The future of osteoarthritis treatment: exploring the potential of exosomes from adipose tissue-derived stem cells

a scoping review

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Aims

This review examines the therapeutic potential of adipose tissue-derived stem cell (ADSC) exosomes for osteoarthritis (OA), focusing on their anti-inflammator and cartilage regeneration properties.

Methods

A PubMed search (2012 to 2024) was conducted using keywords related to ADSCs, exosomes, and OA. Inclusion criteria focused on studies investigating ADSCs and ADSC-exosomes characteristics, animal OA models, and human OA patients. Exclusion criteria included case reports, case series, and conference abstracts.

Results

ADSCs are an abundant stem cell source with low immunogenicity. ADSC-exosomes exhibit anti-inflammator effects and promote cartilage regeneration via miRNA transport. Preclinical studies demonstrate inhibition of synovial thickening, cartilage destruction, and macrophage activity. Clinical trials suggest that intra-articular ADSCs are safe and effectiv , with higher doses improving pain relief and cartilage regeneration.

Conclusion

ADSC-exosomes are a promising cell-free therapy for OA, with reduced immune rejection and tumorigenicity compared to ADSC transplantation. Standardizing exosome isolation and production remains a challenge. Further research is needed to confirm long-term safety and efficac in humans.

Article focus

- To examine the therapeutic potential of adipose tissue-derived stem cell (ADSC) exosomes for osteoarthritis (OA) treatment, focusing on their anti-inflammator and cartilage regeneration properties.
- To explore the underlying mechanisms by which ADSC-derived exosomes exert therapeutic effects in osteoarthritis, particularly through microRNA-mediated pathways.
- To evaluate the clinical evidence for ADSC therapy in OA patients and assess the translational potential of ADSC-exosome-based cell-free therapies.

Key messages

- ADSC-derived exosomes represent a promising cell-free therapeutic approach for OA that may overcome the limitations of direct cell transplantation, including reduced immune rejection and tumorigenicity risks.
- Exosomal microRNAs serve as key therapeutic cargo that modulate critical pathways in OA pathogenesis, including inflammation suppression, chondrocyte proliferation enhancement, and extracellular matrix homeostasis.
- Clinical trials demonstrate that intra-articular ADSC injections are safe and effectiv for pain relief and functional improvement in knee OA, with higher doses showing superior therapeutic outcomes.

Strengths and limitations

- This is a comprehensive narrative synthesis spanning both preclinical and clinical evidence from 2012 to 2024, providing integrated analysis of ADSC therapy progression from bench to bedside, as well as a systematic evaluation of both direct ADSC transplantation and emerging exosome-based approaches.
- Detailed mechanistic insights into exosomal microRNA pathways and their therapeutic targets, offering valuable translational guidance for future clinical development.
- Absence of formal systematic review methodology with protocol registration and quality assessment tools, potentially affecting the comprehensiveness and objectivity of study selection and evaluation.
- Limited clinical evidence specifically for ADSC-exosome therapy, with most therapeutic data derived from preclinical animal models that may not fully translate to human applications.

Introduction

Osteoarthritis (OA) is a painful and complex degenerative joint disease that affects millions of ageing individuals and causes prolonged pain and altered joint function worldwide.[1] The incidence of OA is correlated with the ageing population and rising prevalence of obesity.[2] The entire joint element is impacted in this degenerative joint condition, resulting in damage to articular cartilage, bone, synovium, and other soft-tissues. The sequence of joint tissue involvement may be influenced by primary causative factors.[3] Several crucial factors contribute to OA pathogenesis, including biomechanical factors, proinflammator mediators, and proteases.[4] Recent studies have highlighted that OA pathogenesis involves not only cartilage degradation, but also subchondral bone remodelling, chronic low-grade synovial inflammation, and neuroinflammation, all of which contribute to joint destruction and pain chronicity.[3,5] These pathological processes are driven by molecular and cellular mechanisms, including matrix metalloproteinases (MMPs) and ADAMTS-mediated extracellular matrix degradation, osteoclast activation, and ectopic ossification in subchondral bone, synovial macrophage activation and pro-inflammator cytokine secretion (e.g. IL-1β, IL-6, TNF-α), as well as neoinnervation, angiogenesis, and central sensitization, which exacerbate chronic pain.[5] Currently, there are no approved disease-modifying OA drugs, and conservative therapy and pain-relieving drugs provide only temporary relief of osteoarthritic symptoms and delay the need for surgical management.[6,7] Surgical treatment of OA is dominated by total joint replacement (TJR), which is highly efficacious in patients with advanced OA and results in greater pain relief and functional improvement.[8] However, the incidence of serious adverse events associated with TKA is higher than that associated with non-surgical treatment. The two most common serious adverse events are deep venous thrombosis and stiffness, which require brisement force.[9,10] Additionally, prostheses with a limited lifetime will inevitably affect a patient's quality of life. Therefore, further research is required to explore other innovative therapies.

Many types of MSC-based therapies for tissue regeneration and anti-inflammation are currently undergoing clinical trials, among which adipose tissue-derived stem cells (ADSCs) are used in the treatment of articular cartilage injury, owing to their ease of harvest and high potential for cartilaginous production capacity.[11,12] For OA treatment, numerous types of RNA, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) may be delivered from MSCs to OA cells. However, transplantation of MSCs carries the potential risks of immune rejection and disease transmission.[13]

Exosomes are a subset of extracellular vesicles. They play an important role in cellular communication by transferring biological cargo such as functional proteins, metabolites, and nucleic acids to recipient cells.[14] The primary clinical applications of exosomes include their use as biomarkers, cell-free therapeutics, drug delivery carriers, fundamental analysis of exosome kinetics, and cancer vaccines. Exosomes function as biomarkers that can aid in diagnosis, prognosis, disease progression, and chemoresistance assessment.[15]

Exosomes in OA synovial fluid have also been analyzed by numerous research groups: healthy articular chondrocytes treated with OA-derived exosomes have exhibited downregulated expression of anabolic genes and upregulated expression of catabolic- and inflammation-related genes.[16,17]

Exosomes derived from different types of MSCs have the potential to be a new approach for treating OA because of the ability of these multipotent cells to proliferate and differentiat .[18] Previous studies have demonstrated the efficac of ADSC-derived exosomes against tissue damage, suggesting that ADSC-derived exosomes may be a promising treatment for OA.[19,20] In this review, we outline the therapeutic potential and underlying mechanisms of ADSC-derived exosomes in OA. Given the persistent limitations of conventional OA therapies, this review focuses on the novel therapeutic potential of ADSCs and their exosomes, highlighting recent advances and future directions.

Methods

A comprehensive narrative synthesis was undertaken to explore the therapeutic potential of ADSCs and their exosomes in OA. To identify relevant studies, we conducted an extensive PubMed search using both Medical Subject Headings and free-text terms encompassing ADSCs ("adipose derived stem cell", "adipose mesenchymal stem cell", "ADSC"), exosomes ("exosome", "extracellular vesicle"), and osteoarthritis ("osteoarthritis", "OA", "degenerative joint disease"). This search spanned January 2012—when exosome research in regenerative medicine began to flourish—through December 2024, and was restricted to English-language publications involving human or animal models.

Studies were selected on the basis of clinical relevance and scientific rigour rather than a rigid checklist. We focused on preclinical animal investigations, in vitro mechanistic studies using chondrocytes or related cell types, and clinical trials in OA patients that offered insights into ADSC or ADSC-exosome characteristics, mechanisms of action, therapeutic outcomes, or safety profiles. Conference abstracts, editorials, commentaries, and studies centred solely on non-ADSC mesenchymal stem cells were excluded, although we hand-searched reference lists of review articles and key papers to capture any additional relevant reports.

Two investigators (PHH, TCL) independently screened titles and abstracts for potential inclusion. Full texts of promising articles were then reviewed in depth, and decisions to include or exclude studies were resolved by consensus; a third reviewer (SYL) was consulted if disagreements persisted. Although we did not follow a formal protocol registration process, this flexible approach allowed us to adapt our inclusion criteria as emerging themes guided our review.

Data extraction embraced a structured yet adaptable framework. For ADSC studies, we noted study design, source of adipose tissue (for example, subcutaneous fat or infrapatellar fat pad), cell preparation methods, dosing, delivery routes, outcome measures (such as pain assessment, functional scores, and imaging findings), efficac results, and safety observations. For exosome studies, we recorded experimental models, exosome isolation and purification techniques, key bioactive cargo (including miRNAs and proteins), mechanistic findings, therapeutic effects, and any reported adverse events.

Rather than performing formal quality assessments, we leveraged our clinical expertise in regenerative medicine to interpret study strengths, limitations, and translational relevance. Findings were woven into a cohesive narrative organized around three themes: 1) the therapeutic characteristics and applications of ADSCs in OA, 2) the emerging mechanisms and potential of ADSC-derived exosomes, and 3) clinical outcomes and safety considerations. This narrative format highlights patterns, emerging insights, and knowledge gaps, providing a clear, expert-driven synthesis of ADSC and exosome research in OA.

