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REVIEW

Mechanosensitive miRNAs in Cartilage and Subchondral Bone Remodeling: Emerging Targets for Osteoarthritis Therapy

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Abstract: Osteoarthritis (OA) is a chronic degenerative joint disorder characterized by cartilage degradation and bone remodeling. Mechanical stimuli play fundamental roles in maintaining joint homeostasis by regulating cellular metabolism and the composition and stiffness of the extracellular matrix (ECM). Consequently, targeting mechanics-associated factors represent a promising therapeutic direction for OA. MicroRNAs (miRNAs), a class of short non-coding RNAs, negatively regulate target mRNAs at the posttranscriptional level and modulate gene expression in recipient cells without altering gene sequences. Growing interest surrounds the impact of mechanical forces on cellular responses and associated epigenetic gene expression. Therefore, investigating miRNA expression under mechanical loading conditions is crucial for elucidating the role of mechanosensitive miRNAs in articular cartilage and bone metabolism. This highlights specific miRNAs as potential therapeutic targets to disrupt the pathological feedback loops in OA. In this review, we examine the current applications of mechanosensitive miRNAs and delivery systems for OA therapy. We further analyze potential factors influencing their application. Significantly, extracellular vesicles (EVs) may facilitate the transport of mechanosensitive miRNAs across the bone–cartilage interface under mechanical stress. This mechanism provides a novel perspective for fully understanding the bidirectional communication between chondrocytes and osteocytes in response to physiological loading, and how its dysregulation contributes to OA pathology. Advancing research on EVs and their miRNA cargo is essential for the effective application of mechanosensitive miRNA-based regulation in intercellular and tissue interactions during OA treatment.

Keywords: osteoarthritis, mechanosensitive, microRNAs, extracellular vesicles

Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by cartilage degeneration, bone remodeling, and synovitis involvement throughout its onset and progression.[1,2] During this pathological process, mechanical stimuli critically regulate joint homeostasis through dynamic control of cellular metabolism and extracellular matrix (ECM) composition and stiffness.[3–5] Targeting mechanosensitive factors represents a promising therapeutic direction for OA by converting detrimental mechanical forces into beneficial signals. Therefore, manipulating mechanotransduction pathways offers opportunities to halt OA progression. Recently, several mechanosensors, including pericellular matrix (PCM) and ECM components, mechanically gated ion channels and porins (such as transient receptor potential vanilloid 4 and Piezo), integrins, mitochondria, cytoskeleton, and primary cilia have been discovered as the first responders to mechanical force.[6–8] However, the downstream effectors that enact alterations in gene expression profiles during mechanotransduction signaling remain incompletely characterized, despite the established roles of several transcription factors (eg, nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB], Yes-associated protein [YAP]) in mediating cellular responses to mechanical stimuli.[9–13] However, traditional therapeutic approaches targeting growth factors or small-molecule inhibitors face significant challenges in clinical translation due to inherent limitations in specificity and stability, coupled with high production costs. Consequently, small oligonucleotides—including microRNAs (miRNAs)

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that regulate mechanosensitive cellular metabolism—represent a promising alternative for modulating physiological systems.[14–17]

As short non-coding RNAs averaging ~22 nucleotides, miRNAs provide a simple, cost-effective, and scalable approach to direct cellular activities by regulating gene expression through mRNA degradation or translational repression.[18] Recently, the impact of mechanical forces on cellular mechanotransduction and their role in mechanics-induced epigenetic regulation of gene expression have garnered significant scientific attention.[19] Although the interplay between mechanical forces and biological responses constitutes a highly intricate process that modulates multiple cellular events—including proliferation, differentiation, inflammation, senescence, and apoptosis—its core regulatory mechanism may be mediated through mechanosensitive miRNAs. This mechanism has been extensively investigated in the context of OA, particularly during the degenerative processes affecting articular cartilage and subchondral bone.[20]

Therefore, investigating miRNA expression under mechanical loading conditions will elucidate the systemic effects of mechanotransduction signaling during bone and cartilage degeneration. Furthermore, advances in delineating the multifunctional roles of mechanosensitive miRNAs in articular cartilage and bone metabolism will underscore their potential as therapeutic targets for interrupting disease-driving circuits in OA.[21,22]

This review will critically evaluate current research on mechanosensitive miRNAs in cartilage and bone biology, highlighting their therapeutic potential for OA treatment. Subsequently, we will summarize emerging delivery systems—particularly extracellular vesicles (EVs)—that enable targeted transfer of mechanosensitive miRNAs as a paradigm for precision therapeutics. Finally, key challenges in the clinical translation of mechanosensitive miRNA-based therapies and future research directions will be analyzed.

Mechanosensitive miRNAs in Cartilage

Physiological mechanical forces—encompassing compressive, tensile, and shear stresses—are indispensable for sustaining articular cartilage homeostasis by orchestrating anabolic-catabolic equilibrium, chondrocyte phenotypic stability, and ECM integrity. These forces regulate mechanotransduction pathways that activate key transcription factors (eg, YAP/TAZ) and epigenetic modulators (eg, mechanosensitive miRNAs), thereby maintaining tissue functionality and joint health.[23] As the sole cellular constituents in cartilage, chondrocytes sense dynamic alterations in the mechanical microenvironment and transduce extracellular forces into biochemical signals that regulate cellular activities, thereby modulating PCM properties and tissue homeostasis.[24] Cartilage chondrocytes sense extracellular mechanical forces through specialized mechanoreceptors (eg, integrins, TRPV/PIEZO channels) and ion channels, activating downstream signaling cascades—including calcium-dependent pathways and focal adhesion kinase (FAK) phosphorylation—that regulate pivotal cellular processes in OA pathology, such as the synthesis, secretion, and EV-mediated transfer of miRNAs.[5]

By integrating miRNA microarray profiling with quantitative reverse transcription polymerase chain reaction (qRT-PCR), Dunn et al pioneered the identification of spatially resolved miRNA expression patterns in bovine articular cartilage, revealing mechanosensitive miRNAs (eg, miR-221/222) that are significantly upregulated in weight-bearing regions (anterior medial condyle, M1) compared to non-weight-bearing zones (posterior medial condyle, M4).[25] As the first identified mechanosensitive miRNAs in mammalian articular cartilage, miR-221 and miR-222 exhibit spatially stratified upregulation, and this mechano-activated miRNA pair targets key regulators of cartilage homeostasis.[26] While acknowledging the developmental and species-specific limitations of bovine cartilage models, Hecht et al, further validated this mechanosensitive axis in mature tissue-engineered human cartilage. Their study demonstrated that non-physiological static loads downregulate miR-222 expression, leading to derepression of ADAMTS5 and increase in aggrecan degradation (proteomic analysis). Concomitantly, these loads upregulated miR-221, which inhibited PTEN, triggered hyperactivation of the PI3K/Akt pathway, and ultimately induced chondrocyte hypertrophy and apoptosis. Collectively, these results establish miR-221/222 as central mediators of OA mechanopathology, providing a mechanistic rationale for miRNA-targeted therapies aimed at recalibrating dysregulated mechanotransduction pathways.[20] Similarly, Stadnik et al demonstrated that mechanical stress dynamically upregulates the expression of mechanosensitive miRNAs —including miR-221, miR-222, miR-21-5p, and miR-27a-5p—in both ex vivo cartilage explants subjected to

incremental load magnitudes and in vivo joint cartilage exposed to abnormal loading.[27] These findings further support the involvement of epigenetic mechanisms in transducing mechanical cues into cellular activities during OA progression.

In situ, chondrocytes reside within a dynamic and spatially heterogeneous mechanical microenvironment characterized by multi-modal loading modalities—compression, hydrostatic pressure, shear stress, osmotic stress, and tensile strain—which exhibit significant zonal variations due to depth-dependent differences in ECM composition and chondrocyte morphology (flattened in superficial vs columnar in deep zones).[28] Through integrated in vivo joint loading models and in vitro 3D hydrogel systems replicating zone-specific mechanical cues, studies have demonstrated that chondrocytes differentially transduce these biomechanical signals via mechanosensitive ion channels (eg, TRPV4/PIEZO1) and purinergic Ca^{2+} signaling, ultimately modulating the expression of mechanosensitive miRNAs (eg, miR-221/222, miR-140-5p, miR-23b-3p).[29–32] These miRNAs, as cataloged in Table 1, function as critical epigenetic regulators of cartilage homeostasis by targeting key anabolic/catabolic pathways in a load-dependent manner.

However, in the human body, articular cartilage experiences complex combinations of stress patterns. Consequently, while individual stress patterns can be effectively analyzed in the lab to investigate specific molecular changes in detail, they fail to replicate the in vivo cellular and molecular responses within human cartilage. Given that mechanical stress-induced injury is a primary aetiological factor in OA, investigating mechanosensitive miRNAs induced by actual mechanical injury—rather than by individual stress patterns—is of particular significance. Such miRNAs represent potential therapeutic targets themselves and could be harnessed as therapeutic agents. For example, miR-140 is specifically and highly expressed in human articular cartilage.[42] Previous studies have identified that miR-140 plays an important homeostatic and chondroprotective role in adult joints and can be modulated by mechanically driven signals.[43] Chaudhry et al demonstrated a groundbreaking approach by achieving CRISPR-Cas9-mediated editing of miR-140 with 90–98% efficiency in primary human articular chondrocytes—the first study to accomplish such high-precision genetic manipulation in this cell type. Their genome-wide screening identified novel mechanosensitive targets of miR-140 (including ADAMTS5, MMP13, and TGF-βR2), which coordinately regulate ECM degradation and inflammatory

Table 1 Expression and Clinical Relevance of Mechanosensitive miRNAs in Cartilage

miRNA	Target	Mechanical Force	Function	Literature	Clinical Relevance
miR-9-5p	KLF5	Tensile strain	Intra-articular injection of exosome-mediated miR-9-5p could prevent OA progression	Li et al 2023[33]	Cartilage
miR-214	NA	Treadmill exercise	Suitable mechanical load induced expression of miR-214 may be chondroprotective.	Cao et al 2022[34]	Cartilage
miR-140	Mechanosensitive targets	Cartilage injury	The expression of miR-140 is down-regulated upon cartilage injury and play a vital role in cartilage homeostasis.	Chaudhry et al 2022[35]	Cartilage
miR-221-3p	P27/TIMP3/TCF4/ARNT	NA	Chondrocyte-derived EVs could inhibit the bone formation capability of osteoblasts.	Shang et al 2021[36]	Cartilage
miR-221/222 miR-21/27a	TIMP3/CPEB3	Mechanical loading	Mechanically regulated miRNAs were identified in cartilage under mechanical stress.	Stadnik et al 2021[27]	Cartilage
miR-365	HDAC4	Cyclic tensile strain	Cyclic tensile strain could increase miR-365 expression and promote chondrogenesis of BMSCs	Chen et al 2019[37]	Cartilage
miR-365	HDAC4	Cyclic loading	miR-365 could participate into the regulation of mechanical stress and contribute to cartilage catabolism.	Yang et al 2016[38]	Cartilage
miR-365	HDAC4	Cyclic loading	miR-365 is mechanically responsive microRNA and directly targets HDAC4.	Guan et al 2011[39]	Cartilage
miR-203	ERα	Mechanical stress	Mechanical stress could reduce ERα expression by regulating miR-203 activity in chondrocytes.	Tian et al 2019[40]	Cartilage
miR-146a	Smad4	Mechanical injury	miR-146a could increase the expression of VEGF and damaging the TGF-β pathway via targeting Smad4 in cartilage.	Jin et al 2014[41]	Cartilage

Note: NA: Information not reported or not investigated in the source study.

responses. Single-cell RNA sequencing further confirmed that edited miR-140 simultaneously suppressed IL-6/STAT3 signaling and metalloproteinase activity, significantly enhancing chondrocyte resilience to mechanical stress. This pioneering work establishes gene-edited mechanosensitive miRNAs as precision therapeutic tools targeting OA pathogenesis at the epigenetic level.[35] Similarly, Yang et al provided mechanistic evidence that cyclic tensile strain (10% elongation, 0.5 Hz) upregulates miR-365 expression by 3.7-fold in human chondrocytes, directly targeting HDAC4's 3′-UTR confirmed by dual-luciferase reporter assays.[38] This epigenetic modulation suppresses HDAC4-mediated deacetylation of histone H3 at lysine 9, consequently enhancing SOX9-dependent collagen type II and aggrecan transcription. Crucially, pathological mechanical loading (15% strain) reversed this protective effect, inducing miR-365-mediated promotion of MMP-13 and ADAMTS-5 via NF-κB hyperactivation—demonstrating its dual role as a mechanoadaptive switch in OA progression.[38] Earlier work by Guan et al first established miR-365-HDAC4 axis in chondrogenesis, revealing its necessity for mechanical loading-induced differentiation of mesenchymal stem cells.[39] Thus, targeting mechanosensitive miRNAs in articular chondrocytes holds potential as a novel therapeutic strategy for both preventing and treating OA.

