Lipid nanoparticle-based gene therapies for osteoarthritis: A review

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ABSTRACT

Osteoarthritis (OA) remains a leading cause of disability and lacks approved disease-modifying pharmacotherapies, affecting over 500 million people worldwide. Over the past decade, advances in joint biology, molecular research on cartilage and subchondral bone degeneration, and nanomaterial studies for targeted delivery have driven gene therapy strategies for OA. Early clinical studies employing local delivery of anti-inflammatory or anabolic transgenes through adeno-associated virus, helper-dependent adenovirus, or plasmids have demonstrated intra-articular expression and initial safety, establishing regulatory and translational pathways. Recent advances in molecular biology and nanotechnology have enabled the emergence of RNA-based therapies delivered via lipid nanoparticles (LNPs). LNPs, clinically validated through their use in mRNA COVID-19 vaccines, offer a modular and scalable system for nucleic acid delivery. They provide stability for RNA constructs, enhance joint retention, and facilitate penetration into the dense extracellular matrix of cartilage. Preclinical studies have demonstrated that intra-articular administration of LNP-encapsulated small interfering RNAs and messenger RNAs can suppress inflammatory mediators, silence catabolic enzymes, and promote cartilage regeneration. This review summarizes recent studies on the design, optimization, and translational progress of LNP-based RNA therapies for OA, addressing ongoing challenges related to durability, re-dosing, scalability, and immunogenicity. It outlines a roadmap for achieving disease-modifying RNA therapeutics in OA.

Keywords:
Osteoarthritis; Gene therapy; Lipid nanoparticle; Gene delivery

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1. Introduction

Osteoarthritis (OA) is the most common degenerative joint disease and a leading cause of pain and disability in aging populations. Globally, more than 500 million individuals are affected, with prevalence expected to rise further as life expectancy and obesity rates increase.[1,2] The disease is characterized by the progressive loss of articular cartilage, subchondral bone remodeling, synovial inflammation, and the formation of osteophytes. These structural changes result in pain, stiffness, and impaired mobility, ultimately leading to significant socioeconomic and healthcare burdens. Despite the high prevalence and impact, effective disease-modifying OA drugs (DMOADs) remain elusive.

Currently available treatments are primarily symptomatic. Non-pharmacological core approaches, including weight management and exercise, remain foundational to effective treatment. Pharmacological treatments such as non-steroidal anti-inflammatory drugs and intra-articular corticosteroids offer short-term relief but do not alter disease progression. Advanced cases often necessitate surgical interventions, including total joint replacement, which is invasive, expansive, and associated with significant risks.[3] As shown in **Figure 1**, current OA treatment strategies primarily focus on pain control and functional improvement, rather than targeting the molecular drivers of joint degeneration.

The failure to develop effective DMOADs stems from the multifactorial and heterogeneous nature of OA. Cartilage, subchondral bone, synovium, and meniscus are dynamically interconnected,

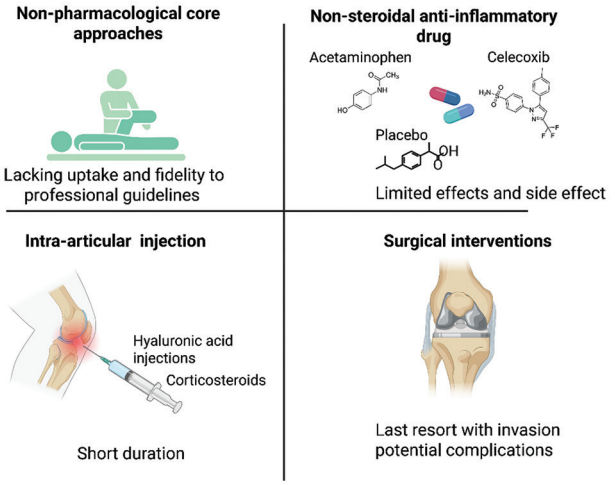

Figure 1. Current treatment approaches for osteoarthritis include non-pharmacological interventions, pharmacological treatments, and surgical procedures. While these methods alleviate symptoms, they do not modify disease progression.[3] Created in BioRender.com (Qinghao Zhang *et al.*) 2025 https://BioRender.com/calsoad.

creating a complex microenvironment that resists mono-therapeutic interventions. The avascular structure and dense extracellular matrix (ECM) of cartilage present formidable barriers to drug penetration and retention. Moreover, systemic drug delivery is hampered by rapid clearance, poor joint-specific bioavailability, and the risk of off-target toxicity.[4] These challenges highlight the urgent need for novel delivery systems capable of transporting therapeutic molecules directly into the joint and maintaining their activity *in situ*.[5]

Against this backdrop, nucleic acid-based therapeutics—particularly RNA-based modalities—have emerged as a promising frontier. Messenger RNAs (mRNAs), small interfering RNAs (siRNAs), and circular RNAs (circRNAs) can modulate gene expression with high precision, allowing suppression of catabolic mediators, blockade of inflammatory pathways, and enhancement of anabolic signaling.[6,7] Currently, RNA therapeutics can target an increasing number of genes, expanding the therapeutic landscape for OA.

The clinical validation of lipid nanoparticle (LNP)-based RNA delivery in vaccines has catalyzed their exploration in musculoskeletal disorders.[8,9] LNPs encapsulate RNA, protecting it from nuclease degradation and facilitating cellular uptake, while enabling controlled and localized expression. Recent preclinical work demonstrates that intra-articular injection of LNPs can silence inflammatory cytokines, inhibit matrix metalloproteinases (MMPs), and promote cartilage repair.[10] Moreover, strategies combining LNPs with hydrogel depots or engineering circRNA payloads have enhanced retention times and improved therapeutic durability.[11,12] These findings underscore the potential of LNP-based RNA delivery systems to shift OA treatment from symptomatic management to disease modification.

2. Pathophysiological mechanisms of OA

OA is increasingly recognized as a multifactorial disease characterized not only by cartilage degradation but also by a complex interplay of pathological events involving the synovium, subchondral bone, and periarticular tissues.[13,14] Unlike inflammatory arthritides such as rheumatoid arthritis, which are primarily driven by systemic immune dysregulation, OA develops insidiously through biomechanical stress, cellular senescence, low-grade inflammation, and metabolic dysfunction. This multifaceted and synergistic pathophysiology underscores the need for multi-targeted therapeutic strategies, making programmable RNA-based therapeutics delivered via LNPs particularly attractive, as they can be designed to modulate multiple pathogenic pathways simultaneously.[1,15,16]

2.1. Cartilage degeneration and ECM breakdown

The primary hallmark of OA is the progressive deterioration of articular cartilage, a highly specialized tissue composed mainly of type II collagen and aggrecan.[17] Chondrocytes are the sole resident cells responsible for maintaining cartilage homeostasis, balancing anabolic processes that synthesize ECM proteins with catabolic mechanisms that degrade them. In OA, this balance is disrupted, favoring catabolism. MMPs, especially MMP-13, aggrecanases such as disintegrin, and metalloproteinase with thrombospondin type 1 motif (ADAMTS)-4 and ADAMTS-5, are markedly upregulated, driving collagen and proteoglycan degradation.[18-20] Their expression is stimulated by pro-inflammatory cytokines, notably interleukin (IL)-1β and tumor necrosis factor-α (TNF-α).[21]