Results

Study selection

A total of 241 records were identified through database searching, of which 12 duplicates were removed, leaving 229 articles for title and abstract screening. Overall, 76 full-text articles were assessed for eligibility and, following exclusions, 26 studies met the inclusion criteria and were included in the final analysis; the study selection process is depicted in Figure 1.

Among the included studies, ten clinical investigations evaluated autologous or allogenic ADSC therapy in patients with Kellgren–Lawrence grade II to IV knee OA.[21] Seven of these were randomized controlled trials, with the remaining three comprising cohort or single-arm designs. All interventions used intra-articular injection of ADSCs—predominantly autologous cells harvested from subcutaneous adipose tissue, although a minority employed allogenic sources—with follow-up durations ranging from six to 24 months. Sample sizes ranged from 11 to 125 participants (mean age 52 to 68 years). Across these trials, consistent improvements in pain scores, functional assessments, and imaging parameters were reported (Table I).

A total of 16 preclinical studies investigated ADSC-derived exosomes. Ten combined in vivo and in vitro experiments, fiv were exclusively in vitro, and one was solely in vivo. Rodent OA models—induced by destabilization of the medial meniscus, anterior cruciate ligament transection, or monosodium iodoacetate—were used for in vivo work, with exosomes delivered via intra-articular injection; in vitro studies typically stimulated chondrocytes with interleukin-1β or hydrogen peroxide to assess inflammation, extracellular matrix production, and cell proliferation. Exosomes were sourced from ADSCs isolated from subcutaneous fat, infrapatellar fat pad, or groin adipose tissue. These studies uniformly demonstrated that ADSC exosomes attenuate inflammation, enhance cartilage matrix synthesis, and support chondrocyte viability (Table II).

ADSCs and their therapeutic application in OA

ADSCs are a type of mesenchymal stem cell with proven self-renewal ability and multilineage differentiation potential. They are used in the treatment of articular cartilage injuries because of their ease of harvesting and high capacity for cartilage production. In vitro studies have shown that these cells contain CD73, CD90, CD105, and CD106 markers that are necessary for their differentiation into cartilage.[48,49]

The two common sources of ADSCs are the infrapatellar fat pad (IPFP) and subcutaneous fat.[50] The IPFP is located in the extrasynovial area of the anterior compartment of the knee joint, and is often routinely removed and disposed of as surgical waste during arthroscopic or open knee surgery. In contrast, subcutaneous fat, which can easily be harvested via liposuction, offers a more accessible and abundant source. Compared with subcutaneous fat, IPFP has more blood vessels and nerves, and is more similar to visceral fat.[41] Wang et al[51] found that despite being derived from adipose tissue, IPFP-derived stem cells and subcutaneous fat-derived stem cells exhibit significant divergence in both proliferation and differentiation potential. Stem cells from subcutaneous fat exhibit significantly higher proliferation and adipogenic capacity, whereas stem cells from IPFP display significantly higher chondrogenic potential. The distinctive properties of ADSCs, including their accessibility, proliferative and multilineage differentiation capacities, and the secretion of paracrine factors and exosomes underscore their potential in OA treatment, which has been increasingly supported by recent clinical trials.

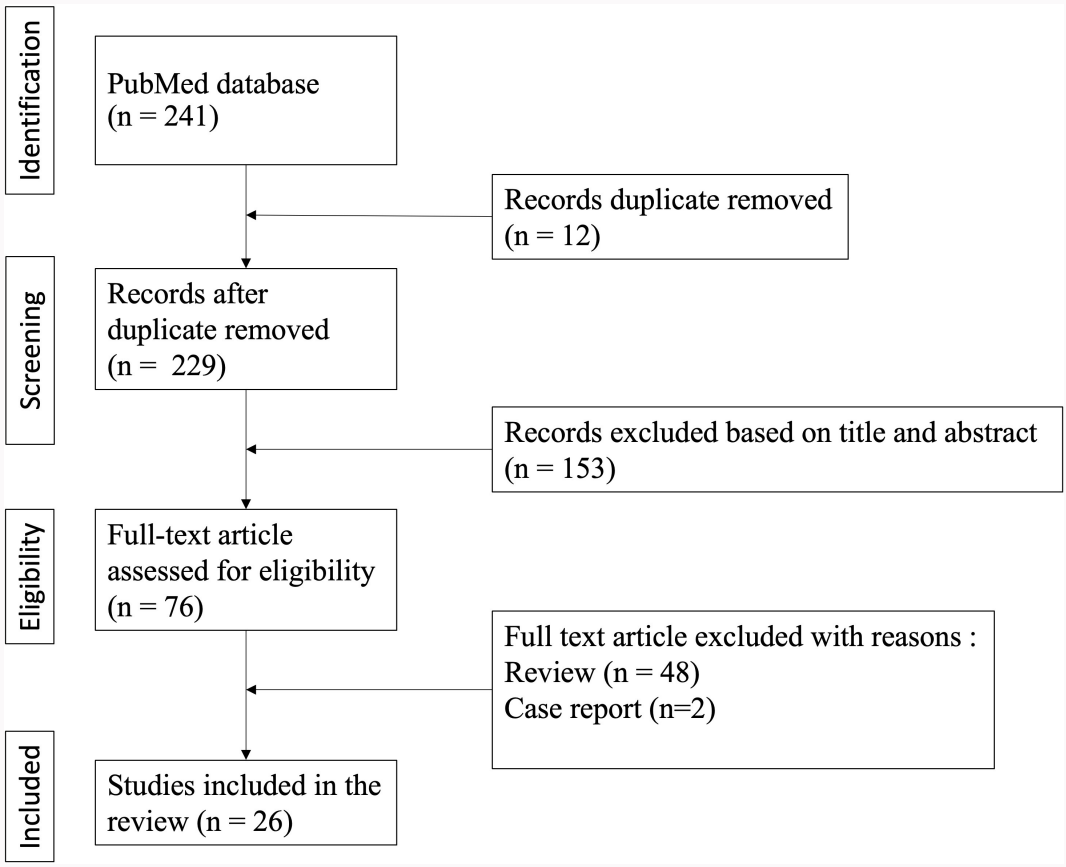

Fig. 1
PRISMA flowchart showing the study selection process for the narrative review of adipose-derived stem cells and their exosomes in osteoarthritis treatment. The flowchart illustrates the systematic identification, screening, and inclusion of studies from the initial PubMed database search through to the final selection of 26 studies for analysis.

Several preclinical animal studies have investigated the safety and effects of ADSCs in OA mouse models. In 2012, ter Huurne et al[52] demonstrated that in a collagenase-induced early phase OA model, a single injection of 2×10^4 autologous ADSCs into the knee joints of mice inhibited synovial lining thickening, enthesophyte formation associated with ligaments, and cartilage destruction by suppressing macrophage activity, with the treatment demonstrating a favourable safety profile. The authors also showed that ADSCs expressed high levels of mRNA for tissue inhibitors of metalloproteinases (TIMPs), which may partly block the induction of IL-1/MMP-mediated ligament destruction, particularly TIMPs 1 and 3, in vitro. In another study, Mei et al[53] reported the efficac of allogenic ADSCs in an ACLT-induced OA rat model. Compared to the control group, intra-articular injection of 1×10^6 allogenic ADSCs attenuated ACLT-induced cartilage degeneration without any local adverse reactions in the treatment group. In addition, they investigated the paracrine effect of ADSCs on chondrocytes, and the results indicated that ADSC-secreting cytokines mitigated the IL-1β-induced upregulation of MMP-3 and MMP-13 in chondrocytes. Additionally, co-culture with ADSCs downregulated the pro-inflammator cytokines TNF-α and IL-6 but upregulated the anti-inflammator cytokine IL-10 in IL-1ß-stimulated chondrocytes. In addition to their intra-articular application in OA models, ADSCs have also demonstrated regenerative potential in other orthopaedic contexts. Notably, Fu et al[54] fabricated a biomimetic vascularised bone-periosteum construct by combining endothelial-differentiated ADSCs with a periosteum-mimetic cell sheet, both derived from ADSCs, and applied this construct in a rabbit spinal fusion model. The results showed significant enhancement of angiogenesis and new bone formation at the fusion site, as confirmed by imaging, histological, and biomechanical analyses. These findings further highlight the osteogenic and angiogenic capacities of ADSCs, and suggest broader applications for ADSC-based therapies in bone tissue engineering and repair.

