrophages can induce the osteogenic differentiation of BMSCs, promote bone tissue formation, and improve the pathological changes of the femoral heads in rats with alcoholic ONFH head. MiR-135b-5p and miR-122-5p can also be used as diagnostic markers of ONFH (Wu, Wang, et al. 2021).

4.4 | EVs and Intervertebral Disc

The pathological characteristics of IVDD are painful disc degeneration caused by an imbalance in the anabolic and catabolism of intervertebral disc (Krut et al. 2021). The intervertebral disc consists of the nucleus pulposus, annulus fibrous and cartilage endplate to maintain flexibility and elasticity of the spine. Disc cell death, ECM component changes, oxidative stress, and increased inflammation are key factors in disc degeneration (Stergar et al. 2019). In addition, genetic factors, mechanical load, nutritional factors and aging interact with each other, resulting in degeneration of the intervertebral disc (Vo et al. 2016). The degeneration mechanisms of IVDD include metabolic disorders of nucleus pulposal cells (NPC), release of inflammatory cytokines and activation of inflammasomes, apoptosis and aging of nucleus pulposal cells (Johnson et al. 2015; Yang et al. 2021). The vesicles released by degenerated NPCs have the ability to transport miR-27a-3p and target the PPARγ/NFκB/PI3K/AKT signalling pathway, thereby influencing the M1 polarization of macrophages and exacerbating the degeneration of IVDD (Zhao et al. 2023). CircRNA_0000253 transported by sEVs has been confirmed through in vivo and in vitro experiments to promote IVDD by adsorbing miRNA-141-5p and down-regulating SIRT1 (Song et al. 2020).

The therapeutic significance of MSC-derived sEVs for IVDD is emphasized (Wuertz et al. 2008). It can promote NPC proliferation, reduce apoptosis and inflammation, and increase ECM synthesis and deposition (Bhujel et al. 2022). sEVs inhibit the apoptosis-related signalling pathways PI3K/Akt and MAPK signalling pathways by transmitting miRNAs, such as miR-21, miR-532-5p and miR-142-3p, thereby inhibiting NPC apoptosis (Wen et al. 2021; Hingert et al. 2020). Moreover, EVs can delay the aging of intervertebral disc cells by regulating the Sirtuin signalling pathway, increasing the expression of Sirtuin 1 and 6 (Sun et al. 2021; Tao, Xue, et al. 2024). EVs can also carry antioxidant proteins, such as peroxidase-1 and glutathione peroxidase 4, to eliminate reactive oxygen species and reduce the damage to intervertebral disc cells by oxidative stress (Xia et al. 2019). EVs play an anti-inflammatory role in the recovery of IVDD by inhibiting the release of inflammatory mediators and activation of NLRP3 inflammasomes (Xia et al. 2019; Yu et al. 2023). In addition, miRNAs such as miR-410, miR-302c and miR-26a-5p carried by EVs can inhibit the activation of inflammasomes and reduce the release of inflammatory cytokines (Zhang et al. 2020; Yu et al. 2023). The circRNAs carried by circ_0072464 and circ_0050205 can inhibit ferrodynamic death of nucleus pulposterior cells and promote cell proliferation and matrix synthesis (Yu, Xu, et al. 2022, Yu, Liu et al. 2022). MiR-431 targets and inhibits NRF2 expression, and circ_0072464 inhibits the expression of miR-431 by competitively binding to miR-431, upregulates NRF2 expression, thereby inhibiting ferrody death of NPCs (Yu, Xu, et al. 2022). LncRNA is involved in the regulation of DNA methylation, chromatin modification, transcription and translation processes (Qian et al. 2019). For example, lncRNAs such as CAHM and MALAT1 can inhibit inflammatory responses and reduce apoptosis of nucleus pulposterior cells (Li, Xu, and Chen 2022; Tao, Xue, et al. 2024). MSC-EVs can also increase the production of aggrecan, type I collagen, and TIMP-1, reduce the expression of MMP-3 and MMP-13, and regulate ECM metabolism (Hu et al. 2017). In addition, recent study has also demonstrated that sEVs can reduce ferroptosis and degeneration of NPC. They exert their effects by regulating the p62/KEAP1/NRF2 axis and can effectively alleviate the progression of IVDD in a rat model (Chen et al. 2025). MSC-EVs carry thioredoxin (TXN) and enter nucleus pulposus stem cells (NPSCs), where they promote endogenous TXN production by activating the NRF2/AP-1 positive feedback loop, inhibit cellular senescence, and alleviate IVDD (Chen et al. 2025).

4.5 | EVs Crosstalk in Musculoskeletal System

As we have discussed previously, EVs are rich in bioactive factors such as proteins, RNA, DNA, and lipids, and play a crucial role in intercellular communication. Research has shown that exercise can stimulate the rapid release of EVs into the circulation and may affect the activities of various organs (Frühbeis et al. 2015; Whitham et al. 2018). As the most active tissue during exercise, skeletal muscle may be the main potential source. Numerous studies have demonstrated that Mu-EVs reach tissues and organs such as bone, adipose tissue, kidney and liver through the circulation, which all indicate the key role of EVs in organ communication (Figure 4).

4.5.1 | Crosstalk Within the Musculoskeletal System

4.5.1.1 | Muscle-Bone Crosstalk. The interorgan communication between bone and skeletal muscle plays a vital role in human health. The crosstalk between bone and muscle is regarded as an intrinsic mechanism that preserves the structural integrity and functional coordination of these two tissues across the lifespan. Disruption of this crosstalk has been linked to various age-related disorders (Kirk et al. 2025). As an important medium of intercellular communication, EVs play a key role in muscle-skeletal crosstalk. Mu-EVs can reach the bones through

TABLE 3 | Summary of cells secreting extracellular vesicles in various musculoskeletal tissues, their miRNA cargo, and proposed role in bone.

Tissue/cell source	cargo	Target cell	Function	Reference
Osteoclast	miR-324	MSCs	Regulation of osteogenic differentiation	(Liang et al. 2021)
Osteoclasts	miR-23a-5p	Osteoblasts	Inhibit osteogenic differentiation	(Yang et al. 2020)
Osteoclasts	miR-146a-5p, miR-322-3p	Osteoclasts, osteoblasts	Inhibit osteoclast function and promote osteoblast differentiation	(Minami et al. 2025)
Osteoclasts	miR-331-3p	Osteoblasts	Regulate osteoblast function	(Zhang, Zhang et al. 2024)
Osteoclasts	RANK	Osteoblasts	Promote osteogenesis	(Ma et al. 2021)
Osteoblasts	miR-503-3p	OCPs	Inhibit osteoclast differentiation	(Wang et al. 2021)
Osteoblasts	circ_0008542	OCPs	Promote osteoclast differentiation and bone resorption	(Wang et al. 2021)
Osteoblasts	miR-143-3p	Osteoblasts, OCPs	Inhibit osteoblast differentiation	(Uenaka et al. 2022)
Osteoblasts	—	MSCs	Decrease osteogenic differentiation	(de Souza et al. 2023)
MSCs	miR-122-5p	Macrophages	Suppress RANKL-induced osteoclast differentiation	(Choi et al. 2024)
UCMSCs	—	Endothelial cells	Enhance fracture healing by promoting angiogenesis	(Zhang, Hao, et al. 2019)
BMSCs	miR-590-3p	Osteoblasts	Induce osteoblast differentiation and osteogenesis	(Luo et al. 2025)
BMSCs	—	Macrophages, osteoblasts	Promote M2 macrophage polarization and enhance osteogenic differentiation	(Zhang, Bai, et al. 2024)
BMSCs	miR-935	Osteoblasts	Promote osteoblast proliferation and differentiation	(Zhang et al. 2021)
BMSCs	miR-22-3p	Osteoblasts	promote osteogenic differentiation	(Zhang et al. 2020)
BMSCs	LncTUG1	Osteoblasts	Enhance osteoblast activity	
BMSCs	LncRNA MALAT1	Osteoblasts	Enhance osteoblast activity	(Yang et al. 2019)
BMSCs	miR-15b-5p	Osteoclasts	Reduce osteoclast differentiation	(Xu et al. 2024)

(Continues)

TABLE 3 | (Continued)

Tissue/cell source	cargo	Target cell	Function	Reference
BMSCs	—	Older BMSCs	Enhance proliferation and osteogenic differentiation	(Jia et al. 2020)
BMSCs	—	Osteoblasts, HUVECs	Promote osteogenesis and angiogenesis	(Zhang et al. 2021)
BMSCs	miR-151-3p	OCPs	Promote osteoclastogenesis	(Dong et al. 2025)
ASCs	—	Osteoclasts	Suppress NLRP3 inflammasome activation	(Zhang et al. 2021)
ASCs	miR-21	Osteoclasts	Inhibiting osteoclast activity	(Hu et al. 2022)
Macrophages	miR-365-2-5p	Osteoblasts	Promote osteoblast osteogenic differentiation	(Hou et al. 2024)
M2 macrophages	Glutamate	OCPs	Downregulate osteoclast-specific gene expression	(Huang et al. 2024)
Macrophages	miR-155 (M1), miR-378a (M2)	MSCs	M1-EVs inhibit bone regeneration; M2-EVs promote bone regeneration	(Kang et al. 2020)
Macrophages	—	BMSCs	Promote osteogenesis	(Pu et al. 2023)
M1 macrophages	miR-98	Osteoblast—like cells	Exacerbate bone loss and osteoporosis	(Yu et al. 2021)
M1 macrophages	miR-21a-5p	BMSCs	Promote osteogenic differentiation	(Liu et al. 2021)
M2 macrophages	—	Osteoclast-like cells	Inhibit osteoclast differentiation	(Guo et al. 2025)
M2 macrophages	miR-122	BMSCs	Promote osteogenic differentiation	(Le et al. 2025)
Bone marrow macrophages	miR-140, miR-378a	Skeletal stem/progenitor cells	miR-140 promotes adipogenesis, miR-378a promotes osteogenesis	(He et al. 2024)

Abbreviations: BMSCs, bone marrow mesenchymal stem cells; HUVECs, human umbilical vein endothelial cells; MSCs, mesenchymal stem cells; OCPs, osteoclast precursors.

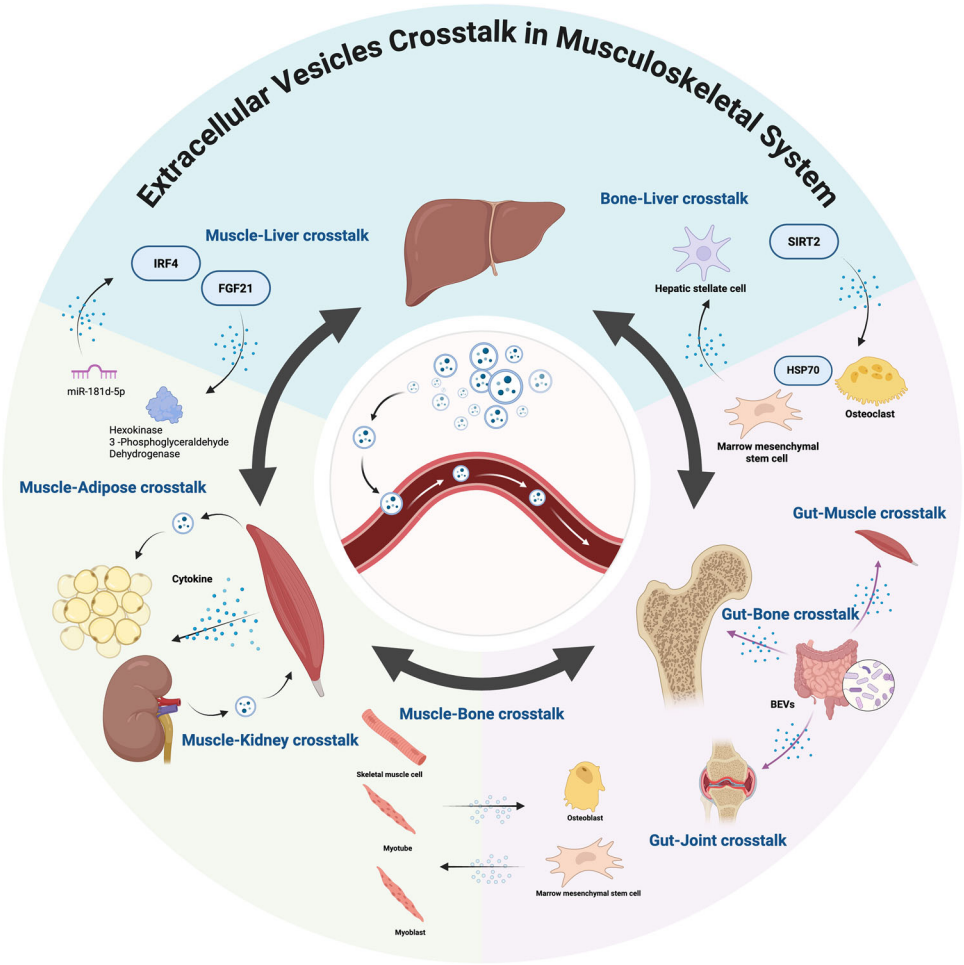

FIGURE 4 | The role of EVs in inter-organ communication as an important medium.

