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# siRNA therapy in osteoarthritis: targeting cellular pathways for advanced treatment approaches

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Osteoarthritis (OA) is a common joint disorder characterized by the degeneration of cartilage and inflammation, affecting millions worldwide. The disease's complex pathogenesis involves various cell types, such as chondrocytes, synovial cells, osteoblasts, and immune cells, contributing to the intricate interplay of factors leading to tissue degradation and pain. RNA interference (RNAi) therapy, particularly through the use of small interfering RNA (siRNA), emerges as a promising avenue for OA treatment due to its capacity for specific gene silencing. siRNA molecules can modulate post-transcriptional gene expression, targeting key pathways involved in cellular proliferation, apoptosis, senescence, autophagy, biomolecule secretion, inflammation, and bone remodeling. This review delves into the mechanisms by which siRNA targets various cell populations within the OA milieu, offering a comprehensive overview of the potential therapeutic benefits and challenges in clinical application. By summarizing the current advancements in siRNA delivery systems and therapeutic targets, we provide a solid theoretical foundation for the future development of novel siRNA-based strategies for OA diagnosis and treatment, paving the way for innovative and more effective approaches to managing this debilitating disease.

## KEYWORDS

osteoarthritis, siRNA, chondrocytes, fibroblast-like synoviocytes, osteoblasts

## 1 Introduction

Osteoarthritis (OA) is a prevalent chronic joint disease characterized by the degeneration of cartilage and inflammation (1). The risk factors for OA encompass obesity, injury, genetic predisposition, among others. It is noteworthy that the incidence is higher among females compared to males, and age stands as the foremost risk factor (2, 3). The pathogenesis of osteoarthritis primarily involves the articular cartilage, subchondral bone, and synovium, yet its specific mechanisms remain not fully elucidated (4). Therapeutic interventions for OA mainly

include non-pharmacologic management, pharmacologic management, and surgical interventions. Recommended non-pharmacological approaches include education, self-management, exercise, and weight loss (5). Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are frontline pharmaceuticals in the treatment of OA, recommended for use in clinical guidelines. However, the cautious administration of NSAIDs is imperative to avert potential adverse effects. While acetaminophen's efficacy falls short of that of NSAIDs, its safety profile renders it suitable for patients contraindicated for NSAIDs (6). Surgical interventions exhibit notable efficacy in long-term improvement of patients' physiological function and alleviation of pain; nevertheless, they are not exempt from potential side effects (7). Moreover, an increasing body of evidence suggests a correlation between psychological factors and the onset of OA pain. Utilizing psychological approaches, such as coping skills training (CST) and emotional disclosure, has proven effective in alleviating OA pain (8). As the pathogenic mechanisms of OA are continually elucidated, an increasing number of pharmaceuticals targeting the pathophysiological mechanisms of the disease are under development to replace the current predominantly palliative treatments, such as chondroitin sulfate and hyaluronan, collectively known as disease-modifying osteoarthritis drugs (DMOADs). These drugs, targeting cartilage, inflammatory pathways, and subchondral bone, hold promising prospects (9).

RNA interference (RNAi) denotes the duplex RNA's inhibitory effect on genes, constituting a natural mechanism within organisms to silence genes (10). Small interfering RNA (siRNA) represents a category of double-stranded RNA molecules, spanning 21–23 nucleotides, formed through enzymatic cleavage of double-stranded RNA (11). siRNA associates with various proteins to form the RNA-induced silencing complex (RISC). Subsequently, it pairs with target mRNA, cleaving the mRNA and ultimately impeding the transcriptional process (12). Given its selective ability to silence almost any gene, siRNA therapy holds promise as a clinical approach for targeting specific genes in the treatment of OA. The first siRNA therapy was approved in 2018, utilized for the treatment of transthyretin-mediated amyloidosis. Since then, siRNA-based therapies for various diseases have entered clinical trials, indicating the broad prospects of siRNA in treating diseases (13). Furthermore, diverse delivery systems based on siRNA have been developed to enhance the efficiency of siRNA reaching its target, encompassing polymers, lipids, antibodies, nanocarriers, and peptide segments (14). This review comprehensively summarizes the progress in utilizing siRNA for the treatment of OA from a cellular perspective, including targeting chondrocytes, fibroblast-like synoviocytes, and osteoblasts, offering a novel outlook on the application of siRNA in OA therapy.