Related clinical trials reported that intra-articular injection of ADSCs appears to be a safe and effectiv therapy for knee OA and may prevent disease progression.[25] Jo et al[22] conducted a phase I/II trial on 18 knee OA patients, administering autologous ADSCs at low (1.0×10^7), medium (5.0×10^7), and high (1.0×10^8) doses. After six months, the results indicated that intra-articular injection of ADSCs into osteoarthritic knees was not associated with apparent adverse events, and only the high-dose group showed significant improvement in WOMAC scores and pain relief. MRI and arthroscopy also confirmed hyaline cartilage regeneration in the high-dose group, while the low- and medium-dose groups did not show any improvement. In a phase I single-arm trial, Pers et al[23] investigated the safety and efficac of intra-articular ADSC injections in 18 knee OA patients using a dose-escalation protocol (low: 2×10^6, medium: 10×10^6, high:

Table I. Characteristics of included clinical studies investigating adipose tissue-derived stem cells (ADSCs) in osteoarthritis (OA) treatment. All reported knee OA, and all used intra-articular injections.

Study	Type of study	Control group patients	Treatment group patients	Mean age, yrs	OA K-L grade	ADSC source	Follow-up, mths
Jo et al (2014)[22]	Prospective cohort study	0	18	61.8	III - IV	Subcutaneous fat	6
Pers et al (2016)[23]	Prospective single arm clinical trial	0	18	64.6	III - IV	Subcutaneous fat	6
Song et al (2018)[24]	Prospective double blinded RCT	0	18	54.8	II - III	Subcutaneous fat	24
Freitag et al (2019)[25]	Prospective non-blinded RCT	10	20	53.6	II - III	Subcutaneous fat	12
Lee et al (2019)[26]	Prospective double blinded RCT	12	12	62.7	II - IV	Subcutaneous fat	6
Lu et al (2019)[27]	Prospective double blinded RCT	26	26	57.3	II - III	Subcutaneous fat	12
Chen et al (2021)[28]	Prospective single blind RCT	8	49	67.6	I - III	Allogenic ADSCs	24
Sadri et al (2023)[29]	Prospective triple blinded RCT	20	20	52.8 (SD 7.5)	II - III	Allogenic ADMSC	12
Kim et al (2023)[30]	Prospective double blinded RCT	127	125	63.75 (SD 7.1)	III	Subcutaneous fat	6
Chen et al (2024)[31]	Non-randomized cohort study	0	11	65.3	II - IV	Allogenic ADSCs	12

K-L, Kellgren-Lawrence; RCT, randomized controlled trial.

50 × 10^6). After six months, all groups showed pain reduction and WOMAC improvement without adverse events, but only the low-dose group achieved statistical significanc . This inverse dose effect may be due to higher baseline inflammation in the low-dose group, suggesting ADSCs exert stronger immunoregulatory effects in an inflammator milieu. Song et al[24] conducted a prospective double-blind randomized controlled trial (RCT), first confirming the safety of ADSCs in BALB/c-nu nude mice. After confirming no-observed-effect level for toxicity, no tumorigenicity, or death, 18 knee OA patients were then divided into three groups (low: 1 × 10^7, medium: 2 × 10^7, high: 3 × 10^7) and received three intra-articular ADSC injections. Over 96 weeks, no apparent adverse events (AEs) or serious adverse events (SAEs) were reported. The high-dose group showed the greatest pain relief and functional improvement, along with increased cartilage volume, particularly at 48 weeks.

A RCT on 30 knee OA patients compared controlled, single-injection, and double-injection groups (100 × 10^6 autologous ADSCs). Both treatment groups showed similar pain and functional improvement with good tolerability, although moderate AEs slightly increased after the second injection in the double-injection group. MRI Osteoarthritis Knee Scores (MOAKS)[55] revealed that only the double-injection group exhibited cartilage loss improvement and achieved a trend of greater disease stabilization. The observed stabilization, rather than cartilage regrowth, suggests that ADSCs act via paracrine and supportive pathways rather than direct chondrocyte differentiation.[25] In a prospective double-blind randomized controlled trial, Lee et al[26] evaluated the effects of a single intra-articular injection of autologous ADSCs versus saline in patients with knee OA. At six months, the ADSC-treated group exhibited significant clinical and functional improvement, with a 55% reduction in WOMAC score and no adverse events. In addition, MRI findings indicated that cartilage defects remained stable in the ADSCs group, whereas the control group showed progression of cartilage deterioration. Lu et al[27] conducted a double-blind RCT to assess the efficac and safety of intra-articular injections of Re-Join (human adipose-derived mesenchymal progenitor cells) versus hyaluronic acid (HA) in 52 knee OA patients. After 12 months of follow-up, the Re-Join group had a significantly higher proportion of patients achieving 50% and 70% Western Ontario and McMaster Universities osteoarthritis index (WOMAC)[56] improvement compared to the HA group. Meanwhile, MRI also showed a notably greater increase in articular cartilage volume in the Re-Join group. In another double-blind RCT, Kim et al[30] enrolled 261 patients with K-L grade 3 knee OA, who received a single injection of 1 × 10^8 autologous ADSCs or a placebo. At six months, the ADSCs group showed significantly greater improvements in VAS, WOMAC, KOOS, and IKDC scores than controls, with similar adverse event rates, confirming safety. However, no significant differences were found in cartilage status or radiological measures.

Chen et al[28] performed a single-blind RCT to assess intra-articular injection of allogenic ADSCs (ELIXCYTE) in knee OA patients. Among 57 patients, those receiving ELIXCYTE (16 × 10^6, 32 × 10^6, or 64 × 10^6 cells) had earlier and longer-lasting pain relief than the HA group, with superior WOMAC,

Table II. Characteristics of included preclinical studies investigating adipose tissue-derived stem cell (ADSC)-derived exosomes in osteoarthritis (OA) models.

Study	Model	OA induction	ADSC origin	Delivery method	In vitro/in vivo
Zhao et al (2023)[32]	Rats and mice	Rats (DMM+ ACLT), mice (DMM) IL-1β induced chondrocyte	Human subcutaneous fat	In vivo: intra-articular injections In vitro: co-incubate ADSC-exosomes with the IL-1β-treated chondrocytes	Both in vivo and in vitro
Wu et al (2019)[33]	Mice	DMM-induced OA model, IL-1β induced chondrocyte	Human IPFP	In vivo: intra-articular injections In vitro: co-incubate ADSC-exosomes with the IL-1β-treated chondrocytes	Both in vivo and in vitro
Li et al (2023)[34]	Rats	MIA-induced OA model, IL-1β induced chondrocyte	Human subcutaneous thigh adipose tissues	In vivo: intra-articular injections In vitro: co-incubate ADSC-exosomes with the IL-1β-treated chondrocytes	Both in vivo and in vitro
Li et al (2023)[35]	Mouse chondrocyte	IL-1β-treated chondrocytes arthritis model	Mouse adipose MSC	Co-incubate ADSC-exosomes with the IL-1β-treated chondrocytes	In vitro
Meng et al (2023)[36]	Rats	Iodoacetate induced OA model, IL-1β induced chondrocyte	Male Sprague-Dawley rats	In vivo: intra-articular injections In vitro: co-incubate ADSC-exosomes with the IL-1β-treated chondrocytes	Both in vivo and in vitro
Zhao et al (2020)[37]	Human articular chondrocyte	H2O2 induced chondrocyte	Liposuction surgery of a healthy donor	Co-incubate ADSC-exosomes with the H2O2-treated chondrocytes	In vitro
Chang et al (2023)[38]	Rats and human articular chondrocyte	ACLT-induced OA model, IL-1β induced chondrocyte	Human subcutaneous adipose tissue	In vivo: intra-articular injections In vitro: co-incubate ADSC-exosomes with the IL-1β-treated chondrocytes	Both in vivo and in vitro
Li et al (2022)[39]	Mice	IL-1β-induced ATDC5 cells	Mouse ASCs	Co-incubate ADSC-exosomes with the IL-1β-induced ATDC5 cells	In vitro
Zhao et al (2023)[40]	Mice	LSI-induced OA models	White adipose tissue from mouse groin	Tail vein injection	In vivo
Yin et al (2023)[41]	Mice	DMM-induced OA model, IL-1β induced chondrocyte	Mouse IPFP and subcutaneous ADSCs	In vivo: intra-articular injections In vitro: co-incubate ADSC-exosomes with the IL-1β-treated chondrocytes	Both in vivo and in vitro
Meng et al (2023)[42]	Rats	ACLT induced OA model, IL-1β induced chondrocyte	Rat ADSCs	In vivo: intra-articular injections In vitro: co-incubate ADSC-exosomes with the IL-1β-treated chondrocytes	Both in vivo and in vitro
Shao et al (2021)[43]	White rabbits	Articular cartilage injury model	Rabbit IPFP	In vivo: intra-articular injections In vitro: co-incubate IPFP-MSC exosome with chondrocytes showing good rates of growth from passage 3	Both in vivo and in vitro
Wang et al (2022)[44]	Rats and human articular chondrocytes	DMM-induced OA model IL-1β induced chondrocyte	Human subcutaneous adipose tissues	In vivo: intra-articular injections	Both in vivo and in vitro

(*Continued*)

(*Continued*)