the blood flow, where they are engulfed by BMSCs. Mu-EVs promote glycolysis of BMSC by delivering lactate dehydrogenase A to BMSC cells, and promote the differentiation of BMSCs into osteoblasts, and has a protective effect on mice waste osteoporosis (Ma et al. 2023). In addition, mechanical stress-induced myoblast-derived EVs containing miR-92a-3p can promote BMSCs proliferation and osteogenic differentiation through the miR-92a-3p/PTEN/AKT signalling pathway (Xu et al. 2023). An in vivo experiment has shown that Mu-EVs from normal mice can effectively reverse disposable osteoporosis by promoting bone formation and inhibiting bone resorption (Huang et al. 2023). C2C12 myoblast-derived sEVs, increasing the level of miR-27a-3p in receptor cells, thereby reducing the expression of adenomatos polyposis coli target, activates the β-catenin signalling pathway, and can promote the differentiation of pre-osteogenic MC3T3-E1 cells into mature osteoblastic cells (Qin and Dallas 2019). Human skeletal myoblasts secrete EVs containing miR-873-3p. These EVs target human hBMSCs. MiR-873-3p promotes the osteogenic differentiation of hBMSCs by targeting H2 calmodulin (CNN 2). This process enhances bone formation and helps prevent osteoporosis (Chen, Li, Zhang, et al. 2024). Myotubes secrete sEVs containing FNDC5/irisin. These sEVs target osteoblasts and promote osteoblast proliferation and inhibit ferroptosis. They contribute to the exercise-induced protective effects on bone (Tao, Wang, et al. 2024). Myoblast sEVs miR-669a-5p and miR-450b-5p have also been shown to be new targets for regulating osteoblast differentiation and treatment of senile osteoporosis (Chen, Zheng, et al. 2024). Similarly, BMSC-EVs containing miR-486-5p targets C2C12 myotube cells. Dexamethasone can induce muscle atrophy, and BMSC-EVs can inhibit this process through the miR-486-5p/FoxO1 axis (Li et al. 2021). EVs released from human bone marrow mesenchymal stem cells hBMSCs are able to impede the over-activation of the ubiquitin-proteasome system (UPS) as well as the autophagy-lysosome pathway. They can also restrain oxidative stress and inflammatory reactions, reverse the transformation of muscle fibre types, postpone muscle atrophy induced by hindlimb unloading, and improve muscle function (Chang et al. 2025).

In addition, muscle-released myostatin acts directly on osteocytes, prompting them to produce more bone regulatory factors, inhibiting the expression of miR-218 in osteocyte-derived sEVs, and suppressing osteoblastic differentiation via the Wnt signalling pathway. Exogenous miR-218 can reverse this inhibitory effect (Qin et al. 2017). Under normal circumstances, miR-218 can inactivate the Wnt inhibitors SOST, DKK2, and SFRP2, thereby stimulating the Wnt/β-catenin signalling pathway and promoting the osteogenic differentiation of bone marrow stromal cells (Hassan et al. 2012). However, myostatin causes miR-218 to decrease, Wnt inhibitor activity increases, inhibiting the Wnt/β-catenin signalling pathway. After the Ocy454 cell sEVs containing less miR-218 were internalized by MC3T3 cells, the osteogenic

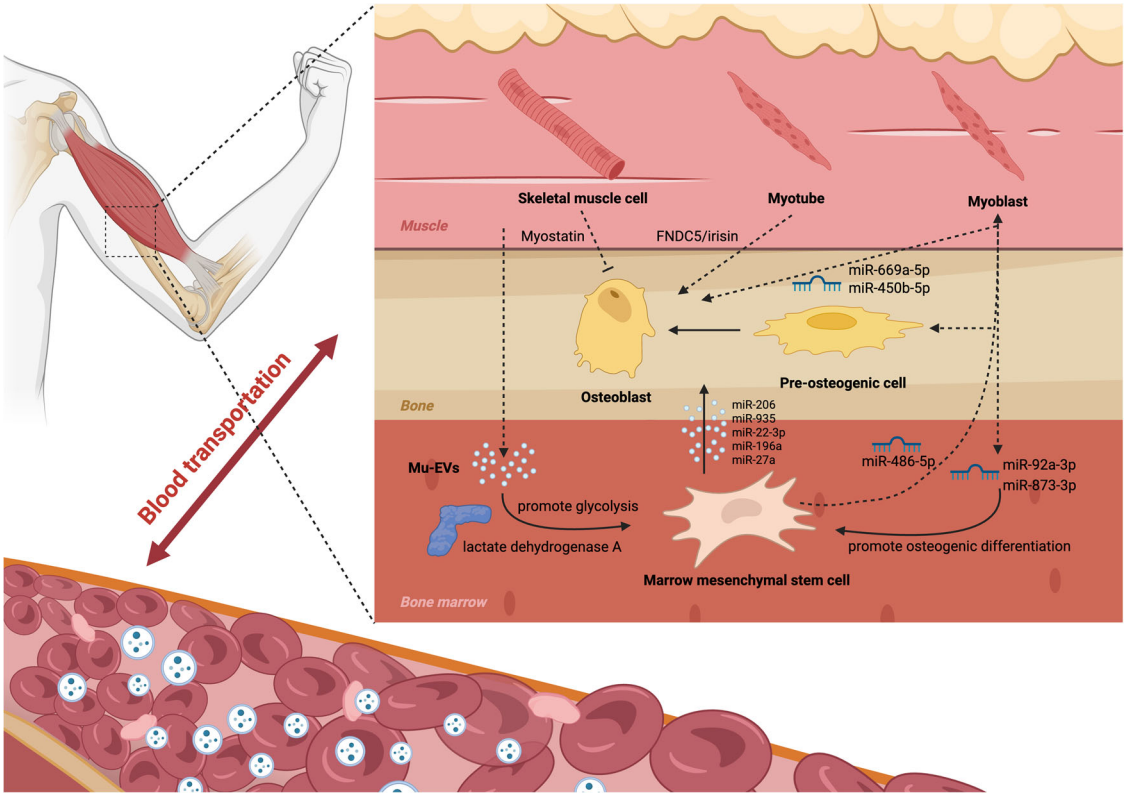

FIGURE 5 | The role of EVs in muscle-skeleton crosstalk as an important medium for intercellular communication. Extracellular vesicles secreted by skeletal muscle (Mu-EVs) reach the bone through the bloodstream and are phagocytosed by bone marrow mesenchymal stem cells (BMSCs), promoting osteogenic differentiation. BMSC-derived EVs (BMSC-EVs) can also target myotube cells to alleviate muscle atrophy. Proteins and the miRNA myostatin secreted by muscles can also act directly on bone cells through EVs to regulate bone metabolism.

differentiation of MC3T3 cells was further inhibited (Qin and Dallas 2019) (Figure 5).

4.5.1.2 | Muscle-Adipose Crosstalk. Although skeletal muscle and adipose tissue have distinct structures and functions, they are closely interconnected in the body and act as endocrine organs by releasing cytokines (Rome 2022). Therefore, studying muscle-adipose crosstalk is crucial for understanding the mechanisms regulating tissue homeostasis in the body. Adipose tissue-derived EVs play a key role in regulating skeletal muscle metabolism, particularly in insulin resistance and metabolic dysfunction. For example, miR-27a, highly expressed in the serum of obese individuals and pre-diabetic patients, is secreted by adipocytes into the circulation. Adipocyte-derived EVs carrying miR-27a induce insulin resistance in C2C12 skeletal muscle cells by suppressing peroxisome proliferator-activated receptor γ (PPARγ) and its downstream genes, linking obesity to muscle metabolic impairment (Yu et al. 2018; Kim et al. 2022). Additionally, adipocyte EVs from high-fat diet-fed mice increase triglyceride accumulation and reduce glucose uptake in myocytes, exacerbating insulin resistance (Yu et al. 2018). Under circadian rhythm disruption, adipocyte-derived miR-22-3p is taken up by skeletal muscle cells, inducing insulin resistance (IR) in vitro, with circulating miR-22-3p levels positively correlated with clinical IR markers, suggesting its potential as a biomarker for skeletal muscle IR (Zhang, Zhang, et al. 2023). Aging-related adipose tissues such as perimuscular adipose tissue release EVs enriched in let-7d-3p, a miRNA that targets HMGA2, a key transcription factor for muscle stem cell (MuSC) self-renewal. This leads to reduced MuSC proliferation and promotes the development of sarcopenia, indicating that EVs mediate age-related muscle atrophy (Itokazu et al. 2022). Furthermore, adipocyte-derived EVs influence fibro-adipogenic progenitors (FAPs) during muscle repair: FAP-released EVs containing miR-127-3p promote MuSC differentiation by inhibiting S1pr3, while Mu-EVs with miR-127a/b-3p and miR-126-3p suppress FAP adipogenic differentiation by targeting PPARγ, c-Met, and Runx1, reducing intramuscular fat infiltration during regeneration (Yu et al. 2024; Zhai et al. 2017). In addition, miR-146a-5p derived from sEVs of white adipose tissue can regulate myocyte mitochondrial autophagy and delay skeletal muscle senescence through the Fbx32/FoxO3 signalling axis (Qin et al. 2025). Mu-EVs regulate adipose tissue homeostasis through EVs-miRNA mediated signalling. Under mechanical overload (MOV) or resistance exercise, skeletal muscle releases EVs containing miR-1, which are preferentially taken up by epididymal white adipose tissue (eWAT). In eWAT, miR-1 targets Tfap2α (an inhibitor of β3-adrenoceptor Adrβ3 expression), enhancing adrenergic signalling and lipolysis (Vechetti et al. 2021). Mu-EVs also regulate adipogenesis and lipid accumulation. For example, miR-146a-5p in Mu-EVs inhibits adipogenesis by directly targeting growth differentiation factor 5 (GDF5) and suppressing PPARγ signalling, reducing fatty acid uptake in adipocytes (Qin et al. 2023). Conversely, EVs from slow-twitch muscle fibres promotes lipid accumulation in intramuscular adipocytes, revealing fibre-type-specific roles in muscle-adipose

crosstalk (Zhao et al. 2024). In obesity, insulin-resistant skeletal muscle releases EVs with altered lipid and miRNA profiles, such as reduced RAB35 and cholesterol enrichment, which induce lipid storage in adipocytes and exacerbate metabolic dysfunction (Jalabert et al. 2021). EVs serve as key mediators of bidirectional communication between muscle and adipose tissue, coordinating metabolic homeostasis and disease progression. Adipose-derived EVs, such as those carrying miR-27a and let-7d-3p, promote muscle insulin resistance and age-related atrophy, while Mu-EVs, such as those containing miR-1 and miR-146a-5p, regulate adipocyte lipolysis, browning and intramuscular fat deposition. These findings highlight EVs as potential biomarkers and therapeutic targets for metabolic diseases, such as obesity and sarcopenia, offering opportunities to restore tissue balance by intervening in EV-mediated crosstalk.