## 2 Targeting chondrocytes

The pathological manifestations of OA are diverse, with the degeneration of articular cartilage being a primary characteristic. Articular cartilage primarily comprises water and organic extracellular components. Chondrocytes represent the exclusive

cell type within the cartilage matrix, responsible for maintaining the synthesis and degradation equilibrium of the extracellular matrix (ECM) (15). Upon exposure to mechanical, inflammatory, and metabolic factors, anomalies arise in the function of chondrocytes. This results in a reduction in the generation of ECM molecules and an augmentation in the production of proteinases. The disruption of ECM homeostasis is thus initiated, consequently promoting the degeneration of articular cartilage (16).

### 2.1 Targeting the apoptosis of chondrocytes

The proliferation and apoptosis of chondrocytes undergo alterations in OA. Research indicates a diminished proliferation and an increased apoptosis of chondrocytes in OA, which is associated with the progression of OA (17–19). Targeting the proliferation and apoptosis of chondrocytes holds the potential to alleviate the progression of OA.

Downregulating the expression of DNA methyltransferase 3 alpha (*DNMT3A*) using siRNA can reduce apoptosis and induce proliferation of chondrocytes in knee OA rats (20). 15-Lipoxygenase-1 (15-LOX-1), a lipid metabolism enzyme, can facilitate apoptosis of chondrocytes induced by sodium nitroprusside (SNP) and inhibit chondrocyte proliferation. Inhibiting arachidonate 15-lipoxygenase (*ALOX15*) expression using siRNA significantly mitigates the destruction of articular surface and bone, as well as the formation of osteophytes, thereby considerably alleviating destabilization of the medial meniscus (DMM) induced OA in rats (21). The expression of KH RNA binding domain containing, signal transduction associated 1 (*KHDRBS1*) increases in chondrocytes of OA model rats stimulated by tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). *KHDRBS1* siRNA inhibits the activation of the nuclear factor kappa B (NF- $\kappa$ B) signaling pathway and significantly reduces chondrocyte apoptosis by reducing caspase-3 expression (22). Secreted phosphoprotein 1 (SPP1) is an extracellular matrix molecule that induces apoptosis of OA chondrocytes by activating the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (AKT) pathway and inhibits proliferation. Knocking down SPP1 using siRNA promotes chondrocyte proliferation and inhibits chondrocyte apoptosis through the reduction of caspase-3 and caspase-9 expression (23). Phosphatase and tensin homologue (*PTEN*) is a crucial tumor suppressor gene, and its expression is significantly upregulated in OA chondrocytes. *PTEN* affects cell proliferation by inhibiting the PI3K/AKT pathway. *PTEN* siRNA significantly inhibits apoptosis and promotes proliferation of OA chondrocytes (24). Downregulating ribosomal protein L38 (*RPL38*) using siRNA, leading to the upregulation of suppressor of cytokine signaling 2 (*SOCS2*) expression and activation of the janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathway, resulted in a reduction of chondrocyte apoptosis induced by interleukin 1 $\beta$  (IL-1 $\beta$ ). This process also alleviated histological phenomena such as reduction of articular chondrocytes, cartilage degradation and erosion in OA mice, thereby delaying the progression of OA (25).

## 2.2 Targeting chondrocyte senescence

In OA, chondrocyte senescence increases, and it can propagate to adjacent healthy chondrocytes through cell communication, inducing senescence (26). The aggregation of senescent chondrocytes promotes the progression of OA by disrupting the ECM homeostasis (27). The senescence-associated secretory phenotype (SASP) expressed by senescent chondrocytes is one of the key contributors to ECM impairment, causing an imbalance between ECM synthesis and degradation through the secretion of various cytokines and proteases such as interleukin 6 (IL-6), matrix metalloproteinases 13 (MMP13), and a disintegrin and metalloprotease with thrombospondin motifs 5 (ADAMTS5) (28). Research targeting cellular senescence provides insights for siRNA therapy.