Mechanosensitive miRNAs in Subchondral Bone Remodeling

Subchondral bone remodeling, characterized by the coupled processes of bone resorption and formation, is dynamically regulated by mechanosensitive miRNAs in OA pathophysiology. Given its intimate link to articular cartilage as an adjacent tissue, subchondral bone critically contributes to OA pathogenesis and progression.[44–46] Direct mechanical loading of articular cartilage activates intracellular signaling pathways, leading to biochemical responses; these alterations in cartilage homeostasis further mediate stress transfer to the underlying subchondral bone.[47–49] As a dynamic tissue, subchondral bone undergoes continuous remodeling governed by the balance between osteogenic activity and bone resorption. This process is mediated by interactions among osteoblasts, osteoclasts, and osteocytes within the subchondral microenvironment. Accumulating evidence indicates that miRNAs serve as key regulators in mechanosensing and mechanotransduction, modulating bone homeostasis through post-transcriptional silencing of critical transcription factors and signaling pathway modulators.[33,50] For instance, mechanoresponsive miR-103a directly targets Runx2 (runt-related transcription factor 2) in osteoblasts by binding its 3′-untranslated region (3'UTR), thereby suppressing osteogenic differentiation through post-transcriptional repression of this master transcription factor. Concurrently, mechanosensitive miR-154-5p inhibits osteolineage commitment of adipose-derived mesenchymal stem cells (ADSCs) by silencing core components of the canonical Wnt/β-catenin signaling pathway, including Wnt5a and downstream effectors.[51,52] Pathological subchondral remodeling in OA emerges from dichotomous mechanical stressors: disuse-induced trabecular resorption and overloading-triggered sclerotic thickening. This imbalance disrupts biomechanical reciprocity across the osteochondral unit, fueling OA progression through uncoupled joint loading and inflammatory amplification via cytokine-mediated crosstalk.[52] Mechanosensitive miRNAs thus emerge as pivotal regulators of these pathways. Arfat et al employed a hindlimb unloading (HLU) mouse model to simulate mechanical underuse, screening for differentially expressed miRNAs in long bones. They discovered that miR-208a-3p suppresses osteogenesis during remodeling by directly targeting ACVR1 in MC3T3-E1 cells, a core receptor for bone morphogenetic protein (BMP) signaling.[53] Crucially, this study demonstrated that antagomiR-208a-3p administration enhanced osteogenic differentiation in MC3T3-E1 preosteoblasts by suppressing miR-208a-3p. Concurrently, it reversed mechanical unloading-induced bone loss in HLU mice. These findings establish miR-208a-3p inhibition as a promising therapeutic strategy for bone-related pathologies, including OA, by restoring mechanotransductive homeostasis. Additional mechanosensitive miRNAs regulating bone metabolism are cataloged in Table 2.

The osteochondral functional unit, comprising articular cartilage and subchondral bone, exhibits a critical bidirectional interaction driving OA progression.[71] As established in prior work,[36] mechanosensitive miRNAs undergo paracrine transport via chondrocyte-derived EVs (eg, miR-221) across the osteochondral interface. This process is structurally facilitated by microchannels, evidenced by Taheri et al's identification of 3D CMMC networks.[72] Biomechanically, early subchondral bone loss reduces load-absorbing capacity, increasing shear stress on cartilage, while late-stage sclerosis transmits excessive force directly to articular surfaces. As a result, pathological alterations within subchondral bone can significantly impact cartilage integrity.[73] For instance, osteoclast-mediated bone resorption

Table 2 Expression and Clinical Relevance of Mechanosensitive miRNAs in Subchondral Bone Remodeling

miRNA	Target	Mechanical Force	Function	Literature	Clinical Relevance
miR-212-3p	Hmgb1	Mechanical unloading	The expression of miR-212-3p is increased under mechanical unloading and osteogenic differentiation capability could be suppressed by directly targeting Hmgb1.	Zhang et al 2023[54]	Bone Remodeling
miR-9-5p	KLF5	Tensile strain	Intra-articular injection of exosome mediated miR-9-5p could alleviate OA progression.	Li et al 2023[33]	Bone Remodeling
miR-20a	BAMBI SMAD6	Fluid shear stress	miR-20a could enhance osteoblast differentiation udder fluid shear stress.	Peng et al 2022[55]	Bone Remodeling
miR-100	FZD5 FZD8	Fluid shear stress	miR-100 could mediate mechanosensitive interaction between TGFβ and Wnt pathway in osteocytes under fluid shear stress.	Dole et al 2021[56]	Bone Remodeling
miR-203a-3p	NA	Hindlimb unloading	EV mediated miR-203a-3p is mechanistically regulated to protein synthesis and degradation.	Pelt et al 2020[57]	Bone Remodeling
miR-337-3p	IRS1 Nox4	Cyclical mechanical loading	Overexpression of mechanosensitive miR-337-3p could alleviate ectopic ossification.	Geng et al 2020[58]	Bone Remodeling
miR-132-3p	Ep300	Mechanical unloading	Inhibited expression miR-132-3p in the bone can preserve bone mass, microstructure.	Hu et al 2020[59]	Bone Remodeling
miR-30 family	Runx2	Mechanical unloading	miR-30 family members participate into the regulation of the dysfunction of osteoblasts under unloading environment.	Zhang et al 2020[60]	Bone Remodeling
miR-138-5p	MACF1	Treadmill exercise Cyclic stretching	miR-138-5p is a mechanoresponsive miRNA in the bone.	Chen et al 2020[61]	Bone Remodeling
miR-208a-3p	ACVR1	Hindlimb unloading	Inhibition of miR-208a-3p may be protective for relieving bone loss.	Arfat et al 2018[53]	Bone Remodeling
miR-195-5p	WNT3A, FGF2, and BMPR1A	Cyclic tension strain	miR-195-5p is a mechanosensitive and could regulate osteogenic differentiation.	Chang et al 2017[62]	Bone Remodeling
miR-148a-3p	Kdm6b	NA	miR-148a-3p participates into the regulation of adipocyte and osteoblast differentiation.	Tian et al 2017[63]	Bone Remodeling
miR-503-5p	NA	Cyclical stretch	miR-503-5p is mechanosensitive and could inhibit osteogenic differentiation.	Liu et al 2017[64]	Bone Remodeling
miR-33-5p	Hmga2	Microgravity Fluid shear stress	miR-33-5p is a mechanosensitive miRNA and could promote osteogenic differentiation.	Wang et al 2016[65]	Bone Remodeling
miR-494-3p	Fgfr2 Rock1	Compressive force	Compressive force could inhibit cell proliferation by upregulating miR-494-3p expression.	Iwaki et al 2015[66]	Bone Remodeling
miR-153	BMPR2	NA	miR-153 is a mechanosensitive miRNA and could regulates osteogenic differentiation.	Cao et al 2015[67]	Bone Remodeling
miR-103	Cav1.2	Microgravity	miR-103 could inhibit osteoblast proliferation via suppressing Cav1.2 expression under simulated microgravity environment.	Sun et al 2015[68]	Bone Remodeling
miR-103a	Runx2	Cyclic mechanical stretch	miR-103a is a mechanosensitive miRNA and could regulates osteogenic differentiation by targeting Runx2.	Zuo et al 2015[52]	Bone Remodeling
miR17-92 cluster	Periostin, Elk3, Runx2	Mechanical strain	miR17-92 cluster plays a vital role in periosteal bone formation under mechanical strain in type I collagen-producing cells.	Mohan et al 2015[69]	Bone Remodeling
miR-154-5p	Wnt11	Mechanical tension	miR-154-5p could negatively regulate osteogenic differentiation through Wnt/PCP pathway by targeting Wnt11 under tensile stress.	Li et al 2015[51]	Bone Remodeling
miR-20a/21/19b/34/140/200b	NA	Fluid shear stress	A group of miRNAs are involved in the pre-osteoblast differentiation under fluid shear stress.	Mai et al 2013[70]	Bone Remodeling

Note: NA: Information not reported or not investigated in the source study.

releases factors like transforming growth factor-beta (TGF-β) and calcium-phosphate complexes, which promote chondrocyte hypertrophy, apoptosis, and matrix degradation.[74] Concurrently, type H vessel invasion from subchondral bone delivers pro-inflammatory mediators (eg, VEGF, PDGF-BB) into cartilage, further accelerating chondrocyte catabolism.[75,76] Furthermore, osteoclast-derived exosomes containing molecules like let-7a-5p target Smad2 in chondrocytes, driving hypertrophic differentiation and creating a destructive feedback loop.[77] Thus, targeting the crosstalk between articular cartilage and subchondral bone represents a promising therapeutic avenue for OA. Recently, Jing et al developed a bone-targeted extracellular vesicle delivery system to overcome the challenge of drug delivery to subchondral bone. This platform utilizes macrophage-derived vesicles functionalized with bone-targeting peptides, enabling immune evasion and enhanced biological barrier penetration. The engineered system demonstrated low toxicity, high stability, and precise bone targeting both in vitro and in ACLT-induced OA mice. Critically, it successfully inhibited pSmad2/3-dependent TGF-β signaling in subchondral bone, restoring coupled bone remodeling. This strategy provides a novel approach for treating OA by modulating pathological signaling in the subchondral microenvironment. Notably, the platform's capacity to deliver mechanosensitive miRNAs could directly regulate metabolism in both articular cartilage and subchondral bone, offering additional therapeutic leverage against OA progression.[78]