4.5.2 | Crosstalk Between the Musculoskeletal System and Other Organ Systems

4.5.2.1 | Bone-Liver Crosstalk. The liver and skeletal system form a complex bidirectional regulatory network via EVs, playing a critical role in physiological homeostasis and diseases, particularly osteoporosis. Growing evidence indicates that osteoporosis is a common complication in patients with chronic liver disease (CLD), especially in cirrhosis and cholestatic liver diseases (Wakolbinger et al. 2019). The role of EVs in liver-bone crosstalk has garnered increasing attention, as studies on the EV-mediated liver-bone axis homeostasis are essential for understanding osteoporosis progression. Epigenetic research has demonstrated that SIRT1 and SIRT6 are associated with bone metabolism (Louvet et al. 2020; Kim et al. 2020). A working model of liver-bone communication has been revealed: hepatic SIRT2 regulates the pro-osteoclastic NF-κB p65 signalling in osteoclasts through sEVs containing leucine-rich α-2-glycoprotein 1 (LRG1). The interorgan SIRT2-sEV-LRG1-NF-κB-NFATc1 axis is essential for maintaining bone homeostasis. When intracellular NF-κB p65-NFATc1 signalling is overactivated in osteoclasts, hepatic-derived sEV-LRG1 transferred to osteoclasts acts as a brake on osteoclastic activity to maintain bone balance. This axis represents a promising therapeutic target for primary osteoporosis, with targeting hepatic SIRT2 or sEV-LRG1 emerging as potential treatment strategy (Lin et al. 2023). Additionally, hepatic EVs from type 2 diabetes patients carry fatty acid synthase (Fasn), which induces ectopic fatty acid synthesis in periodontal ligament cells (PDLC), activates the NLRP3 inflammasome and Gasdermin D cleavage, and triggers PDLC pyroptosis, exacerbating diabetes-related alveolar bone loss (Liu, Dou, et al. 2024).

Bone marrow-derived dendritic cells (DCs) secrete EVs carrying heat shock protein 70 (HSP70), which promote the differentiation of naive T cells into regulatory T cells Tregs and inhibit Th17 cell polarization by activating the PI3K/mTOR pathway. In a hepatic ischemia-reperfusion injury (HIRI) model, injection of HSP70-EVs reduces intrahepatic inflammatory cell infiltration and alleviates liver damage by controlling the Th17/Treg cell ratio through the PI3K/mTOR axis (Zheng et al. 2018). BMSC-EVs play a multidimensional role in the regulation of liver fibrosis. BMSC-EVs carrying miR-148a-5p can specifically target Smad4, significantly reducing the activation of hepatic stellate cells (HSCs) and collagen deposition. This mechanism has been confirmed in a CCl_4-induced liver fibrosis mouse model, which showed a decrease in the proportion of α-SMA-positive cells and collagen fiber area in liver tissue (Xuan et al. 2022). Similarly, miR-192-5p carried by BMSC-EVs targets PPP2R3A in activated HSC-T6 cells, slowing down the progression of liver fibrosis (Tan et al. 2023). BMSCs treatment can exert anti-fibrotic effects by downregulating the lnc-BIHAA1/rno-miR-667-5p signalling pathway in HSCs (Feng et al. 2022). Meanwhile, BMSC-EVs promote autophagy in HSC-T6 cells by inhibiting the PI3K/Akt/mTOR signalling pathway, a process that partially relies on the delivery of anti-fibrotic miRNAs (such as miR-7045-5p), thereby accelerating the degradation of the ECM and alleviating liver fibrosis (Liu, Jiang, et al. 2025). Notably, quercetin priming enhances the expression of miR-136-5p in BMSC-EVs. Upon delivery of miR-136-5p to macrophages, it alleviates M1 macrophage polarization via the GNAS/PI3K/ERK/STAT3 pathway, thereby reducing intrahepatic inflammatory responses and improving liver function, which provides a new direction for the treatment of CLD (Jiang et al. 2024). On the other hand, miR-223 carried by BMSC-EVs significantly reduces intrahepatic macrophage infiltration by inhibiting the NLRP3 inflammasome, effectively alleviating hepatocyte injury in an autoimmune hepatitis model (Chen et al. 2018).

4.5.2.2 | Muscle-Liver Crosstalk. The relationship between the liver and muscle has garnered increasing attention. In skeletal muscle of mice with non-alcoholic steatohepatitis (NASH), the expression of interferon regulatory factor 4 (IRF4) is significantly upregulated. The IRF4-FSTL1-DIP2A/CD14 signalling pathway links skeletal muscle cells to hepatic pathogenesis in NASH (Guo et al. 2023). Hepatic fibroblast growth factor 21 (FGF21) mediates liver-muscle interaction by inhibiting the PI3K/Akt pathway to impair muscle regeneration, providing a novel therapeutic strategy for decompensated cirrhosis-related sarcopenia (Zhou et al. 2024). The concept of tissue crosstalk as a mechanism for the physiological effects of exercise was proposed decades ago (Goldstein 1961). Skeletal muscle is now recognized as an endocrine organ capable of producing and secreting hundreds of myokines that act in autocrine, paracrine or endocrine manners. To maintain glucose homeostasis during exercise, muscle glucose uptake is accompanied by increased hepatic glucose production (Severinsen and Pedersen 2020). Pulse-chase and intravital imaging experiments demonstrate that exercise-released EVs tend to localize in the liver and transfer their protein cargo (Whitham et al. 2018). For example, EVs deliver glycolytic enzymes such as hexokinase and glyceraldehyde-3-phosphate dehydrogenase to enhance glucose metabolism in hepatocytes, with in vitro studies showing increased glucose uptake rates in EVs-treated hepatocytes (Whitham et al. 2018). Mu-EVs play a critical role in mediating the anti-metabolic dysfunction-associated steatohepatitis (MASH) effects of remote ischemic conditioning (RIC) treatment by facilitating the transfer of sEVs loaded with miR-181d-5p to the liver. Identification of the novel miR-181d-5p/Nr4a3 signalling pathway underlying RIC's therapeutic effects provides new insights into the mechanisms supporting liver-muscle crosstalk (Zhao et al. 2025). A recent study has found that overtraining leads to lactate accumulation in skeletal muscles, promoting the sorting of F-box protein 2 into sEVs. These sEVs enter the liver and activate the BAX/BAK signalling pathway,

triggering liver fibrosis. Salidroside can alleviate overtraining-related hepatic fibrosis by inhibiting lactate production in muscles and blocking this muscle-liver crosstalk (Liu, Zhou, et al. 2025).

4.5.2.3 | Muscle-Kidney Crosstalk. Skeletal muscle atrophy, a common complication of chronic kidney disease (CKD), is characterized by loss of muscle mass, strength and function (Robinson et al. 2020). An early study identified 12 differentially expressed miRNAs in skeletal muscles of normal and CKD mice. Specifically, CKD suppresses miR-29 in muscles, leading to increased expression of the transcription factor Ying Yang-1 (YY1), which inhibits myogenesis (Wang et al. 2011). Studies indicate that the expression of certain EVs-associated miRNAs in CKD is exercise-sensitive. Low-frequency electrical stimulation reduces the expression of miRNA-1 and -206, improving CKD-induced skeletal muscle atrophy by upregulating the IGF-1 signalling pathway, thereby enhancing protein metabolism and promoting myogenesis (Hu et al. 2015). Exercise can increase the levels of miR-23a and miR-27a in nephrectomised mice, activating Akt signalling and reducing the expression of TRIM63/MuRF1 and FBXO32/atrogin-1 proteins to mitigate muscle atrophy in CKD (Wang et al. 2017). In streptozotocin-induced diabetic mice, elevated muscle miR-23a/27a improves muscle atrophy, concurrently increasing their levels in serum sEVs and kidneys, reducing renal collagen deposition and pSMAD2/3 expression, and alleviating renal fibrosis. AAV-GFP tracing shows Mu-EVs transfer to kidneys, confirming miR-23a/27a mediates muscle-kidney protective crosstalk via EVs (Zhang et al. 2018). Treatment with EVs encapsulating miR-26a leads to miR-26a overexpression in muscles, increasing skeletal muscle cross-sectional area, reducing the upregulation of FBXO32/atrogin-1 and TRIM63/MuRF1, and improving cardiac fibrosis lesions to prevent CKD-induced muscle atrophy and mitigate cardiomyopathy. These results provide a potential strategy for using EVs to deliver therapeutics for CKD complications (Wang et al. 2019). In a separate investigation, intramuscular administration of EVs loaded with miR-26 was shown to mitigate muscle wasting through inhibition of FoxO1. Concurrently, this treatment also ameliorates renal fibrosis by suppressing connective tissue growth factor expression, highlighting dual therapeutic effects against tissue degeneration (Zhang, Wang, et al. 2019).

4.5.2.4 | Gut-Joint Crosstalk. Recent research has uncovered dysbiosis of the gut microbiota in individuals with OA, establishing associations between multiple gut-derived microbial metabolites and the disease pathogenesis (Boer et al. 2019; Rushing et al. 2022; Van Pevenage et al. 2023). Building on this, a functional gut-joint axis, the gut microbiota-GUDCA-intestinal FXR-GLP-1-joint axis has been revealed (Yang et al. 2025). Bacterial extracellular vesicles (BEVs) have been considered as a potential bridge in the gut-joint axis in OA (Niu et al. 2025), suggesting that BEVs may regulate gut barrier permeability and immune-inflammatory responses by transmitting membrane-associated components such as lipopolysaccharides, LPS, cytoplasmic metabolites such as tryptophan derivatives, and genetic materials. Among these components, LPS has been the most extensively studied and has shown the most promising results related to OA (Huang and Kraus 2016). Evidence supports the association between elevated serum LPS levels and the radiographic severity and clinical symptoms of OA (Huang et al. 2016). Studies have also found that patients with RA exhibit gut microbiota dysbiosis and increased intestinal permeability, while probiotic-derived EVs can exert anti-RA effects through immunomodulation and maintenance of gut microbiota homeostasis (Bungau et al. 2021; Chen, Li, Xie, et al. 2024; Lin, Zhang, et al. 2023). Immunomodulation serves as the core mechanism: probiotic-derived EVs can alleviate RA symptoms in preclinical models by promoting M2 macrophage polarization and inhibiting pro-inflammatory cytokines (Dell'Atti et al. 2025). However, many mechanisms underlying the transportation of EVs in this context remain to be elucidated. Future research could focus on in-depth analysis of the functions of specific biomolecules within EVs, utilize advanced omics techniques to comprehensively map the molecular profiles of EVs in the gut-joint axis, and clarify the complete signalling pathways of EVs from release in the gut, transportation to joints, to their functional effects. This would provide a more detailed molecular basis for understanding the complex mechanisms of the gut-joint axis.

