

Nanotherapeutic Strategies for Osteoarthritis: Targeting Aging, Metabolism and Inflammation

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Abstract: Osteoarthritis (OA) is no longer viewed as a mere “wear-and-tear” disease, but rather as a multifactorial joint failure syndrome driven by cellular senescence, metabolic dysregulation, and low-grade chronic inflammation. These pathological pillars synergistically disrupt cartilage homeostasis, subchondral bone remodeling, and synovial inflammation, collectively fueling disease progression. While conventional therapies offer only symptomatic relief, they fail to reverse or reprogram the underlying pathological microenvironment. Consequently, there is an urgent need to develop disease-modifying interventions that can simultaneously target these pathological pillars. Here, we critically examine how nanomaterial-based platforms—leveraging tailorable surface chemistry, cartilage-penetrating dimensions, and stimuli-responsive cargo release—enable precision targeting of these interconnected mechanisms. We highlight advances in senolytic delivery for senescent cell clearance, redox-modulating nanozymes for metabolic reprogramming, and immunoregulatory strategies for macrophage repolarization, emphasizing designs that transcend passive drug delivery to actively remodel the joint microenvironment. By integrating mechanistic insights with engineering innovation, this review outlines a roadmap for next-generation disease-modifying nanomedicines that promise not merely to slow OA progression, but to restore the biological clock of the joint. We also discuss current translational barriers and propose future directions for personalized OA therapy.

Keywords: osteoarthritis, nanomaterials, aging, metabolism, inflammation, immune modulation, nanotherapeutic strategies

Introduction

Osteoarthritis (OA) is the most common type of arthritis and a major contributor to joint pain and disability, impacting over 7% of people worldwide (528 million people).^{1,2} OA is a disabling chronic joint disease characterized by joint pain, tenderness, deformity, and functional impairment.^{3,4} The strain, trauma and deformity of knee, hip and other weight-bearing joints can cause cartilage damage and bone hyperplasia, leading to the occurrence of OA.^{5,6} The incidence rate is increasing year by year, which has seriously affected the life quality of OA patients and increased the heavy burden on social medical resources.^{2,7} To date, no therapy has proved capable of halting or reversing OA. Management remains purely symptomatic—weight loss, tailored exercise, physiotherapy, and analgesics—until the joint is deemed beyond salvage. At that point, total joint replacement offers the only exit, but its steep price, intensive perioperative demands, and risk of complications weigh heavily on patients, families, and health-care systems.^{8,9}

While OA is traditionally framed as “wear-and-tear,” it is emergingly recognized as a whole-joint failure syndrome in which three inter-locking mechanisms—cellular senescence, metabolic homeostasis disorder and low-grade chronic inflammation—cooperate to dismantle cartilage, subchondral bone and synovial integrity.^{10–12} Senescent chondrocytes

(SnChos) and synovial cells release senescence-associated secretory phenotype (SASP) factors, including pro-inflammatory cytokines and matrix-degrading enzymes, which promote synovial inflammation and accelerate cartilage matrix breakdown.¹³ Inflammatory mediators such as IL-1 β and TNF- α further induce stress responses in chondrocytes, increase oxidative stress, and promote additional cellular senescence, thereby linking inflammation to aging-related cell dysfunction.^{14,15} At the same time, metabolic disturbances, particularly mitochondrial dysfunction and reactive oxygen species (ROS) imbalance, enhance cartilage catabolism and increase tissue sensitivity to inflammatory signaling.^{16,17} Systemic metabolic factors, including obesity-associated adipokines and chronic low-grade inflammation, also contribute to sustained inflammatory activation within the joint and impair tissue repair capacity.^{18,19} As a result, damage extends beyond cartilage to involve the synovium and subchondral bone, supporting the concept of OA as a whole-joint failure syndrome rather than a disorder confined to a single tissue.²⁰

Traditional treatment approaches, including non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief and joint replacement surgeries for advanced cases, have limitations.^{3,21} NSAIDs may cause gastrointestinal and cardiovascular side effects,²² while surgical interventions are invasive and associated with risks such as infection and prosthesis failure.²¹ To overcome these limitations, there is an urgent need for innovative drug delivery platforms in clinical OA management.²³ In recent years, advanced nanoparticle-based delivery systems—such as liposomes, polymer vesicles, solid lipid nanoparticles, dendrimers, and hybrid nanocarriers—have been developed to enhance drug penetration into cartilage and prolong drug retention within the joint cavity.^{24–28} These novel nano-delivery systems distinguished by their cartilage-penetrating dimensions and tailorable surface chemistry, showing promising potential in improving intra-articular drug targeting, extending therapeutic duration, and enabling stimulus-responsive precision delivery.^{25,27} Due to their excellent biocompatibility, biodegradability, and environment-responsive cargo release properties, these nano-systems allow for localized, controlled drug delivery at OA-affected sites, offering strong translational prospects for future clinical applications.^{24–28} Alternative biological approaches, particularly intra-articular mesenchymal stromal cell (MSC) therapies, have shown variable efficacy in pain reduction and functional improvement.²⁹ However, widespread adoption is constrained by inconsistent outcomes across cell sources and protocols, batch-to-batch variability, and complex regulatory hurdles.^{30,31} Nanomaterial-based systems circumvent these limitations by offering superior controllability—enabling precise drug loading, cartilage-targeted surface modification, and prolonged intra-articular retention—thereby presenting a more readily translatable strategy for OA management.²⁶