Study	Model	OA induction	ADSC origin	Delivery method	In vitro/in vivo
				In vitro: co-incubate ADSC-exosomes with the IL-1β-treated chondrocytes	
Sevimli et al (2023)[45]	Chondrocyte	N/A	hSF-MSCs hAD-MSCs	Co-culture chondrocytes with hADMSC exosomes or hSFMSC exosomes	In vitro
Xie et al (2022)[46]	Human ADSCs	N/A	human subcutaneous adipose tissue	Co-culture third-passage ADSCs with ADSCs exosomes	In vitro
Wu et al (2024)[47]	Mice and human chondrocyte	DMM-induced OA model H2O2 induced chondrocyte	IPFP	In vivo: intra-articular injections In vitro: co-incubate IPFP-MSC exosome with the H2O2-induced chondrocytes	Both in vivo and in vitro

ACLT, anterior cruciate ligament transection; DMM, destabilization of the medial meniscus; hAD-MSCs, human adipose derived mesenchymal stem cells; H2O2, hydrogen peroxide; hSF-MSCs, human synovial fluid mesenchymal stem cells; IPFP, infrapatellar fat pad; LSI, lumbar spinal instability; MIA, monosodium iodoacetate; MSC, mesenchymal stem cell; N/A, not available.

visual analogue scale (VAS), and KSCRS scores.[57] However, MRI showed no cartilage regeneration or structural modifications in this study. Sadri et al[29] compared the effect of intra-articular injection of 100×10^6 allogenic ADSCs with placebo (normal saline) in 40 patients with knee OA. They concluded that the intra-articular injection of ADSCs in patients with knee OA was safe. Laboratory data, MRI findings, and clinical examination of patients at different timepoints showed notable articular cartilage regeneration and significant improvement. In a non-randomized cohort study, Chen et al[31] assess the safety and efficac of allogenic ADSCs (GXCPC1) in 11 patients with knee OA. After one year of follow-up, GXCPC1 treatment was found to be safe and well-tolerated without treatment-related severe adverse events. Both low-dose (6.7×10^6) and high-dose (4×10^7) groups showed improved pain and knee function, with greater VAS and WOMAC score improvements in the high-dose group. Overall, both autologous and allogenic ADSCs have demonstrated significant therapeutic potential for knee OA, showing pain relief, functional improvement, and, in some studies, structural benefits. These findings suggest that intra-articular ADSCs injection is a promising and well-tolerated approach for OA management (Table III).

Nevertheless, the promising methods using ADSCs presently are cell viability constraints and the potential risk of tumours associated with the application of ADSCs. Some studies suggested that ADSCs may foster tumour cell proliferation and invasion by secreting pro-inflammator cytokines such as IL-6 and IL-8, as well as matrix metalloproteinases (MMP-2, MMP-9). Additionally, ADSCs may interact with the tumour microenvironment, they can remotely home to the cancer site, mediate tumour expansion, epithelial-to-mesenchymal transition, and interact with cancer stem cells and immunomodulatory cells, potentially creating an immunosuppressive environment. Further, ADSCs also contribute to the formation of cancer-associated fibroblasts and cancer-associated adipocytes, thereby supporting tumour progression.[58] Consequently, researchers are increasingly focusing on exosomes derived from ADSCs as a novel cell-free therapeutic approach.

Exosomes

Numerous studies have shown that the efficac of mesenchymal stem cell (MSC) therapy depends on the differentiation potential of MSCs, or rather, it depends on the paracrine effect of MSCs, particularly the secretion of exosomes.[59]

According to MISEV 2023, the term 'exosome' represents a subtype of small extracellular vesicles from internal compartments of the cell that are released via the multivesicular body, thereby confirming their origin from the endosomal system.[60]

Exosomes are membranous vesicles ranging from 40 to 150 nm in diameter that are formed by multivesicular bodies carrying intraluminal vesicles that fuse with the cell membrane.[61] These vesicles have been reported to have pivotal functions in various biological processes such as angiogenesis, apoptosis, antigen presentation, intercellular communication, and inflammation. Consequently, exosomes have significant effects on the pathophysiology of various diseases. Among them, the ability to promote chondrocyte regeneration, inhibit apoptosis, and improve anti-inflammation and the extracellular matrix (ECM) balance significantly contributes to OA treatment.[62] Figure 2 summarizes the principal mechanisms through which ADSC-derived exosomes exert therapeutic effects in osteoarthritis.

Exosomes exhibit properties that vary according to the origin, type, and state of the cell from which they are derived. For instance, exosomes derived from bone marrow MSCs and adipose-derived MSCs have been reported to exhibit significant differences in RNA composition.[11]

MSC-exosomes contain biomarkers such as CD63, CD81, CD9, ALIX, ANXA5, LAMP1, HSP70, and TSG101.[50] Potential biomarkers of ADSC-exosomes include CD109, CD166, HSPA4, TRAP1, RAB2A, RAB11B, and RAB14.[63] The biofunction of exosomes depends on their internal composition, including a variety of miRNA, proteins, cytokines, lipids, and non-coding RNA.[64] Among these cargo types, miRNAs have garnered significant attention due to their ability to post-transcriptionally regulate gene expression by targeting specific mRNAs. Through this mechanism, miRNAs influenc

Table III. Summary of clinical outcomes and safety profiles of adipose tissue-derived stem cell (ADSC) therapy in osteoarthritis.

Study	Study group and doses	Outcome measures	Result	AEs
Jo et al (2014)[22]	Low-dose group, 1×10^7cells of ADMSCs Medium-dose group, 5×10^7 cells of ADMSCs High-dose group, 1×10^8 cells of ADMSCs	WOMAC, VAS, KSS, K-L, joint space width, mechanical axis with weightbearing line, and anatomical axis, ICRS grade	High-dose group showed significant improvement in WOMAC, VAS, KSS, and ICRS grade. No significant changes were observed in low- or medium-dose groups, except KSS function score, which improved in the low-dose group. Radiological measures remained unchanged across all groups.	No treatment-related AE or SAE in any group.
Pers et al (2016)[23]	2×10^6, 10×10^6, and 50×10^6 cells	WOMAC, VAS, KOOS, SAS, SF-36	Statistically significant improvements in WOMAC, VAS, KOOS, and SAS scores were only found in the low dose group. No improvements in the SF-36 in any groups.	No adverse events related to liposuction or injection were observed. 1 SAE, unstable angina pectoris, was reported in 1 patient 3 mths after ASC injection. 5 minor AEs reported by 4 patients reported minor, procedure-related events, including mild knee pain and effusion within the first week.
Song et al (2018)[24]	Low-dose group, 1×10^7 cells Medium-dose group, 2×10^7 cells High-dose group, 5×10^7 cells Three injections	WOMAC, NPRS-11, SF-36	WOMAC scores improved over time in all groups. Significant NRS-11 reductions were seen in the low- and high-dose groups at week 12 after the first injection. SF-36 showed a transient decline, with significant changes at weeks 12 and 96 only. Knee cartilage volume increased throughout follow-up, especially in the high-dose group.	No death or SAEs was reported. Mild to moderate AEs occurred in all groups (low-dose: 67%, medium-dose: 58%, high-dose: 50%), mostly transient joint pain and swelling resolving within 7 days. 1 patient experienced mild oedema and cramps of bilateral lower limbs, which were relieved in 21 days without treatment and not related to the MSC treatment.
Freitag et al (2019)[25]	One-injection group: 100×10^6 cells of ADMSCs Two-injection group: 100×10^6 cells of ADMSCs (baseline and 6 mths)	NPRS, KOOS, WOMAC, MOAKS	Both treatment groups showed NPRS improvement from baseline. All KOOS subscales analysis improved consistently through follow-up. WOMAC scores (inverse %) increased from 59.6/54.4 at baseline to 84/87.3 at 12 mths. Structure analyzed by MOAKS analysis revealed that in the one-injection group, 30% had further cartilage loss and 50% developed osteophyte progression. In the two-injection group, 89% showed cartilage improvement or no progression.	Minor discomfort, swelling, and bruising were common but self-limiting in both groups. 2 participants experienced prolonged pain and swelling (lasting 4 wks) that impacted daily activities and were classified as severe adverse events.
Lee et al (2019)[26]	ADMSC group, 1×10^8 cells of ADMSCs Control group, 3 ml of saline (NaCl 9 mg/ml)	WOMAC, VAS, KOOS, MRI	At 6 mths post-injection, WOMAC total, pain, stiffness, and function scores improved by 54% to 59%. VAS and KOOS scores also showed significant improvement. However, no significant changes were observed in K-L grade, joint space width, HKA angle, or MRI-assessed cartilage defect size.	Treatment-related adverse events were reported in 8 patients in the MSC group, including arthralgia in 6 patients and joint effusion in 2 patients, and in 1 patient in the control group with joint effusion.
Lu et al (2019)[27]	haMPC group, 5×10^7 haMPCs Control group, HA	WOMAC, VAS, SF-36, MRI of knees	Both haMPCs and HA groups showed significant WOMAC improvement. VAS and SF-36 scores were significantly better in the haMPCs group at 6 and 12 mths. MRI revealed increased cartilage volume in the haMPCs group, while the HA group showed a decreasing trend over 12 mths.	Adverse events occurred in 73% of the haMPCs group and 54% of the HA group, mostly mild to moderate joint pain and swelling resolving within 7 days. One serious adverse event (1.9%) occurred in the HA group (knee joint