4.5.2.5 | Gut-Bone Crosstalk. EVs secreted by intestinal commensals, probiotics and pathogenic bacteria have been demonstrated to possess the ability to regulate the intestinal microenvironment and host health (Liu et al. 2021; Díaz-Garrido et al. 2021). Intestinal bacteria can promote the maturation and development of the host immune system via BEVs (Kaparakis-Liaskos and Ferrero 2015). The emerging BEV-based gut-bone axis reveals the relationship between the gut and bones more directly compared to the early gut-bone axis centred on the immune and endocrine systems (Liu, Li, et al. 2025). Probiotics are defined to be live microorganisms capable of conferring beneficial effects on host health when supplied in adequate amounts (Hill et al. 2014). Studies have shown that probiotics can prevent bone loss induced by sex hormone deficiency and inflammation (Ohlsson and Sjögren 2015; Huidrom et al. 2021; Gao, Kuraji, et al. 2022). A meta-analysis further validated the positive effect of probiotic supplements on bone health in postmenopausal women (Wang, Wei, et al. 2024). The latest research has confirmed that *Bacillus coagulans* can ameliorate post-menopausal osteoporosis by regulating the gut-immune-bone axis, re-emphasizing the therapeutic potential of probiotics in bone regeneration through gut-bone crosstalk (Sapra et al. 2025; Fu et al. 2025). BEVs isolated from probiotics have also exhibited anti-osteoporotic effects in models, showing clinical prospects in the treatment of bone diseases (Wei et al. 2025). For instance, BEVs derived from *Proteus mirabilis* can downregulate the expression of miR-96-5p and upregulate its target gene Abca1, leading to mitochondria-dependent apoptosis of osteoclasts, thereby inhibiting osteoclast differentiation and bone resorption activity (Wang et al. 2022). In animal models, probiotic-derived EVs significantly improve trabecular bone structure and reduce bone resorption markers, providing novel bacteria-derived biotherapeutic targets for the treatment of osteolytic diseases such as osteoporosis and RA (Wang et al. 2022). Furthermore, bacteria possess advantages, including large-scale fermentation capability, diverse gene editing methods, and mature high-density fermentation technologies (Liu, Wang, et al. 2020), endowing BEVs with unique characteristics of easy engineering modification and clinical translation (Liu et al. 2022). BEVs have been widely used in preclinical studies for osteoporosis treatment (Liu, Song, et al. 2024; Kong et al. 2025). By using the probiotic *Escherichia coli* Nissle 1917 (ECN) as a chassis cell, the surface of BEVs secreted by ECN

was engineered to simultaneously display bone morphogenetic protein 2 (BMP-2) and chemokine receptor 4 (CXCR4) via the fusion protein ClyA, resulting in excellent bone-targeting ability (Liu, Song, et al. 2024). Another study on the engineering of BEVs derived from ECN involved conjugating the osteoclast precursor fusion protein DC-STAMP to the surface of BEVs, followed by physical electroporation to load the osteoclastogenesis-inhibiting peptide FRATtide, achieving targeted delivery to bone tissue (Kong et al. 2025). These engineering strategies further enhance the functionality of BEVs, providing novel biotherapeutics with both targeting ability and osteogenic activity, as well as potential for large-scale production, for osteoporosis treatment. Existing preclinical studies on probiotic-derived BEVs still lack standardized quality control. The molecular details underlying the cross-organ regulation of BEVs as key mediators in the gut-bone axis remain unclear. In the future, it is necessary to decipher the precise regulatory network of BEVs in the gut-bone axis, and based on this, optimize BEVs engineering strategies to advance the process of clinical translation.

4.5.2.6 | Gut-Muscle Crosstalk. As correlations between the decline in skeletal muscle mass and function and alterations in gut microbiota composition have been observed in animal experiments (Wu et al. 2020; Lahiri et al. 2019), the gut and skeletal muscle that both equipped with signal-transducing capabilities have been logically linked. These findings highlight the gut-muscle axis as a physiological target for reducing the risk of sarcopenia (Prokopidis et al. 2021). A mechanistic connection exists between the gut microbiota and muscle atrophy, whereby the gut microbiota can modulate the sensitivity of skeletal muscle to anabolic stimuli (Grosicki et al. 2018; Casati et al. 2019). Early studies have identified a crucial role of BEVs in this mechanism, EVs derived from *Pseudomonas panacis* can penetrate the intestinal barrier, distribute to insulin-sensitive organs such as skeletal muscle and adipose tissue, and induce insulin resistance and glucose intolerance by blocking the insulin signalling pathway (Choi et al. 2015). The role of probiotics has also been emphasized. Probiotics have been shown to limit the loss of skeletal muscle mass in animal models, supplements of *Bifidobacterium* and *Lactobacillus* can increase muscle mass and strength in aged mice (Ni, Yang, et al. 2019). *Lactobacillus casei Shirota* can significantly ameliorate age-related decline in muscle function in a mouse model of accelerated aging by regulating the gut-muscle axis, restoring intestinal short-chain fatty acids, and modulating the gut microbiota (Chen, Chang, et al. 2022). Probiotic-derived EVs have emerged as more promising candidates for sarcopenia treatment due to their enhanced targeting ability and bioactivity. Heat-inactivated *Lactobacillus plantarum* HY7715-derived EVs can simultaneously improve muscle regeneration and intestinal homeostasis by regulating the gut-muscle axis (Lee et al. 2025). Probiotics have been demonstrated to effectively improve muscle mass and function in rodents under both anabolic and catabolic conditions. However, when translating these findings to humans, the situation remains unclear. Although multiple meta-analyses have confirmed that probiotics serve as an effective intervention for sarcopenia in humans (Prokopidis et al. 2023; Shokri-Mashhadi et al. 2023), there remain limitations—including a paucity of well-designed studies and the challenges in achieving accurate and reproducible measurement of muscle mass and function (Giron et al. 2022).

5 | Clinical Significance of EVs in the Musculoskeletal System

Now commonly used treatments for bone metabolism diseases such as osteoporosis and OA. Oestrogen replacement and calcitonin are routinely used to treat drugs, but there are problems such as poor organ selectivity and many side effects in long-term use. For example, oestrogen replacement treatments include Risk of cancer. Drugs for treating RA have adverse effects on immunosuppression, radiation therapy can damage normal tissues, and artificial bone materials will have problems with infection, rejection, and integration (Li et al. 2019).

EVs have many characteristics for the treatment of musculoskeletal system diseases. Excellent biocompatibility: high compatibility with human tissues and cells, and low risk of immune response. Good targeting ability: sEVs are naturally able to target specific tissues or cells, accurately transport biologically active substances, and target them more accurately after engineering modification. Strong penetrability: With a particle size of 30–150 nm, it can penetrate physiological barriers and deliver therapeutic substances to difficult places for traditional drugs to reach. It contains bioactive molecules such as nucleic acids, proteins and lipids. It can also participate in intercellular communication and can be used as biomarker. High modifiability: the membrane surface is easy to modify, can connect targeted molecules and drugs, regulate contents, and meet personalized treatment needs (Wang, Li, et al. 2023) (Figure 6).

5.1 | EVs Dosing in Pre-Clinical Studies

To validate the potential of EVs as therapeutic agents, well-designed in vitro and in vivo studies are essential. To gain a broader understanding of EVs dosing strategies and appropriate dosages, we summarized several recent preclinical studies on EVs for musculoskeletal system diseases, which used natural or engineered EVs as therapeutic interventions in vitro and in vivo (Table 4). These studies used EVs from different sources, administered at different concentrations in vitro and in vivo by direct mixing into culture media or injection into defect sites with small volumes of PBS. Notably, there was a wide variation in the effective dose range of EVs. For instance, different studies on RA used concentrations ranging from 20 μg/mL (Chen, Shi, et al. 2024) to 80 μg/mL (Wu, Su, et al. 2025). Similar inconsistencies were observed in studies using particle number for EVs dosing quantification, such as those on osteoporosis with varying particle dose specifications (Chang et al. 2024; Lee et al. 2021). However, a concentration of 1×10^{10} particles/mL appears to be widely used and accepted in OA studies using particle number for EVs dosing. In these summarized preclinical studies, the rationale for EVs dose selection and treatment frequency was largely lacking. For example, in studies on IVDD, different administration frequencies (weekly or biweekly injections) were used without clear justification for the choices (Xia et al. 2019; Zhou et al. 2022). In studies on ONFH (Zhang et al. 2020; Chen, Du, et al. 2020), dose selection also lacked uniform standards and clear theoretical support. Additionally, systemic administration routes often used higher doses than local routes (such as intra-articular injection and direct injection into injury sites), regardless of the specific disease model. For example, in osteoporosis studies, intravenous

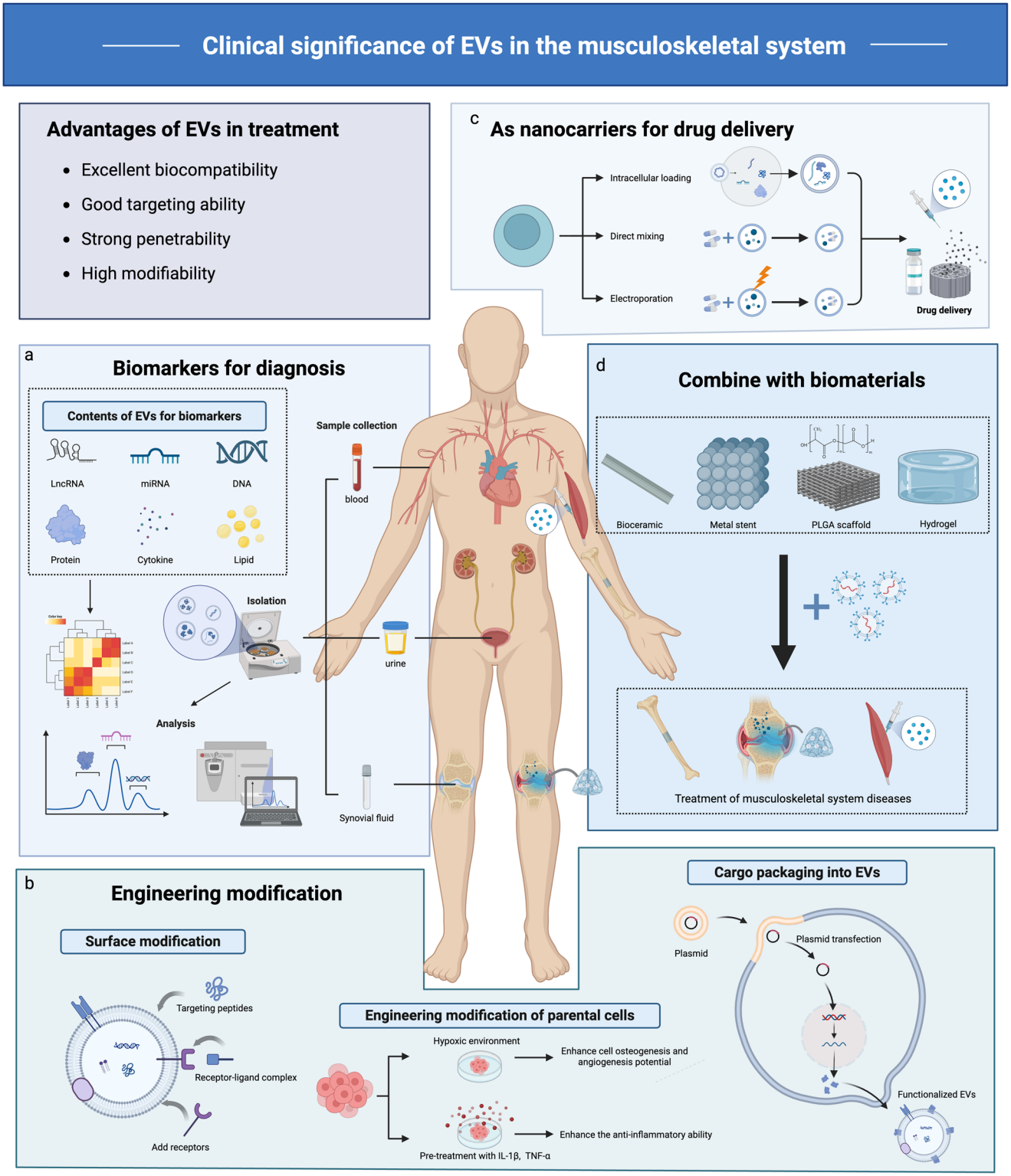

FIGURE 6 | The clinical significance of EVs in the musculoskeletal system. (**a**) EVs include DNA, miRNA, lncRNA, proteins, cytokines and lipids, have therapeutic potential as diagnostic biomarkers. (**b**) The engineering modification of EVs, including surface modification, modification of parental cells and cargo packaging into EVs. (**c**) EVs can serve as nanocarriers for drug delivery. The drug-loading strategies of EVs include loading drugs in EV-derived cells and loading drugs after EVs isolation. In addition, electroporation can also achieve loading by stimulating the formation of pores in the membrane. (**d**) EVs combined with biomaterials are used to treat musculoskeletal system diseases. EVs can serve as nanocarriers for drug delivery.

TABLE 4 | Application of EVs in the research of treating musculoskeletal diseases and corresponding dosages.