Despite the burgeoning development of nanomaterial-based interventions, a fundamental understanding of how nanotherapeutic strategies engage with and modulate OA pathogenic mechanisms remains incompletely elucidated. In this review, we critically synthesize recent advances in rationally engineered nanotherapeutics targeting key pathogenic mechanisms of OA: cellular senescence, metabolic dysregulation, and immune-mediated inflammation (Figure 1). First, we dissected nano-enabled strategies for senescent cell clearance and quiescence, encompassing targeted delivery of senolytics and senomorphic nucleic acids, mitochondrial quality control, and SASP neutralization. Subsequently, we examined metabolic reprogramming approaches, including ROS scavenging, iron chelation, ferroptosis inhibition, and restoration of mitochondrial bioenergetics. Furthermore, we deliberate on immunomodulatory nanotherapeutic strategies centered on macrophage M1-to-M2 repolarization and pro-inflammatory cytokine neutralization. By delineating the molecular mechanisms underpinning these interventions, critically evaluating cartilage-specific delivery strategies, and identifying translational bottlenecks, we outline a roadmap for next-generation “disease-modifying nanomedicines”—therapeutic platforms that promise not merely to decelerate OA progression but to restore the biological clock of the joint.

Nanotherapeutic Strategies Targeting Aging Pathogenesis in OA

OA is the most common joint disease in the middle-aged and elderly population.³² Emerging researches indicate that the mechanisms underlying the pathogenesis of OA are multifaceted, with aging being a key factor in promoting OA progression.^{33,34} The aging mechanism of OA is due to factors involved in stress induction of chondrocytes,³⁵ telomere shortening,³⁶ DNA damage^{37,38} and epigenetic changes.³⁹ Since aging-associated targets in OA are spatially confined within the dense, negatively charged cartilage extracellular matrix (ECM) and are exposed to rapid synovial clearance, conventional drugs often show limited penetration, poor retention, and insufficient cell specificity.⁴⁰ In this context,