Senescent cells reduce apoptosis by producing apoptosis inhibitor proteins (IAPs). Knocking down genes encoding anti-apoptotic proteins baculoviral IAP repeat containing 2 (*BIRC2*), baculoviral IAP repeat containing 3 (*BIRC3*), and X-linked inhibitor of apoptosis (*XIAP*) induces the clearance of senescent cells. Furthermore, the IAP inhibitor (AT-406) further alleviated cartilage degeneration and tibial subchondral bone reconstruction in rats with post-traumatic osteoarthritis (PTOA), thereby decelerating the progression of OA (29). Asporin is an extracellular matrix protein that induces chondrocyte senescence by targeting transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1)–Smad family member 2 (SMAD2) pathway. Knocking down asporin using siRNA inhibits senescence in chondrocytes and alleviates cartilage destruction in DMM-induced OA mice through TGF- $\beta$ 1 pathway (30). Inhibiting excitatory amino acid transporter protein 1 (*EAAT1*) enhances the response of senescent chondrocytes to ferroptosis, inducing cell death, with no significant impact on normal cells. Moreover, the *EAAT1* inhibitor (UCPH-101) induced the clearance of senescent chondrocytes and mitigated cartilage degeneration (31). Mitofusin 2 (*MFN2*) regulates mitochondrial fusion, which plays a role in cell metabolism and aging, while dysregulation of *MFN2* can lead to cartilage destruction. The expression of *MFN2* is elevated during OA and aging, while knocking down *MFN2* using siRNA can reverse age-related metabolic changes in rat chondrocytes (32). Additionally, tribbles homolog 3 (*TRB3*) siRNA reduces senescence in OA chondrocytes by reducing p16 and p21 levels, presenting another target for addressing chondrocyte senescence (33).

## 2.3 Targeting chondrocyte autophagy

The relationship between chondrocyte autophagy and apoptosis is intricate. Chondrocyte autophagy eliminates aged organelles and proteins, thereby maintaining internal homeostasis and protecting cells from apoptosis. Under the influence of external pathological factors, cellular autophagy is impaired, leading to the progression of OA (34). Hence, utilizing siRNA to restore chondrocyte autophagic function might be a means to treat OA.

The mechanistic target of rapamycin (mTOR) pathway is a crucial cellular autophagy inhibition pathway, regulated by PI3K/AKT and AMP-activated protein kinase (AMPK) (35). MicroRNA

7 (*miR-7*) siRNA inhibits the phosphorylation of the PI3K/AKT/mTOR pathway by reducing interleukin 17A (*IL-17A*) expression, and promotes the conversion of microtubule associated protein light chain 3 (LC3) from LC3-I to LC3-II, enhances beclin 1 (*BECN1*) expression, and suppresses sequestosome 1 (*SQSTM1*) expression, thereby restoring autophagic dysfunction in IL-1 $\beta$  induced chondrocytes. This significantly reduces cartilage destruction and the progression of OA in model rats (36). The upregulation of *MFN2* in OA model mice, through activating the NF- $\kappa$ B and p38 mitogen-activated protein kinase (MAPK) pathways and inhibiting the PI3K/AKT/mTOR pathway, promotes inflammation and leads to excessive autophagy in chondrocytes. Knocking down *MFN2* can suppress inflammation and cartilage degeneration in OA rat chondrocytes, thereby slowing down the progression of OA (37). The upregulation of transient receptor potential cation channel subfamily V member 5 (*TRPV5*) expression in OA is mitigated by *TRPV5* siRNA, which reduces intracellular Ca<sup>2+</sup> influx and enhances autophagy in MIA-induced OA rat chondrocytes. Furthermore, ruthenium red (a *TRPV5* inhibitor) delays OA progression by reducing cartilage destruction (38). *TRB3* inhibits autophagy by suppressing the autophagic receptor p62 and is upregulated in TNF- $\alpha$ -induced OA chondrocytes. Knocking down *TRB3* using siRNA promotes autophagy in chondrocytes, making it a potential target for targeting chondrocyte autophagic function (33).