Application	EVs source	In vitro cell study/dosage	In vivo model/dosage	References
RA	M2 macrophages	CTLL2 cells; 80 μg/mL	Mouse collagen-induced arthritis model; 150 μL (80 μg/mL)	(Wu et al. 2025)
OA	Chondrocytes	Chondrocytes, macrophages, osteoblasts; 5×10^8 particles/mL	Rat ACLT model; 50 μL (10^9 /mL) weekly for 4 weeks	(Xu et al. 2025)
OA	MSCs	Chondrocytes; 5×10^8 particles/mL	Rat DMM OA model; 1×10^{10} particles/mL weekly for 4 weeks	(Li, Lu, et al. 2025)
OA	MSCs	Chondrocytes; 100 μg/mL	Rat DMM OA model; 10 μL (100 μg/mL) injected weekly	(Wang et al. 2025)
Cartilage repair	UCMSCs	Chondrocytes; 50 μg/mL	Rabbit knee osteochondral defect model; 100 μg/mL	(Chen, Zhou, et al. 2024)
CEP degeneration	HEK293T cells	CEP cells; 100 μg/mL	Rat CEP degeneration model; 20 μL (100 μg/mL) injected weekly	(Lin et al. 2024)
OA	HEK293T cells	Chondrocytes; 20 μg/mL	Rat cartilage defect model and OA model; 100 μg/50 μL	(Wu, Tao, et al. 2025)
OA	MSCs	Chondrocytes; 1×10^{10} particles/mL	Mouse post-traumatic OA model; 1×10^{10} particles/mL	(Feng et al. 2025)
ONFH	MSCs	MG-63 and U-2 cells; 100 μg/mL	Rat ONFH model; 1×10^{12} particles/mL	(Zhang et al. 2020)
RA	MSCs	CD3+ T cells; 20 μg/mL	Mouse CIA model; 100 μg/mouse on days 0, 15, 30	(Chen, Shi, et al. 2024)
Osteoporosis	Endothelial cells	—	Mouse OVX model; 100 μg	(Song et al. 2019)
Osteoporosis	UCMSCs	—	Mouse GIOP model; 100 μg every 2 days for 8 weeks	(Zhao et al. 2025)
Osteoporosis	BMSCs	—	Mouse OVX model; 100 μg weekly for 2 months	(Li, Tang, et al. 2024)
Osteoporosis	BMSCs	MC-3T3 cells, RAW264.7 cells; 20 μg/mL	Mouse OVX model;100 μg/100 μL twice a week for 8 weeks	(Wang, Zou, et al. 2023)
Cartilage repair	MSCs	Chondrocytes; 1, 5, 10 μg/mL	Rat osteochondral defect model; 100 μg/100 μL, injected weekly for 12 weeks	(Zhang, Chuah, et al. 2018)
Osteoporosis	MSCs	MC3T3-E1 cells, osteoblasts; 1×10^7 particles/mL	Mouse OVX model; 1 mg/kg (1.4×10^9 vesicles) 3 times/week for 4 weeks	(Cha et al. 2023)
OA	Dioscorea japonica	Primary human chondrocytes; 10 μg/mL	Rat OVX OA model; 1 mg/kg/day	(Hwang et al. 2023)
OA	Embryonic stem cells	Human chondrocytes; 1×10^{10} particles/mL	ACLT-induced OA mice model; 1×10^1 particles/mL twice/week for 12 weeks	(Shen et al. 2023)
Diabetic bone disease	BMSCs	Osteoblasts; 20 μg/mL	Rat model of type 2 diabetes mellitus; 200 μg/mL	(Li, Zhang, et al. 2023)
Muscle regeneration	BMSCs	C2C12 myoblasts; 80 μg/mL	Mouse tibialis anterior injury in model; 30 μg	(Ye et al. 2023)
Skeletal muscle regeneration	Myogenic progenitor cells	Muscle satellite cells; 5×10^9 particles/mL	Mouse gastrocnemius muscle injury model; 50 μL (2.3×10^{10} particles/mL) every other day	(Cao et al. 2024)
Osteoporosis	MSCs	Bone marrow monocytes, HUVECs; 5×10^9 particles/mL	Mouse OVX model; 100 μg (5×10^9 particles/mL) every 3 days for 8 weeks	(Chang et al. 2024)
Osteoporosis	BMSCs	—	Mouse GIONFH model; 500 μg/500 μL	(Gui et al. 2024)
Infected bone defects	Osteoclasts	MC3T3-E1 osteoblasts; 20 μg/mL	Rat model of infected bone defects; 0.2 mg/kg twice a week	(Zhang, Zhang et al. 2024)
Ischemic bone disease	MSCs	HUVECs; 50 μg/mL	Rat GIONFH model; 500 μg/500 μL	(Jiang et al. 2024)
Bone regeneration	ASCs	HUVECs, RAW264.7 cells; 150 μg/mL	Rat femoral defect model; 40 μL	(Qi et al. 2024)
Osteoarthritis pain	MSCs	Chondrocytes, Schwann cells; 15 μg	Mouse DMM OA model; 15 μL every 2 weeks for 8 weeks	(Lu et al. 2023)
OA	iPSCs	Human primary chondrocytes, RAW 264.7 cells; 10 μg/mL	Rabbit ACLT OA model; 100 μg weekly for 3 weeks	(Hsueh et al. 2023)
OA	UCMSCs	Chondrocytes; 5×10^6 particles/mL	Rat MIA-induced OA model; 1×10^{10} particles/mL weekly for 4 weeks	(Liu, Liu, et al. 2023)
OA	UCMSCs	IL-1β-induced chondrocytes; 200 μg/mL	Rat OA model; 5×10^9 particles	(Yang et al. 2024)

(Continues)

TABLE 4 | (Continued)

Application	EVs source	In vitro cell study/dosage	In vivo model/dosage	References
OA	ASCs	Chondrocytes, macrophages; 10 μg/mL	Rat DMM OA model; 20 μL (10 μg/mL) weekly	(Wang et al. 2022)
Temporomandibular joint OA	MSCs	Chondrocytes, macrophages; 1, 2, 5 μg/mL	Rat MIA-induced OA model; 100 μg/50 μL	(Zhang, Teo, et al. 2019)
Osteoporosis	BMSCs	RAW264.7 cells, BMDMs; 100 μg/mL	Mouse OVX model; 100 μg thrice a week	(Yang et al. 2022)
OA	Wharton's jelly MSCs	Chondrocytes, RAW264.7 cells; 1, 5 μg/mL	Rat OA model; 30 μg/200 μL	(Chen, Tang, et al. 2022)
IVDD	BMSCs	NP cells; 100 μg/mL	Rabbit IVDD model; 100 μg	(Xia et al. 2019)
ONFH	USCs	HNPCs, HMECs; 100 μg/mL	Rat GC-induced ONFH model; 500 μg/200 μL	(Chen, Du, et al. 2020)
IVDD	MSCs	HNPCs; 100 μg/mL	Rat IVDD model; 100 μg	(Zhou et al. 2022)
Osteoporosis	Skeletal muscle	Monocytes; 100 μg/mL	Rat osteoporosis model; 200 μg/200 μL twice weekly	(Huang et al. 2023)
RA	UCMSCs	RA synovial fibroblasts; 1 μg/μL	Rat Collagen II adjuvant-induced RA model; 100 μL (1 μg/μL) weekly	(Huang et al. 2022)
OA	MSCs	Mouse chondrocytes; 200 μg/mL	Mouse OA model; 200 μg	(Li et al. 2021b)
OA	ASCs	Mouse chondrocytes; 50 μg/mL	Mouse cartilage injury model; 100 μg weekly	(Li et al. 2021a)
Glucocorticoid-induced osteoporosis	Platelet lysate	Endothelial progenitor cells; 50 μg/mL	Rat GIOP model; 100 μg weekly	(Zheng et al. 2022)
Muscle atrophy	C2C12 cells	C2C12 myotubes; 1×10^{10} particles/mL	Mouse muscle atrophy model; 8.5×10^{10} particles/mouse weekly for 5 weeks	(Chen, Yuan, et al. 2022)
Fracture nonunion	BMSCs	HUVECs, mouse osteoblast precursor cells; 20, 40 μg/mL	Rat femoral nonunion model; 40 μg/100 μL weekly for 6 weeks	(Zhang et al. 2020)
OA	BMSCs	Rat chondrocytes; 20, 40 μg/mL	Rat OA model; 40 μg/100 μL weekly for 6 weeks	(He et al. 2020)
IVDD	iMSCs	Senescent NPCs; 1×10^{10} particles/mL	Rat IVDD model; 2 μL weekly for 8 weeks	(Sun et al. 2021)
Bone fracture	BMSCs	MC3T3, MG63 cells; 100 μg/mL	Mouse fracture model; 100 μL, Days 1 and 8 post-surgery	(Hu, Wang, et al. 2021)
Bone regeneration	BMSCs	—	Rat calvarial defect model; 4.5×10^9 particles/rat	(Kang et al. 2022)
Osteoporosis	ASCs	—	Mouse OVX osteoporosis model; 1×10^8or 5×10^8 particles/100 μL thrice a week for 2 weeks	(Lee et al. 2021)
Osteoporosis	MSCs	—	Rat OVX osteoporosis model; 750 μg twice a week	(Wang et al. 2020)
OA	Dendritic cells	Human chondrocytes; 50 μg/mL	ACLT-induced OA mouse model; 100 μg/100 μL weekly for 4 weeks	(Liang et al. 2020)
IVDD	MSCs	TNF-α-treated NPCs; 100 μg/mL	Ex vivo disc organ culture model; 100 μg/mL	(Liao et al. 2021)
Osteoporosis	MSCs		Mouse OVX osteoporosis model; 100 μL (1×10^{11} particles/mL) weekly for 6 weeks	(Cui et al. 2022)
Shoulder stiffness	BMSCs	CDFs, NIH3T3 cells; 20–50 μg/mL	Mouse immobilization model; 50 μL (20–50 μg/mL), weekly for 3 weeks	(Luo et al. 2022)
OA	M2 macrophages	M1 macrophages; 50 μg/mL	ACLT-induced OA mouse model; 10 mg/10 μL weekly for 5 weeks	(Qin et al. 2023)
Bone repair	ASCs	HUVECs, RAW264.7 cells; 10 μg/mL	Rat femoral defect model; 40 μL	(Wu et al. 2023)
OA	ASCs	Chondrocytes, synovial fibroblasts; 10 μg/mL	Rat OA model; 100 μg/250 μL	(Li et al. 2023)
Osteoporosis	UCMSCs	RAW264.7 cells; 100 μg/mL	Mouse osteoporosis model; 100 μg/100 μL	(Hu et al. 2020)
Ischemic muscle injury	UCMSCs	C2C12 cells; 100 μg/mL	Hindlimb ischemia mouse model; 100 μg	(Yan et al. 2020)
Cartilage degeneration	ASCs	Chondrocytes, RAW264.7 cells; 1×10^8 and 2×10^8 particles/mL	Rat OA model, DMM mouse model; 1×10^8 particles weekly	(Woo et al. 2020)

doses were 100 μg in some studies (Song et al. 2019; Li, Tang, et al. 2024), while intra-articular injections were relatively lower, such as 1 mg/kg (approximately 1.4×10^9 vesicles) (Cha et al. 2023). Similar patterns were observed in OA studies, where intra-articular injection doses varied widely but were generally lower than systemic doses (Xu et al. 2025; Li, Lu, et al. 2025).

Thus, there is a need for quantitative reference strategies for EVs administration that can account for various factors associated with different therapeutic EVs production methods. The primary obstacle to EVs quantification standardization is the biological heterogeneity of EVs, which are multicomponent entities containing over 1000 proteins and complex nucleic acid arrays (Fan et al. 2024; Wiklander et al. 2019). Therefore, prioritizing particle number over total protein content can avoid dose bias caused by EVs heterogeneity. On this basis, engineered EVs (such as with targeting peptides) can facilitate concentration quantification based on the amount of engineered proteins displayed on their surface or loaded into their lumen (Lewis et al. 2021; Qu et al. 2018). Pre-clinical studies on EVs for musculoskeletal diseases exhibit significant inconsistencies and ambiguities in dosing strategies, which may affect the reliability and comparability of research results and pose challenges for subsequent clinical translation. Future studies need to comprehensively consider multiple factors such as biodistribution, production processes, treatment objectives and administration routes to address dose optimization and standardization, thereby advancing the practical application of EVs in treating musculoskeletal diseases.