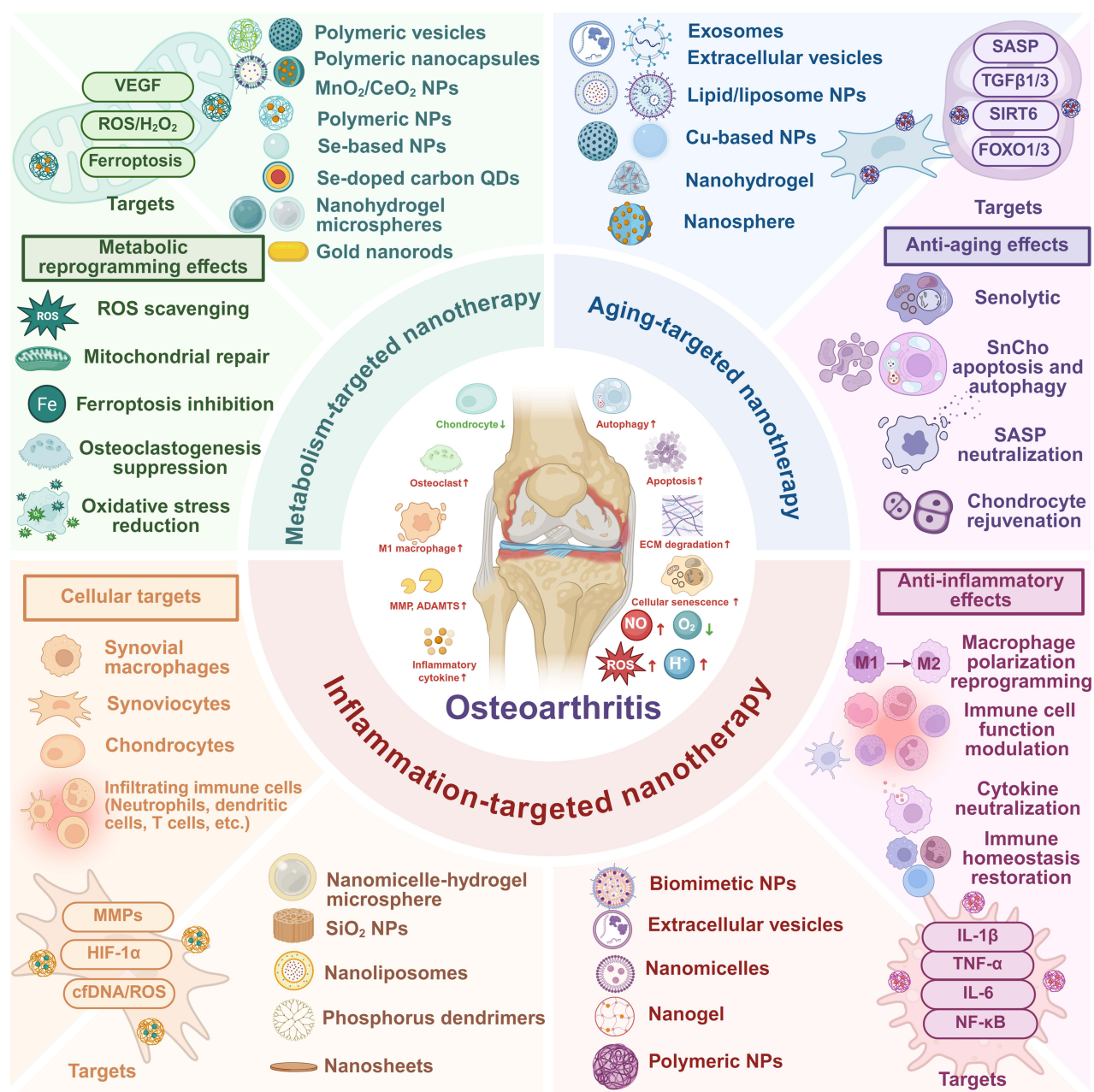


Figure 1 Schematic illustration of recent advances in nanotherapeutic strategies for osteoarthritis targeting aging, metabolism, and inflammation. The diagram presents an integrated framework connecting pathological targets, core nanomaterial platforms, and mechanism-specific therapeutic effects across three interconnected disease mechanisms.

nanomaterial-based platforms can be engineered for cartilage-targeted binding, deep tissue penetration, and microenvironment-responsive release, thereby improving local bioavailability and enabling precise delivery of senotherapeutics or pro-regenerative cues.⁴¹ Therefore, exploring the aging mechanism of OA and potential nanotherapeutic strategies targeting aging will bring new possibilities for prospective treatment options for OA.^{42,43}

Nanotherapeutic Strategies Preventing Cellular Senescence

Cellular senescence, a core hallmark of aging, is typically triggered by persistent stress signals, including DNA damage, telomere attrition, oxidative stress, and mitochondrial dysfunction.⁴⁴ These triggers activate checkpoint pathways, primarily the p53/p21 and p16^{INK4a}/Rb axes, locking cells into stable cell-cycle arrest.^{10,45} Concurrently, senescent

cells undergo profound metabolic and phenotypic remodeling, developing a senescence-associated secretory phenotype (SASP) characterized by the release of pro-inflammatory cytokines (IL-6, IL-8), chemokines, and matrix-degrading enzymes (MMPs, ADAMTSs).^{10,45} In OA, these aging-related processes prominently manifest in articular chondrocytes. During aging and disease progression, chondrocytes progressively acquire a senescent phenotype characterized by diminished anabolic capacity, heightened catabolic activity, and increased inflammatory output, thereby disrupting cartilage homeostasis and accelerating degeneration.⁴⁶ Therapeutic strategies targeting senescence include senolytics to selectively remove senescent cells, as well as NAD⁺-boosting agents and mitophagy inducers.⁴⁷ Senolytics are agents that selectively eliminate senescent cells by exploiting their apoptotic vulnerabilities, thereby removing the source of SASP factors and creating space for tissue regeneration. Conversely, senomorphics suppress or reprogram the harmful SASP without necessarily killing the cells, targeting upstream signaling pathways (JAK/STAT, mTOR, MAPK, NF- κ B) that drive inflammatory and catabolic secretions.^{48–50} Nanomaterial-based delivery systems provide a versatile platform to implement these strategies in OA because they can enhance cartilage retention, improve penetration through the dense extracellular matrix, and enable cell- or microenvironment-responsive delivery, potentially increasing efficacy while limiting off-target exposure.^{41,43} Below, we systematically review nano-enabled senolytic approaches that directly remove SnChos, followed by nanotherapeutic senomorphic strategies that modulate SASP as well as inflammatory signaling and other novel strategies.

The pioneering work by Jeon et al established that selective clearance of SnChos in mouse models reduced histologic OA severity, improved pain behavior, decreased MMP-13 expression, and potentially stimulated cartilage regeneration.⁵¹ Building on this foundation, nanomaterial-based senolytic delivery has emerged as a promising approach to eliminate SnChos while sparing healthy chondrocytes.⁵² Efferocytosis, an intrinsic regulatory mechanism to eliminate apoptotic cells, will be suppressed due to the delayed apoptosis process in aging-related diseases.⁵³ However, the further efferocytosis effect and the secondary alteration of tissue homeostasis are always ignored, especially in the in situ degenerative lesion. Based on this, Xiong et al⁵⁴ engineered an innovative in situ senolytic platform termed A-Lipo/PAHM — aldehyde/methacrylic-anhydride modified hyaluronic acid microspheres prepared by micro-fluidic photo-cross-linking. After Schiff-base anchoring to collagen-II fragments within the degraded cartilage surface, the spheres release ABT263-loaded liposomes plus PDGF-BB; the former drives senescent-cell apoptosis, while the latter recruits surrounding MSCs. In-situ efferocytosis converts neighboring macrophages to a pro-resolving phenotype, halving p16^{INK4a} abundance and restoring glycosaminoglycan (GAG) content in an anterior cruciate ligament transection (ACLT) porcine cartilage explant OA model.