Delivery Systems of Mechanosensitive miRNAs

Mechanosensitive miRNA expression is dynamically modulated by mechanical stress at the single-cell level.[20] Externally applied forces trigger cells in articular cartilage and subchondral bone to produce miRNAs, which diffuse locally to influence both the producing cells (autocrine) and surrounding cell populations (paracrine), mediating crosstalk across the osteochondral interface.[79] Compelling evidence confirms that mechanosensitive miRNAs orchestrate OA development by dynamically modulating mRNA targets involved in chondrocyte metabolism and osteogenic differentiation.[33] Mechanical stress imbalance triggers pathological bidirectional miRNA crosstalk across the osteochondral interface, establishing self-reinforcing feedback cycles.[7,19,79] For instance, under abnormal loading, osteoclast-derived EVs deliver miR-212-3p targeting Smad2 in chondrocytes, suppressing TGF-β signaling and accelerating matrix degradation,[80] while EV-transported miR-214-3p inhibits ATF4, compromising cartilage anabolism.[81] Injured chondrocytes release miR-221-enriched EVs that target Runx2 in osteoblasts, impairing bone formation and exacerbating subchondral sclerosis.[36] Bone sclerosis increases shear stress on articular surfaces while cartilage degradation products (eg, TGF-β) further activate osteoclasts, establishing a "subchondral sclerosis-cartilage degradation" vicious cycle.[45,78,82]

However, the therapeutic potential of extracellular miRNAs is limited by their rapid degradation by nucleases in biological fluids.[83,84] Particularly in OA joints, therapeutic macromolecules such as miRNA-based agents are subject to rapid clearance by synovial fluid dynamics.[85,86] Furthermore, extracellular miRNAs administered via joint injection can trigger innate immune activation, which not only amplifies inflammatory responses in OA but also poses biosecurity risks.[87,88] Moreover, the densely packed and negatively charged cartilage ECM impedes cellular uptake and penetration of miRNA therapeutics due to their large size, anionic charge, and hydrophilicity. Concurrently, lysosomal degradation poses an additional barrier to achieving functional bioavailability. Consequently, advanced miRNA delivery systems that enhance nuclease resistance, prolong intra-articular retention, facilitate cellular internalization, and promote endosomal escape are essential to realizing the therapeutic potential of miRNA-based OA interventions.[89] Leveraging advances in nucleic acid chemistry and nanodelivery systems, engineered miRNA-based therapies—including polyplexes, liposomes, and exosomes—are emerging as clinically impactful modalities for OA treatment. These systems enable durable and targeted modulation of pathological drivers through site-specific delivery of miRNA mimics or antagonists encapsulated in polymeric/lipid vehicles.[90–92] Optimal delivery platform selection must account for spatiotemporal disease progression, where nanoparticle-based systems show advantages in early synovial inflammation targeting,[93] while EV-mediated approaches may better penetrate sclerotic subchondral bone in late OA.[94,95]

As nanoscale vesicles secreted by cells, EVs carry cargoes including DNA, mRNA, proteins, lipids, and miRNAs, enabling rapid intertissue transport.[96] Their capacity to traverse microcrack channels and vascular conduits at the bone–cartilage interface facilitates bidirectional communication, as depicted in Figure 1.[97,98] The lipid bilayer of EVs confers functional versatility by shielding miRNAs from extracellular nucleases during intercellular transit, thereby preserving their structural integrity and bioactivity. For instance, Liu et al demonstrated that mechanical stress triggers osteocytes in

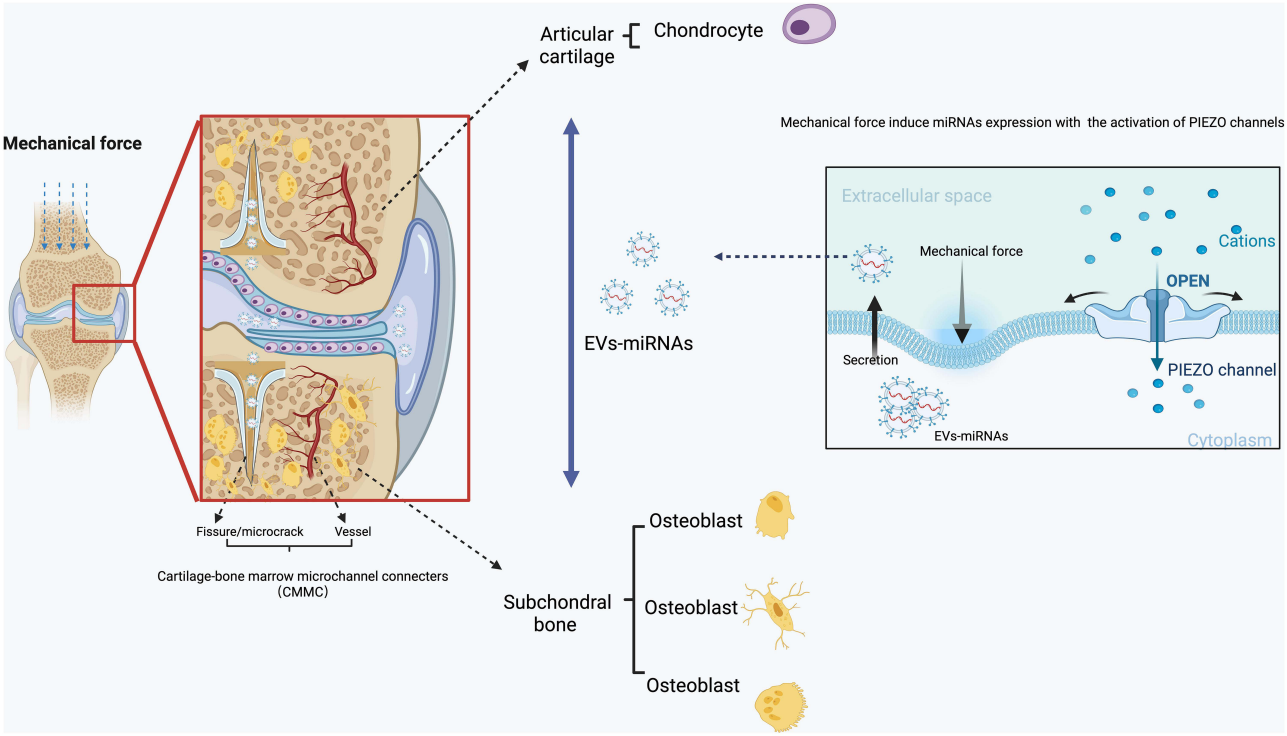

Figure 1 Mechanical loading can regulate the expression of mechanosensitive miRNAs in articular cartilage and subchondral bone with the activation of PIEZO channels. Under the protection of EVs transport, the mechanosensitive signal communication between the bone–cartilage structure is carried out through cartilage-bone marrow microchannel connectors (CMMC) such as fissure, microcrack, and vessel across the bone–cartilage interface, and then intervenes to regulate osteochondral metabolism.

subchondral bone to secrete EVs, accelerating cartilage metabolic dysregulation in both human patients and male mice. The EV-encapsulated miR-23b-3p promotes cartilage catabolism and suppresses anabolism by targeting OTUD4, thereby disrupting chondrocyte mitophagy. Suppression of miR-23b-3p in osteocytes or chondrocytes attenuates cartilage degeneration and halts OA progression in male mice. Collectively, these findings establish osteocyte-derived EVs as mediators of bone-cartilage crosstalk and nominate miR-23b-3p as a potential therapeutic target for OA.[98] Mirroring this protective mechanism, synoviocyte-derived EVs deliver functional miR-150-3p to chondrocytes, attenuating inflammation and degeneration via Trim14/NF-κB/IFNβ axis regulation—a potential cartilage-protective pathway for OA therapy.[99] Although EV-mediated miRNAs can potentially transmit mechanosensitive signals between chondrocytes and fibroblast-like synoviocytes, their free movement across the dense, avascular ECM of cartilage remains challenging. To address this limitation, Liang et al engineered exosomes by fusing chondrocyte-affinity peptides (CAPs). These CAP-modified exosomes efficiently encapsulated miR-140 and delivered the cargo into chondrocytes in vitro. Moreover, these engineered exosomes effectively delivered miR-140 to deeper cartilage regions, inhibited cartilage-degrading proteases, and slowed OA progression in vivo. This approach provides a promising targeted, cell-free therapeutic strategy for OA.[100] Moreover, miR-223 was identified as a key mediator through which human umbilical cord-derived extracellular vesicles (hUC-EVs) exert anti-inflammatory and chondroprotective effects by targeting the NLRP3 inflammasome.[101] To enhance the targeting efficiency and therapeutic efficacy of RNA delivery to cartilage, this study employed a dual-engineering strategy: exogenous miR-223 was loaded into hUC-EVs via electroporation, while the vesicle surface was modified with a collagen II-targeting peptide using genetic engineering. Consequently, these dual-engineered EVs significantly attenuated OA progression by suppressing NLRP3 inflammasome activation and chondrocyte pyroptosis, thereby establishing a novel theoretical framework for engineered EV-mediated miRNA therapy in OA treatment.[101]

Beyond facilitating EV transport within cartilage, EV-mediated miRNAs critically regulate subchondral bone remodeling by modulating osteoclast–osteoblast balance. For instance, Li et al demonstrated that osteoclast-derived exosomal miR-214-3p suppresses osteoblastic bone formation in ovariectomized mice by targeting ATF4.[81] In parallel to

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natural EV-mediated intercellular transfer, mechanosensitive miRNAs can be delivered via engineered polymer-based systems. These include poly(lactic-co-glycolic acid) (PLGA), chitosan, polyethyleneimine (PEI), and polyamidoamine (PAMAM) dendrimers.[100] A representative example is the miR-140-activated collagen hydrogel developed by Rajagopal et al, which promotes mesenchymal stem cell (MSC) chondrogenic differentiation and hyaline cartilage production by: Upregulating cartilage-specific genes (COL2A1, SOX9, ACAN), suppressing hypertrophic markers (eg, COL10A1), and sustaining miRNA bioavailability through controlled release from the hydrogel matrix.[102] Similarly, Zhao et al demonstrated that a short peptide-conjugated chitosan complex (pNNS-CS) delivering miR-140 and IGF-1 effectively protected chondrocytes and enhanced cartilage repair. This was achieved both through in vitro transfection into chondrocytes and in vivo intra-articular injection into knee joints.[103] In parallel, Carthew et al engineered a mechanoresponsive polyethylene glycol/gelatin-norbornene hydrogel (GelNB-PEG) encapsulating mechanosensitive miR-100-5p and miR-143-3p. This system significantly promoted the in situ osteogenic differentiation of mesenchymal stem cells (MSCs), demonstrating dual capabilities: Facilitating bone and cartilage repair via mechanosensitive miRNA action, and providing a translatable platform for bone tissue engineering applications.[104] Consequently, developing self-regulating, mechanoresponsive delivery systems holds significant potential for addressing the critical unmet therapeutic needs in OA as shown in Table 3.