(*Continued*)

(*Continued*)

Study	Study group and doses	Outcome measures	Result	AEs
				infection), leading to study withdrawal.
Chen et al (2021)[28]	ADSC group, 64×10^6 cells, 32×10^6 cells, 16×10^6 cells of ADSCs (ELIXCYTE) Control groups, Hya Joint Plus synovial fluid supplement	WOMAC, VAS, KSCRS	All ADSC groups showed significant reductions in WOMAC and VAS scores from baseline to Week 48, with pain improvement evident as early as Week 2. KSCRS scores significantly increased in the 16×10^6 cells group and pooled ADSC groups, while a decline was observed in the HA group.	A total of 77.2% of patients reported treatment-emergent adverse events, most commonly musculoskeletal and connective tissue issues (40.4%), general disorders and administration site conditions (29.8%), infections (21.1%), and gastrointestinal symptoms (12.3%). Treatment-related AEs included injection site joint pain (15.8%), arthralgia (14.0%), and joint swelling (12.3%).
Sadri et al (2023)[29]	ADMSC group, 100×10^6 cells of ADMSCs Control group, placebo (normal saline)	WOMAC, VAS, KOOS, SF-36, MRI, biomarkers	The ADMSC group showed significant reductions in WOMAC and VAS scores over 12 mths ($p < 0.001$), along with increased KOOS (total and subscales) and improved SF-36 scores. MRI revealed slight cartilage thickening, significant in the medial anterior and posterior tibial regions. Serum levels of HA and COMP decreased ($p < 0.05$), while IL-10 increased at Week 1 ($p < 0.05$) and inflammator markers declined by Month 3 ($p < 0.001$). CD3, CD4, and CD8 expression also showed a decreasing trend over 6 mths.	2 patients of the ADMSCs group had mild and self-limiting local swelling and pain in the injected knee joint, which relieved after 2 to 3 days. No SAEs were observed in any of the patients.
Kim et al (2023)[30]	ADMSC group, 1×10^8 cells of ADMSCs Control group, normal saline	WOMAC, VAS, PROMs, KOOS, SF-36, IKDC subjective knee score, KL grades, WORMS	VAS, total WOMAC, and other PROMs improved significantly more in the ADMSC group compared to controls. However, radiological outcomes—including K-L grade, HKA angle, joint space width, and MRI-based WORMS—showed no significant change in either group at 6 mths.	Adverse events occurred in 38.4% of the ADMSC group and 32.3% of the control group. Serious AEs were reported in 1 ADMSC patient (pneumonia) and 3 control patients (COVID-19, herpes zoster, spondylolisthesis), all unrelated to treatment. Procedure-related joint pain and swelling occurred in 3 ADMSC patients (2.4%) and 1 control patient (0.8%).
Chen et al (2024)[31]	Low-dose group, 6.7×10^6 cells of ADSCs (GXCPC1) High-dose group, 4×10^7 cells of ADSCs (GXCPC1)	WOMAC, VAS, SF-12	Both high- and low-dose cohorts showed decreasing trends in WOMAC and VAS scores. Greater improvement in WOMAC was observed in the high-dose group. Significant VAS reductions occurred at Weeks 12 and 24 in the low-dose group, and at Weeks 4, 8, and 12 in the high-dose group. SF-12 physical scores increased in both cohorts, while mental scores remained unchanged.	Grade > 3 AEs occurred in 60% of the low-dose cohort and 16.7% of the high-dose cohort. Treatment-related AEs were more frequent in the high-dose group (100%) than in the low-dose group (40%), but none were severe. SAEs requiring or prolonging hospitalization occurred in two low-dose and one high-dose subject, all unrelated to treatment.

AEs, adverse events; COMP, cartilage oligomeric matrix protein; HA, hyaluronic acid; haMPCs, human adipose-derived mesenchymal progenitor cells; HKA angle, hip-knee-ankle angle; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; K-L, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; KSCRS, Knee Society Clinical Rating System; KSS, Knee Society Score; NPRS, numerical pain rating scale; NRS, numerical rating scale; PROMs, patient-reported outcome measures; SAE, severe adverse events; SAS, Short Arthritis Assessment Scale; SF-12, 12-Item Short Form Survey; SF-36, 36-Item Short Form Survey; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities osteoarthritis index; WORMS, Whole-Organ MRI Score.

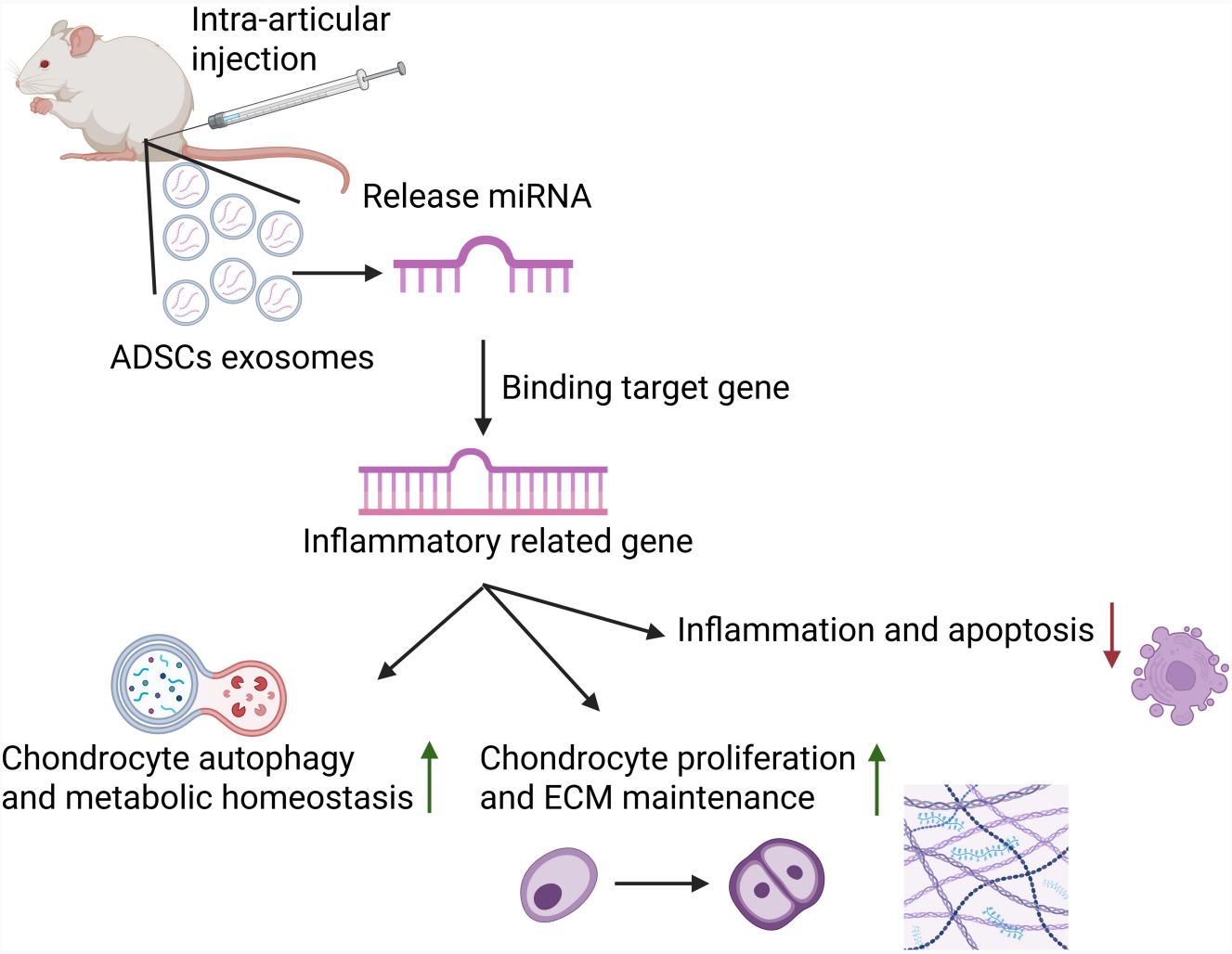

Fig. 2
Schematic illustration of the proposed mechanisms by which adipose tissue-derived stem cell (ADSC)-derived exosomes exert therapeutic effects in osteoarthritis. Following intra-articular injection, exosomal microRNAs (miRNAs) modulate the expression of inflammation-related genes in chondrocytes, leading to reduced inflammation and apoptosis, enhanced autophagy and metabolic homeostasis, and promotion of chondrocyte proliferation and extracellular matrix (ECM) maintenance.

a wide range of biological processes, including physiological functions and disease progression.[65] For example, exosomes carrying miRNA-376c-3p have been shown to alleviate OA-induced chondrocyte degradation and synovial fibrosis through targeting WNT3 or WNT9a in Wnt–β-catenin pathway.[34] Recent studies have further elucidated the role of exosomal cargo in skeletal tissue homeostasis and OA pathogenesis. For example, Yao et al identified miR-494-3p as a key exosomal component derived from senescent osteocytes; its downregulation impaired osteogenic differentiation and accelerated age-related bone loss via activation of the PTEN/PI3K/AKT pathway, while restoration of exosomal miR-494-3p rescued osteogenic potential both in vitro and in vivo.[66] In addition, Li et al[67] described a cartilage-derived exosomal circular RNA, circStrn3, which acts as a competitive sponge for miR-9-5 p, thereby modulating Wnt signalling. In a DMM-induced OA model, downregulation of circStrn3 or restoration of miR-9-5p levels attenuated cartilage degeneration and subchondral bone remodelling. Given this emerging evidence, miRNAs may represent a key therapeutic component of ADSC exosomes in OA treatment.