Enzyme-like Cu-based nanoparticles would favor the elimination of SnChos. Moreover, several previous studies indicate that Cu-based materials can promote MSCs chondrogenesis and cartilage repair.^{55,56} Hence, Cu-based nanomaterials promote a chondrogenic microenvironment in articular cartilage after the clearance of SnChos. Wang et al⁵⁷ developed antibody-functionalized copper sulfide nanoparticles (B2M-CuS NPs) that target senescent chondrocytes via anti- β 2-microglobulin (B2M) antibodies, a surface marker upregulated in cellular senescence. These nanoparticles exhibit peroxidase-like activity, converting endogenous H₂O₂ into toxic hydroxyl radicals ($\bullet$ OH) specifically within SnChos, inducing selective apoptosis while showing no toxicity to normal chondrocytes. Notably, Cu²⁺ released from the nanoparticles further promotes the chondrogenesis of surviving normal chondrocytes, creating a pro-regenerative microenvironment following senolytic clearance. Intra-articular injection into surgery-induced OA mice demonstrated effective cartilage regeneration.⁵⁷ However, long-term safety concerns regarding copper accumulation in subchondral bone and potential systemic ion release necessitate comprehensive biosafety evaluation.

Besides, recent advances in extracellular vesicle engineering have enabled RNA interference-based senolytic strategies.⁵⁸ In this regard, versatile engineered WPD-sEVssiMDM2 are loaded with siRNA targeting mouse double minute 2 homologue (siMDM2) and decorated with cartilage-targeting peptide WYRGRL-PEG2K-DSPE (WPD). This multifunctional modification enhances cellular uptake, cartilage penetration, and joint retention. By silencing MDM2, a negative regulator of p53, the system reactivates p53-driven apoptotic pathways specifically in SnChos, effectively eliminating senescent cells via the MDM2-p53 axis. The nanoplatform restored matrix homeostasis in OA and aged mouse models and reduced senescence in human explants⁵⁹ (Figure 2A).