Traditional pharmacological attempts to inhibit MMPs have failed due to off-target toxicity and insufficient selectivity. In contrast, RNA-based approaches, such as siRNAs, offer a promising strategy to specifically silence MMP-13 or ADAMTS-5 expression. Preclinical studies have demonstrated that targeted delivery of siRNAs against MMP-13, encapsulated in nanoparticles, can significantly attenuate cartilage destruction in rodent OA models.[22,23]

2.2. Inflammatory pathways and synovial activation

OA is now recognized as a low-grade inflammatory disease, characterized by synovial tissue infiltration with macrophages and activation of innate immune signaling. This creates a pro-inflammatory milieu characterized by elevated levels of IL-1β, TNF-α, and IL-6, which amplify catabolic cascades in chondrocytes and sensitize nociceptive neurons, as illustrated

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in **Figure 2**. Central to this process is the nuclear factor kappa B (NF-κB) pathway. The activation of NF-κB promotes the transcription of pro-inflammatory cytokines, chemokines, and matrix-degrading enzymes, perpetuating a vicious cycle of joint destruction and pain.[24] Importantly, synovial inflammation and the resulting cytokine release directly exacerbate cartilage catabolism and subchondral bone remodeling, illustrating the critical crosstalk between joint tissues that necessitates therapeutic strategies capable of intervening at multiple levels.

Another critical pathway is the Janus kinase/signal transducer and activator of transcription (JAK/STAT), which regulates both inflammatory and catabolic genes. Targeting these intracellular signaling cascades using siRNAs or antisense oligonucleotides has shown promise in preclinical models of OA. For example, RNA therapeutics directed against NF-κB subunits have been shown to reduce synovial hyperplasia and protect cartilage in rodent studies.[25,26] In summary, the low-grade inflammatory milieu in OA, driven by synovial activation and key signaling pathways such as NF-κB and JAK/STAT, is a central driver of disease progression and pain, presenting a compelling target for LNP-encapsulated RNA inhibitors.

2.3. Subchondral bone remodeling

Subchondral bone changes are integral to OA pathogenesis. The early stages are characterized by increased bone remodeling and bone marrow lesions, followed by sclerosis and the formation of osteophytes. These alterations not only contribute to mechanical stress on cartilage but also influence biochemical signaling within the joint. The Wnt/β-catenin pathway plays a pivotal role, with overactivation driving osteophyte formation and insufficient activity leading to bone fragility. RNA-based therapeutics offer the opportunity to modulate this pathway with high specificity. For example, mRNA delivery of Wnt antagonists or siRNA-mediated silencing of sclerostin has been investigated as a strategy to restore homeostasis in subchondral bone remodeling.[27]

2.4. Anabolic, reparative, and microenvironment-modulating pathways

To achieve long-term disease modification, effective therapeutic strategies must extend beyond suppressing catabolism and inflammation to actively promoting anabolic repair and addressing the broader pathologic joint microenvironment. Transforming growth factor-β (TGF-β) and bone morphogenetic proteins are among the most potent regulators of cartilage repair, stimulating chondrocyte survival and matrix synthesis. However, dysregulated TGF-β signaling in aged or osteoarthritic joints can paradoxically drive osteophyte formation and synovial fibrosis, highlighting the importance of precise modulation.[28,29] Recent studies have highlighted insulin-like growth factor 1 (IGF1) and fibroblast growth factor 18 (FGF18) as particularly promising anabolic targets. LNP-encapsulated mRNA encoding *IGF1* or *FGF18* has been shown in animal models to enhance matrix regeneration and restore cartilage structure more effectively than recombinant protein injections, owing to sustained intra-articular expression.[30,31] The OA microenvironment is further shaped by epigenetic regulation, where microRNAs (miRNAs) such as miR140, miR146a, and miR27b fine-tune cartilage homeostasis. Their dysregulation contributes to OA pathogenesis, making miRNA mimics or inhibitors delivered through LNPs a viable strategy to restore regulatory networks.[32-34] Emerging roles for long

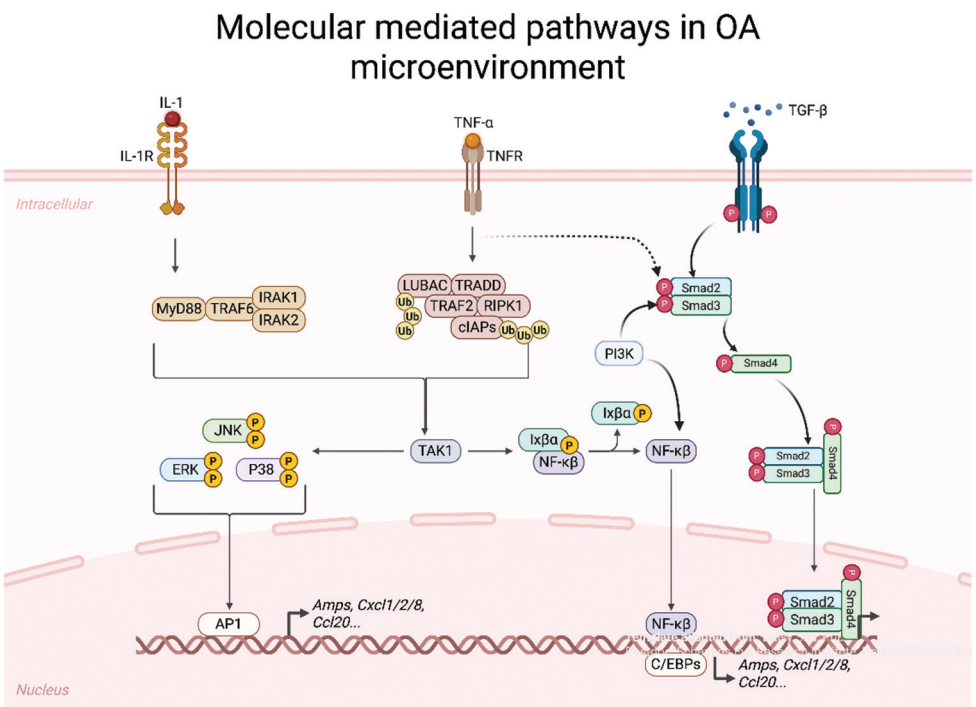

Figure 2. The NF-κB and JAK/STAT activation pathways in OA synovium, highlighting potential RNA therapeutic targets for modulating inflammation and catabolism.[25,26] Created in BioRender.com (Qinghao Zhang *et al.*). 2025 https://BioRender.com/041eagd.
Abbreviations: JAK: Janus kinase; NF-κB: Nuclear factor kappa B; OA: Osteoarthritis; STAT: Signal transducer and activator of transcription.

non-coding RNAs (lncRNAs) and circRNAs further expand the therapeutic landscape for microenvironment modulation.[35,36]

Finally, pain, a defining feature of the OA microenvironment mediated by factors such as nerve growth factor (NGF), represents a critical therapeutic target. While anti-NGF antibodies show efficacy, RNA-based approaches targeting NGF or downstream mediators offer potential for localized, precisely tunable analgesia with reduced systemic side effects.[37-39] Thus, the joint microenvironment presents multiple interconnected targets—anabolic, epigenetic, and nociceptive—for LNP-based RNA therapies aiming to achieve comprehensive disease modification. Collectively, the pathophysiological landscape of OA is complex and interconnected, involving cartilage breakdown, inflammation, bone changes, pain signaling, and epigenetic dysregulation. This underscores the rationale for employing versatile LNP-encapsulated RNA therapeutics that can be co-formulated or sequentially administered to target multiple pathways for enhanced efficacy.