## 2.4 Targeting chondrocyte secretion

In OA, the aberrant function of chondrocytes leads to the release of degradative enzymes, such as matrix metalloproteinases (MMPs) and a disintegrin and metalloprotease with thrombospondin motifs (ADAMTSs) (4). These enzymes further contribute to cartilage degradation. The degradation products of cartilage can serve as damage-associated molecular patterns (DAMPs), entering the synovium and inducing the production of inflammatory factors. This, in turn, further stimulates chondrocytes to produce degradative enzymes, forming a vicious cycle (39).

*MMP13* is upregulated in PTOA and contributes to cartilage destruction by degrading type II collagen. Using a nano-platform to deliver *MMP13* siRNA reduces cartilage degradation, synovial hyperplasia and osteophyte growth in PTOA mice model, slowing down the progression of PTOA with favorable long-term therapeutic effects (40). Intra-articular injection of *MMP13* siRNA and/or *ADAMTS5* siRNA inhibited cartilage degradation in early-stage OA mice model (41). The use of nanoparticle delivery for lysine demethylase 6B (*KDM6B*) siRNA lowered the expression of *MMP13* in mice model, and significantly alleviated the progression of OA by reducing cartilage degradation (42). The level of  $\beta$ -catenin is increased in chondrocytes of OA mice. Catenin beta 1 (*CTNNB1*) encodes  $\beta$ -catenin, and knocking down *CTNNB1* reduces the expression of matrix metalloproteinases 3 (*MMP3*), *MMP13*, and a disintegrin and metalloprotease with thrombospondin motifs 4 (*ADAMTS4*). This suggests that *CTNNB1* siRNA may inhibit cartilage degradation (43). Jian Zhang et al. discovered a drug that co-delivers curcumin and endothelial PAS domain protein 1

(*EPAS1*) siRNA, which alleviates mice cartilage degradation and slows down the progression of OA by reducing the expression of *MMP3*, *MMP13*, *ADAMTS5* in OA chondrocytes (44). The activation of the interleukin 1 (IL-1) signaling pathway can lead to the progression of OA. Matrix metalloproteinases 9 (*MMP9*) siRNA reduces the shedding of syndecan-4 (*SDC4*), thereby lowering the sensitivity of chondrocytes to the IL-1 signaling pathway (45). Furthermore, *miR-7* siRNA inhibits the expression of *MMP3*, *MMP13*, and *ADAMTS5* in IL-1 $\beta$ -induced chondrocytes, thereby promoting ECM homeostasis and delaying OA progression (36).

### 3 Targeting fibroblast-like synoviocytes

Synovial inflammation is another characteristic feature of OA. The aberrant function of chondrocytes leads to the secretion of proteolytic enzymes, causing the production of inflammatory and metabolic products that affect the adjacent synovium. The progression of synovial inflammation can further exacerbate cartilage damage (46).

The production of pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , IL-6, can exacerbate cartilage degradation and is associated with hyperalgesia in OA (47, 48). Silencing NLR family pyrin domain containing 1 (*NLRP1*) reduces the production of IL-1 $\beta$  induced by P2X4 purinoceptor (P2X4) in OA fibroblast-like synoviocytes (49). *RELA* proto-oncogene, NF- $\kappa$ B subunit (*RELA*) siRNA significantly inhibits the induction of IL-1 $\beta$  and TNF- $\alpha$  in the synovial fluid, thereby alleviating synovial inflammation and cartilage degradation in early-stage OA rats through inhibition of the NF- $\kappa$ B pathway (50). Utilizing nanoparticles to deliver cyclin dependent kinase inhibitor 2A (*CDKN2A*) siRNA results in a reduction of *IL-1 $\beta$* , *IL-6*, and *TNF- $\alpha$*  expression in fibroblast-like synoviocytes of model rats, and reduces cartilage destruction and pain (51). Hyaluronan contributes to the composition of synovial fluid for joint lubrication. In OA, hyaluronan degradation occurs, promoting inflammation. The expression of cell migration inducing hyaluronidase 1 (*CEMIP*) increases in OA fibroblast-like synoviocytes, and knocking down *CEMIP* reduces the degradation of hyaluronan in OA fibroblast-like synoviocytes (52). Glutaminase (*GLS*) siRNA inhibits glutamine–glutamate metabolism, reducing the IL-6 inflammatory response in OA fibroblast-like synoviocytes (53).