Table 3 Delivery Vehicles of Mechanosensitive miRNAs and Clinical Relevance in OA

miRNA	Target	miRNA source	Delivery vehicles	Function	Literature	Clinical relevance
miR-23b-3p	OTUD4	Osteocyte	EVs	Targeted delivery of miR-23b-3p via engineered EVs facilitates bone-cartilage crosstalk, offering a promising OA treatment approach.	Liu et al 2025[98]	Cartilage
miR-212-3p	Smad2	Osteoclasts	Exosomes	Exosome mediated osteoclast-derived miR-212-3p delivery could promote chondrocyte dysfunction and cartilage degradation.	Dai et al 2024[80]	Cartilage
miR-26b-5p	TLR3 and COL10A1	Macrophage	Exosomes	Exosome mediated macrophage-derived miR-26b-5p delivery could protect cartilage and ameliorate gait abnormalities in OA mice.	Qian et al 2024[105]	Cartilage
miR-223	NLRP3	Exogenous	WYRGRL-EVs	Dual-engineered EVs mediated miR-223 delivery inhibits the activation of NLRP3 inflammasome and chondrocyte proptosis.	Liu et al 2023[101]	Cartilage
miR-140	NA	Exogenous	CPP-NPs	CPP-NPs demonstrates outstanding penetrability and accumulation in cartilage.	Zhao et al 2023[106]	Bone Remodeling
miR-146b-5p	TRAF6	MSCs	Exosomes	Exosome mediated miR-146b-5p delivery suppresses inflammatory responses and ECM degradation and protects cartilage.	Lou et al 2023[107]	Cartilage
miR-199a-3p	mTOR	MSCs	CAP-exosomes	CAP binding MSCs-exosomes transfer miR-199a-3p to protect chondrocytes.	Zhao et al 2023[108]	Cartilage
miR-224-5p	PTX3	Exogenous	G5-AHP nanoparticle	G5-AHP nanoparticles mediated miR-224-5p delivery could inhibit cartilage degeneration and synovial inflammation.	Chen et al 2023[109]	Cartilage
miR-9-5p	KLF5	Chondrocytes	Exosomes	Reduction of circStrn3 could increase miR-9-5p expression and be protective for mechanical instability-induced OA.	Li et al 2023[33]	Cartilage

(*Continued*)

Table 3 (Continued).

miRNA	Target	miRNA source	Delivery vehicles	Function	Literature	Clinical relevance
miR-148a	DNMT-1	Cow's milk	EVs	CMEVs carrying TGFβ and miR-148a could regulate chondrocyte homeostasis and protect cartilage.	Pieters et al 2022[110]	Cartilage
miR-150-3p	Trim14	FLSs	EVs	EVs-mediated miR-150-3p delivery could be a novel therapeutic strategy of OA.	Wang et al 2022[99]	Cartilage
miR-29b-5p	TET1	MSCs	SKP@miR	Stem cell-homing hydrogel-based miR-29b-5p delivery could promote cartilage regeneration in OA.	Zhu et al 2022[111]	Cartilage
miR-486-5p	PTEN	ADSCs	Exosomes	miR-486-5p modified exosomes could alleviate chondrocyte apoptosis.	Wang et al 2022[112]	Cartilage
miR-100-5p miR-143-3p	mTOR	MSCs	GelNB-PEG hydrogel	GelNB-PEG hydrogel could increase MSC osteogenic capability without multi-step transfection procedures.	Carthew et al 2020[104]	Bone Remodeling
miR-140	MMP-13 Adamts-5	Chondrocytes	CAP-exosomes	Engineered exosomes mediated miR-140 delivery in chondrocytes could alleviates OA progress.	Liang et al 2020[100]	Cartilage
miR- 100-5p	mTOR	MSCs	Exosomes	MSCIPFP-derived exosomes could inhibit cartilage degeneration and ameliorate gait abnormality in OA.	Wu et al 2019[113]	Cartilage
miR-221	NA	Exogenous	(FB/HA) hydrogel	FB/HA hydrogel loaded with antimiR-221/ lipofectamine could promote cartilage repair.	Lolli et al 2019[114]	Cartilage
miR-100-5p miR-143-3p	mTOR	MSCs	Gelatin-PEG hydrogel	Modulating the expression of mechanosensitive miRNAs could enhance osteogenesis capability in Gelatin-PEG hydrogel.	Frith et al 2018[115]	Bone Remodeling
miR-140-5p	RalA	MSCs	Exosomes	exosomes mediated miR-140-5p could enhance the proliferation and migration of chondrocytes.	Tao et al 2017[116]	Cartilage
miR-199a-5p	HIF1a	MSCs	Chitosan-nanoparticle	Chitosan-nanoparticle mediated miR-199a-5p agomir delivery could improve osteogenic capability of mesenchymal stem cells.	Chen et al 2015[117]	Bone Remodeling
miR-149-5p	FUT-1	Exogenous	polysaccharide-nanoparticles	Polysaccharide-nanoparticles mediated microRNA-149-5p delivery could achieve a collaborative impact on cartilage regeneration.	Celik et al 2019[118]	Cartilage
miR365	NA	Exogenous	NPs-YCWP-oral system	NPs-YCWP-oral system mediated miR365 antagomir delivery could improve the symptoms of PTOA.	Zhang et al 2020[119]	Cartilage

Note: NA: Information not reported or not investigated in the source study.

Discussion and Future Perspective

Emerging evidence underscores the pivotal role of mechanosensitive miRNAs in orchestrating multi-tissue responses to mitigate OA pathogenesis. At the inflammation level, miR-146a-5p potently suppresses synovitis by targeting TRAF6, effectively dampening NF-κB signaling and reducing IL-1β-driven TNF-α production in chondrocytes.[41] Complementarily, miR-140-5p demonstrates dual regulatory capacity—inhibiting IL-6/STAT3 pro-inflammatory cascades while directly suppressing MMP13 and ADAMTS5 expression to preserve cartilage integrity.[116] The discovery that synovial macrophage-derived exosomes transport miR-223-3p across tissue barriers to inhibit NLRP3 inflammasome

activation in chondrocytes further illustrates how miRNA signaling coordinates joint-wide anti-inflammatory responses.[101] Beyond inflammation control, these regulatory molecules critically influence cellular differentiation and matrix homeostasis. Chondrocyte autophagy—a key protective mechanism against degradation—is enhanced by miR-199a-3p through ATG7 pathway activation,[108] while miR-365 promotes collagen synthesis via HDAC4 inhibition and subsequent SOX9 upregulation.[38] In subchondral remodeling, miR-100-5p modulates Wnt/β-catenin signaling by targeting DKK2, preventing pathological osteophyte formation, whereas miR-208a-3p fine-tunes osteoblast differentiation through ACVR1 repression.[53]

Notably, miRNA-mediated osteochondral crosstalk constitutes a critical pathological axis. Chondrocyte-derived exosomes deliver miR-221 to osteoblasts, suppressing Runx2 expression and bone formation,[36] while osteoclast-secreted miR-214-3p accelerates cartilage breakdown through apoptotic pathway activation.[81] This bidirectional feedforward cascade highlights why targeted interventions—such as chitosan nanoparticles delivering miR-140—concurrently ameliorate cartilage erosion and subchondral sclerosis preclinical models.[103] Collectively, these mechanisms demonstrate how miRNAs integrate inflammation resolution, metabolic equilibrium, and structural remodeling across joint tissues, establishing them as master regulators of OA pathophysiology with significant therapeutic implications.

Although mechanosensitive miRNAs offer novel insights into OA progression and present promising therapeutic targets, clinically reliable outcomes remain limited. To date, clinical trials investigating miRNA-based OA diagnostics and therapeutics are scarce, with only five registered studies on ClinicalTrials.gov (NCT03869229, NCT05683769, NCT04851210, NCT03866330, NCT05869630; summarized in Table 4). This scarcity largely stems from inconsistent methodologies in miRNA handling across studies,[120–123] including variations in: Sample processing (eg, RNA extraction protocols from synovial fluid vs serum); Analytical platforms (eg, qPCR, RNA-seq, nanopore detection); Delivery systems (eg, exosomes, hydrogels, polymer carriers). Addressing these methodological gaps requires standardization of key procedures:[120–123] Establishing uniform protocols for biofluid collection, storage, and miRNA isolation to minimize degradation; Defining sensitivity/specificity thresholds for miRNA biomarkers across detection platforms; Optimizing targeted delivery systems (eg, CAP-exosomes, peptide-conjugated polymers) to enhance joint bioavailability; Determining effective miRNA mimic/inhibitor concentrations while minimizing off-target effects. Resolving these issues is essential before miRNA-based therapies can advance to clinical application.

Firstly, the effects of specific miRNAs, including miR-146a, are not consistent across different studies.[124–126] This miRNA plays a vital role in cartilage integrity and is crucial for maintaining joint homeostasis. Consequently, miR-146a-based therapies have garnered significant attention in OA research, with numerous epigenetic studies aiming to enhance chondrogenesis and inhibit cartilage degeneration by targeting it.[42,127–129] However, contrasting findings present a challenge: miR-146a is reported to be highly expressed in early-stage OA cartilage but downregulated in severe OA. Furthermore, some studies indicate that the overexpression of miR-146a can reduce IL-1β-induced TNF-α production in chondrocytes, highlighting its complex and context-dependent regulatory functions.[43]

Secondly, the precise quantitative determination of effective doses for miRNA-based therapeutics or inhibitors presents a major translational challenge prior to clinical application of mechanosensitive miRNAs. Both in vivo and in vitro, mechanical stresses (eg, compression, shear stress, tension, hydrostatic pressure, and fluid flow) dynamically

Table 4 Current Clinical Trials About miRNAs in the Diagnosis and Treatment of OA

NCT Number	Study Title	Study Status	Study Type
NCT03869229	Adipose-derived Mesenchymal Stem Cells in Osteoarthritis	Unknown	Interventional
NCT05683769	microRNA in Erosive Hand Osteoarthritis and Psoriatic Arthritis	Completed	Observational
NCT04851210	Identification of miRNAs Associated with Gender Difference in Osteoarthritis Patients	Recruiting	Observational
NCT03866330	Wharton's Jelly-derived Mesenchymal Stem Cells in Osteoarthritis	Unknown	Interventional
NCT05869630	Exercise on microRNA in Osteoarthritis	Completed	Interventional

Abbreviation: NCT, National Clinical Trial.

regulate miRNA synthesis and secretion in articular chondrocytes and osteocytes, enabling cellular adaptation to environmental changes.[130,131] However, the heterogeneity of mechanical stimuli leads to divergent miRNA expression profiles, which subsequently modulate downstream signaling pathways in a context-dependent manner. Key pathways implicated in OA pathogenesis—including NF-κB, Wnt/β-catenin, SIRT1/p53, and SDF1/CXCR4—are differentially regulated by miRNAs under varying biomechanical conditions,[130,131] complicating the quantification of therapeutic efficacy. Moreover, translational barriers remain substantial. Most reported therapeutic outcomes derive from animal models, where miRNA interventions show efficacy in alleviating OA pathology.[14] Notably, species-specific differences in miRNA targeting mechanisms (eg, miR-122 targeting distinct TGF-β pathway components in humans vs mice) raise concerns about human applicability. Safety profiles of systemic miRNA delivery (eg, off-target effects, immunogenicity) also require rigorous evaluation before clinical translation.[122]

In particular, delivery systems for mechanosensitive miRNAs—especially EVs that act as intercellular messengers—have become a major focus of cartilage regeneration and OA research, owing to their ability to deliver bioactive factors.[132] However, the heterogeneous molecular cargo within EVs could compromise the therapeutic efficacy of encapsulated drugs. Moreover, key challenges must be addressed before clinical translation, including efficient drug loading into EVs, achieving targeted delivery, and scaling up EV production.[84,133]

Beyond direct mechanical regulation of miRNA expression, mechanical stimuli may also directly modulate the corresponding miRNA target molecules themselves, independently influencing downstream signaling pathways.