3. Advances in gene delivery systems for OA

The efficacy of RNA-based therapeutics in OA hinges on the development of efficient and safe delivery systems that can overcome the unique anatomical and biological barriers of the joint. Over the past two decades, multiple gene delivery platforms have been investigated, including viral vectors, non-viral biologically derived systems, and biomaterial-based carriers, as illustrated in **Figure 3**. While viral vectors initially dominated the field due to their high transduction efficiency, concerns regarding safety, immunogenicity, and re-dosing limitations have spurred the transition toward non-viral systems. Among these, LNPs have emerged as the most clinically validated and versatile vehicles, benefiting from rapid progress catalyzed by the COVID-19 mRNA vaccine experience.[16,40]

3.1. Viral vectors

Adeno-associated viruses (AAVs) have been widely explored in musculoskeletal research due to their ability to transduce both dividing and non-dividing cells, low pathogenicity, and relatively stable expression. Preclinical studies have demonstrated that intra-articular injection of AAVs encoding anti-inflammatory proteins, such as IL-1 receptor antagonist, or anabolic growth factors, like IGF1, leads to local protein expression and symptomatic improvement in OA models.[41] However, limitations quickly became apparent. Immune responses against AAV capsids restricted the feasibility of repeated dosing, a critical issue given the chronic nature of OA. In addition, the restricted packaging capacity of AAVs limited their ability to deliver complex constructs, such as multi-cistronic RNAs or large circRNAs.

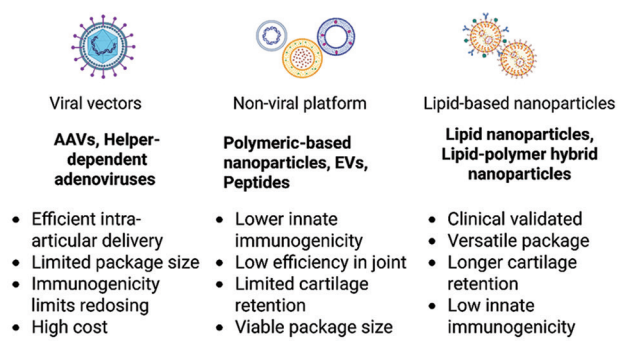

Figure 3. Overview of viral vectors, non-viral platforms, and lipid-based nanoparticle gene delivery systems investigated for OA, along with their respective advantages and limitations.[16,41,46] Created in BioRender.com (Qinghao Zhang *et al.*) 2025 https://BioRender.com/jnyr8vx.
Abbreviations: AAV: Adeno-associated virus; EV: Extracellular vesicles; OA: Osteoarthritis.

3.2. Non-viral biologically derived systems

Non-viral biologically derived carriers, such as engineered bacteria or extracellular vesicles (EVs), have been applied in gene delivery.[42,43] For example, attenuated *Escherichia coli* strains have been used to deliver plasmids encoding therapeutic genes.[44,45] It is important to note that EVs, including exosomes and microvesicles, exhibit substantial heterogeneity. Different EV subtypes (e.g., based on cellular origin or isolation method) can have significantly different RNA loading capacities, cartilage penetration efficiencies, and immunogenic profiles, which must be carefully considered when comparing them to synthetic vectors such as LNPs. These systems benefit from their intrinsic cell-penetrating properties and potential for delivering large payloads. However, their translation to OA therapy remains limited due to significant concerns regarding safety, unpredictability of host responses, and regulatory complexity.

3.3. Polymer-based nanoparticles

Polymeric nanoparticles represent another important non-viral platform. Cationic polymers such as polyethyleneimine (PEI) and chitosan have been tested for intra-articular delivery of plasmid DNA and siRNAs targeting catabolic enzymes.[46] For instance, PEI-condensed siRNA against MMP-13 reduced cartilage matrix degradation in OA.[47] More recently, biodegradable poly β-amino esters have been engineered to mitigate the cytotoxicity associated with earlier cationic polymers while maintaining efficient nucleic acid delivery.[48-50] Nevertheless, challenges remain regarding the reproducibility of synthesis, scalability, and ensuring penetration into the dense cartilage ECM.

3.4. LNPs development in clinical settings

The breakthrough in LNP technology for RNA delivery has redefined the gene therapy landscape.[51] Clinically validated through their use in mRNA vaccines against SARS-CoV-2, LNPs provide a scalable, safe, and versatile platform well-suited for intra-articular applications. Structurally, LNPs consist of ionizable lipids, cholesterol, helper lipids, and polyethylene glycol (PEG)-conjugated lipids, which together encapsulate and protect RNA from degradation, facilitate endosomal escape, and enable controlled release. Unlike viral vectors, LNPs allow repeat dosing without significant risk of neutralizing immune responses, a critical advantage for chronic conditions such as OA.[2,16,52]

In preclinical OA models, intra-articular administration of siRNA–LNPs targeting catabolic enzymes such as ADAMTS-5 has been shown to reduce cartilage erosion and improve joint function.[53,54] Similarly, mRNA-based LNPs encoding IGF1 have been demonstrated to stimulate anabolic signaling and enhance cartilage repair, with superior outcomes compared to recombinant protein injections due to sustained local expression.[55-57] Recent studies have further demonstrated the potential of circRNA/LNP formulations, which combine the stability of circRNAs with the delivery efficiency of LNPs, thereby enabling prolonged therapeutic activity in OA joints.[58-60] **Figure 4** provides a comparative overview of these delivery systems.

3.5. Transition from viral to LNP platforms

The trajectory from viral vectors to LNP-based systems reflects the broader shift in gene therapy for OA.[61] As summarized in **Table 1**, each delivery platform possesses distinct advantages and limitations. Viral systems provided the initial proof of concept for localized gene expression, but were hindered by immune responses and re-dosing barriers.[62-64]

LNPs now combine the scalability, safety, and efficiency required for clinical translation, representing the most promising platform for achieving sustained, tunable RNA expression in OA joints. Importantly, the modularity of LNPs allows for future integration with targeting ligands, responsive hydrogels, and combinatorial RNA payloads to address the multifactorial pathology of OA.[60] Among RNA-based therapeutics, circRNAs have recently emerged as a particularly promising approach for OA treatment. **Figure 5** illustrates the mechanisms of the LNP-based circRNA delivery system in chondrocytes.

In summary, while viral vectors pioneered gene therapy for OA and non-viral alternatives explored safer options, LNPs have emerged as the leading platform, successfully balancing efficacy, safety, manufacturability, and re-dosing potential, thereby paving the way for clinical translation of RNA therapeutics.