Proliferation of fibroblast-like synoviocytes is one of the characteristics of synovial inflammation and can lead to hyperplasia of the synovial lining (54). Knocking down latent transforming growth factor beta binding protein 1 (*LTBP-1*) using siRNA reduces fibroblast-like synoviocytes proliferation by downregulating the transforming growth factor  $\beta$  (TGF- $\beta$ ) signaling pathway (55).

Methyltransferase like 3 (*METTL3*) mediated m6A modification inhibits autophagy in OA fibroblast-like synoviocytes by regulating autophagy related 7 (*ATG7*) RNA and promotes cell senescence. *METTL3* siRNA is able to inhibit expression of SASP-related genes and alleviate senescence in fibroblast-like synoviocytes. Furthermore, intra-articular injection of *METTL3* siRNA delayed the progression of DMM-induced OA

in mice (56). Fibroblast-like synoviocytes are considered the primary cells involved in synovial fibrosis in OA, and chronic joint pain is closely associated with synovial fibrosis (57). Inhibiting the upregulated expression of hypoxia inducible factor 1 subunit alpha (*HIF-1A*) in knee OA model rats reduces pyroptosis in fibroblast-like synoviocytes and significantly decreases the expression of synovial fibrogenic markers (58).

## 4 Targeting osteoblasts

In OA, subchondral bone undergoes remodeling due to excessive loading and changes in mechanical environment (59). The abnormal remodeling of subchondral bone can further exacerbate cartilage degradation (60). Osteoblasts regulate bone formation, remodeling and mineralization (61). Osteoblasts undergo changes in phenotype in OA, such as elevated alkaline phosphatase activity and increased secretion of osteocalcin. Additionally, alterations in signaling pathways like wingless-type MMTV integration site family (WNT) and TGF- $\beta$  contribute to the abnormal remodeling of subchondral bone (62, 63). Hence, targeting osteoblasts with siRNA represents a potential therapeutic approach.

In OA, there is an increased production of endogenous hepatocyte growth factor (HGF), which, by stimulating the production of TGF- $\beta$ 1, inhibits osteoblast responsiveness to bone morphogenetic protein 2 (BMP-2), leading to abnormal mineralization. *HGF* siRNA restores osteoblast responsiveness to BMP-2 and upregulates the WNT signaling pathway to nearly normal levels (64). Leptin expression is significantly increased in OA osteoblasts and can lead to elevated levels of alkaline phosphatase and osteocalcin, as well as increased osteoblast proliferation. Partially reducing the alkaline phosphatase activity and osteocalcin release is possible by inhibiting leptin or its receptor using siRNA, indicating the potential to inhibit bone remodeling (65). Silencing *ALOX15* promotes AMPK phosphorylation, inhibits mechanistic target of rapamycin complex 1 (mTORC1) phosphorylation, thereby suppressing expression levels of *TGF- $\beta$ 1*. This, in turn, enhances osteoblast autophagy and ultimately alleviates the progression of OA (66). Activation of Toll-like receptor 4 (TLR4) and innate immune activation can exacerbate cartilage degradation in OA. The antidepressant amitriptyline can bind to TLR4, inhibiting TLR4, IL-1 receptor, and NLR family pyrin domain containing 3 (*NLRP3*) dependent innate immune responses in OA chondrocytes, synoviocytes, and osteoblasts. Similarly, silencing *NLRP3* using siRNA has a comparable effect (67).

## 5 Targeting other cells

The pathological changes in OA involve the entire joint, and current research predominantly focuses on the abnormalities in cartilage. Research on other cells to treat OA is limited, such as macrophages or mesenchymal stem cells (68). Nevertheless, siRNA targeting these cells has shown promising prospects.