Notably, significant sex- and age-related differences in mechanosensitive miRNA expression critically influence OA pathogenesis and therapeutic response. Postmenopausal women exhibit diminished estrogen receptor α (ERα) expression, unleashing miR-203 overexpression, which targets ERα and amplifies cartilage degradation, explaining higher OA incidence versus age-matched males.[40,109,134] More importantly, Erα have been reported to play important roles in the etiology of OA by being involved in the regulation of mechanotransduction pathways. A recent study showed that ERα levels were decreased in knee cartilage chondrocytes under mechanical overload, implying that ERα may be highly responsive to mechanical stress, and regulation of ERα levels may provide a novel therapeutic target for the treatment of OA.[134] Meanwhile, Erα has also been reported to be the target of mechanosensitive miR-203, and a study demonstrated that intra-articular injection of a miR-203 inhibitor could attenuate cartilage degradation by elevating ERα levels in vivo, and this undoubtedly adds complexity to the regulation of the mechanotransduction process and represents a new method to treat OA.[40,57,135] However, although sex-dependent differences may play a vital role in the mechanical stress-induced mechanotransduction of articular cartilage, decreased ERα levels result in different responses to mechanical force between old male and female chondrocytes remain to be reported.[136] Besides, aging also fundamentally reprograms miRNA mechanoresponsiveness: senescent chondrocytes show blunted miR-140 induction but sustained miR-365 overexpression under cyclic strain, disrupting TGF-β/HDAC4 crosstalk essential for ECM homeostasis.[38,54] These findings necessitate sex- and age-stratified therapeutic approaches, such as ERα-stabilizing miR-203 inhibitors for postmenopausal women and EV-mediated miR-100-5p delivery to restore osteochondral mechanotransduction in elderly patients.[40,56,86,113,137]

Similarly, the TGFβ signaling pathway plays a critical role in chondrocyte anabolism. Impairing TGFβ activity diminishes the anabolic response to mechanical stress, highlighting TGFβ's vital function in mediating mechanical signals within articular cartilage. Previous studies confirm that maintaining physiological TGFβ levels is essential for articular cartilage homeostasis, as dysregulation (either excessive or insufficient activation) proves detrimental.[138] Consequently, precise modulation of TGFβ expression in chondrocytes remains unclear. Notably, recent research suggests mechanical stress may induce TGFβ activation in articular cartilage, potentially contributing to OA development.[139] Intriguingly, research on mechanosensitive miRNAs provides a potential molecular explanation for how chondrocytes sense mechanical stress and dynamically modulate their miRNA expression profiles. For instance, Jin et al demonstrated that applying 10 MPa mechanical stress for 60 minutes upregulated miR-146a expression in human chondrocytes. This increase contributed to chondrocyte mechanical injury by interfering with the TGF-β signaling pathway via targeted inhibition of Smad4.[41] Similarly, Zhang et al observed that mechanical unloading upregulated miR-212-3p in MC3T3-E1 cells. This miRNA subsequently inhibited osteogenic differentiation by directly targeting High Mobility Group Box 1 protein (HMGB1) in vivo, highlighting its mechanosensitive nature.[54] Furthermore, Dai et al

revealed that osteoclast-derived miR-212-3p, transferred via EVs, targeted Smad2 in chondrocytes. This mechanism induced chondrocyte dysfunction and accelerated cartilage matrix degradation in both OA patients and mouse models. Collectively, these findings underscore the interaction between mechanosensitive miRNAs and the TGF-β signaling pathway as a promising therapeutic target for OA prevention and treatment, particularly given the critical role of mechanical loading in articular cartilage and subchondral bone remodeling during OA progression.[80]

Critically, mechanosensitive miRNAs orchestrate OA pathogenesis through hierarchical regulation of core mechanotransduction pathways in a loading-dependent manner. The YAP/TAZ pathway is suppressed by miR-103a targeting Runx2 under physiological cyclic stretch, but pathologically amplified by unloading-induced miR-30 overexpression, which stabilizes nuclear YAP.[52,60] Concurrently, Wnt/β-catenin signaling is gated by mechanical thresholds: physiological fluid shear upregulates miR-100-5p to inhibit DKK2, sustaining Wnt activation for bone homeostasis, whereas abnormal compression induces miR-154-5p-mediated Wnt5a degradation, disrupting sclerostin regulation.[51,56] For NF-κB inflammation, miR-146a serves as a mechanical rheostat—degrading TRAF6 to resolve physiological inflammation at <5 MPa compression, but failing catastrophically at >10 MPa where IL-1β hyperactivation overrides its suppression.[41] Most pivotally, TGF-β/Smad signaling exhibits bidirectional miRNA control: physiological loading induces miR-140 to enhance TGFβR2 sensitivity for ECM maintenance, while pathological shear stress triggers osteoclast-derived miR-212-3p transfer via EVs to silence Smad2 in chondrocytes, uncoupling anabolic responses.[80] This paradigm explains how miRNAs convert mechanical energy into precise epigenetic instructions across the osteochondral unit.

Finally, the spatiotemporal dynamics of mechanical forces—encompassing load magnitude, frequency, duration, and type—critically orchestrate stage-specific miRNA responses during OA progression. In early OA, physiological low-magnitude cyclic compression induces protective miR-140 and miR-146a expression, maintaining cartilage homeostasis by suppressing NF-κB-mediated inflammation and MMP13/ADAMTS5-driven matrix degradation.[27,140] Conversely, progressive OA is characterized by sustained pathological compression, which upregulates miR-365 and miR-21-5p.[38,141] These miRNAs drive catabolic ECM breakdown through HDAC4 suppression and TGF-β pathway dysregulation, accelerating joint degeneration.[38,56,141] Within subchondral bone, low-to-moderate shear stress during early remodeling activates osteogenic miR-100-5p and miR-20a, enhancing Wnt/β-catenin signaling for physiological adaptation.[48,56] However, high-magnitude/low-frequency loads (eg, joint malalignment or impact trauma) in late-stage OA trigger pathological overexpression of miR-208a-3p and miR-212-3p.[53,80] These miRNAs promote aberrant bone sclerosis through Runx2 inhibition and Smad2 silencing, ultimately disrupting osteochondral crosstalk.[53,80,82] This dynamic regulation establishes miRNAs as mechanically gated rheostats that convert physical stimuli into stage-specific pathological signals across the osteochondral unit.

Conclusion

Emerging evidence solidifies the pivotal role of mechanosensitive miRNAs as key regulators in OA pathogenesis, dynamically orchestrating cartilage and bone homeostasis in direct response to mechanical cues. This review synthesizes critical advances, revealing that specific miRNAs (eg, miR-140, miR-365, miR-221/222) act as mechanoresponsive mediators, critically linking aberrant mechanical loading to OA progression through their regulation of ECM degradation, inflammation, and subchondral bone remodeling. Furthermore, EVs have emerged as crucial facilitators, enabling the transfer of these regulatory miRNAs across the osteochondral interface and unveiling a novel pathway for bidirectional mechanotransduction communication between chondrocytes and osteocytes. The significant therapeutic potential is underscored by promising strategies employing engineered EVs (eg, CAP-exosomes) and advanced biomaterial-based delivery systems (like peptide-modified hydrogels), which demonstrably enhance cartilage penetration and miRNA stability, yielding encouraging results in preclinical OA models. However, translating this exciting potential into tangible clinical benefits necessitates addressing key hurdles. Future efforts must prioritize establishing standardized methods for profiling miRNA mechanosensitivity across diverse OA stages and mechanical environments, developing dose-optimized delivery platforms capable of overcoming synovial clearance and immune activation challenges, and conducting rigorous validation of EV cargo specificity and long-term safety in robust large-animal models. Looking forward, the field must focus on integrating multi-omics approaches to comprehensively map the intricate networks governed by miRNA-

mechanotransduction, designing next-generation "smart" biomaterials offering spatiotemporal control for site-specific miRNA release, and advancing into well-designed clinical trials evaluating EV-based miRNA therapies (such as NCT03869229) specifically in early OA patient cohorts. Successfully harnessing the power of mechanosensitive miRNAs as precision therapeutics holds immense promise to fundamentally redefine OA management strategies by restoring healthy joint mechano-homeostasis and effectively halting disease progression.

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References

1. Tang S, Zhang C, Oo WM, et al. Osteoarthritis. *Nat Rev Dis Primers*. 2025;11(1):10. doi:10.1038/s41572-025-00594-6
2. Courties A, Kouki I, Soliman N, Mathieu S, Sellam J. Osteoarthritis year in review 2024: epidemiology and therapy. *Osteoarthritis Cartilage*. 2024;32(11):1397–1404. doi:10.1016/j.joca.2024.07.014
3. Lei L, Wen Z, Cao M, et al. The emerging role of Piezo1 in the musculoskeletal system and disease. *Theranostics*. 2024;14(10):3963–3983. doi:10.7150/thno.96959
4. Ma Z, Vyhlidal MJ, Li DX, Adesida AB. Mechano-bioengineering of the knee meniscus. *Am J Physiol Cell Physiol*. 2022;323(6):C1652–C1663. doi:10.1152/ajpcell.00336.2022
5. Hodgkinson T, Kelly DC, Curtin CM, O'Brien FJ. Mechanosignalling in cartilage: an emerging target for the treatment of osteoarthritis. *Nat Rev Rheumatol*. 2022;18(2):67–84. doi:10.1038/s41584-021-00724-w
6. Vincent TL, McClurg O, Troeberg L. The extracellular matrix of articular cartilage controls the bioavailability of pericellular matrix-bound growth factors to drive tissue homeostasis and repair. *Int J Mol Sci*. 2022;23(11):6003. doi:10.3390/ijms23116003
7. Steinecker-Frohnwieser B, Lohberger B, Toegel S, et al. Activation of the mechanosensitive ion channels Piezo1 and TRPV4 in primary human healthy and osteoarthritic chondrocytes exhibits ion channel crosstalk and modulates gene expression. *Int J Mol Sci*. 2023;24(9):7868. doi:10.3390/ijms24097868
8. Dieterle MP, Husari A, Rolauffs B, Steinberg T, Tomakidi P. Integrins, cadherins and channels in cartilage mechanotransduction: perspectives for future regeneration strategies. *Expert Rev Mol Med*. 2021;23:e14. doi:10.1017/erm.2021.16
9. Wang Y, Jin Z, Jia S, Shen P, Yang Y, Huang Y. Mechanical stress protects against chondrocyte pyroptosis through TGF-β1-mediated activation of Smad2/3 and inhibition of the NF-κB signaling pathway in an osteoarthritis model. *Biomed Pharmacother*. 2023;159:114216. doi:10.1016/j.biopha.2023.114216
10. Bjerre-Bastos JJ, Hamrouni N, Henrotin Y, Thudium CS, Bihlet AR. Joint biomarker response to mechanical stimuli in osteoarthritis - A scoping review. *Osteoarthr Cartil Open*. 2023;5(4):100390. doi:10.1016/j.ocarto.2023.100390
11. Smirnova O, Efremov Y, Klyucherev T, et al. Direct and cell-mediated EV-ECM interplay. *Acta Biomater*. 2024;186:63–84. doi:10.1016/j.actbio.2024.07.029
12. Jin P, Liu H, Chen X, Liu W, Jiang T. from bench to bedside: the role of extracellular vesicles in cartilage injury treatment. *Biomater Res*. 2024;28:0110. doi:10.34133/bmr.0110
13. Sheth M, Sharma M, Kongsomros S, et al. Matrix stiffness modulated release of spheroid-derived extracellular vesicles and discovery of Piezo1 cargo. *bioRxiv*. 2025;2025.
14. Szala D, Kopańska M, Trojniak J, et al. The role of MicroRNAs in the pathophysiology of osteoarthritis. *Int J Mol Sci*. 2024;25(12):6352. doi:10.3390/ijms25126352
15. Lin J, Jia S, Zhang W, et al. Recent advances in small molecule inhibitors for the treatment of osteoarthritis. *J Clin Med*. 2023;12(5):1986. doi:10.3390/jcm12051986
16. Liu D, Li X, Zhang L, et al. Small molecule inhibitors of osteoarthritis: current development and future perspective. *Front Physiol*. 2023;14:1156913. doi:10.3389/fphys.2023.1156913
17. Lafont JE, Moustaghfir S, Durand A-L, Mallein-Gerin F. The epigenetic players and the chromatin marks involved in the articular cartilage during osteoarthritis. *Front Physiol*. 2023;14:1070241. doi:10.3389/fphys.2023.1070241
18. Lu TX, Rothenberg ME. MicroRNA. *J Allergy Clin Immunol*. 2018;141(4):1202–1207. doi:10.1016/j.jaci.2017.08.034
19. Jin L, Ma J, Chen Z, et al. Osteoarthritis related epigenetic variations in miRNA expression and DNA methylation. *BMC Med Genomics*. 2023;16(1):163. doi:10.1186/s12920-023-01597-6
20. Hecht N, Johnstone B, Angele P, Walker T, Richter W. Mechanosensitive MiRs regulated by anabolic and catabolic loading of human cartilage. *Osteoarthritis Cartilage*. 2019;27(8):1208–1218. doi:10.1016/j.joca.2019.04.010
21. Kim M, Rubab A, Chan WCW, Chan D. Osteoarthritis year in review 2022: genetics, genomics and epigenetics. *Osteoarthritis Cartilage*. 2023;31(7):865–875. doi:10.1016/j.joca.2023.03.003
22. Mihanfar A, Shakouri SK, Khadem-Ansari MH, et al. Exosomal miRNAs in osteoarthritis. *Mol Biol Rep*. 2020;47(6):4737–4748. doi:10.1007/s11033-020-05443-1
23. Zhang K, Wang L, Liu Z, et al. Mechanosensory and mechanotransductive processes mediated by ion channels in articular chondrocytes: potential therapeutic targets for osteoarthritis. *Channels*. 2021;15(1):339–359. doi:10.1080/19336950.2021.1903184
24. Lee W, Leddy HA, Chen Y, et al. Synergy between Piezo1 and Piezo2 channels confers high-strain mechanosensitivity to articular cartilage. *Proc Natl Acad Sci U S A*. 2014;111(47):E5114–5122. doi:10.1073/pnas.1414298111