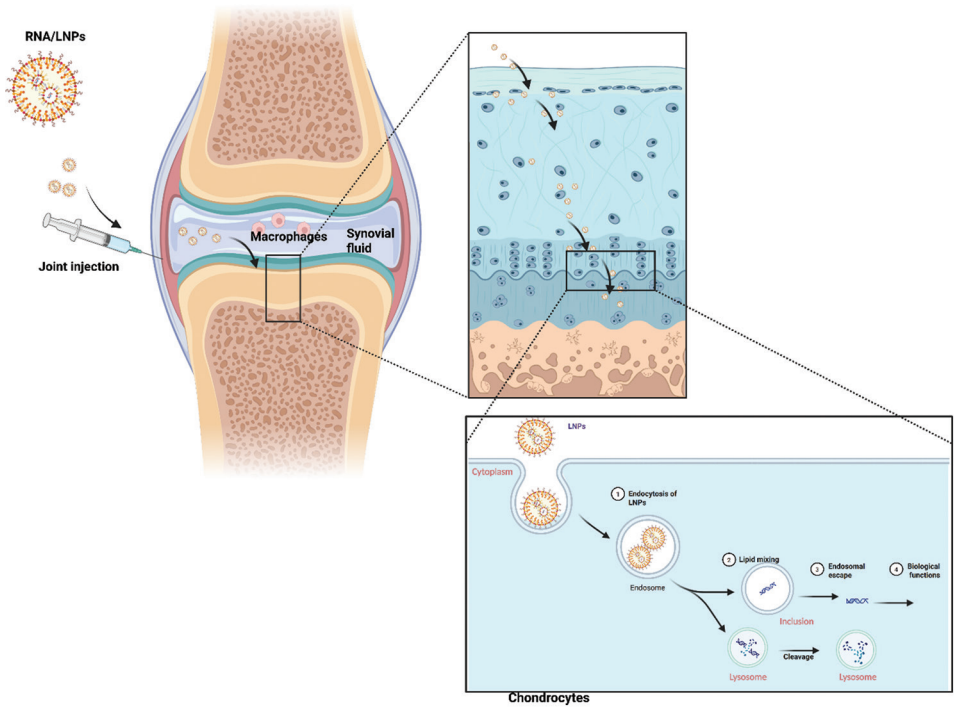

Figure 4. Lipid nanoparticle (LNP) structure and mechanism of intra-articular RNA delivery, showing LNP administration, cartilage penetration, and cellular uptake.[53,55,58] Created in BioRender.com (Qinghao Zhang *et al.*) 2025 https://BioRender.com/q6o1jp8.

Table 1. Comparison of major nucleic acid delivery platforms

Delivery platform	Advantages	Disadvantages
Lipid nanoparticles	Low immunogenicity; high engineering flexibility; suitable for repeat dosing; large payload capacity; scalable manufacturing	Efficiency, stability, and tissue targeting can be suboptimal
Adeno-associated virus	Low immunogenicity; tissue tropism; long-term/durable transgene expression	Small cargo capacity (~4.7 kb); can elicit immune responses; delayed onset of expression; high production costs
Lentivirus	Transduces both dividing and non-dividing cells; larger cargo capacity than adeno-associated virus	Random integration risk (insertional mutagenesis); high immunogenicity
Polymeric nanoparticles	High biocompatibility; tunable structure; low immunogenicity	Lower transfection efficiency; instability; complex *in vivo* behavior
Extracellular vesicles	High biocompatibility; low immunogenicity; high stability	Complex manufacturing and isolation; rapid hepatic clearance; significant heterogeneity among extracellular vesicle subtypes

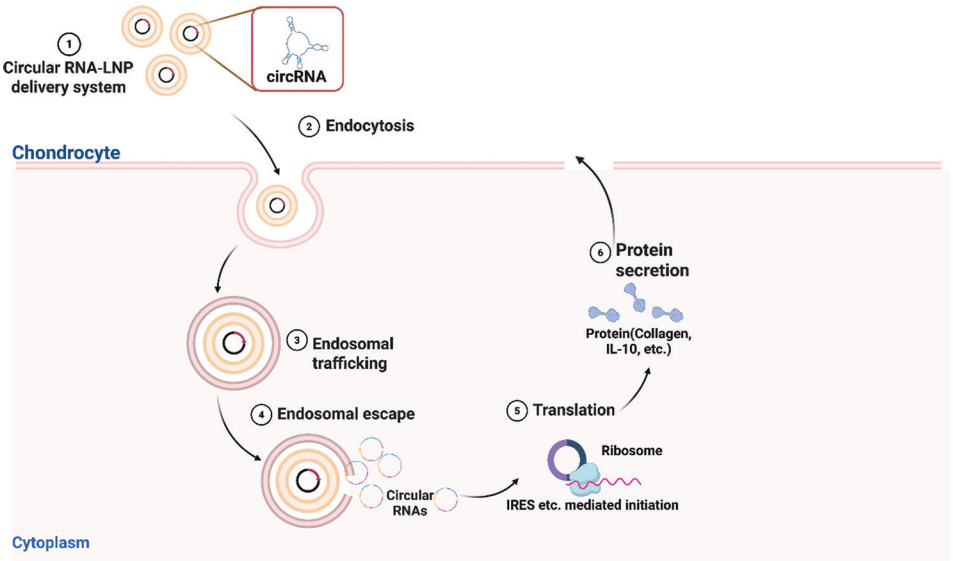

Figure 5. CircRNA-based LNP delivery system in chondrocytes.[53,59,60] Created in BioRender.com (Qinghao Zhang *et al.*) 2025 https://BioRender.com/mk0o8a7.
Abbreviations: CircRNA: Circular RNA; IRES: Internal ribosome entry site; LNP: Lipid nanoparticle.

4. Preclinical progress in LNP-based RNA therapeutics for OA

Building upon the clinical success of LNP-based mRNA vaccines, researchers have adapted this technology to address the unique challenges of intra-articular delivery.[65,66] Recent preclinical studies have demonstrated the feasibility of using LNPs to deliver a range of RNA payloads, including siRNAs, mRNAs, and circRNAs, to modulate key pathogenic pathways in OA, resulting in significant structural and symptomatic improvements.[67-71]

Recent preclinical studies have demonstrated the efficacy of LNP-based mRNA delivery for the treatment of OA. As shown in **Figure 6**, intra-articular injection of LNP-encapsulated FGF18-modified mRNA significantly enhanced FGF18 expression in mouse joints, activating the forkhead box O3a-mediated autophagy pathway to alleviate chondrocyte senescence and cartilage degeneration. Furthermore, optimizing formulation parameters such as the water-to-ethanol ratio, nitrogen-to-phosphorus ratio, PEG percentage, and dialysis buffer concentration proved crucial for enhancing the accumulation and retention of LNPs within the joint cavity, as evidenced by luciferase mRNA imaging.[71]

4.1. LNP-delivered siRNAs targeting catabolic pathways

Silencing catabolic enzymes represents a major focus in LNP-delivered siRNA therapeutic strategies for OA. MMP-13 and aggrecanases (e.g., ADAMTS-4 and ADAMTS-5) are among the most critical mediators of ECM degradation. Recent studies have demonstrated that the intra-articular administration of LNP-encapsulated siRNAs targeting MMP-13 in rodent models resulted in a significant reduction in cartilage erosion and osteophyte formation, accompanied by improved gait and mobility scores compared to controls. For example, Zhao *et al.*[67] reported a novel LNP-based siRNA formulation targeting fibroblast activation protein (FAP), which is upregulated in senescent chondrocytes. FAP-siRNA/LNP complex effectively reduced the senescent chondrocyte burden, suppressed NF-κB–driven senescence-associated secretory phenotype, and preserved cartilage and subchondral bone integrity.[68,69]