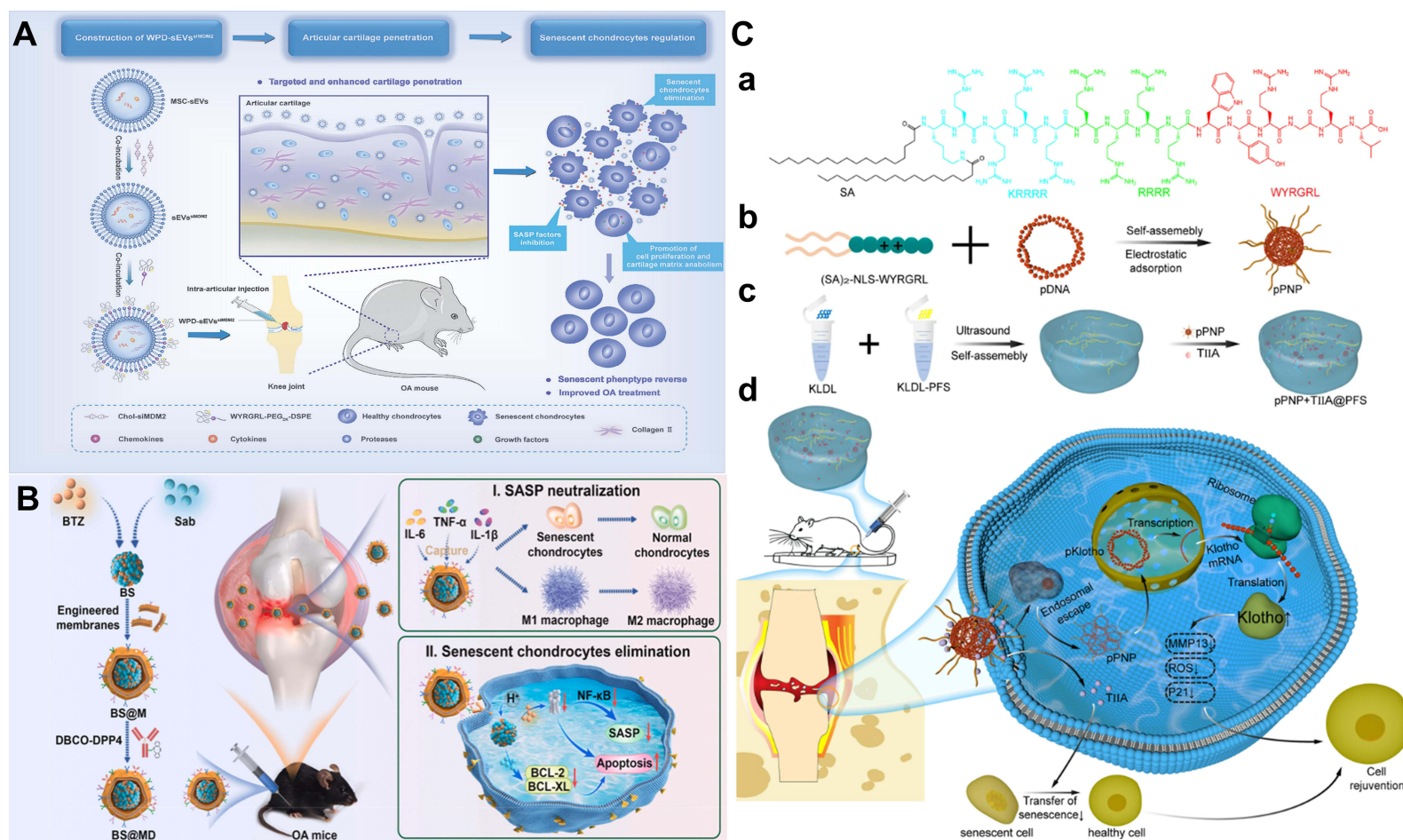


Figure 2 Nanotherapeutic strategies preventing cellular senescence. **(A)** Schematic illustration showing the construction process of and mechanism of multifunctionally engineered WPD-sEVssiMDM2 with enhanced cartilage penetration ability and targeted senescent chondrocytes elimination effect for OA treatment. Intra-articular injection of WPD-sEVssiMDM2 successfully reduced the percentage of senescent chondrocytes, inhibited SASP factors production, and retarded cartilage degeneration in OA mice. Reproduced from Feng et al.⁵⁹ Copyright 2025, Wiley. **(B)** Schematic illustration of the BS@MD preparation and intra-articular injection for OA treatment by SASP neutralization and senescent chondrocytes elimination. Reproduced from Peng et al.⁶⁰ Copyright 2026, Elsevier. **(C)** Schematic illustration of locoregional generation of Klotho protein to mitigate OA. (a) Chemical structure of the NPs featuring a nuclear localization sequence (NLS) peptide as the hydrophilic moiety and stearic acid (SA) as the hydrophobic domain. (b) Schematic illustration of the preparation of plasmid DNA (pDNA)-laden peptide NPs (pPNPs). (c) Schematic illustration of the pPNP coating on hydrogel. (d) The pPNP-gel generates Klotho protein to ameliorate the aging microenvironment and delay arthritis progression. In the anterior cruciate ligament transection (ACLT) rat model, this approach ameliorates arthritis and promotes osteogenesis. Reproduced from Wang et al.⁶¹ Copyright 2024, Springer Nature.

While senolytics remove senescent cells, senomorphics offer an alternative model: suppressing the deleterious SASP without eliminating the cells, thereby preserving any beneficial functions senescent cells may retain while neutralizing their inflammatory and catabolic output.⁴⁸ Yang et al⁶² synthesized copper-silicate nanoparticles loaded with astragaloside-IV (CSP@AS-IV) that exploit the mildly acidic synovial milieu of inflamed OA joints. The particle lattice dissolves in response to acidic pH, enabling tandem release of Cu^{2+} and AS-IV. Cu^{2+} provides antioxidant and anti-inflammatory signals, whereas AS-IV suppresses MMP13 and upregulates Col-II, collectively shifting cartilage metabolism toward matrix synthesis. Nevertheless, pH-triggered dissolution introduces sensitivity to lesion heterogeneity; acidity variations across synovial fluid, cartilage regions, and disease stages may cause inconsistent dissolution kinetics, underscoring the need for optimized microenvironment-responsive designs.⁶²

While endogenous cue-responsive nanosystems (eg, pH-triggered dissolution) offer energy-free release, their performance can be limited by lesion heterogeneity and insufficient “on demand” controllability.⁶³ To achieve tighter spatiotemporal control beyond endogenous cues, some nanoplateforms incorporate externally triggered release using near-infrared (NIR) light, which can be delivered noninvasively and provides rapid, switch-like activation at the illuminated site. In this regard, Xu et al⁶⁴ introduced an NIR-sensitive multifunctional heterostructure: EGCG (epigallocatechin gallate)-decorated Au–Ag nano-jars (E@Au–Ag). NIR activation enables on-demand release at the target joint, reducing reliance on repeated intra-articular injections. However, potential thermal effects on superficial collagen structures require careful optimization of irradiation parameters to balance responsive release with tissue safety.⁶⁴ Complementing this approach, Shi et al⁶⁵ engineered molybdenum nanodots (MNDs) that act as broad-spectrum scavengers of ROS and reactive nitrogen species (RNS) at physiological temperature, while generating mild photo-thermal heating upon 808 nm NIR irradiation. This dual mechanism restored mitochondrial fusion proteins, down-regulated fission proteins, and reversed chondrocyte senescence.⁶⁵

Recognizing that senolytics and senomorphics may act synergistically, Peng et al developed a dual-engineered macrophage membrane-camouflaged nanoplateform (BS@MD) that combines both modalities⁶⁰ (Figure 2B). The system acts as a “nanosponge” to broadly neutralize heterogeneous SASP components while simultaneously delivering senolytic cargo. Anti-DPP4 surface conjugation enables selective targeting of SnChos, releasing bortezomib and sabutoclax to synergistically inhibit the NF- κ B and BCL-2 pathways, thereby inducing SnChos apoptosis and suppressing SASP production. This dual mechanism effectively disrupts the senescence-inflammation feedback loop, addressing limitations of therapies that lack cell-specific targeting or fail to neutralize diverse SASP factors.

Nicotinamide adenine dinucleotide (NAD^+) serves as an essential metabolic cofactor whose age-dependent decline accelerates cellular senescence and inflammation.^{66–68} While NAD^+ supplementation can reverse aging indicators and modulate macrophage polarization, its anionic nature and membrane impermeability necessitate high-dose systemic administration, and intra-articular delivery is hindered by ECM penetration resistance and rapid lymphatic clearance.⁶⁹ To overcome these barriers, Lin et al⁷⁰ developed injectable, self-lubricating hydrogel microspheres (NAD@NPs@HM) that continuously release NAD^+ to simultaneously block chondrocyte senescence and repolarize synovial macrophages. Photo-cross-linked chondroitin-sulfate beads encapsulating lactoferrin-modified NAD-liposomes extend intra-articular residence while converting sliding friction into rolling friction. Single-injection treatment suppressed Src-driven glycolysis and shifted M1-to-M2 macrophages, interrupting the senescence-inflammation loop in aged mice.⁷⁰