TABLE 1 Gene targets, cell activity and pathways table.

Cell	Cell Activity	Gene	Pathway	Reference
Chondrocytes	Proliferation	DNMT3A, ALOX15, KHDRBS1, SPP1, PTEN, RPL38	NF-κB PI3K/AKT/mTOR JAK/STAT3 TGF-β1-SMAD2 p38 MAPK IL-1	(20–25, 29, 30) (31–33, 36–38, 40–45)
	Senescence	BIRC2, BIRC3, XIAP, asporin, EAAT1, MFN2, TRB3		
	Autophagy	miR-7, MFN2, TRPV5, TRB3		
	Secretion	MMP13, ADAMTS5, KDM6B, CTNNB1, EPAS1, MMP9, miR-7		
Fibroblast-like synoviocytes	Inflammation	NLRP1, RELA, CDKN2A, CEMIP, GLS, LTBP-1	NF-κB TGF-β	(49, 50–55, 56, 58)
	Senescence and pyroptosis	METTL3, HIF-1A		
Osteoblasts	Bone remodeling	HGF, leptin, ALOX15, NLRP3	WNT AMPK	(64–67)

Xu Chen et al. engineered nanoparticles capable of releasing nitric oxide and notch receptor 1 (*NOTCH1*) siRNA. By inhibiting macrophage inflammatory responses, these nanoparticles reduced OA cartilage damage without significant side effects (69).

Mesenchymal stem cells derived from bone marrow are ideal for tissue repair due to their differentiation potential. Inhibiting *BLACAT1* overlapping *LEMD1* locus (*BLACAT1*) promotes the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells under inflammatory conditions, demonstrating potential for treating OA (70).

## 6 Discussion

OA is a chronic degenerative joint disease that, as it progresses, often leads to disability and pain, significantly impacting the quality of life (71). Currently, the treatment approach for OA primarily focuses on mitigating disease symptoms and arresting its progression. In recent years, with an increasingly profound understanding of OA, it is recognized as a comprehensive, multifactorial joint disorder, intimately connected to the interactions among articular cartilage, synovium, subchondral bone, and their constituent cells. Due to its