25. Dunn W, DuRaine G, Reddi AH. Profiling microRNA expression in bovine articular cartilage and implications for mechanotransduction. *Arthritis Rheum*. 2009;60(8):2333–2339. doi:10.1002/art.24678
26. Ramos YFM, Rice SJ, Ali SA, et al. Evolution and advancements in genomics and epigenomics in OA research: how far we have come. *Osteoarthritis Cartilage*. 2024;32(7):858–868. doi:10.1016/j.joca.2024.02.656
27. Stadnik PS, Gilbert SJ, Tarn J, et al. Regulation of microRNA-221, −222, −21 and −27 in articular cartilage subjected to abnormal compressive forces. *J Physiol*. 2021;599(1):143–155. doi:10.1113/JP279810
28. Vazquez KJ, Andreae JT, Henak CR. Cartilage-on-cartilage cyclic loading induces mechanical and structural damage. *J Mech Behav Biomed Mater*. 2019;98:262–267. doi:10.1016/j.jmbbm.2019.06.023
29. Nims R, Palmer DR, Kassab J, Zhang B, Guilak F. The chondrocyte 'mechanome': activation of the mechanosensitive ion channels TRPV4 and PIEZO1 drives unique transcriptional signatures. *FASEB J*. 2024;38(13):e23778. doi:10.1096/fj.202400883R
30. Li Q, Yu H, Zhao F, et al. 3D printing of microenvironment-specific bioinspired and exosome-reinforced hydrogel scaffolds for efficient cartilage and subchondral bone regeneration. *Adv Sci*. 2023;10(26):e2303650. doi:10.1002/advs.202303650
31. Lv M, Zhou Y, Chen X, Han L, Wang L, Lu XL. Calcium signaling of in situ chondrocytes in articular cartilage under compressive loading: roles of calcium sources and cell membrane ion channels. *J Orthop Res*. 2018;36(2):730–738. doi:10.1002/jor.23768
32. Chen Z, Zhang Y, Liang C, Chen L, Zhang G, Qian A. Mechanosensitive miRNAs and BONE FORMATIon. *Int J Mol Sci*. 2017;18(8):1684.
33. Li B, Ding T, Chen H, et al. CircStrn3 targeting microRNA-9-5p is involved in the regulation of cartilage degeneration and subchondral bone remodelling in osteoarthritis. *Bone Joint Res*. 2023;12(1):33–45. doi:10.1302/2046-3758.121.BJR-2022-0231.R1
34. Cao H, Zhou X, Li H, Wang M, Wu W, Zou J. Study on the role of MicroRNA-214 in the rehabilitation of cartilage in mice with exercise-induced traumatic osteoarthritis. *Curr Issues Mol Biol*. 2022;44(9):4100–4117. doi:10.3390/cimb44090281
35. Chaudhry N, Muhammad H, Seidl C, et al. Highly efficient CRISPR-Cas9-mediated editing identifies novel mechanosensitive microRNA-140 targets in primary human articular chondrocytes. *Osteoarthritis Cartilage*. 2022;30(4):596–604. doi:10.1016/j.joca.2022.01.005
36. Shang X, Böker KO, Taheri S, Lehmann W, Schilling AF. Extracellular vesicles allow epigenetic mechanotransduction between chondrocytes and osteoblasts. *Int J Mol Sci*. 2021;22(24):13282. doi:10.3390/ijms222413282
37. Chen J, Wu X. Cyclic tensile strain promotes chondrogenesis of bone marrow-derived mesenchymal stem cells by increasing miR-365 expression. *Life Sci*. 2019;232:116625. doi:10.1016/j.lfs.2019.116625
38. Yang X, Guan Y, Tian S, Wang Y, Sun K, Chen Q. Mechanical and IL-1β responsive miR-365 contributes to osteoarthritis development by targeting histone deacetylase 4. *Int J Mol Sci*. 2016;17(4):436. doi:10.3390/ijms17040436
39. Guan Y-J, Yang X, Wei L, Chen Q. MiR-365: a mechanosensitive microRNA stimulates chondrocyte differentiation through targeting histone deacetylase 4. *FASEB J*. 2011;25(12):4457–4466. doi:10.1096/fj.11-185132
40. Tian L, Su Z, Ma X, Wang F, Guo Y. Inhibition of miR-203 ameliorates osteoarthritis cartilage degradation in the postmenopausal rat model: involvement of estrogen receptor α. *Hum Gene Ther Clin Dev*. 2019;30(4):160–168. doi:10.1089/humc.2019.101
41. Jin L, Zhao J, Jing W, et al. Role of miR-146a in human chondrocyte apoptosis in response to mechanical pressure injury in vitro. *Int J Mol Med*. 2014;34(2):451–463. doi:10.3892/ijmm.2014.1808
42. Duan L, Liang Y, Xu X, Xiao Y, Wang D. Recent progress on the role of miR-140 in cartilage matrix remodelling and its implications for osteoarthritis treatment. *Arthritis Res Ther*. 2020;22(1):194. doi:10.1186/s13075-020-02290-0
43. Ghafouri-Fard S, Bahroudi Z, Shoorei H, Abak A, Ahin M, Taheri M. microRNA-140: a miRNA with diverse roles in human diseases. *Biomed Pharmacother*. 2021;135:111256. doi:10.1016/j.biopha.2021.111256
44. Zhang H, Wang L, Cui J, et al. Maintaining hypoxia environment of subchondral bone alleviates osteoarthritis progression. *Sci Adv*. 2023;9(14):eabo7868. doi:10.1126/sciadv.abo7868
45. Hu W, Chen Y, Dou C, Dong S. Microenvironment in subchondral bone: predominant regulator for the treatment of osteoarthritis. *Ann Rheum Dis*. 2021;80(4):413–422. doi:10.1136/annrheumdis-2020-218089
46. Li G, Yin J, Gao J, et al. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. *Arthritis Res Ther*. 2013;15(6):223. doi:10.1186/ar4405
47. Shao Y, Zhang H, Guan H, et al. PDZK1 protects against mechanical overload-induced chondrocyte senescence and osteoarthritis by targeting mitochondrial function. *Bone Res*. 2024;12(1):41. doi:10.1038/s41413-024-00344-6
48. Wang S, Li W, Zhang P, et al. Mechanical overloading induces GPX4-regulated chondrocyte ferroptosis in osteoarthritis via Piezo1 channel facilitated calcium influx. *J Adv Res*. 2022;41:63–75. doi:10.1016/j.jare.2022.01.004
49. Chen L, Zhang Z, Liu X. Role and mechanism of mechanical load in the homeostasis of the subchondral bone in knee osteoarthritis: a comprehensive review. *J Inflamm Res*. 2024;17:9359–9378. doi:10.2147/JIR.S492415
50. Desjardin C, Vaiman A, Mata X, et al. Next-generation sequencing identifies equine cartilage and subchondral bone miRNAs and suggests their involvement in osteochondrosis physiopathology. *BMC Genomics*. 2014;15(1):798. doi:10.1186/1471-2164-15-798
51. Li J, Hu C, Han L, et al. MiR-154-5p regulates osteogenic differentiation of adipose-derived mesenchymal stem cells under tensile stress through the Wnt/PCP pathway by targeting Wnt11. *Bone*. 2015;78:130–141. doi:10.1016/j.bone.2015.05.003
52. Zuo B, Zhu J, Li J, et al. microRNA-103a functions as a mechanosensitive microRNA to inhibit bone formation through targeting Runx2. *J Bone Miner Res*. 2015;30(2):330–345. doi:10.1002/jbmr.2352
53. Arfat Y, Basra MAR, Shahzad M, Majeed K, Mahmood N, Munir H. miR-208a-3p suppresses osteoblast differentiation and inhibits bone formation by targeting ACVR1. *Mol Ther Nucleic Acids*. 2018;11:323–336. doi:10.1016/j.omtn.2017.11.009
54. Zhang L, Xu L, Wang Y, et al. Histone methyltransferase Setdb1 mediates osteogenic differentiation by suppressing the expression of miR-212-3p under mechanical unloading. *Cell Signal*. 2023;102:110554. doi:10.1016/j.cellsig.2022.110554
55. Peng Z, Mai Z, Xiao F, et al. MiR-20a: a mechanosensitive microRNA that regulates fluid shear stress-mediated osteogenic differentiation via the BMP2 signaling pathway by targeting BAMBI and SMAD6. *Ann Transl Med*. 2022;10(12):683. doi:10.21037/atm-22-2753
56. Dole NS, Yoon J, Monteiro DA, et al. Mechanosensitive miR-100 coordinates TGFβ and Wnt signaling in osteocytes during fluid shear stress. *FASEB J*. 2021;35(10):e21883. doi:10.1096/fj.202100930
57. Van Pelt DW, Vechetti IJ, Lawrence MM, et al. Serum extracellular vesicle miR-203a-3p content is associated with skeletal muscle mass and protein turnover during disuse atrophy and regrowth. *Am J Physiol Cell Physiol*. 2020;319(2):C419–C431. doi:10.1152/ajpcell.00223.2020