The Klotho protein, an essential component of endocrine fibroblast growth factor (FGF) receptor complexes,^{71–73} is a potent anti-aging factor downregulated in OA joints, suppressing chondrocyte catabolism via ZIP8 and MMP13 inhibition.^{74–76} Tanshinone IIA (TIIA) complements this by inhibiting cellular communication network factor 1 (CCN1)-driven chondrocyte cluster formation and senescence.^{77,78} Wang et al⁶¹ capitalized on this mechanistic synergy by engineering pPNP+TIIA@PFS—a stem cell-homing nanohydrogel that co-delivers Klotho plasmid and TIIA to achieve tripartite action: nuclear-targeted gene expression, dual-compartment ROS scavenging, and endogenous MSC recruitment (Figure 2C). Single intra-articular injection in ACLT rats elevated Klotho, suppressed catabolic markers ZIP8 and MMP13, alongside reduced osteophyte volume.⁶¹ However, optimization of formulation parameters and long-term safety profiling are warranted for clinical translation.

In conclusion, emerging nanotherapeutic designs that engage apoptotic clearance, exploit pathological microenvironment cues, or enable light-triggered on-demand release broaden the therapeutic toolbox for senescence-targeted OA

beyond direct SASP suppression. Senolytic nanoplateforms offer the advantage of permanently removing deleterious cell populations, while senomorphic strategies provide a reversible, potentially safer alternative for chronic management. Moving toward clinical translation will require improving robustness across heterogeneous lesions and disease stages, defining safe and practical treatment regimens, and clarifying long-term biosafety issues such as ion retention and cumulative tissue exposure through rigorous *in vivo* and real-world evaluations.

Nanotherapeutic Strategies Regulating Autophagic Homeostasis

Emerging evidence underscores that defective autophagy, an evolutionarily conserved intracellular degradation system essential for maintaining cellular homeostasis, serves as a critical pathogenic driver in joint aging and OA progression.^{79,80} During OA pathogenesis, compromised autophagic flux results in the accumulation of damaged organelles and misfolded proteins, thereby exacerbating chondrocyte dysfunction, accelerating cartilage matrix degradation, and ultimately promoting cell death.⁸¹ Central to this pathological cascade, the forkhead box O (FoxO) transcription factor, especially FoxO1 and FoxO3, emerge as pivotal regulators of cartilage homeostasis and autophagic activity.^{82,83} Consequently, recent nanotherapeutic strategies have shown considerable promise in modulating autophagic homeostasis to enhance chondrocyte survival and attenuate inflammatory responses.⁸⁴ Specifically, nanomaterial-based delivery systems targeting FoxO represent an innovative therapeutic strategy, offering disease-modifying potential by restoring autophagic homeostasis and decelerating OA progression.⁸ For instance, Li et al⁸⁵ developed a CD90⁺ MCS-derived micro-vesicle (CD90@MV)-coated nanoparticle (CD90@NP). Poly (lactic-co-glycolic acid) (PLGA) nanoparticle was coated with CD90@MV, and a model glucocorticoid, triamcinolone acetonide (TA), was encapsulated in the CD90@NP (T-CD90@NP). T-CD90@NP promoted the regeneration of chondrocytes, reduced cellular senescence and apoptosis via the FOXO pathway, exhibiting significant chondroprotective effect in the rabbit and rat OA models. Besides, Feng et al delivered embryonic stem-cell-derived small extracellular vesicles (ESC-sEVs) that alleviate non-early-stage OA by rejuvenating SnChos. Notably, ESC-sEVs exert their anti-aging effects through activation of the FOXO1A-autophagy axis, without inducing apoptosis (Figure 3A). The approach attenuates OA progression in both mechanical-stress-induced and naturally aged mice models, and reverses the senescent phenotype in ex-vivo cultured human end-stage OA cartilage explants.⁸⁶ However, the FOXO1A-autophagy axis is only one of several senescence-regulatory networks, and additional ESC-sEV-mediated pathways remain undefined. Moreover, weekly intra-articular administration is clinically impractical, necessitating the development of slow-release or depot-formulated ESC-sEVs.