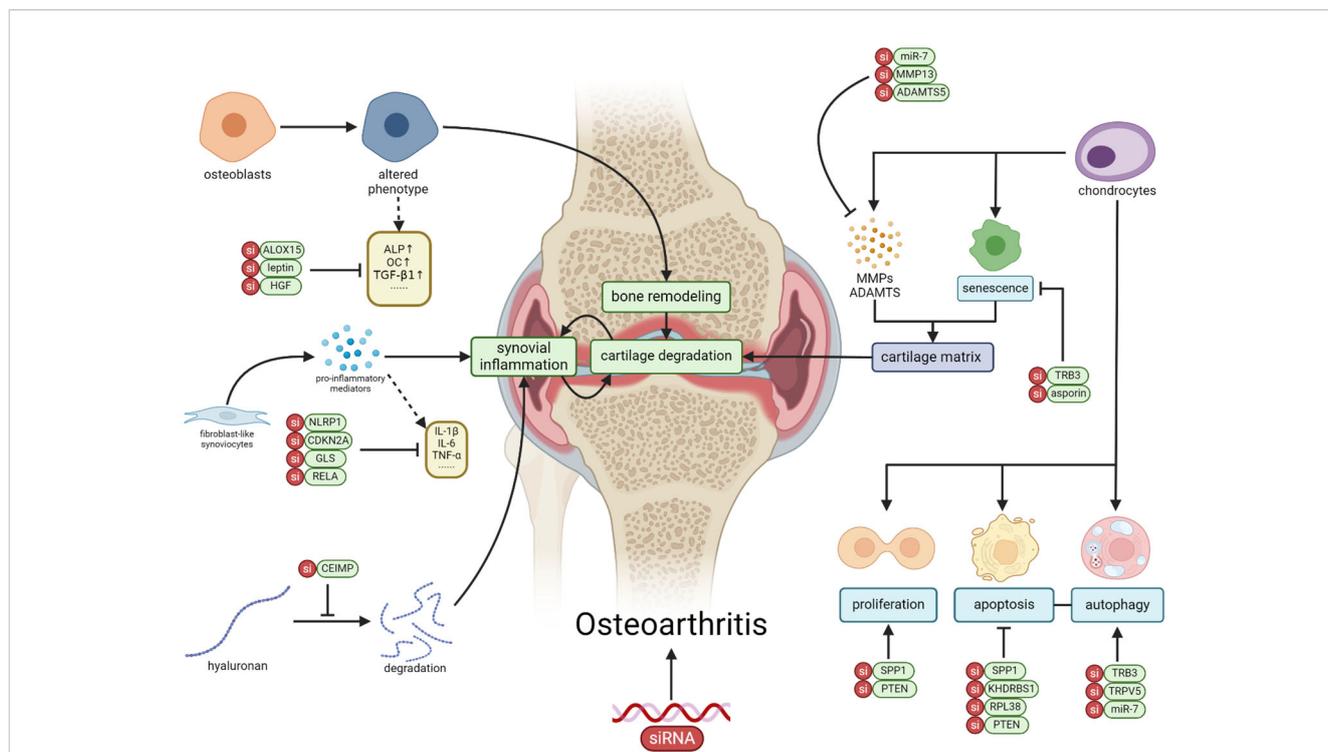


FIGURE 1

The application of siRNA therapy in OA involves targeting genes and signaling pathways in various cell types within OA, including chondrocytes, synovial fibroblasts, osteoblasts, macrophages, and mesenchymal stem cells. Through the correction of cellular activities such as proliferation, apoptosis, senescence, autophagy, and inflammation, siRNA exhibits the potential to alleviate the progression of OA (Created with BioRender.com).

inherent property of selectively silencing genes, siRNA stands as a potential candidate among DMOADs. Recent investigations have disclosed that employing siRNA to target chondrocytes, fibroblast-like synoviocytes, osteoblasts, and other cells and molecules involved in the development of OA can effectively decelerate the progression of the ailment. Additionally, a substantial volume of research centered around siRNA delivery systems has enhanced the precision and duration of siRNA delivery to target tissues. While there is currently no siRNA therapy specifically targeting osteoarthritis (according to [clinicaltrials.gov](https://clinicaltrials.gov)), an increasing number of siRNA therapies targeting various diseases are entering clinical trials or gaining approval. These include cancer, hypertension, hypercholesterolemia, as well as some rare genetic disorders such as hemophilia and primary hyperoxaluria (72). These studies collectively highlight the broad potential of employing siRNA in the treatment of OA.

However, the constraints of current siRNA therapies cannot be disregarded. The primary method of siRNA therapy involves intravenous administration using nano-carriers, including lipid carriers, polymer carriers, and inorganic carriers (12). Lipid carriers, due to their positively charged nature, may undergo aggregation with serum proteins (73). On the other hand, negatively charged siRNA can distribute through the bloodstream to the reticuloendothelial system (RES) and are more readily phagocytosed, compared to neutral or positively charged counterparts (11). Furthermore, siRNA permits a degree of mismatch with the target mRNA, resulting in the silencing of non-target genes, known as off-target effects (74). Competition with the endogenous RNAi pathway and off-target effects can lead to hepatotoxicity (75). Cationic lipids and polymers, among other delivery methods involving internalization, can also induce immune responses by activating Toll-like receptor 7 (TLR7) and Toll-like receptor 8 (TLR8) (76). To address these issues, numerous improvement strategies have been applied to optimize siRNA delivery, including chemical modifications, siRNA-ligand conjugation, siRNA-polymer conjugation, and others (77).