Apart from their therapeutic potential, the production of exosomes in the synovial fluid of patients with OA has been reported to be significantly higher than that in healthy individuals. As OA progresses, the levels of lncRNA prostat -specific transcript 1 (PCGEM1) and chemokines that can promote inflammation and inhibit cartilage proliferation gradually increase, making them useful markers for identifying the stage of OA.[68]

Recent studies have demonstrated that exosomes can be modified by incorporating a wide variety of compounds or drugs, and can be delivered to specific cells or tissues. Additionally, their small size, stable structure, non-immunogenicity, and non-toxic nature render them highly promising tools for targeted drug delivery.[69]

Compared to ADSC therapy, ADSC exosome treatment is a cell-free therapy that not only simulates the capability of the original ADSCs but also effectively avoids limited cell survival, immune rejection, convenient processing, and potential tumorigenicity.[70]

Owing to their ability to transfer small molecule substances to target cells, exosomes play a pervasive role

in the fundamental processes of both innate and adaptive immunity, as well as in modulating immune-mediated processes.[71] Moreover, considering the abundant source of adipose tissue, low harvesting comorbidity, and limited availability of other MSCs sources, ADSCs and ADSC exosomes have attracted the attention of researchers. The potency of ADSC exosome therapy has been demonstrated in experimental OA animal models. Of these, destabilization of the medial meniscus (DMM) and anterior cruciate ligament transection (ACLT) mouse models, which are more representative of human OA, are the most widely used to assess the efficac of MSC-exosome-based therapy.[32]

Among the two common ADSC-exosomes, IPFP exosomes and subcutaneous fat exosomes, it was proven that IPFP exosomes demonstrate better potency than subcutaneous fat exosomes in treating certain aspects of OA owing to their abundant expression of miR-99b-3p, which may alleviate the development of OA by suppressing the expression of ADAMTS4 and reducing the loss of ECM.[41] Later, overexpression of miR-99b-3p in subcutaneous fat exosomes was demonstrated to result in greater efficac in promoting cartilage regeneration and anabolism-related protein expression than that in IPFP-exosomes.[41] An in vitro study confirmed that ADSC exosomes exerted a strong stimulatory effect on chondrocyte migration and proliferation with the upregulation of miR-145 and miR-221. Additionally, these exosomes attenuated inflammation by reducing the levels of key inflammator biomarkers, including IL-6, TNF-α, and NF-κB, in an H_2O_2-induced oxidative stress model.[37] Li et al[34] confirmed that human ADSCs exosomes could potentially mitigate OA-induced chondrocyte degradation and synovial fibrosis both in vivo and in vitro in rat models. The mechanism involves miR-376c-3p in human ADSC exosomes, restraining the Wnt–β-catenin pathway by targeting WNT3 or WNT9a. Meng et al[36] showed that ADSC exosomes could be absorbed by chondrocytes to promote chondrocyte proliferation through miR-429. In addition, exosomal miR-429 in ADSCs promotes autophagy in chondrocytes by targeting FEZ2 to ameliorate OA progression. miR-127-5p is an essential miRNA for cartilage differentiation and is downregulated during OA progression. Sevimli et al[45] compared the exosomal miRNA-127-5p expression profiles of chondrogenic differentiated human foetal chondroblast cells (hfCCs) with human ADSCs and human synovial fluid-derived stem cells (hSFDSCs). Their results suggested that there was no significant differenc between hADSCs and hfCC exosomes. However, the expression of miR-127-5p in hSFDSCs exosomes was significantly lower than that in hfCC exosomes. This indicates that hADSCs exosomes are a rich source of miRNA-127-5p and may be essential for cartilage regeneration.

Zhao et al[32] demonstrated that subcutaneous fat MSC-derived exosomes could deliver miR-199a-3p to chondrocytes. Enhanced miR-199a-3p specifically targets the 3′-UTR of mTOR mRNA, enhancing chondrocyte autophagy and resulting in increased anabolism and suppressed catabolism in OA cartilage. In another DMM-induced OA model, IPFP-derived exosomes attenuated articular cartilage damage and promoted gait function through exosomal miR-100-5 p, which inhibits rapamycin (mTOR), maintains cell proliferation, and promotes autophagy and ECM synthesis.[33]

In an IL-1β-treated chondrocyte arthritis model, ADSC exosomal miR-93-5p was shown to inhibit autophagy and apoptosis of IL-1β-treated chondrocytes by targeting ADAMTS9 to activate the PI3K/AKT/mTOR pathway, thereby inhibiting inflammation and alleviating OA.[35] Exosomes secreted from miR-338-3 -modified ADSCs inhibited the expression of prostaglandin E2 (PGE2), IL-6, IL-1β, and TNF-α, which promoted ATDC5 cell proliferation. The underlying mechanism is the transfer of miR-338-3p by exosomes targeting the RUNX2 gene, which is responsible for inducing the expression of matrix-degrading enzymes, such as MMP13 and ADAMTS5.[39] In IL-1β pre-conditioned chondrocytes, Wang et al[44] observed miR-486-5p ADSC exosomes exhibited better attenuating effect on the ER stress induced apoptosis compared with miR-486-5p ADSCs, normal ADSC exosomes and miR-486-5 p. This effect was confirmed by the decreasing trend of the ER stress markers CHOP and GRP78, the apoptosis marker cleaved Caspase-3, and cytokine release of IL-6 and TNF-α. In addition, miR-486-5p ADSC exosomes showed the greatest effect in restoring cartilage matrix component type II collagen expression and inhibiting the cartilage degradation protease MMP13 expression. In a DMM-induced OA model, miR-486-5p exosomes remarkably reversed the increased expression of the pro-inflammator M1 macrophage marker iNOS and decreased the anti-inflammator M2 macrophage marker CD163 in the synovium. These results validated the superiority of miR-486-5p exosomes in attenuating chondrocyte apoptosis and OA progression.

Several studies have shown that appropriate modifications or preconditioning of ADSC exosomes can further enhance their delivery efficienc , targeting accuracy, and therapeutic effects in OA.[44,72]

Hypoxia-pretreated ADSC-derived exosomes were shown to have a better effect on the suppression of OA progression than normoxic ADSC exosomes, as evidenced by improved weightbearing function, articular cartilage integrity, and normal matrix levels (collagen type II and GAG), as well as decreased levels of matrix degradative enzymes (MMP13 and ADAMPs) and the inflammator mediator IL-1β in ACLT rats.[38] Hypoxia also enhanced the protective effect of ADSC exosomes in lumbar spinal instability-induced OA models, as demonstrated by the lower facet joint OA scores of the articular cartilage and less proteoglycan loss in the lumbar facet joint cartilage than in the ADSC exosome group. Moreover, hypoxia-treated ADSC exosomes normalized uncoupled bone remodelling and aberrant H-type vessel formation in subchondral bone.[40]

Tropoelastin (TE) pretreatment increased the ability of ADSCs to secrete exosomes. Moreover, compared to normal ADSC exosomes, TE-pretreated ADSCs exosomes exhibited superior therapeutic advantages in the ACLT-induced OA model, as shown by the decreased cartilage damage and promotion of cartilage regeneration. This therapeutic effect was possibly caused by the upregulation of miR-451-5p induced by TE pre-treatment.[42]

Kartogenin (KGN) pretreatment has also been shown to enhance the capacity of exosomes to induce chondrogenic differentiation of stem cells. The proliferation rate of chondrocytes in the exosome and KGN exosome groups was significantly higher than that in the control group. However, in in vivo experiments, the KGN exosome group exhibited better

cartilage repair and a larger amount of hyaline cartilage-like tissue regeneration at the defect site than the exosome group.[43] In another study, Xie et al[46] first induced ADSCs with different concentrations of KGN, and the results suggested that 5 μM KGN had an optimal effect on the chondrogenic differentiation of ADSCs. Subsequently, they assessed the effect of KGN-induced ADSCs exosomes on chondrogenic differentiation of ADSCs. Compared with ADSCs exosomes, KGN-induced ADSC exosomes can significantly improve the proliferation, clone formation, migration, and chondrogenic differentiation of ADSCs and inhibit apoptosis.