Nanohydrogels or nanoparticles can be engineered to activate autophagy, primarily through the modulation of key regulatory signaling axes such as the mTOR/FOXO3a pathway.⁸⁹ These bioactive delivery systems not only function as vehicles for therapeutic cargo but also actively enhance local autophagic flux, thereby ameliorating age-related degenerative phenotypes at the tissue and organ levels. In this regard, Kong et al addressed the limitations of traditional protein delivery by developing an mRNA-LNP system for FGF18. The study explored a method that enables deeper cartilage penetration and sustained FGF18 expression, activating the FOXO3a-autophagy pathway to reduce chondrocyte senescence (Figure 3B). In both DMM and senile OA models, intra-articular injection LNP significantly alleviated OA symptoms by targeting autophagy and mitigating the aging phenotype.⁸⁷ Mitochondrial dynamics during mitosis are tightly coupled with selective macro-autophagy (mitophagy).⁹⁰ This coordination between mitochondrial fission and autophagic activation maintains energy homeostasis, which is critical for cartilage integrity.⁹¹ Recent nanomaterials advances enable synergistic modulation of this axis for OA therapy. For example, biomaterials can be designed to activate mitophagy pathways selectively, such as the PINK1/Parkin pathway,⁹² which is responsible for recognizing and eliminating damaged mitochondria. These materials can selectively target mitochondria in chondrocytes or synovial cells, reducing oxidative stress and improving cellular function. One promising example is a study by Chen et al developing a FoxO3-NETT@SMs composite system centred on CRISPR/Cas9-based FOXO3 gene editing, delivered via the NETT nanocarrier and encapsulated within sodium alginate-hybridised exosome hydrogel microspheres (Figure 3C). The injectable nanoengineered hydrogel system can activate mitophagy via the PINK1/Parkin pathway, restore mitochondrial function, promote chondrocyte activity, and alleviate OA progression.⁸⁸ Therefore, autophagy-related transcription factors that regulates autophagy and mitophagy may suggest a promising point to explore aging-targeted materials for OA treatment. Through targeted regulation of these critical cellular processes, functional nanomaterials emerge as disease-modifying agents capable of mitigating aging-driven osteoarthritic changes, thus providing therapeutic avenues for treatment.

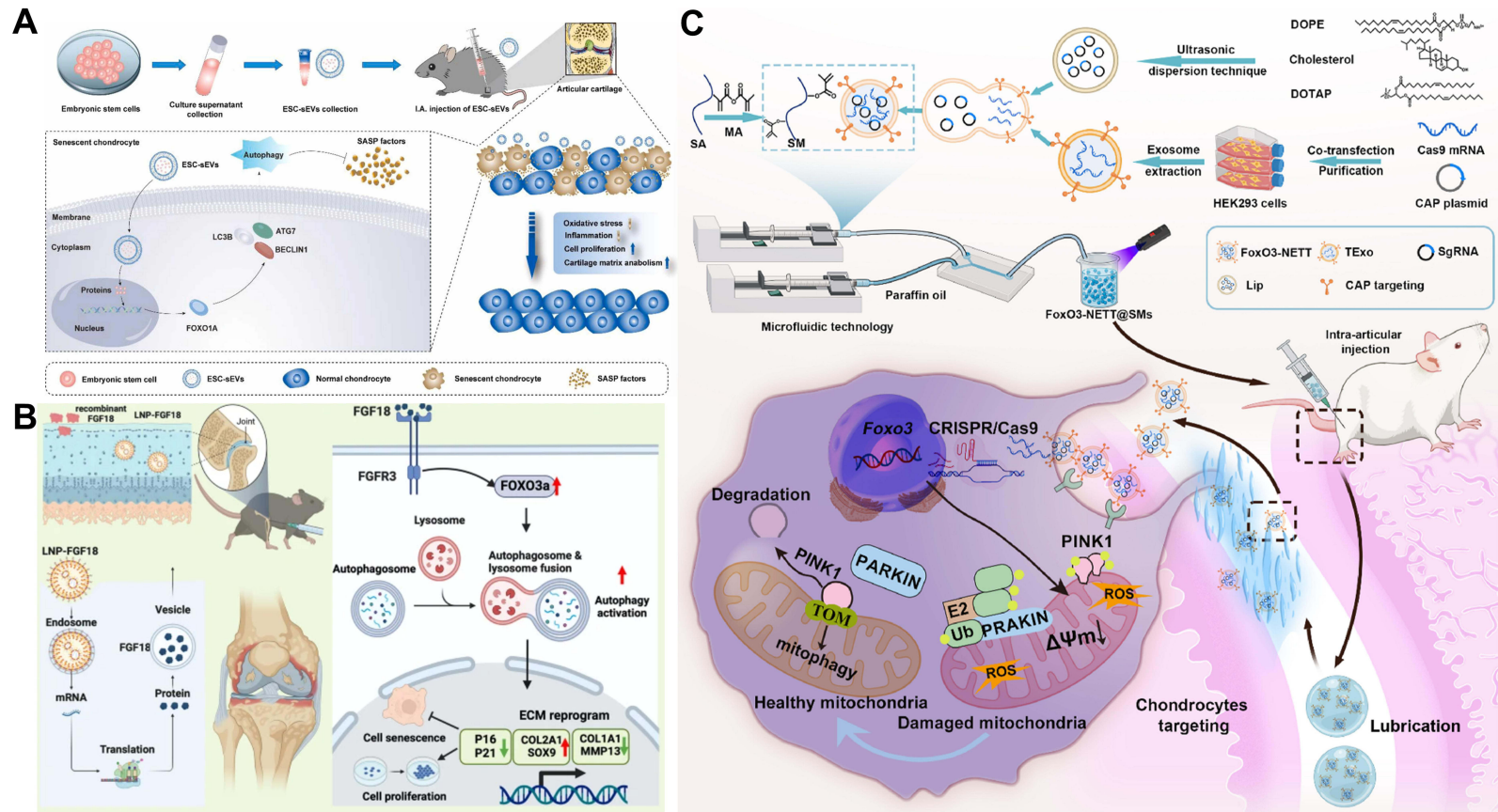


Figure 3 Nanotherapeutic strategies in the regulation of autophagic homeostasis. **(A)** Schematic diagram of the harvest and application of ESC-sEVs for locally intra-articular injection in posttraumatic OA mice and naturally aged mice. Reproduced from Feng et al⁸⁶ Copyright 2024, Elsevier. **(B)** Delivery of FGF18 using mRNA-LNP protects the cartilage against degeneration via alleviating chondrocyte senescence. Reproduced from Kong et al⁸⁷ Copyright 2025, Springer Nature. **(C)** Schematic of FoxO3-NETT@SMs targeting-regulated Foxo3 gene in vivo to modulate mitochondrial dynamics for osteoarthritis therapy. Reproduced from Chen et al⁸⁸ Copyright 2022, Elsevier.