Beyond the inherent limitations of siRNA therapy, the selection of target genes represents one of the challenges in utilizing siRNA therapy for OA treatment. Given that OA is a disease affecting the entire joint, silencing target genes for OA may also potentially diminish therapeutic efficacy through the impact on physiological activities of other tissues, or even inadvertently accelerate disease progression. The activation of the PI3K/AKT/mTOR pathway can enhance skeletal muscle protein synthesis, whereas inhibition of the PI3K/AKT/mTOR pathway can increase protein breakdown, marking a signature of muscle atrophy. Moreover, muscular weakness constitutes a risk factor in the development of OA (78, 79). IL-6 is released during and after exercise to enhance muscle energy supply and plays a crucial role in the repair of acute muscle injuries by activating satellite cells (80, 81). Inhibiting IL-6 could have repercussions on muscle function, potentially exacerbating the progression of OA.

In this review, we summarized the advancements in utilizing siRNA to target various cells for the treatment of OA, including chondrocytes, fibroblast-like synoviocytes, osteoblasts, and others (Table 1 and Figure 1). These studies, encompassing both *in vitro* experiments and *in vivo* trials, consistently demonstrate the potential of siRNA therapy. However, siRNA therapy still confronts numerous challenges, such as the selection of therapeutic targets, more efficient carriers for siRNA delivery, and addressing the immunogenicity of siRNA. Hence, the therapeutic potential of siRNA remains vast, with significant room for further advancement.

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## Conflict of interest

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## Glossary

DNMT3A	DNA methyltransferase 3 alpha
ALOX15	Arachidonate 15-lipoxygenase
KHDRBS1	KH RNA binding domain containing, signal transduction associated 1
TNF- $\alpha$	Tumor necrosis factor $\alpha$
NF- $\kappa$ B	Nuclear factor kappa B
SPP1	Secreted phosphoprotein 1
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
AKT	Protein kinase B
PTEN	Phosphatase and tensin homologue
RPL38	Ribosomal protein L38
SOCS2	Suppressor of cytokine signaling 2
JAK	Janus kinase
STAT3	Signal transducer and activator of transcription 3
IL-1 $\beta$	Interleukin 1 $\beta$
IL-6	Interleukin 6
MMP13	Matrix metalloproteinases 13
ADAMTS5	A disintegrin and metalloprotease with thrombospondin motifs 5
BIRC2	Baculoviral IAP repeat containing 2
BIRC3	Baculoviral IAP repeat containing 3
XIAP	X-linked inhibitor of apoptosis
TGF- $\beta$ 1	Transforming growth factor $\beta$ 1
Smad2	Smad family member 2
EAAT1	Excitatory amino acid transporter protein 1
MFN2	Mitofusin 2
TRB3	Tribbles homolog 3
mTOR	Mechanistic target of rapamycin
AMPK	AMP-activated protein kinase
miR-7	MicroRNA 7
IL-17A	Interleukin 17A
BECN1	Beclin 1
SQSTM1	Sequestosome 1
p38 MAPK	p38 mitogen-activated protein kinase
TRPV5	Transient receptor potential cation channel subfamily V member 5
KDM6B	Lysine demethylase 6B
CTNNB1	Catenin beta 1
MMP3	Matrix metalloproteinases 3
ADAMTS4	A disintegrin and metalloprotease with thrombospondin motifs 4

(Continued)

## Continued

EPAS1	endothelial PAS domain protein 1
IL-1	Interleukin 1
MMP9	Matrix metalloproteinases 9
NLRP1	NLR family pyrin domain containing 1
RELA	RELA proto-oncogene, NF- $\kappa$ B subunit
CDKN2A	Cyclin dependent kinase inhibitor 2A
CEMIP	Cell migration inducing hyaluronidase 1
GLS	Glutaminase
LTBP-1	Latent transforming growth factor beta binding protein 1
TGF- $\beta$	Transforming growth factor $\beta$
METTL3	Methyltransferase like 3
ATG7	Autophagy related 7
HIF-1A	Hypoxia inducible factor 1 subunit alpha
WNT	Wingless-type MMTV integration site family
HGF	Hepatocyte growth factor
BMP-2	Bone morphogenetic protein 2
mTORC1	Mechanistic target of rapamycin complex 1
TLR4	Toll-like receptor 4
NLRP3	NLR family pyrin domain containing 3
NOTCH1	Notch receptor 1
BLACAT1	BLACAT1 overlapping LEMD1 locus