In another study conducted by Wu et al,[47] exosomes were harvested from IPFP-MSCs pre-conditioned with TNF-α and it was found that EV secretion was enhanced by upregulating ATG16L1 levels through the PI3K/AKT signalling pathway. After intra-articular administration, IPFP-MSC-EXOs$^{TNF-\alpha}$ exhibited superior efficac in ameliorating gait abnormalities and pathological changes compared to IPFP-MSC-EXOs^{naive} in the joints of DMM mice. They also validated that the underlying mechanism of the chondroprotective effect was the significant enrichment of exosomal low-density lipoprotein receptor-related protein 1 (LRP1) in IPFP-MSC-EXOs$^{TNF-\alpha}$. Exosomal LRP1 protein plays a role in promoting the catabolism of ECM-degrading MMPs and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), indirectly upregulating aggrecan expression.

To address the short half-life of exosomes, Yin et al[41] developed an injectable hybrid hydrogel via Michael addition of hyperbranched polyethylene glycol diacrylate and thiolated hyaluronic acid. Their results indicated that hyaluronan-based hydrogel microparticles (HMPs) exhibited favourable characteristics such as extended exosome retention, enhanced biocompatibility, and facilitated ECM synthesis in chondrocytes. Furthermore, in a murine OA model, exosomes encapsulated by HMPs exhibited gradual degradation and sustained release, which exerted long-term inhibitory effects on ECM degradation while promoting the repair of damaged cartilage in OA. These in vitro and in vivo studies have demonstrated the therapeutic potential of ADSC exosomes in enhancing cartilage regeneration, reducing joint inflammation, maintaining ECM homeostasis, and improving overall joint function in OA models (Table IV).

Discussion

To provide an integrated overview of the principal mechanisms identified in recent studies, Figure 2 summarizes how ADSC-derived exosomes exert their therapeutic effects in OA. We have summarized several clinical studies investigating the use of ADSCs in the treatment of knee OA. The results of these clinical studies indicate that both autologous and allogenic ADSCs are promising, effectiv , and safe therapeutic options for knee OA, offering pain relief and functional improvement (e.g. WOMAC and VAS scores), with some evidence of preventing disease progression. Studies by Jo et al[24] and Song et al[24] reported that autologous ADSCs at high dosages (1.0×10^8 or 3×10^7 cells) can lead to increased hyaline cartilage regeneration and better pain reduction compared to low dosages. Freitag et al[25] demonstrated that double injection of ADSCs exhibited cartilage loss improvement, while Song et al[24] reported that three injections further enhance therapeutic effects, suggesting that injection frequency may influenc the efficac of ADSC treatment. Nonetheless, the inverse dose effect in the study by Pers et al,[23] where the lowest (2×10^6 cells) provided the most significant benefit in patients with the most elevated baseline pain levels, indicates that the therapeutic effect may not be solely dose-dependent, but also influenced by baseline levels of inflammation. This deduction is in accord with a similar study by Jo et al,[22] showing that the highest dose (100×10^6 cells) exhibited the greatest efficac in patients with the highest baseline pain scores (VAS and WOMAC). Moreover, there is a lack of consistency across studies regarding structural improvement. Kim et al's[30] large-scale RCT (261 patients), Chen et al's[28] study with ELIXCYTE (up to 64×10^6 cells) and Pers et al's[23] trial report significant clinical benefits but no detectable cartilage status change by MRI after six to 12 months. Similarly, studies by Lee et al[26] and Freitag et al[25] demonstrated functional improvement and stabilization of the cartilage defect rather than structural repair. These discrepancies could stem from several factors: the relatively short follow-up periods (e.g. 6 months in Kim et al's[30] study) may be insufficient to identify slow regenerative phenomena; imaging techniques such as MOAKS might not be sensitive enough to detect subtle structural changes, as suggested by Freitag et al;[25] small sample sizes, such as in Chen et al[31] (57 patients) and Lee et al[26] (24 patients), may limit the statistical power to recognize cartilage restoration; or ADSCs primarily have immunomodulatory and paracrine actions with little contribution from direct chondrogenesis, as shown by cartilage stabilization instead of regrowth in studies by Freitag et al[25] and Lee et al.[26] Numerous studies have further confirmed that ADSCs can secrete a variety of growth factors, cytokines, and extracellular vesicles through paracrine effects, thereby modulating inflammation and promoting chondrocyte regeneration.[73–75] These paracrine effects, particularly those mediated by exosomes, offer new research directions for OA treatment.

Inspired by the paracrine effects of ADSCs, recent researches have shifted focus to ADSC-derived exosomes as a cell-free therapeutic strategy for OA. Our review of ADSC exosome studies underscores the complex and diverse roles of exosomes from IPFP, subcutaneous fat tissue, and preconditioned ADSCs in promoting chondrocyte proliferation, sustaining ECM homeostasis, regulating autophagy, and inhibiting inflammation and apoptosis. Central to these effects is the role of miRNAs as critical cargo within ADSC exosomes, which significantly regulate the pathological process of OA.[65] In Yin et al's[41] study, IPFP-derived exosomes were more effectiv than subcutaneous fat exosomes at protecting against ECM loss, which was attributed to their higher expression of miR-99b-3p, reducing ADAMTS4 expression. Notably, exosome-mediated cartilage regeneration can also be promoted when miR-99b-3p is overexpressed in subcutaneous fat exosomes, indicating that exosome composition can be tailored for improved regenerative potential. Similarly, Wang et al[44] found that miR-486-5p-loaded exosomes were superior to ADSCs in apoptosis alleviation and matrix regeneration of chondrocytes. This may result from an inflammator environment, leading to a significant impact on the secretome of ADSCs.

At the mechanistic level, the therapeutic potential of exosomes in OA is mediated through a variety of miRNAs targeting pivotal genes and signalling cascades. In particular,

Table IV. Overview of the mechanisms and functions of adipose tissue-derived stem cell (ADSC)-derived exosomes in osteoarthritis (OA) models.

Study	Model	Bioactive ingredients	ADSC origin	Function	Mechanism
Zhao et al (2023)	Rats (DMM+ ACLT), Mice (DMM) IL-1β induced chondrocyte	miR-199a-3p	Human subcutaneous fat	Significant cartilage regeneration Ameliorate the pathological severity degree of cartilage	The enhanced miR-199a-3p expression in chondrocytes specifically targeted the 3′ UTR region of mTOR mRNA, resulting in the decrease of mTOR protein level and the related downstream signal pathway. The repressive mTOR signal also increased chondrocyte autophagy, which increased anabolism and suppressed catabolism in OA cartilage.
Wu et al (2019)	DMM-induced OA mice, IL-1β induced chondrocyte	miR-100-5p	Human IPFP	Promote chondrocyte proliferation Enhanced matrix synthesis Reduced the expression of catabolic factor	miR-100-5p could bind to the 3′-untranslated regions (3′UTR) of mTOR and decreased mTOR signalling pathway, then enhance autophagy level in chondrocytes.
Li et al (2023)	Monosodium iodoacetate -induced rat OA model, IL-1β induced chondrocyte	miR376 c3p	Human subcutaneous thigh adipose tissues	Mitigate OA-induced chondrocyte degradation and synovial fibrosis	miR-376c-3p targeted the 3′-untranslated regions of WNT3 or WNT9a, then repressed the WNT-beta-catenin signalling pathway.
Li et al (2023)	IL-1β-treated chondrocytes arthritis model	miR-93-5p	Mouse adipose mesenchymal stem cell	Inhibited the autophagy and apoptosis of IL-1β-treated chondrocytes	miR-93-5p inhibited the autophagy and apoptosis of IL-1β-treated chondrocytes by targeting ADAMTS9 to activate the PI3K/AKT/mTOR pathway.
Meng et al (2023)	Iodoacetate induced OA model, IL-1β induced chondrocyte	miR-429	Male Sprague-Dawley rats	Promote chondrocyte proliferation Ameliorate cartilage injury	mir-429 target FEZ2 and promote autophagy (increase Beclin 1, collagen II, and LC3-II/I expression, decrease FEZ2 expression)
Zhao et al (2020)	H2O2 induced cartilage injury	miR-145, miR-221	Liposuction surgery of a healthy donor	Stimulate chondrocyte proliferation Promote mesenchymal differentiation Anti-inflammation	ADSC-exosomes induced Runx2, Sox9, Col II and β-catenin, and Col II mRNA expression. Reduced levels of inflammator biomarkers, IL-6, TNF-α and nF-κB, while increased levels of IL-10
Chang et al (2023)	IL-1β induced OA like in vitro cell model, ACLT induced model	miR-381-3p, miR-122-5p, miR-143-3p, miR-206, miR-30a-5p, miR-22-3p, miR-151a-5p	Subcutaneous adipose tissue	Enhanced cartilaginous matrix synthesis and inhibited fibrous/degenerated cartilage Suppress inflammator cytokines and degradation enzymes	Hypoxia-ADSC-Exo increased the mRNA expression of aggrecan, col2a1, and PTHrP, and inhibited the mRNA expression and protein level of type I and type X collagen Hypoxia-ADSC-Exo suppressed the mRNA expression of the inflammator -related genes CEBPβ, COX-2, IL-6, and TNF-α and catabolic genes MMP-13 and ADAMT5.
Li et al (2022)	IL-1βinduced ATDC5 cells	miR-338-3p	Mouse ASCs	Reduced inflammation and degradation of chondrocytes Stimulated cell proliferation and inhibited cell apoptosis	miR-338-3p targeted RUNX2 to inhibit the expression of prostaglandin E2 (PGE2), IL-6, IL-1β, and TNF-α, and promoted the expression of Col2a1 and aggrecan
Zhao et al (2023)	Lumbar spinal instability (LSI)-induced LFJ OA models.	Unclear	White adipose tissue of the mouse groin	Alleviated CGRP+ nerves in subchondral bone Showed better pressure tolerance and less retraction frequency of the hind paw Alleviate cartilage degeneration and synovial inflammation	Unclear