4.2. LNP-delivered mRNAs promoting cartilage regeneration

An equally promising avenue involves the delivery of mRNAs encoding anabolic and reparative factors. *FGF18* and *SOX9* are among the most widely studied genes.[30,70] A study introduced a cartilage-optimized LNP system engineered for intra-articular mRNA delivery, which achieved higher joint-specific expression of *FGF18* compared to conventional LNPs while minimizing off-target liver uptake.[71] Optimization of the untranslated regions (UTRs) and nucleoside modifications of *FGF18* mRNA has been shown to extend intra-articular expression to nearly 1 week.[71-74] This formulation effectively reduces chondrocyte senescence and sustains cartilage homeostasis.[30]

4.3. circRNA–LNP delivery systems

Recently, circRNAs have emerged as an innovative RNA modality for OA therapy due to their structural stability and multifunctionality.[75] As illustrated in **Figure 7**, circRNAs can be engineered for high-efficiency protein translation through optimized UTRs, internal ribosome entry site elements, and N6-methyladenosine modifications (**Figure 7A**), or for sequence-specific interference, functioning as miRNA sponges, protein decoys, or antisense molecules (**Figure 7B**).

Their covalently closed loops confer resistance to exonuclease degradation, which may offer advantages within the inflammatory environment of OA.[76] Moreover, circRNAs act as miRNA sponges and protein scaffolds, providing multilayered regulation of pathogenic pathways.[77]

In a previous study, a circRNA construct encoding a super-repressor of NF-κB was delivered via LNPs, achieving significant

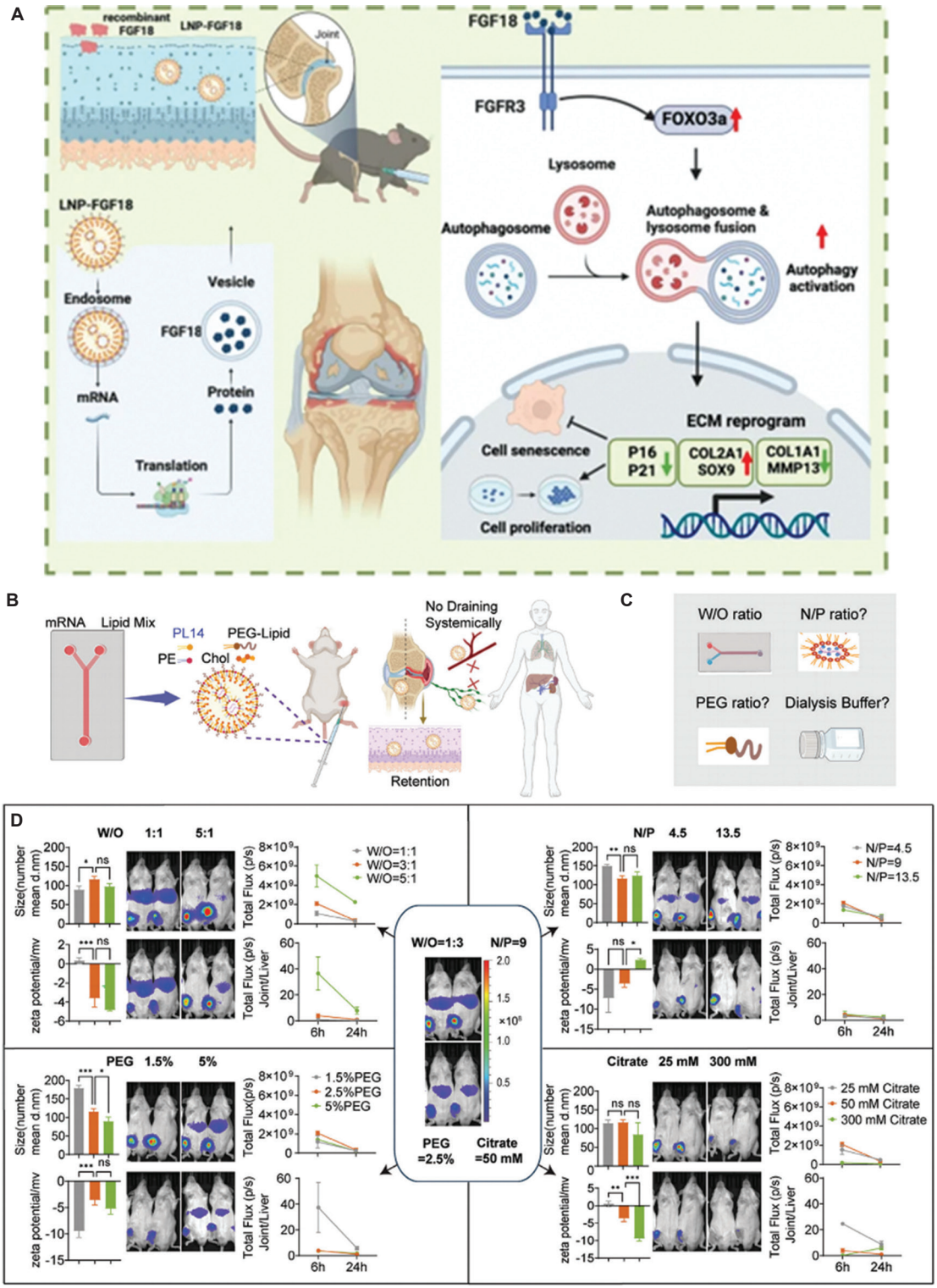

Figure 6. Schematic diagram of the LNP delivery system for osteoarthritis therapy and *in vivo* experimental results. (A) Intra-articular delivery of LNP-encapsulated FGF18 modified mRNA for osteoarthritis therapy. Injection of LNP–FGF18 into the mouse joint cavity significantly increased FGF18 expression *in vivo*, activating the FOXO3a-mediated autophagy pathway and protecting cartilage by attenuating chondrocyte senescence and degeneration. (B) Schematic illustration of the nanoparticle preparation method. (C) Illustration of enhanced accumulation of luciferase–mRNA LNPs in cartilage cavity through optimization of the W/O ratio, the N/P ratio, the percentage of PEG, and the concentration of dialysis buffer. (D) Size, zeta potential, and bioluminescence imaging of ICR mice (n = 3) after intra-articular injection of LNP–luciferase mRNA (2 μg mRNA) in different formulations. The fluorescent scale bar unit is photons/sec/cm^2/sr, with a radiance scale of 1.0×10^7–2×10^8. Data were represented as mean ± standard error of the mean. Statistical significance was calculated via one-way analysis of variance, followed by Dunnett's multiple comparisons test (*p < 0.05, **p < 0.01, and ***p <0.001).[71] Reprinted with permission from Sun *et al.*[71] Copyright © 1999–2025 John Wiley & Sons, Inc.

Abbreviations: FOXO3a: Forkhead box O3a; ICR: Institute of Cancer Research; LNP: Lipid nanoparticle; mRNA: Messenger RNA; N/P: Nitrogen-to-phosphorus; PEG: Polyethylene glycol; W/O: Water-to-ethanol.