58. Geng Y, Zhao X, Xu J, et al. Overexpression of mechanical sensitive miR-337-3p alleviates ectopic ossification in rat tendinopathy model via targeting IRS1 and Nox4 of tendon-derived stem cells. *J Mol Cell Biol*. 2020;12(4):305–317. doi:10.1093/jmcb/mjz030
59. Hu Z, Zhang L, Wang H, et al. Targeted silencing of miRNA-132-3p expression rescues disuse osteopenia by promoting mesenchymal stem cell osteogenic differentiation and osteogenesis in mice. *Stem Cell Res Ther*. 2020;11(1):58. doi:10.1186/s13287-020-1581-6
60. Zhang L, Li G, Wang K, et al. MiR-30 family members inhibit osteoblast differentiation by suppressing Runx2 under unloading conditions in MC3T3-E1 cells. *Biochem Biophys Res Commun*. 2020;522(1):164–170. doi:10.1016/j.bbrc.2019.11.057
61. Chen Z, Zhao F, Liang C, et al. Silencing of miR-138-5p sensitizes bone anabolic action to mechanical stimuli. *Theranostics*. 2020;10 (26):12263–12278. doi:10.7150/thno.53009
62. Chang M, Lin H, Fu H, Wang B, Han G, Fan M. MicroRNA-195-5p regulates osteogenic differentiation of periodontal ligament cells under mechanical loading. *J Cell Physiol*. 2017;232(12):3762–3774. doi:10.1002/jcp.25856
63. Tian L, Zheng F, Li Z, et al. miR-148a-3p regulates adipocyte and osteoblast differentiation by targeting lysine-specific demethylase 6b. *Gene*. 2017;627:32–39. doi:10.1016/j.gene.2017.06.002
64. Liu L, Liu M, Li R, et al. MicroRNA-503-5p inhibits stretch-induced osteogenic differentiation and bone formation. *Cell Biol Int*. 2017;41 (2):112–123. doi:10.1002/cbin.10704
65. Wang H, Sun Z, Wang Y, et al. miR-33-5p, a novel mechano-sensitive microRNA promotes osteoblast differentiation by targeting Hmga2. *Sci Rep*. 2016;6:23170. doi:10.1038/srep23170
66. Iwawaki Y, Mizusawa N, Iwata T, et al. MiR-494-3p induced by compressive force inhibits cell proliferation in MC3T3-E1 cells. *J Biosci Bioeng*. 2015;120(4):456–462. doi:10.1016/j.jbiosc.2015.02.006
67. Cao Y, Lv Q, Lv C. MicroRNA-153 suppresses the osteogenic differentiation of human mesenchymal stem cells by targeting bone morphogenetic protein receptor type II. *Int J Mol Med*. 2015;36(3):760–766. doi:10.3892/ijmm.2015.2275
68. Sun Z, Cao X, Hu Z, et al. MiR-103 inhibits osteoblast proliferation mainly through suppressing Cav1.2 expression in simulated microgravity. *Bone*. 2015;76:121–128. doi:10.1016/j.bone.2015.04.006
69. Mohan S, Wergedal JE, Das S, Kesavan C. Conditional disruption of miR17-92 cluster in collagen type I-producing osteoblasts results in reduced periosteal bone formation and bone anabolic response to exercise. *Physiol Genomics*. 2015;47(2):33–43. doi:10.1152/physiolgenomics.00107.2014
70. Mai Z, Peng Z, Zhang J, et al. miRNA expression profile during fluid shear stress-induced osteogenic differentiation in MC3T3-E1 cells. *Chin Med J*. 2013;126(8):1544–1550. doi:10.3760/cma.j.issn.0366-6999.20123137
71. Goldring SR, Goldring MB. Changes in the osteochondral unit during osteoarthritis: structure, function and cartilage-bone crosstalk. *Nat Rev Rheumatol*. 2016;12(11):632–644. doi:10.1038/nrrheum.2016.148
72. Taheri S, Winkler T, Schenk LS, et al. Developmental transformation and reduction of connective cavities within the subchondral bone. *Int J Mol Sci*. 2019;20(3):E770. doi:10.3390/ijms20030770
73. Hunt MA, Charlton JM, Esculier J-F. Osteoarthritis year in review 2019: mechanics. *Osteoarthritis Cartilage*. 2020;28(3):267–274. doi:10.1016/j.joca.2019.12.003
74. Zhang R-K, G-W L, Zeng C, et al. Mechanical stress contributes to osteoarthritis development through the activation of transforming growth factor beta 1 (TGF-β1). *Bone Joint Res*. 2018;7(11):587–594. doi:10.1302/2046-3758.711.BJR-2018-0057.R1
75. Xie H, Cui Z, Wang L, et al. PDGF-BB secreted by preosteoclasts induces angiogenesis during coupling with osteogenesis. *Nat Med*. 2014;20 (11):1270–1278. doi:10.1038/nm.3668
76. Romeo SG, Alawi KM, Rodrigues J, Singh A, Kusumbe AP, Ramasamy SK. Endothelial proteolytic activity and interaction with non-resorbing osteoclasts mediate bone elongation. *Nat Cell Biol*. 2019;21(4):430–441. doi:10.1038/s41556-019-0304-7
77. Dai J, Dong R, Han X, et al. Osteoclast-derived exosomal let-7a-5p targets Smad2 to promote the hypertrophic differentiation of chondrocytes. *Am J Physiol Cell Physiol*. 2020;319(1):C21–C33. doi:10.1152/ajpcell.00039.2020
78. Jing Z, Zhang G, Cai Y, Liang J, Lv L, Dang X. Engineered extracellular vesicle-delivered TGF-β inhibitor for attenuating osteoarthritis by targeting subchondral bone. *J Tissue Eng*. 2024;15:20417314241257781. doi:10.1177/20417314241257781
79. Veronesi F, Costa V, Bellavia D, Basoli V, Giavaresi G. Epigenetic modifications of MiRNAs in osteoarthritis: a systematic review on their methylation levels and effects on chondrocytes, extracellular matrix and joint inflammation. *Cells*. 2023;12(14):1821. doi:10.3390/cells12141821
80. Dai J, Hu Z, Zeng F, et al. Osteoclast-derived exosomal miR-212-3p suppressed the anabolism and accelerated the catabolism of chondrocytes in osteoarthritis by targeting TGF-β1/Smad2 signaling. *Arch Biochem Biophys*. 2024;751:109827. doi:10.1016/j.abb.2023.109827
81. Li D, Liu J, Guo B, et al. Osteoclast-derived exosomal miR-214-3p inhibits osteoblastic bone formation. *Nat Commun*. 2016;7:10872. doi:10.1038/ncomms10872
82. Jia H, Ma X, Wei Y, et al. Loading-induced reduction in sclerostin as a mechanism of subchondral bone plate sclerosis in mouse knee joints during late-stage osteoarthritis. *Arthritis Rheumatol*. 2018;70(2):230–241. doi:10.1002/art.40351
83. Hickerson RP, Vlassov AV, Wang Q, et al. Stability study of unmodified siRNA and relevance to clinical use. *Oligonucleotides*. 2008;18 (4):345–354. doi:10.1089/oli.2008.0149
84. Shang X, Fang Y, Xin W, You H. The application of extracellular vesicles mediated miRNAs in osteoarthritis: current knowledge and perspective. *J Inflamm Res*. 2022;15:2583–2599. doi:10.2147/JIR.S359887
85. Meng Z, Lu M. RNA interference-induced innate immunity, off-target effect, or immune adjuvant? *Front Immunol*. 2017;8:331. doi:10.3389/fimmu.2017.00331
86. Hu B, Zhong L, Weng Y, et al. Therapeutic siRNA: state of the art. *Signal Transduct Target Ther*. 2020;5(1):101. doi:10.1038/s41392-020-0207-x
87. Nakamura A, Ali SA, Kapoor M. Antisense oligonucleotide-based therapies for the treatment of osteoarthritis: opportunities and roadblocks. *Bone*. 2020;138:115461. doi:10.1016/j.bone.2020.115461
88. Crooke ST, Baker BF, Crooke RM, Liang X-H. Antisense technology: an overview and prospectus. *Nat Rev Drug Discov*. 2021;20(6):427–453. doi:10.1038/s41573-021-00162-z
89. DeJulius CR, Walton BL, Colazo JM, et al. Engineering approaches for RNA-based and cell-based osteoarthritis therapies. *Nat Rev Rheumatol*. 2024;20(2):81–100. doi:10.1038/s41584-023-01067-4