(*Continued*)

(*Continued*)

Study	Model	Bioactive ingredients	ADSC origin	Function	Mechanism
Yin et al (2023)	IL-1βinduced cell model, DMM-induced OA model	miR-99b-3p	IPFP, subcutaneous-ADSCs	Promote ECM synthesis (increased ACAN, COMP and collagen II protein level)	miR-99b-3p down-regulates ADAMTS4, and increase the expression of ACAN and COMP
Meng et al (2023)	ACLT induced OA model, IL-1β induced chondrocyte	miR-451-5p	Rat ADSC	Enhance the matrix synthesis of chondrocytes Maintain the chondrocyte phenotype in vitro and promote cartilage repair in OA rats	Unclear
Shao et al (2021)	Articular cartilage injury	Unclear	Rabbit IPFP	Exosomes promoted the proliferation of chondrocytes Exosomes induced phenotypic changes in chondrocytes	KGN-exosomes superiorly increased the expression of Sox9, Aggrecan, and Col II
Wang et al (2021)	DMM-induced OA mice, IL-1β induced chondrocyte	miR-486-5p	Subcutaneous adipose tissues	Attenuating the ER stress-induced apoptosis Cartilage regeneration and inflammation modulation	miR-486-5p inhibit the ER stress induced apoptosis through inhibited the expression of CHOP, then the apoptosis marker cleaved Caspase-3 and ER stress marker GRP78 showed decreasing pattern. miR-486-5p further reduced the cytokine release of IL-6 and TNF-α. miR-486-5p increased expression of ACAN, COL2A1 and decreased expression of MMP13.
Sevimli et al (2023)	N/A	miR-127-5p	hADSCs hSFDSCs	Significantly higher levels of miR-127-5 p expression in hADSCs exosomes than hSFDSCs	miR-127-5p promote cartilage differentiation via increasing the expression of Sox9, Col II and aggrecan and decreasing the expression of Runx2, IL-β-induced MMP13.
Xie et al (2022)	N/A	N/A	Human subcutaneous adipose tissue	KGN-induced ADSC-exosomes significantly promote the chondrogenic differentiation of ADSC	KGN-induced ADSC-exosomes increase the expression levels of chondrogenesis-related genes, including aggrecan, Col III, Col II, and SOX9, and inhibited the expression of chondrolysis-related genes, including MMP-3, ADAMTS4, and ADAMTS5
Wu et al (2024)	DMM-induced OA mice, H2O2 induced chondrocyte	LRP1	IPFP	Ameliorate gait abnormalities and pathological changes Exosomal LRP1 protein derived from IPFP MSC EXOs TNF-α exerts a chondroprotective effect	TNFα precondition enhances the EVs secretion of IPFP MSCs by upregulating ATG16L1 levels LRP1 serves as the primary endocytic receptor for extracellular matrix-degrading MMPs and ADAMTSs in chondrocytes and promotes the catabolism of ECM degrading MMPs and ADAMTSs, indirectly leading to an upregulation of aggrecan expression

LRP1, low-density lipoprotein receptor related protein 1.

miR-99b-3p and miR-338-3p target ADAMTS4 and RUNX2 to suppress ECM degradation,[39,41] whereas miR-376c-3p inhibits Wnt–β-catenin via WNT3/WNT9a to mitigate chondrocyte degradation and synovial fibrosis.[65] In addition, miR-145 and miR-221 has been observed to downregulate inflammator markers (e.g. IL-6, TNF-α, NF-κB),[37] while miR-486-5p was shown to attenuate ER stress-induced apoptosis and MMP13 expression, consequently promoting restoration of type II collagen.[44] To further enhance these effects, preconditioning strategies have been explored to optimize exosome functionality. Hypoxia-pretreated ADSC exosomes improve cartilage integrity and suppress inflammation,[38,40] while KGN preconditioning enhances chondrogenic differentiation and cartilage repair.[43,46] Furthermore, TNF-α preconditioning upregulates exosomal LRP1 to protect ECM,[47] and hydrogel encapsulation

improves the stability and bioavailability of exosomes, and extends their release for prolonged therapeutic benefits.[41]

However, these studies have several limitations. For instance, most investigations depend on single miRNA target validation without investigating their interaction with other miRNAs, signalling pathways, or regulatory factors. This singular focus results in some contradictory effects: miR-93-5p suppresses autophagy, thereby inhibiting inflammation and ameliorating OA, whereas miR-199a-3p and miR-100-5p activate autophagy to promote chondrocyte survival and ECM synthesis, implying uninvestigated synergistic or antagonistic interactions between these pathways. Moreover, the primary use of preclinical animal models (e.g. DMM, ACLT) or in vitro cellular models raises uncertainties about whether these therapeutic effects translate to humans. A previous study has demonstrated that cartilage thickness has a significant influenc on intra-articular drug delivery.[76] To date, there are no completed large animal or clinical trials to help evaluate the therapeutic effect of ADSC exosomes. Improving our understanding of the interplay of multiple miRNAs and signalling pathways, combined approaches with biomaterials, and interactions within the joint microenvironment could facilitate the development of exosome-based therapies for OA.

OA is a prevalent degenerative disease that severely affects joint function and the quality of life. Currently, OA treatment mainly focuses on alleviating pain and delaying the need for TKA. However, both conservative therapy and TKA are limited in their capacity to address the underlying causes of OA. To date, no disease-modifying agents have been developed to underscore the need for novel therapeutic strategies.

Among the emerging approaches, MSC-based therapies, particularly those utilizing ADSCs, have shown promise owing to their advantages of multiple differentiation potentials, easy acquisition without comorbidity, and high yield, which make them an ideal source of MSCs. Numerous preclinical and clinical studies have revealed that intra-articular injections of ADSCs not only alleviate joint pain and ameliorate joint function, but also stimulate the regeneration of chondrocytes, especially in the higher dose group. Although these results provide evidence for the benefits of ADSCs in OA treatment, the potential risks associated with ADSC transplantation, such as tumorigenicity, remain a concern.

Given their stable structure and non-immunogenicity, exosomes as intercellular signal carriers provide a promising cell-free strategy to ameliorate OA progression by transporting various miRNAs and proteins to target inflammator -related genes. Numerous preclinical studies have indicated that ADSCs exosomes can effectively modulate gene expression and affect multiple physiological processes, such as chondrocyte regeneration, inhibition of apoptosis, anti-inflammation, and ECM balance. Moreover, through the implementation of appropriate modifications, such as hypoxia, tropoelastin, KGN, or TNF-α preconditioning, ADSC exosomes can exhibit potent chondroprotective and regenerative effects, thereby reinforcing their therapeutic capabilities. Additionally, the use of biocompatible materials such as hydrogels prolongs exosome retention, enhances biocompatibility, and facilitates a sustained local drug release system. This can potentially augment the therapeutic effects of exosomes.

Nevertheless, the clinical application of ADSC-derived exosomes in the treatment of OA remains challenging. First, there is no standard procedure for separating and identifying the exosomes. Second, no methods have been reported for large-scale production of exosomes for clinical applications. Third, the existing literature on the therapeutic effect of ADSC exosomes is limited to cellular and rat OA models. There is a paucity of studies exploring the potential of preconditioning and biomaterial applications of ADSC exosomes. In addition, clinical trials are required to confirm its safety, effectiveness, and long-term effects in human patients. Consequently, as a potential candidate for OA treatment, ADSC exosomes deserve further exploration.

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Data sharing

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