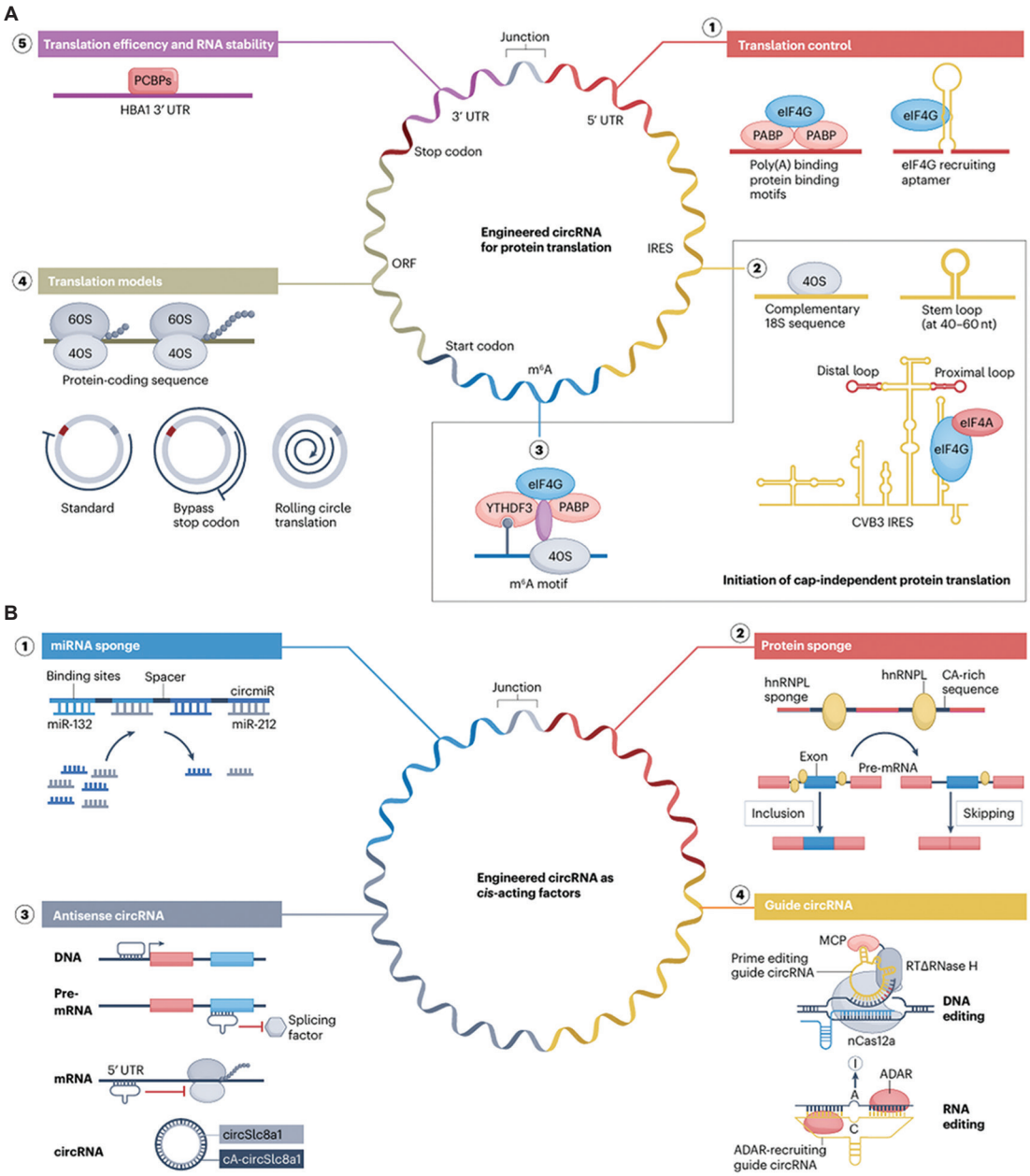

Figure 7. Key components of engineered circRNAs for various purposes. (A) Engineered circRNAs for protein translation. Design of a 5′ UTR to improve the translational efficiency of circRNAs. 5′ UTR, including elements such as poly(A) binding protein motifs and eIF4G-recruiting aptamers (indicated in yellow), which increase circRNA translation by recruiting eIF4G, a key scaffold protein in the translation-initiation step (step 1). Incorporation of an IRES, such as CVB3 IRES, enables cap-independent translation initiation of circRNAs. Short IRES elements, containing a complementary 18S sequence or a stem loop of approximately 40–60 nucleotides, can also initiate circRNA translation. Adding eIF4G-recruiting aptamers at both the distal and proximal positions of CVB3 further increases the translation efficiency of circRNAs (step 2). m6A modification drives circRNA protein translation by recruiting the cytoplasmic m6A reader YTHDF3, which interacts with the 40S and 60S ribosome subunits, and abrogates circRNA immunity without activating RIG-I innate immune signaling (step 3). The protein-coding sequence of circRNA includes a start codon, an ORF, and a stop codon. circRNAs encode proteins via canonical linear ORF translation, stop codon bypass, or rolling circle translation (step 4). Incorporation of the human α-globin 3′ UTR, which interacts with cytoplasmic poly(C) binding proteins forming an α-complex, has been reported to enhance circRNA translation efficiency (step 5). (B) Engineered circRNAs for sequence-based interference. miRNA sponges (circmiR) were engineered with six miR-132 and six miR-212 binding sites prepared by a 6-nucleotide spacer to inhibit miRNA activity (step 1). Protein sponges: artificial hnRNPL sponge circRNAs containing CA-rich sequence clusters modulate pre-mRNA slicing via hnRNPL sequestration (step 2). Antisense circRNAs: through base-pairing, synthetic circRNAs can bind with DNA, pre-mRNA, or mRNA to regulate gene activity (step 3). Guide circRNAs can be used for genome and transcriptome editing (step 4).[76] Reprinted with permission from Cao *et al.*[76] Copyright© 2025 Springer Nature Limited.

Abbreviations: ADAR: Adenosine deaminases acting on RNA; circRNA: Circular RNA; circmiR: Circular RNA microRNA sponge; CVB3: Coxsackievirus B3; eIF4G: Eukaryotic initiation factor 4G; hnRNPL: Heterogeneous nuclear ribonucleoprotein L; IRES: Internal ribosome entry site; m6A: N6-methyladenosine; MCP: MS2 coat protein; nCas12a: Cas12a nickase; ORF: Open reading frame; RIG-I: Retinoic acid-inducible gene I; RT: Reverse transcriptase; UTR: Untranslated region; YTHDF3: YT521-B homology domain family 3.

reductions in inflammatory mediator production and cartilage degradation.[60] Chen *et al.*[78] also reported a double-stranded circRNA aptamer-based therapy for OA by inhibiting protein kinase R activation in a destabilization of the medial meniscus mouse model, achieving notable *in vivo* anti-inflammatory effects. Additionally, circRNA/LNP formulations loaded within hydrogels enabled controlled release and prolonged bone regeneration.[79] Thus, circRNA/LNP systems achieve prolonged therapeutic effects without increasing dosing frequency, aligning well with the long-term treatment needs of OA.

The preclinical progress across these RNA modalities demonstrates the remarkable versatility of LNPs. Whether silencing deleterious genes, expressing therapeutic proteins, or employing multifunctional circRNAs, LNP-based delivery has shown consistent promise in modifying OA disease progression in animal models, paving the way for future clinical applications.