5.2 | EVs in Clinical Studies

In recent years, clinical research has further explored the practical clinical applications of EVs in OA treatment. A triple-blind, randomized, placebo-controlled trial evaluated the safety and efficacy of placental mesenchymal stromal cell-derived extracellular vesicles (PMSCs-EVs) in knee OA patients. However, compared with the placebo, no significant improvement in clinical symptoms or imaging findings was observed with PMSCs-EVs. The authors suggested that the poor efficacy might be attributed to the single injection regimen (Bolandnazar et al. 2024). Two studies focused on umbilical cord Wharton's jelly, a rich source of EVs, growth factors and ECM components (Gupta, Maffulli, Rodriguez, Lee, et al. 2021; Gupta et al. 2021). These studies highlighted the safety of EVs-based therapies in OA but also highlighted challenges such as dosing frequency and variability in EVs sources. More and more basic studies have found that EVs derived from various sources, such as BMSCs (He et al. 2020), hUCMSCs (Li, Yan, et al. 2022) and platelet lysates (Forteza-Genestra et al. 2024), possess the potential to treat musculoskeletal system diseases such as OA and IVDD. Multiple clinical trials using direct intra-articular injection of MSC-EVs to improve OA are also underway (NCT06466850, NCT06431152, NCT05060107). Additionally, one clinical trial combines platelet-rich plasma (PRP) with EVs for intradiscal injection to treat chronic low back pain caused by IVDD (NCT04849429), aiming to integrate the positive effects of PRP growth factors on cartilage growth with the stimulatory activity of MSC-EVs on hyaline cartilage. Existing clinical trials have demonstrated that EVs exhibit the potential to repair cartilage, promote bone regeneration, and modulate immunity in musculoskeletal diseases (Table 5).

5.3 | EVs as Biomarkers for Diagnosis

Components such as protein and miRNA in the EVs differ in health and disease states and can serve as potential diagnostic and prognostic markers for a variety of musculoskeletal diseases (Barile and Vassalli 2017). For example, there are gender differences in miRNA profiles of sEVs in synovial fluid in OA patients, and miRNAs specific to certain female OA patients are correlated with oestrogen response and Toll-like receptor (TLR) signalling, which may explain the prevalence and severity of OA in women the phenomenon of a higher degree (Jiang et al. 2014). There are also relevant clinical trials to determine the role of differentially expressed miRNAs in sEVs in the diagnosis of metabolic bone disease of prematurity (NCT06368154). In addition, synovial fluid-derived sEVs lncRNA-PCGEM1 has some value in distinguishing between early and late OA and circulating ncRNAs show potential to mark different stages of OA (Zhao and Xu 2018). Proteins and ncRNAs in EVs are also important diagnostic indicators. MiR-126-3p in synovial fibroblast-secreted EVs is reduced in OA patients (Zhou et al. 2021). One study showed that PF4 and C1R protein concentrations in EVs differed significantly between sarcopenia patients and healthy individuals and were associated with commonly used sarcopenia diagnostic tests. PF4 and C1R are expected to serve as novel plasma biomarkers for the diagnosis of sarcopenia, helping the early diagnosis of the disease (Aparicio et al. 2024). In plasma sEVs of RA patients, the levels of the let-7 family were significantly higher than those of the healthy control group. The let-7 family can participate in the metabolism, maturation, and activation of immune cells, regulate the immune killing effect of the immune system, and is closely related to the occurrence of a variety of autoimmune diseases (Yang, Wang, et al. 2023). Studies have shown that plasma let-7a-5p can be used as a diagnostic marker for RA, and its expression in PBMCs and synovial fluid macrophages is abnormal, which is also related to the severity of RA (Tang et al. 2022). EVs let-7b Elevated levels in RA synovial fluid can induce arthritis, let-7d-5p increases in serum and $CD8^+$ T cells in RA patients (Liu et al. 2019). In addition, miR-128-3p expression was significantly increased in plasma sEVs in RA patients. Its level is significantly increased in plasma, T cells, and RA-FLS in RA patients, and is involved in the pathogenesis of RA (Peng et al. 2021). MiR-25-3p also significantly increased expression in plasma sEVs in RA patients. It may be involved in regulating potential RNA regulatory pathways of RA by targeting GZMA, and serum sEVs miR-25-3p is associated with early diagnosis of RA (Cheng et al. 2021; Rodríguez-Muguruza et al. 2021).

5.4 | Engineering Modification Strategies of EVs

Some EVs naturally can target specific tissues or cells and can accurately transport the carried biologically active substances to bone tissue or related cells. sEVs derived from MSCs can be highly selectively transferred to the osteosarcoma site through CXCR4/stromal cell-derived factor1 (SDF-1) interaction, achieving targeted delivery (Wei et al. 2022). By engineering modification, targeting can be further enhanced, allowing it to act on the lesion site more accurately. Engineering modification strategies for EVs include surface modification, engineering modification of parental cells, and cargo packaging into EVs.

TABLE 5 | Clinical trials for therapy.

Number	Name	Status	Diseases
NCT06937528	Use of extracellular vesicles (EV) for knee osteoarthrosis	Recruiting	Osteoarthrosis
NCT06466850	Mesenchymal stem cells derived exosomes in osteoarthritis patients	Recruiting	Osteoarthritis
NCT06713902	Extracellular vesicles in fibrin gel for cartilage repair (GelVex)	Recruiting	Joint Disease
NCT06431152	Intra-articular injection of UC-MSC exosome in knee osteoarthritis	Recruiting	Osteoarthritis
NCT05520125	Treatment of patients with bone tissue defects using mesenchymal stem cells enriched by extracellular vesicles	Unknown status	Segmental fracture-bone loss
NCT06463132	Phase 1b clinical trial to evaluate PEP and EUFLEXXA for knee osteoarthritis (KOA)	Not yet recruiting	Knee osteoarthritis
NCT05060107	Intra-articular Injection of MSC-derived Exosomes in Knee Osteoarthritis (ExoOA-1)	Unknown status	Osteoarthritis
NCT06585865	Strength training and resveratrol (STaR)	Not yet recruiting	Sarcopenia
NCT05822856	Gut microbiota: A player in chronic pain in patients with rheumatoid arthritis? (MiSenDol)	Recruiting	Rheumatoid arthritis
NCT04849429	Intra-discal injection of platelet-rich plasma (PRP) enriched with exosomes in chronic low back pain	Completed	Degenerative Disc Disease
NCT05261360	Clinical efficacy of exosome in degenerative meniscal injury (KNEEXO)	Unknown status	Degenerative meniscal injury
NCT06334653	Exercise-regulated organ crosstalk, influence of IL-6 (EVEX)	Completed	Organ crosstalk
NCT06368154	Exosome microRNAs as potential biomarkers of metabolic bone disease of prematurity	Recruiting	Metabolic bone disease of prematurity
NCT05443711	Sarcopenic obesity as a risk of premature aging (SARCOBEAGING)	Active, not recruiting	Sarcopenic obesity
NCT04500769	Training induced muscle exosome release (TIMER)	Active, not recruiting	Metabolic dysfunction
NCT05514639	A prospective pilot study in treating chronic degenerated facet low back pain	Not recruiting	Chronic degenerated facet low back pain
ChiCTR2200063153	Therapeutic effect of human peripheral blood-derived apoptotic extracellular vesicles on temporomandibular joint osteoarthritis	Not recruiting	Temporomandibular joint osteoarthritis
IRCT20210423051054N1	The effect of exosomes in the treatment of knee osteoarthritis	Not recruiting	Knee osteoarthritis
ChiCTR2000031381	Study for exploring the early warning indicators of osteoporosis in healthy people	Recruiting	Osteoporosis

Surface modification is to modify directly on the surface of EVs, connecting ligands to the outer surface of EVs, enhancing EVs targeting capabilities. The main membrane modification methods include lipid insertion, chemical conjugation, enzymatic ligation, affinity binding, and metabolic labelling (Zhang et al. 2024). For example, the complex that binds aptamers to bone marrow stromal cell-derived sEVs can enhance the bone mass of postmenopausal osteoporosis in the mouse model and promote bone healing in the mouse model with femoral fracture (Luo et al. 2019). The addition of CXCR4 on the surface of genetically engineered NIH-3T3 cell-derived sEVs to combine with liposomes carrying antagomir-188 can restore age-related trabecular bone loss in mice and reduce cortical bone porosity (Hu, Li, et al. 2021). Alendronate (Ale) molecules are linked to aside (N3)

to construct Ale-N3, and then alkynes catalysed with copper-catalysed with extracellular vesicles (EVs-DBCO) modified with alkynyl (DBCO). Ale-EVs can be prepared by aside cycloaddition reaction, which can specifically target bone tissue to treat osteoporosis (Smyth et al. 2014). Modified sEVs with bone-targeting peptides for the treatment of osteoporosis, allowing sEVs to specifically transfer siRNA into osteoblasts, silencing the Shn3 gene can enhance osteogenic differentiation, inhibit osteoclast formation and promote angiogenesis (Cui et al. 2022). In the process of constructing novel engineered sEVs modified with targeting peptides and encapsulated by hydrogels, the sEVs are modified through click chemistry to link the targeting peptides. This improves the targeting ability of sEVs in joints and enhances their therapeutic potential for OA (Wan et al. 2023).

Hypoxic environment (0%–10% oxygen tension) can improve the ability and therapeutic effect of MSC secretion of sEVs. For example, hypoxia-pretreated sEVs can enhance cell osteogenesis and angiogenesis potential by upregulating focal adhesion pathways, thyroid hormone synthesis, and VEGF signalling pathways (Gao, Yuan, et al. 2022). One study has demonstrated that hypoxia-apoptotic EVs (H-ApoEVs) isolated from adipose-derived MSCs cultured under hypoxic conditions have a greater impact on cartilage repair than ApoEVs isolated from cells cultured under normoxic conditions (Ding et al. 2024). Hypoxia-pretreated sEVs can enhance cell osteogenesis and angiogenesis through hypoxia-pretreated sEVs can SPRED1/Ras/Erk signalling pathway promote fracture healing (Liu et al. 2020). Hypoxic preconditioning is a novel potential effective method for optimizing the therapeutic effects of MSCs-sEVs. Hypoxia MSCs-sEVs have been used to alleviate intervertebral disc degeneration, promote cartilage repair in OA, and enhance vascularized bone regeneration (Zhou et al. 2022; Zhang, Tian, et al. 2022; Zhuang et al. 2022). In addition, TNF-α pretreatment can increase anti-inflammatory MSC-EVs secretion, enhance its anti-inflammatory, and promote osteogenesis. In bone defect treatment, TNF-α pretreated hASCs-derived sEVs can regulate the proliferation and differentiation of human primary osteoblasts through Wnt signalling (Lu et al. 2017). Compared with unpretreated MSCs, TNF-α pretreatment significantly enhances the vesicle secretion of IPFP-MSCs. The underlying mechanism involves TNF-α pretreatment activating the PI3K/AKT signalling pathway in IPFP-MSCs and upregulating the level of low-density lipoprotein receptor-related protein 1 (LRP1), thereby exerting a chondroprotective effect (Wu, Wu, Xiang et al. 2024). IL-1β pretreated BMSC-derived sEVs can inhibit inflammation and benefit bone regeneration by increasing miRNA-147b expression (Kim et al. 2021). Moreover, chemical signals can alter the MSCs phenotype and sEVs secretion and contents. Kartogenin pretreats hUCMSCs whose origin sEVs can induce cartilage differentiation by promoting miRNA-381-3p secretion (Jing et al. 2020).

EVs-producing cells were genetically engineered by using a plasmid vector encoding a target ligand fused to a transmembrane protein. The chondrocyte-affinity peptide (CAP)-Green Fluorescent Protein (GFP)-Lamp2b plasmid was stably transfected into dendritic cells to obtain CAP-sEVs that specifically bind chondrocytes, delivering miRNA-140 to the deep region of chondrocytes (Liang et al. 2020). CXCR4 Genes were introduced into the NIH-3T3 cell line to obtain sEVs with high expression of CXCR4 for the treatment of age-related osteoporosis (Hu, Li, et al. 2021). Engineered sEVs CAP-Nrf2-Exos were obtained by co-transfecting HEK293T cells with an Nrf2-overexpressing lentiviral vector and the CAP-Lamp2b plasmid. These sEVs can target and deliver Nrf2 to cartilaginous endplate (CEP) cells, protect CEP cells from apoptosis, and improve CEP degeneration in vivo, providing a new and effective strategy for the treatment of IVDD (Lin et al. 2024). However, when intracellular modification, the endoplasmic reticulum protease in the cell may degrade the targeted peptide. For this purpose, the targeted peptide-Lamp2b fusion protein containing glycosylation motifs can be designed to protect the peptide and enhance targeted delivery of EVs (Hung and Leonard 2015).