90. Ye Q-Y, Cui Y, Wang H-Y, et al. Exosomal communication: a pivotal regulator of bone homeostasis and a potential therapeutic target. *Front Pharmacol*. 2024;15:1516125. doi:10.3389/fphar.2024.1516125
91. Cao H, Chen M, Cui X, et al. Cell-free osteoarthritis treatment with sustained-release of chondrocyte-targeting exosomes from umbilical cord-derived mesenchymal stem cells to rejuvenate aging chondrocytes. *ACS Nano*. 2023;17(14):13358–13376. doi:10.1021/acsnano.3c01612
92. Parayath NN, Gandham SK, Amiji MM. Tumor-targeted miRNA nanomedicine for overcoming challenges in immunity and therapeutic resistance. *Nanomedicine*. 2022;17(19):1355–1373. doi:10.2217/nnm-2022-0130
93. Brown S, Kumar S, Sharma B. Intra-articular targeting of nanomaterials for the treatment of osteoarthritis. *Acta Biomater*. 2019;93:239–257. doi:10.1016/j.actbio.2019.03.010
94. Chen X, Tian B, Wang Y, Zheng J, Kang X. Potential and challenges of utilizing exosomes in osteoarthritis therapy (Review). *Int J Mol Med*. 2025;55(3):43. doi:10.3892/ijmm.2025.5484
95. Wu X, Crawford R, Xiao Y, Mao X, Prasadam I. Osteoarthritic subchondral bone release exosomes that promote cartilage degeneration. *Cells*. 2021;10(2):251. doi:10.3390/cells10020251
96. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol*. 2018;19(4):213–228. doi:10.1038/nrm.2017.125
97. Yin B, Ni J, Witherel CE, et al. Harnessing tissue-derived extracellular vesicles for osteoarthritis theranostics. *Theranostics*. 2022;12(1):207–231. doi:10.7150/thno.62708
98. Liu N, Ma Y, Gong W, et al. Osteocyte-derived extracellular vesicles mediate the bone-to-cartilage crosstalk and promote osteoarthritis progression. *Nat Commun*. 2025;16(1):4746. doi:10.1038/s41467-025-59861-5
99. Wang H, Shu J, Zhang C, et al. Extracellular vesicle-mediated miR-150-3p delivery in joint homeostasis: a potential treatment for osteoarthritis? *Cells*. 2022;11(17):2766. doi:10.3390/cells11172766
100. Liang Y, Xu X, Li X, et al. Chondrocyte-targeted MicroRNA delivery by engineered exosomes toward a cell-free osteoarthritis therapy. *ACS Appl Mater Interfaces*. 2020;12(33):36938–36947. doi:10.1021/acsami.0c10458
101. Liu W, Liu A, Li X, et al. Dual-engineered cartilage-targeting extracellular vesicles derived from mesenchymal stem cells enhance osteoarthritis treatment via miR-223/NLRP3/pyroptosis axis: toward a precision therapy. *Bioact Mater*. 2023;30:169–183. doi:10.1016/j.bioactmat.2023.06.012
102. Rajagopal K, Arjunan P, Marepally S, Madhuri V. Controlled differentiation of mesenchymal stem cells into hyaline cartilage in mir-140-activated collagen hydrogel. *Cartilage*. 2021;13(2_suppl):571S–581S. doi:10.1177/19476035211047627
103. Zhao R, Zhang X, Jia L, et al. pNNS-conjugated chitosan mediated IGF-1 and miR-140 overexpression in articular chondrocytes improves cartilage repair. *Biomed Res Int*. 2019;2019:2761241. doi:10.1155/2019/2761241
104. Carthew J, Donderwinkel I, Shrestha S, Truong VX, Forsythe JS, Frith JE. In situ miRNA delivery from a hydrogel promotes osteogenesis of encapsulated mesenchymal stromal cells. *Acta Biomater*. 2020;101:249–261. doi:10.1016/j.actbio.2019.11.016
105. Qian Y, Chu G, Zhang L, et al. M2 macrophage-derived exosomal miR-26b-5p regulates macrophage polarization and chondrocyte hypertrophy by targeting TLR3 and COL10A1 to alleviate osteoarthritis. *J Nanobiotechnology*. 2024;22(1):72. doi:10.1186/s12951-024-02336-4
106. Zhao Y, Deng X, Tan S, et al. Co-polymer carrier with dual advantages of cartilage-penetrating and targeting improves delivery and efficacy of MicroRNA treatment of osteoarthritis. *Adv Healthc Mater*. 2023;12(6):e2202143. doi:10.1002/adhm.202202143
107. Lou C, Jiang H, Lin Z, et al. MiR-146b-5p enriched bioinspired exosomes derived from fucoidan-directed induction mesenchymal stem cells protect chondrocytes in osteoarthritis by targeting TRAF6. *J Nanobiotechnology*. 2023;21(1):486. doi:10.1186/s12951-023-02264-9
108. Zhao S, Xiu G, Wang J, et al. Engineering exosomes derived from subcutaneous fat MSCs specially promote cartilage repair as miR-199a-3p delivery vehicles in Osteoarthritis. *J Nanobiotechnology*. 2023;21(1):341. doi:10.1186/s12951-023-02086-9
109. Chen H, Chen F, Hu F, et al. MicroRNA-224-5p nanoparticles balance homeostasis via inhibiting cartilage degeneration and synovial inflammation for synergistic alleviation of osteoarthritis. *Acta Biomater*. 2023;167:401–415. doi:10.1016/j.actbio.2023.06.010
110. Pieters BCH, Arntz OJ, Aarts J, et al. Bovine milk-derived extracellular vesicles inhibit catabolic and inflammatory processes in cartilage from osteoarthritis patients. *Mol Nutr Food Res*. 2022;66(6):e2100764. doi:10.1002/mnfr.202100764
111. Zhu J, Yang S, Qi Y, et al. Stem cell-homing hydrogel-based miR-29b-5p delivery promotes cartilage regeneration by suppressing senescence in an osteoarthritis rat model. *Sci Adv*. 2022;8(13):eabk0011. doi:10.1126/sciadv.abk0011
112. Wang Y, Fan A, Lu L, et al. Exosome modification to better alleviates endoplasmic reticulum stress induced chondrocyte apoptosis and osteoarthritis. *Biochem Pharmacol*. 2022;206:115343. doi:10.1016/j.bcp.2022.115343
113. Wu J, Kuang L, Chen C, et al. miR-100-5p-abundant exosomes derived from infrapatellar fat pad MSCs protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOR in osteoarthritis. *Biomaterials*. 2019;206:87–100. doi:10.1016/j.biomaterials.2019.03.022
114. Lolli A, Sivasubramaniyan K, Vainieri ML, et al. Hydrogel-based delivery of antimiR-221 enhances cartilage regeneration by endogenous cells. *J Control Release*. 2019;309:220–230. doi:10.1016/j.jconrel.2019.07.040
115. Frith JE, Kusuma GD, Carthew J, et al. Mechanically-sensitive miRNAs bias human mesenchymal stem cell fate via mTOR signalling. *Nat Commun*. 2018;9(1):257. doi:10.1038/s41467-017-02486-0
116. Tao S-C, Yuan T, Zhang Y-L, Yin W-J, Guo S-C, Zhang C-Q. Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells enhance cartilage tissue regeneration and prevent osteoarthritis of the knee in a rat model. *Theranostics*. 2017;7(1):180–195. doi:10.7150/thno.17133
117. Chen X, Gu S, B-F C, et al. Nanoparticle delivery of stable miR-199a-5p agomir improves the osteogenesis of human mesenchymal stem cells via the HIF1a pathway. *Biomaterials*. 2015;53:239–250. doi:10.1016/j.biomaterials.2015.02.071
118. Çelik E, Bayram C, Denkbaş EB. Chondrogenesis of human mesenchymal stem cells by microRNA loaded triple polysaccharide nanoparticle system. *Mater Sci Eng C Mater Biol Appl*. 2019;102:756–763. doi:10.1016/j.msec.2019.05.006
119. Zhang L, Peng H, Zhang W, Li Y, Liu L, Leng T. Yeast cell wall particle mediated nanotube-RNA delivery system loaded with miR365 antagomir for post-traumatic osteoarthritis therapy via oral route. *Theranostics*. 2020;10(19):8479–8493. doi:10.7150/thno.46761
120. Chen B, Dragomir MP, Yang C, Li Q, Horst D, Calin GA. Targeting non-coding RNAs to overcome cancer therapy resistance. *Signal Transduct Target Ther*. 2022;7(1):121. doi:10.1038/s41392-022-00975-3
121. Seyhan AA. Trials and tribulations of MicroRNA therapeutics. *Int J Mol Sci*. 2024;25(3):1469. doi:10.3390/ijms25031469

122. Diener C, Keller A, Meese E. Emerging concepts of miRNA therapeutics: from cells to clinic. *Trends Genet*. 2022;38(6):613–626. doi:10.1016/j.tig.2022.02.006
123. Brillante S, Volpe M, Indrieri A. Advances in MicroRNA therapeutics: from preclinical to clinical studies. *Hum Gene Ther*. 2024;35(17–18):628–648. doi:10.1089/hum.2024.113
124. Ho PTB, Clark IM, Le LT. MicroRNA-based diagnosis and therapy. *Int J Mol Sci*. 2022;23(13):7167. doi:10.3390/ijms23137167
125. Lu Q, Wu R, Zhao M, Garcia-Gomez A, Ballestar E. miRNAs as therapeutic targets in inflammatory disease. *Trends Pharmacol Sci*. 2019;40(11):853–865. doi:10.1016/j.tips.2019.09.007
126. Tafrihi M, Hasheminasab E. MiRNAs: biology, biogenesis, their web-based tools, and databases. *microRNA*. 2019;8(1):4–27. doi:10.2174/2211536607666180827111633
127. Yamasaki K, Nakasa T, Miyaki S, et al. Expression of MicroRNA-146a in osteoarthritis cartilage. *Arthritis Rheum*. 2009;60(4):1035–1041. doi:10.1002/art.24404
128. Shao J, Ding Z, Peng J, et al. MiR-146a-5p promotes IL-1β-induced chondrocyte apoptosis through the TRAF6-mediated NF-kB pathway. *Inflamm Res*. 2020;69(6):619–630. doi:10.1007/s00011-020-01346-w
129. Jones SW, Watkins G, Le Good N, et al. The identification of differentially expressed microRNA in osteoarthritic tissue that modulate the production of TNF-alpha and MMP13. *Osteoarthritis Cartilage*. 2009;17(4):464–472. doi:10.1016/j.joca.2008.09.012
130. Zhang M, Lygrisse K, Wang J. Role of MicroRNA in Osteoarthritis. *J Arthritis*. 2017;6(2):239. doi:10.4172/2167-7921.1000239
131. Uzieliene I, Bironaite D, Bernotas P, Sobolev A, Bernotiene E. Mechanotransducive biomimetic systems for chondrogenic differentiation in vitro. *Int J Mol Sci*. 2021;22(18):9690. doi:10.3390/ijms22189690
132. Yu H, Huang Y, Yang L. Research progress in the use of mesenchymal stem cells and their derived exosomes in the treatment of osteoarthritis. *Ageing Res Rev*. 2022;80:101684. doi:10.1016/j.arr.2022.101684
133. Qi W, Guan W. A comprehensive review on the importance of MiRNA-206 in the animal model and human diseases. *Curr Neuropharmacol*. 2024;22(6):1064–1079. doi:10.2174/1570159X21666230407124146
134. Wang N, Zhang X, Rothrauff BB, et al. Novel role of estrogen receptor-α on regulating chondrocyte phenotype and response to mechanical loading. *Osteoarthritis Cartilage*. 2022;30(2):302–314. doi:10.1016/j.joca.2021.11.002
135. Guo Y, Tian L, Du X, Deng Z. MiR-203 regulates estrogen receptor α and cartilage degradation in IL-1β-stimulated chondrocytes. *J Bone Miner Metab*. 2020;38(3):346–356. doi:10.1007/s00774-019-01062-4
136. Hernandez PA, Moreno M, Barati Z, et al. Sexual dimorphism in the extracellular and pericellular matrix of articular cartilage. *Cartilage*. 2022;13(3):19476035221121792. doi:10.1177/19476035221121792
137. Ramasamy T, Ruttala HB, Munusamy S, Chakraborty N, Kim JO. Nano drug delivery systems for antisense oligonucleotides (ASO) therapeutics. *J Control Release*. 2022;352:861–878. doi:10.1016/j.jconrel.2022.10.050
138. Zhen G, Cao X. Targeting TGFβ signaling in subchondral bone and articular cartilage homeostasis. *Trends Pharmacol Sci*. 2014;35(5):227–236. doi:10.1016/j.tips.2014.03.005
139. Zhen G, Guo Q, Li Y, et al. Mechanical stress determines the configuration of TGFβ activation in articular cartilage. *Nat Commun*. 2021;12(1):1706. doi:10.1038/s41467-021-21948-0
140. Tao S-C, Huang J-Y, Gao Y, et al. Small extracellular vesicles in combination with sleep-related circRNA3503: a targeted therapeutic agent with injectable thermosensitive hydrogel to prevent osteoarthritis. *Bioact Mater*. 2021;6(12):4455–4469. doi:10.1016/j.bioactmat.2021.04.031
141. Lee KS, Lee J, Kim HK, et al. Extracellular vesicles from adipose tissue-derived stem cells alleviate osteoporosis through osteoprotegerin and miR-21-5p. *J Extracell Vesicles*. 2021;10(12):e12152. doi:10.1002/jev2.12152