5. Design and optimization of LNPs for intra-articular delivery

The design and optimization of LNP platforms for OA therapy require strategies tailored to the specific biological and mechanical challenges of the intra-articular environment.[42,75] Unlike systemic drug delivery, which benefits from vascular circulation, intra-articular administration must overcome rapid clearance through synovial fluid turnover, the dense ECM of cartilage, and the need for repeated dosing over the chronic course of disease.[80] Consequently, refinements in both the molecular composition and physicochemical properties of LNPs have been central to recent progress in RNA-based OA therapeutics.

At the structural level, the performance of LNPs is influenced by a balance of four principal components: ionizable lipids, cholesterol, helper lipids, and PEG-conjugated lipids. Ionizable lipids form the functional core of the LNP. Their unique pH-responsive chemistry enables neutral charge at physiological conditions, reducing cytotoxicity, while acquiring a positive charge in the acidic environment of the endosome to mediate electrostatic interactions with endosomal membranes and promote cytoplasmic release of RNA payloads. Modifications in head-group structure, linker biodegradability, and tail saturation have significantly improved RNA encapsulation efficiency and chondrocyte transfection in preclinical models.[81,82] Cholesterol contributes both rigidity and fusogenicity to the bilayer, enhancing intracellular trafficking and endosomal escape.[83,84] Helper lipids such as distearoylphosphatidylcholine support membrane integrity under the mechanical and enzymatic stresses of the joint. PEG-conjugated lipids provide colloidal stability and prevent aggregation, although excessive PEGylation can impair cartilage penetration and cellular uptake. Recent work introducing biodegradable PEG-conjugate lipids has mitigated the risk of anti-PEG immune responses, supporting safe re-dosing in chronic indications such as OA.[85,86]

Furthermore, recent novel designs of ionizable lipids, featuring optimized head-group pKa, biodegradable linkers (e.g., ester-based), and tailored tail saturation, are pushing the boundaries of RNA encapsulation efficiency, chondrocyte transfection potency, and *in vivo* safety profiles.[87,88] While composition defines the baseline performance, engineering strategies have been essential for addressing the barriers of intra-articular delivery. Bio-adhesive coatings, including hyaluronic acid (HA) and chitosan, have been applied in joint models; HA-coated LNPs achieved prolonged joint retention, enhanced chondrocyte uptake, and reduced cartilage degradation compared to unmodified formulations.[89,90] Particle size optimization and surface charge modulation further refine delivery efficiency. While strongly cationic formulations risk inducing cytotoxicity and synovial inflammation, slightly positive charges facilitate ECM binding and deeper penetration without compromising safety.[91]

Chemical innovations have further improved localization and durability. Cholesterol analogues have been incorporated to increase hydrophobic interactions with cartilage ECM. In murine OA models, cholesterol-functionalized siRNA/LNPs targeting MMP-13 exhibited prolonged intra-cartilage retention and significant suppression of ECM degradation.[92] Attaching matrix-penetrating peptides to LNP surfaces also enabled more uniform distribution into deeper cartilage layers, resulting in more consistent chondrocyte transfection and improved histological protection.[93,94]

Despite these advances, the issue of rapid synovial clearance remains. To address this, LNPs have been integrated with hydrogel-based depots, creating hybrid systems that allow sustained release. Natural polymers, such as HA, and synthetic PEG hydrogels have been employed to embed LNPs, allowing RNA payloads to be released gradually over several weeks. In rabbit OA models, hydrogel–LNP hybrids significantly prolonged intra-articular retention and improved cartilage preservation compared with LNPs alone.[95,96] Furthermore, inflammation-responsive hydrogels embedding IL-1 receptor antagonist mRNA/LNPs have been developed to achieve on-demand release under elevated cytokine conditions, ensuring that therapeutic expression aligns with disease flares and minimizes unnecessary exposure.[89,97]

Collectively, the optimization of LNP design can advance RNA therapy for OA toward clinical viability via composition, surface engineering, and integration with advanced biomaterials. By ensuring effective encapsulation, prolonged retention, deep tissue penetration, and compatibility with repeated dosing, these systems address the major barriers of intra-articular RNA delivery and establish a strong foundation for the clinical development of DMOADs.

5.1. Hydrogel–LNP hybrid systems for sustained release

Although LNPs offer efficient encapsulation and cellular delivery, rapid synovial clearance limits their therapeutic window.[98] Hybrid hydrogel/LNP systems have been developed to address this issue. HA-based or gelatin methacryloyl-based hydrogels embedding RNA/LNPs can achieve extended retention in joints, reduce ECM loss, and improve cartilage morphology for longer periods compared with free LNPs.[58,60,99]

Similarly, a cholesterol-modulated hydrogel system co-delivering siRNA–LNPs against cholesterol 25-hydroxylase modulated chondrocyte lipid metabolism and enhanced

anabolic activity. In OA models, this strategy reduced MMP expression, increased SRY-box transcription factor 9 and collagen II levels, and recruited mesenchymal stem cells for cartilage regeneration.[54] Furthermore, advanced "smart" hydrogels that respond to environmental cues (e.g., pH, reactive oxygen species) have been engineered to achieve on-demand release of LNP/RNA payloads during disease flares, thereby enhancing therapeutic specificity.

5.2. Smart environment-responsive hydrogel–LNP hybrid systems

The integration of LNPs with smart, microenvironment-responsive hydrogels represents a cutting-edge strategy to overcome the challenge of rapid synovial clearance and achieve on-demand drug release.

An exemplary system (circ-srIκBα@LNP-SHC) is depicted in **Figure 8**. In this sophisticated design, circRNA-loaded LNPs were surface-modified with both a cartilage-affinity peptide and an anti-FAP single-chain variable fragment for dual targeting of chondrocytes and fibroblast-like synoviocytes (**Figure 8A**). These targeted LNPs were then encapsulated within a silk fibroin composite hydrogel cross-linked via an MMP13-specific substrate peptide. This design ensures that the therapeutic LNPs are released specifically in response to elevated MMP13 levels found in the inflammatory OA joint,