5.5 | Enhancing EV-Based Therapies: The Role of Biomaterial Delivery Systems

The application of EVs involves the direct injection of aqueous solutions into the circulatory system or body cavities to enhance tissue repair (Liu et al. 2021). However, after direct injection of EVs into the damaged area, EVs fail to exert their full biological functions, primarily because free EVs in aqueous solutions are hardly retained in the target region (Imai et al. 2015). Therefore, damage repair requires biomaterial EVs carriers to ensure that EVs are released according to dose and time, as well as the characteristics of no adverse effects on sEVs internalization and appropriate degradation rate (Yu et al. 2020). Studies have demonstrated that EVs can be combined with biomaterials to improve therapeutic efficacy. Present approaches for endowing biological materials with functionalized EVs involve taking advantage of the electrostatic attractions between negatively charged sEVs and positively charged substances, along with their adhesion to the ECM (Yan et al. 2020). Delivery strategies combined with biomaterials have been widely used in recent research on therapeutic applications of EVs (Table 6).

Owing to the outstanding biocompatibility, highly hydrated three-dimensional network structure, and tunable physicochemical properties, hydrogels serve as ideal platforms for the controlled sustained release and delivery of EVs. In recent years, hydrogels have been employed as the primary EV-loading materials (Yan et al. 2020; Yerneni et al. 2022). Moreover, certain hydrogels inherently possess the potential to regulate cell adhesion, proliferation, and differentiation, and thus may further enhance their therapeutic efficacy via synergistic interactions with MSC-EVs (Wang and Feng 2023). The incorporation of EVs into hydrogels can be achieved through various approaches, including physical encapsulation, chemical conjugation or embedding during hydrogel formation (Chyzy et al. 2020). The passive diffusion of EVs within hydrogels is typically driven by the swelling or hydrolytic degradation of the hydrogels. Meanwhile, stimulus-responsive release of EVs in hydrogels triggered by changes in the biological or physicochemical environment, represents an intelligent drug delivery strategy; such stimuli include temperature, photothermal effect, pH, hydrogen peroxide, enzymes and glucose (Fan, Pi, et al. 2024). Novel hydrogels are continuously being developed for combination with MSC-EVs to collectively advance the process of tissue repair. An injectable hydrogel composed of hydroxyapatite embedded in crosslinked hyaluronic acid and alginate can serve as a carrier for MSC-EVs and can effectively promote osteoblast differentiation (Yang et al. 2020). A

TABLE 6 | Delivery of EVs in combination with biomaterials.

Application	EVs source	Biomaterial	References
ACL repair	Embryonic MSCs	Fibrin sealant	(Wong et al. 2025)
Senescent bone repair	ASCs	Hydrogel	(Qi et al. 2025)
IVDD	Engineered HEK-293T cells	cMN	(Zhang et al. 2024)
IVDD	Engineered NPPC	Hydrogel	(Wang et al. 2025)
IVDD	M2 macrophages	Hydrogel	(Zhang, Du, et al. 2024)
IVDD	Preconditioned BMSCs	Hydrogel	(Jin et al. 2024)
OA	Spirulina platensis	Hydrogel	(Liang et al. 2025)
Bone regeneration	M2 macrophages	Electrospun membrane	(Wen et al. 2025)
Tendon-bone interface healing	Tendon stem/progenitor cells	Scaffold	(He et al. 2024)
IVDD	HEK-293T cells	Hydrogel	(Li, Zhai, et al. 2025)
Osteoporotic fracture repair	Engineered *Escherichia coli*	Hydrogel	(Zhou et al. 2025)
RA	hASCs	cMN	(Bui et al. 2024)
Bone regeneration	BMSCs	Hydrogel	(Li, Si, et al. 2024)
Bone repair and regeneration	BMSCs	Hydrogel	(Zhang et al. 2024)
Bone regeneration	Osteoclasts	Hydrogel	(Faqeer et al. 2023)
Cartilage regeneration	MSCs	Hydrogel	(Li, Yuan, et al. 2024)
Senescent bone defect repair	BMSCs	Glass scaffold	(Qi et al. 2024)
Articular cartilage defect	BMSCs	Hydrogel	(Zhu et al. 2024)
RA	Olfactory ecto-MSCs	Hydrogel	(Rui et al. 2023)
OA	BMSCs	Hydrogel	(Wan et al. 2023)
Periprosthetic osteolysis	hUCMSCs	PLGA scaffold	(Xie et al. 2023)
OA	hUCMSCs	Hydrogel	(Yang et al. 2024)
ONFH	hASCs	Hydrogel	(Ikezaki et al. 2024)
Bone regeneration	hMSCs	Scaffolds	(Al-Sharabi et al. 2024)
Osteoporotic bone defect regeneration	hUCMSCs	Hydrogel	(Deluca et al. 2024)
Bone regeneration	Bone marrow neutrophils	Cell sheets	(Wang, Zhang, et al. 2024)
Sarcopenia	BMSCs	Hydrogel	(Dai et al. 2023)
Cartilage repair	BMSCs	Hydrogel	(Liu, Yu, et al. 2023)
Bone regeneration	BMSCs	Hydrogel	(Lu et al. 2024)
OA	MSCs	Hydrogel	(Pang et al. 2023)
Cartilage repair	BMSCs	Hydrogel	(Li et al. 2023)
Osteoporotic tendon-to-bone healing	ASCs	Hydrogel	(Song et al. 2023)
Glucocorticoid-induced ONFH	Preconditioned BMSCs	Hydrogel	(Chen et al. 2023)
Bone repair	BMSCs	Hydrogel	(Chen, Wang, et al. 2024)
Bone regeneration	BMSCs	Hydrogel	(Kuang et al. 2023)
OA	Engineered BMSCs	Hydrogel	(Ma et al. 2024)
Senescent bone repair	BMSCs	Scaffolds	(Wu et al. 2023)
Bone regeneration	BMSCs	Scaffolds	(Ma et al. 2024)
IVDD	MSCs	Hydrogel	(Peng et al. 2023)

(Continues)

TABLE 6 | (Continued)

Application	EVs source	Biomaterial	References
OA	MSCs	Hydrogel	(Yang et al. 2024)
Bone repair	Apoptotic MSCs	Hydrogel	(Yu et al. 2024)
Skeletal muscle injury	Myoblasts	Silk sericin patches	(Song et al. 2022)
Vascularized bone regeneration	Preconditioned BMSCs	Scaffold	(Zhuang et al. 2022)
Bone repair	BMSCs	Hydrogel	(Yang et al. 2023)
IVDD	ASCs	Hydrogel	(Xing et al. 2021)
Tendon repair	BMSCs	Fibrin glue	(Shi et al. 2019)
OA	Preconditioned hBMSCs	Hydrogel	(Sun et al. 2022)
Critical-size bone defect	hUCMSCs	Scaffold	(Hu et al. 2022)
Bone regeneration	Engineered BMSCs	Hydrogel	(Cheng et al. 2022)
Bone regeneration	hMSCs	Scaffold	(Ma et al. 2022)
Fracture healing	HUVECs	Hydrogel	(Lin et al. 2022)
Vascularized bone regeneration	Preconditioned MSCs	PLGA microspheres	(Gao, Yuan, et al. 2022)
Osteoporosis	iMSCs	Hydrogel	(Tao et al. 2021)
Bone regeneration	hBMSCs	Collagen sponge	(Huang et al. 2020)
Osteochondral defect regeneration	Engineered MSCs	Scaffold	(Chen et al. 2019)
Bone repair	hUCMSCs	Hydrogel combined with scaffold	(Zhang, Xie, et al. 2021)
Bone regeneration	Osteoblasts	Hydrogel	(Man et al. 2022)

Abbreviation: cMN, dissolvable microneedles; PLGA, poly(lactic-co-glycolic acid).

new hydrogel composite composed of coral hydroxyapatite, silk fibroin/ethylene glycol chitosan, and bifunctional polyethylene glycol can promote osteoblasts and chondrocytes infiltration, stimulates angiogenesis and deposition of BMP-2, enhances the healing effect of rat bone defect model (Shen et al. 2020). Hydrogels have also been combined with 3D printing technology to enhance the delivery efficiency of MSC-EVs by constructing more appropriate three-dimensional spatial structures. A scaffold composed of a 3D-printed polylactic acid (PLLA) scaffold loaded with calcium peroxide and combined with hydrogel encapsulating sEVs derived from BMSCs can regulate the inflammatory microenvironment, relieve tissue hypoxia and promote new bone formation. It exhibits excellent bone repair ability in in vivo experiments (Zhang et al. 2024). A study has identified a novel type of skeletal stem cells (SSCs) with high differentiation potential and chondrogenic ability from the infrapatellar fat pad. These SSCs were combined with hydrogel to form bio-ink, and a scaffold was constructed using 3D printing technology. The scaffold has demonstrated excellent osteochondral regenerative ability in a rat model of osteochondral defect, promoting synchronous repair of both cartilage and subchondral bone (Lou et al. 2025). In recent studies, researchers are increasingly inclined to combine engineered stem cells with biomaterial-based loading strategies to enhance therapeutic efficacy. Investigators incorporated both the CAP that targets FGF18 and sEVs into a hydrogel. This action efficiently triggered the activation of the FGF18 gene in osteoarthritic chondrocytes at the genomic level within the living body (Chen, Lu, et al. 2024).

Beyond hydrogels, bioceramics such as β-tricalcium phosphate and hydroxyapatite, have good mechanical strength, biocompatibility, and degradability, and are also commonly used in bone tissue engineering scaffold materials (Wang et al. 2015). The study found that combining MSC-EVs with bioceramics can significantly promote bone regeneration. MSC-EVs bind to tricalcium phosphate (TCP) scaffolds to repair critical-size bone defects by enhancing osteoblast differentiation and angiogenesis (Qi et al. 2016). Moreover, through mineral doping and other methods, the uptake and retention of EVs by bioceramics can be improved, and the bone regeneration effect can be further enhanced (Gandolfi et al. 2020). Synthetic degradable polymer systems such as poly (lactic-co-glycolic acid) (PLGA) exhibit tunable release kinetics and serve as an effective delivery platform for EVs. Studies have shown that ASCs-derived sEVs are fixed on PLGA scaffolds, which can be continuously released in vitro and promote bone regeneration in vivo (Li et al. 2018). In addition, copolymer systems such as PLGA-PEG triblock are also used to control the release of sEVs (Swanson et al. 2020). Through surface modification, sEVs can be effectively adsorbed on the metal stent. For example, MSC predifferentiation-secreted sEVs are adsorbed on 3D-printed titanium stents, which can activate MAPK and PI3K/Akt signalling pathways and promote osteogenic differentiation (Swanson et al. 2020). MSC-EVs are incorporated into a mixed scaffold of silver nanoparticles to induce bone formation and can serve as a promising cell-free therapeutic agent for bone regeneration (Lu et al. 2021).

5.6 | EVs Serve as Nanocarriers for Drug Delivery Systems

The lipid bilayer structure of EVs protects internal drugs from rapid degradation within the body. Additionally, EVs exhibit excellent biocompatibility and are less likely to provoke an immune response. They can naturally fuse with cells or be internalized by them, facilitating effective drug delivery. Furthermore, EVs could traverse various biological barriers, including the blood-brain barrier and the blood-tumour barrier. This capability allows for precise drug delivery to specific target tissues or cells, thereby enhancing the therapeutic efficacy of the drugs (Vader et al. 2016). Many chemotherapeutic drugs such as curcumin, paclitaxel, and doxorubicin have been attempted to be delivered via EVs. Research has found that drugs delivered via EVs tend to have higher efficacy, such as curcumin-loaded sEVs three times more anti-inflammatory activity than direct delivery (Zhuang et al. 2011). Drug loading strategies for EVs include loading drugs in EVs-derived cells and loading drugs after EVs isolation. When small RNAs (such as miRNAs and siRNAs) are used to treat diseases, cells can overexpress small RNAs through transfection and use the endogenous RNA secretion mechanism of cells to allow small RNAs to enter EVs. In addition to small RNAs, other therapeutic drugs such as mRNAs, proteins, and small molecules can also be loaded in this way (Gámbaro et al. 2020). For hydrophobic drugs, EVs cargo can be achieved by direct mixing. Simple incubation of curcumin with EVs can increase the in vitro solubility, stability and in vivo bioavailability of curcumin. For hydrophilic compounds such as RNA, passive loading is difficult due to obstruction of the lipid bilayer membrane. Electroporation is a commonly used loading method, which stimulates the membrane to form pores to achieve loading (Herrmann et al. 2021).