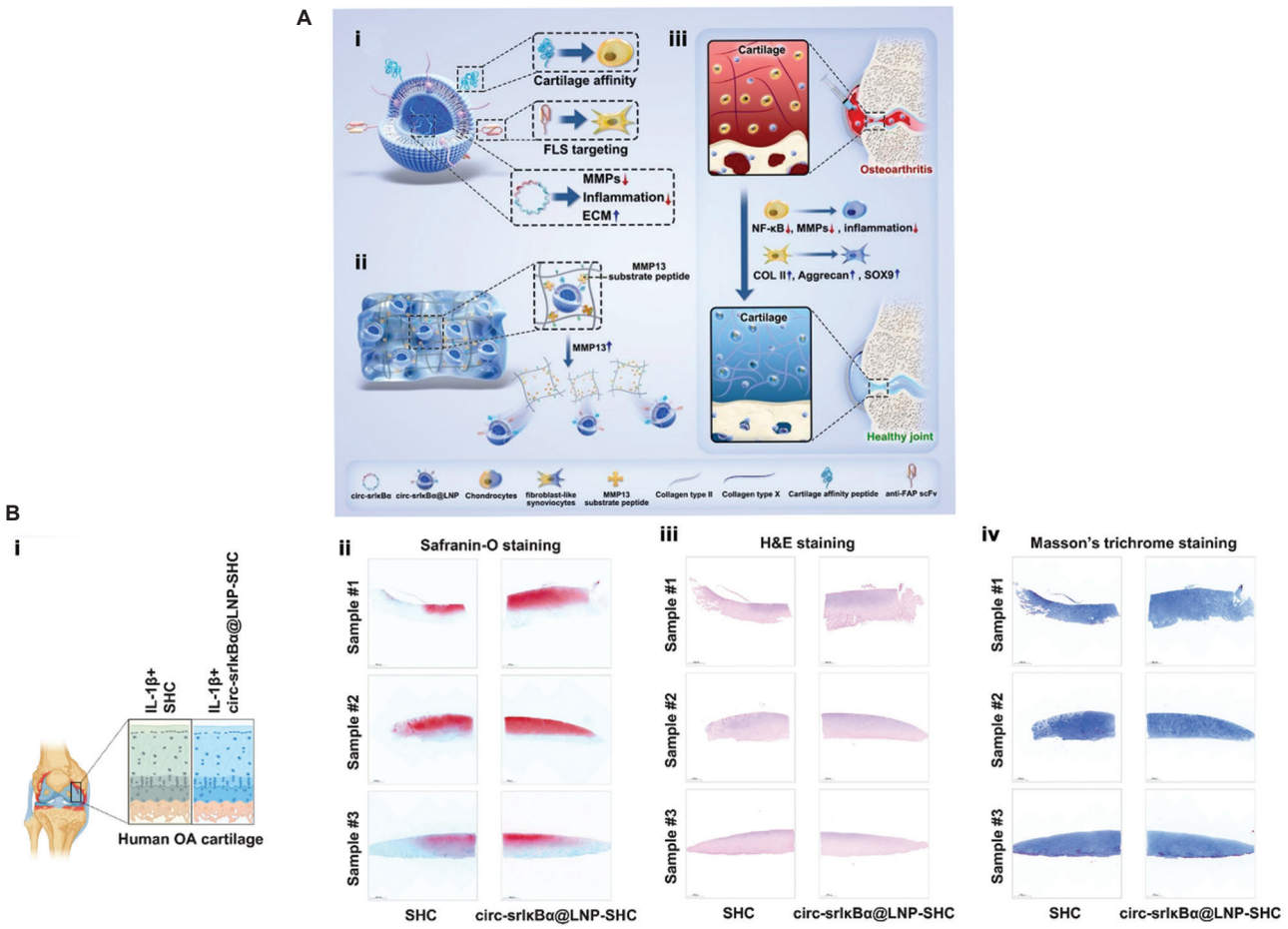

Figure 8. Design and therapeutic evaluation of an environmentally responsive nanoparticle–hydrogel system (circ-srIκBα@LNP-SHC) for the treatment of OA. (A) Schematic diagram of the environment-responsive drug delivery system (circ-srIκBα@LNP-SHC) for OA treatment: (i) circ-srIκBα, which inhibits nuclear translocation of P65, was encapsulated into LNPs. The LNPs were surface-modified with a cartilage-affinity peptide and an anti-FAP single-chain variable fragment to enable specific targeting of chondrocytes and FLS, respectively; (ii) an MMP13-specific substrate peptide was used to cross-link SHC composite hydrogels with circ-srIκBα@LNP, allowing for environmentally responsive release of circ-srIκBα@LNP proportional to MMP13 levels, thereby establishing an intelligent, environment-responsive drug delivery system; and (c) intra-articular injection of circ-srIκBα@LNP-SHC effectively inhibits NF-κB signaling, reduces secretion of MMPs and inflammatory factors, preserves the extracellular matrix, maintains joint microenvironment homeostasis, and mitigates OA progression. (B) Therapeutic effect of circ-srIκBα@LNP-SHC on human OA cartilage explants: (i) Schematic diagram of the procedures for harvesting and treating human OA cartilage explants. Cartilage explants were harvested from the medial condyle of the femur of OA patients undergoing total knee arthroplasty; (ii–iv) representative images of (ii) Safranin O–fast green, (iii) H&E, and (iv) Masson's trichrome staining in IL-1β-maintained explants treated with SHC or circ-srIκBα@LNP-SHC (scale bar: 1,000 μm; magnification: 40×).

Abbreviations: FAP: Fibroblast activation protein; FLS: Fibroblast-like synoviocytes; H&E: Hematoxylin and eosin; IL: Interleukin; LNP: Lipid nanoparticle; MMP: Matrix metalloproteinase; NF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; OA: Osteoarthritis; SHC: Silk fibroin hydrogel composite.

establishing a positive feedback loop for intelligent drug release. Upon intra-articular injection, this system effectively inhibits NF-κB signaling, reduces inflammatory mediators and matrix-degrading enzymes, and preserves the ECM, thereby mitigating OA progression. Importantly, the efficacy of this system was validated not only in animal models but also in human OA cartilage explants, where it significantly reduced MMP13 expression and enhanced the synthesis of key cartilage components, including type II collagen and aggrecan (**Figure 8B**), demonstrating its strong clinical translation potential.[60]

6. Conclusionsz

LNP-based RNA therapeutics represent a transformative strategy for OA, offering a strategy to achieve disease modification beyond symptomatic relief.[100] By enabling localized, programmable, and multifaceted regulation of inflammatory, catabolic, and anabolic pathways, LNP platforms have demonstrated strong preclinical efficacy in preserving cartilage integrity, modulating subchondral bone remodeling, and alleviating pain. The integration of diverse RNA modalities further broadens the therapeutic landscape, highlighting the versatility of LNP systems in addressing the multifactorial nature of OA pathogenesis.

Despite these advances, several critical challenges must be addressed before RNA/LNP therapeutics can be successfully translated into clinical applications. First, the durability of therapeutic effects remains essential, as the chronic course of OA necessitates long-term modulation of pathogenic pathways. Achieving safe and effective re-dosing regimens is equally important, given the need for sustained treatment without triggering adverse immune responses. Finally, the potential for immunogenicity, both from RNA constructs and from repeated LNP administration, necessitates careful optimization of lipid chemistry and RNA design to minimize unintended immune activation.

To accelerate clinical translation, strategic approaches should include the design of cartilage-targeting LNPs with enhanced penetration and retention, and the incorporation of bioresponsive release systems to align therapeutic activity with disease flares. Collaborative frameworks integrating materials science, molecular biology, and clinical orthopedics for gene therapeutics in OA are essential to achieve safe, effective, and truly disease-modifying interventions that can not only alleviate symptoms but also alter the course of joint degeneration. Lipid chemistry, RNA engineering, and intra-articular delivery strategies hold the potential to fundamentally redefine the therapeutic paradigm for OA, shifting treatment from symptomatic management to durable structural restoration and functional recovery.

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The authors declare that they have no conflicts of interest.
Author contributions
Conceptualization: QZ; *Writing–original draft*: All authors; *Writing review & editing*: QZ and JW. All authors have read and approved the final version of the manuscript for publication.
Ethics approval and consent to participate
Not applicable.
Consent for publication
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