In the treatment of sarcopenia, injection of ant-467a loaded EVs (EVs-467a) and ant-874 loaded EVs (EVs-874) can effectively improve sarcopenia in ovariectomy mice, increase muscle mass and strength, and increase the proportion of fast muscle fibres (Dai et al. 2023). In RA treatment, curcumin-loaded MSC-EVs can accurately deliver curcumin to RA lesion sites, regulate the proliferation and inflammatory response of RA-FLS, significantly reducing anti-apoptotic proteins and Levels of inflammatory mediators (He et al. 2023). Folic acid-conjugated ginger-derived extracellular vesicles (FA-GDEVs) can selectively target M1 macrophages in inflamed joints via folate receptors, significantly alleviate the symptoms of RA (Han et al. 2025). In the rat RA model, icariin-loaded EVs regulate the polarization of macrophages, and transform them from pro-inflammatory M1 to anti-inflammatory M2 type, effectively alleviating the symptoms of arthritis and showing good therapeutic effects (Yan et al. 2024). The CAP-sEVs are generated by conjugating CAP with Lamp-2b protein on the surface of sEVs. They can effectively encapsulate miR-140 and deliver it to chondrocytes, thereby inhibiting the activity of cartilage-degrading proteases and slowing the progression of OA (Liang et al. 2020). Additionally, hybrid nanoparticles formed by the fusion of CAP-sEVs and liposomes, utilizing the same targeting mechanism, can transport the CRISPR/Cas9 plasmid into chondrocytes. This process silences the MMP-13 gene, leading to a reduction in the expression of cartilage matrix degradation proteases and further diminishing the decomposition of the ECM (Liang et al. 2022). After MSCs-derived sEVs loaded with doxorubicin, the interaction between MSC-EVs and CXCR4 and SDF-1 on the surface of osteosarcoma cells can be accurately delivered to the bone tumour site, significantly enhancing the therapeutic effect of osteosarcoma and reduce drug toxicity (Wei et al. 2022). EVs derived from BMSCs can also load miR-206 and transport it to osteosarcoma cells, effectively inhibiting the occurrence and development of osteosarcoma by targeting the transformer 2β (TRA2B) gene (Zhang et al. 2020). Engineered carrier M2 sEVs nanocarriers can transform immunosuppressant leukocytes through the interaction of molecules such as lymphocyte function-related antigen-1 (LFA-1) and integrin late antigen-4 (VLA-4) Interlin-10 (IL-10 pDNA) and adrenocorticosteroid drug betamethasone sodium phosphate are delivered to inflammatory joint sites, effectively inhibiting the progression of RA and have less adverse effects on important organs (Li, Feng, et al. 2022). In addition, drug-loaded sEVs are also used in the treatment of osteonecrosis. For example, sEVs derived from adipose stem cells and overexpressing miR-378 can promote osteogenesis and angiogenesis and inhibit glucocorticoid-induced osteonecrosis development by activating the Sonic Hedgehog signalling pathway (Nan et al. 2021). Recent studies have discovered the potential of plant-derived EVs as drug delivery systems and sources of natural bioactive compounds (López de Las Hazas et al. 2023). FA-GDEVs can target M1 macrophages via folate receptors, effectively alleviate the symptoms of RA in mice, and exhibit good safety (Han et al. 2025).

6 | Prospect

EVs are a group of membrane-enclosed vesicles secreted by different types of cells, with good stability and biocompatibility, low immunogenicity and toxicity, and their surface proteins can reflect the surface proteins of the parental cells. They can reach the target cells and transfer their cargo through the cell uptake. EVs have diverse components, including proteins, lipids, nucleic acids and other biologically active molecules (Miao et al. 2022), especially mRNA, miRNA, rRNA, mtDNA and other nucleic acids, miRNAs are involved in intercellular communication and a variety of biological processes. Due to its unique properties, EVs play a crucial role in the musculoskeletal system and are involved in multiple physiological processes such as muscle cell differentiation, muscle regeneration, joint diseases, bone metabolism, and disc degeneration. However, the safety of EVs in humans is still unclear and many in vivo studies are needed to evaluate their distribution, effects and pharmacokinetics to establish safety assessment systems and criteria for assessing treatment effects (Yang et al. 2024). Intravenous EVs have a short half-life in circulation and are easily degraded or cleared by phagocytic cells, in situ delivery through skeletal muscle can prolong the residence time of EVs in the body but may lead to tissue damage. Therefore, various routes of administration, such as subcutaneous injection, and topical injection, also need to be explored to evaluate their therapeutic effects and potential toxic side effects (Ma et al. 2025). In the future, research can be conducted on the use of EVs in combination with other therapeutic methods, such as combination with drug therapy, gene therapy, or cell therapy to improve therapeutic effects. For example, using MSC-EVs in

combination with chemotherapy drugs may enhance the efficacy of chemotherapy while reducing the side effects of chemotherapy drugs (Wei et al. 2022). As a novel nanotherapeutic carrier, EVs have great potential in the treatment of musculoskeletal disorders. However, how to control their biodistribution and targeting to achieve sufficient therapeutic effects remains a major challenge. How to control their biodistribution and targeting to achieve sufficient therapeutic efficacy remains a major challenge (Selvadoss et al. 2024; Villa et al. 2024). A non-invasive treatment approach involving the delivery of sEVs via inhalation, namely, stem cell-derived sEVs nebulization therapy, has demonstrated notable potential in facilitating heart repair after myocardial infarction (Villa et al. 2024). In light of this, it is plausible to postulate that this therapeutic modality may also possess comparable promise in the treatment of musculoskeletal system disorders.

However, the clinical translation of EVs faces multiple obstacles, with the primary bottleneck being the lack of a standardized regulatory framework, as significant disparities exist in global regulations. The US Food and Drug Administration (FDA) has classified EVs as biological products based on its recent announcements and warnings (FDA 2019, 2020). All such products must submit Investigational New Drug Application (IND) and Biologics License Application (BLA). Recently, the European Medicines Agency (EMA) has tended to categorize EV therapies as Advanced Therapy Medicinal Products (ATMPs) (EMA 2007; Salmikangas et al. 2015), which mandates compliance with Good Manufacturing Practice (GMP), comprehensive characterization of source materials, non-clinical safety studies, and clinical trial authorization through the Advanced Therapy Committee (CAT) process (Stawarska et al. 2024). The Centre for Drug Evaluation of China's National Medical Products Administration (NMPA) has also recently classified EVs under ATMPs (NMPA 2025). Countries such as South Korea and Japan have either implemented or are developing unique regulatory strategies that reflect their local scientific priorities and healthcare needs (Verma and Arora 2025). Ultimately, the establishment of a unified global regulatory framework is crucial for maintaining consistent manufacturing standards, eliminating ambiguities in the clinical application of EVs, and ensuring public health safety (Silva et al. 2021). From a technical perspective, the processes of EV isolation and purification require a high degree of standardization to ensure consistency and reproducibility across different batches for clinical use (Wu, Song, et al. 2024). Different isolation methods exhibit preferences for specific EV subpopulations, leading to variations in the composition of miRNAs and surface proteins (Tian, Gong, et al. 2020; Srinivasan et al. 2019). Additionally, EV products typically contain unknown components, including proteins, cell-free DNA, viruses, and vesicular contaminants from other sources, necessitating extensive efforts to address these issues (Jeppesen et al. 2019). Even variations in storage conditions can affect EV heterogeneity (Gelibter et al. 2022). Furthermore, dose-response and biodistribution studies remain scarce in preclinical research on MSC-EVs (Tieu et al. 2021; Tieu et al. 2020). Although MISEV 2023 specifies that concentration should be measured based on particle content, dosage deviations may occur if exogenous nanoparticles are present as contaminants (Webber and Clayton 2013). Currently, there are no standardized guidelines for the practical measurement of EV dosage in preclinical studies (Roefs et al. 2020; Yang et al. 2019). In addition, existing production technologies often fail to produce EVs in commercially viable quantities while maintaining consistent quality (Ahn et al. 2022; Singh et al. 2021). Technical challenges and GMP compliance requirements mean that many academic institutions and early-stage companies lack qualified and comprehensive infrastructure to meet these standards (Ahn et al. 2022). Given the ongoing scientific and technological advancements in this field, regulatory frameworks must be adjusted accordingly in a timely manner to ensure that regulatory policies are both comprehensive and flexible. Beyond government regulations, strict adherence to the Minimum Information for Studies of Extracellular Vesicles (MISEV2018, MISEV2023) issued by the International Society for Extracellular Vesicles (ISEV) (Théry et al. 2018; Welsh et al. 2024), as well as the adoption of existing quantitative characterization methods to ensure batch reproducibility (Witwer et al. 2019; Gimona et al. 2021), will significantly advance standardization in this field.

Future studies should continue to investigate the signalling pathways involved in EVs, including Wnt/β-catenin, PI3K/Akt and MAPK, as well as the mechanisms by which these pathways regulate musculoskeletal cell function, metabolism and differentiation through EVs. For instance, researchers could explore how myostatin's regulatory effects on bone metabolism are mediated by its influence on Wnt inhibitors, and whether EVs exert their therapeutic effects by modulating these signalling pathways (Hassan et al. 2012). Additionally, the mechanisms of action of EV components, such as proteins, nucleic acids, and lipids, warrant further investigation. This includes examining the role of RNA-binding proteins in the packaging and release of miRNAs, and how lipid components affect the membrane structure and function of EVs. For example, the recognition and binding of specific RNA sequences by RNA-binding proteins such as hnRNPA2B1 and SYNCRIP could be studied to understand their role in facilitating miRNA entry into EVs and their subsequent impact on recipient cells (Villarroya-Beltri et al. 2013). Researchers should also aim to identify and characterize new subpopulations of EVs to elucidate the specific expression patterns and functions of these subpopulations in musculoskeletal system diseases. Furthermore, in-depth functional studies of these discovered EV subpopulations should be conducted to clarify their specific roles in muscle cell differentiation, bone metabolism, cartilage repair, and other related processes.

7 | Conclusion

EVs play a crucial role in the musculoskeletal system. They are involved in the processes of myogenesis and muscle regeneration, regulate bone metabolism and also play a key role in inter-organ communication within the musculoskeletal system. Moreover, they are closely related to the pathogenesis of various musculoskeletal diseases. As a novel biological therapeutic vector, EVs have numerous advantages, such as excellent biocompatibility and good targeting ability. These advantages enable them to exhibit great potential in the treatment of musculoskeletal system diseases. With the continuous deepening of research on EVs, their application prospects in the diagnosis, treatment, and prevention of musculoskeletal system diseases will become more and more promising. However, EVs still face a series of challenges during the clinical application process. These include but are not limited

to, technical difficulties in the isolation and purification of EVs, as well as issues regarding the selection and adaptation of biomaterial carriers. We firmly believe that in the future research process, through the collaborative efforts of multiple disciplines such as medical-engineering intersection, innovative breakthroughs in separation techniques, and the continuous conduct of relevant clinical research, EVs are expected to bring significant breakthroughs in the treatment of musculoskeletal system diseases, and thus make more outstanding contributions to human health.

Author Contributions

Peng-jie Fu: conceptualization, writing–review and editing, writing–original draft, visualization, data curation. **Yan Luo**: writing–original draft, writing–review and editing, conceptualization. **Sheng-yuan Zheng**: conceptualization, writing–original draft, writing–review and editing. **Zhe-ru Ma**: methodology, visualization, software, data curation. **Wen-feng Xiao**: writing–review and editing, funding acquisition, project administration. **Hui Li**: writing–review and editing, conceptualization, methodology, supervision. **Yu-sheng Li**: visualization, funding acquisition, writing–review and editing, resources

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Conflicts of Interest

All authors declare that they have no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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