In conclusion, the application of nanotherapeutic strategies in regulating autophagic homeostasis has opened up an exciting new field for the treatment of OA and the improvement of joint health. Future real-world studies are needed to evaluate the additional benefits of autophagy-driven therapies in OA patients.

Nanotherapeutic Strategies Stimulating Cartilage Regeneration

During aging and OA progression, ECM alterations, including advanced glycation end-product accumulation, aggrecan degradation, reduced hydration, and collagen cleavage, progressively disrupt cartilage biomechanics and increase susceptibility to mechanical failure.⁹³ Because the ECM is continuously synthesized and maintained by chondrocytes, restoring the structural and functional integrity of cartilage matrix represents a critical therapeutic objective.¹⁰ However, the aged OA joint presents formidable delivery barriers: the dense, negatively charged cartilage ECM limits therapeutic penetration, while rapid synovial fluid turnover and lymphatic clearance compromise intra-articular retention.⁹⁴ Nanomaterial-based systems have been engineered to overcome these barriers by localizing pro-regenerative cues within cartilage, enabling sustained bioactivity and more efficient repair.⁹⁴ This section examines nanotherapeutic strategies for cartilage regeneration, mainly in the following aspects: (i) biomaterial-mediated structural reinforcement; (ii) stem cell and exosome-based regenerative platforms; and (iii) lubrication restoration and mechanics-senescence axis modulation.

Articular cartilage repair requires simultaneous satisfaction of stringent biomechanical requirements and support for cell-driven regeneration—a combination that conventional hydrogels often fail to achieve. To address the trade-off between mechanical stability and bioactivity, Zhou et al developed a dual physiological signal-responsive KPP@PLEL nanohydrogel. This system integrates a PAMAM dendrimer modified with MMP-13-responsive peptides and loaded with kartogenin (KGN), encapsulated within a thermosensitive PLEL hydrogel. By leveraging body-temperature gelation and MMP-13 responsiveness, KPP@PLEL enables sustained release and improved deep cartilage matrix penetration while extending joint residence. The platform demonstrated reduced inflammation, promoted bone marrow-derived mesenchymal stem/stromal cell (BMSC) chondrogenic differentiation, and enhanced cartilage regeneration with attenuated OA progression compared to free KGN or hydrogel alone.⁹⁵ Complementing synthetic approaches, bioinspired nanocomposites offer superior biomimicry. An injectable nanocomposite hydrogel incorporating 2% silk fibroin nanofibers and glucosamine into a thiolated chitosan matrix achieved in situ gelation following injection. Compared with pristine chitosan hydrogel, this formulation markedly improved compressive mechanical performance while enhancing cellular responses, including proliferation, migration, and chondrogenic differentiation. In a rat osteochondral defect model, the hydrogel promoted seamless tissue integration and articular surface restoration, accompanied by significant upregulation of cartilage markers COL-II and SOX-9.⁹⁶ These studies illustrate that nanoscale material design can simultaneously address the mechanical and biological requirements for functional cartilage repair.

Stem cell exhaustion is recognized as a hallmark of aging, reflecting the progressive loss of stem cell number and function and consequent decline in tissue repair capacity.⁹⁷ In aging-driven OA, this concept provides two practical therapeutic directions: reactivating endogenous stem cells within the joint or replacing impaired repair capacity through cell-based therapy. Mesenchymal stem cells (MSCs) have been widely explored for cartilage repair.⁹⁸ More recently, MSC-derived exosomes have attracted growing attention because they convey many of the anti-inflammatory and senescence-modulating benefits of MSCs while avoiding limitations of live-cell transplantation, including immunogenicity, tumorigenicity risk, and complex regulatory requirements.⁹⁹ However, a critical barrier is that SnChos accumulating in aged cartilage can undermine stem cell-mediated repair. Exposure to SnCho-conditioned environments induces BMSC apoptosis, suppresses proliferation, and impairs chondrogenic differentiation.¹⁰⁰ This suggests that effective regenerative delivery systems should not only provide pro-regenerative cues, but also mitigate the senescent microenvironment so that newly recruited or transplanted cells can survive and deposit healthy matrix.

Umbilical cord-MSC (UCMSC) exosomes offer particular advantages due to their multilineage differentiation potential, immunomodulatory properties, higher proliferation rates, and abundant supply without donor risk compared to adult MSCs.¹⁰¹ In this regard, Cao et al¹⁰² surface-engineered UCMSC-derived exosomes with a collagen-II-binding peptide and embedded them in thiolated hyaluronic acid microgels, creating a two-stage release system that rejuvenates aging chondrocytes in a rat OA model (Figure 4A). The collagen-binding peptide enables targeted delivery to cartilage, while the hydrogel matrix provides sustained release kinetics.

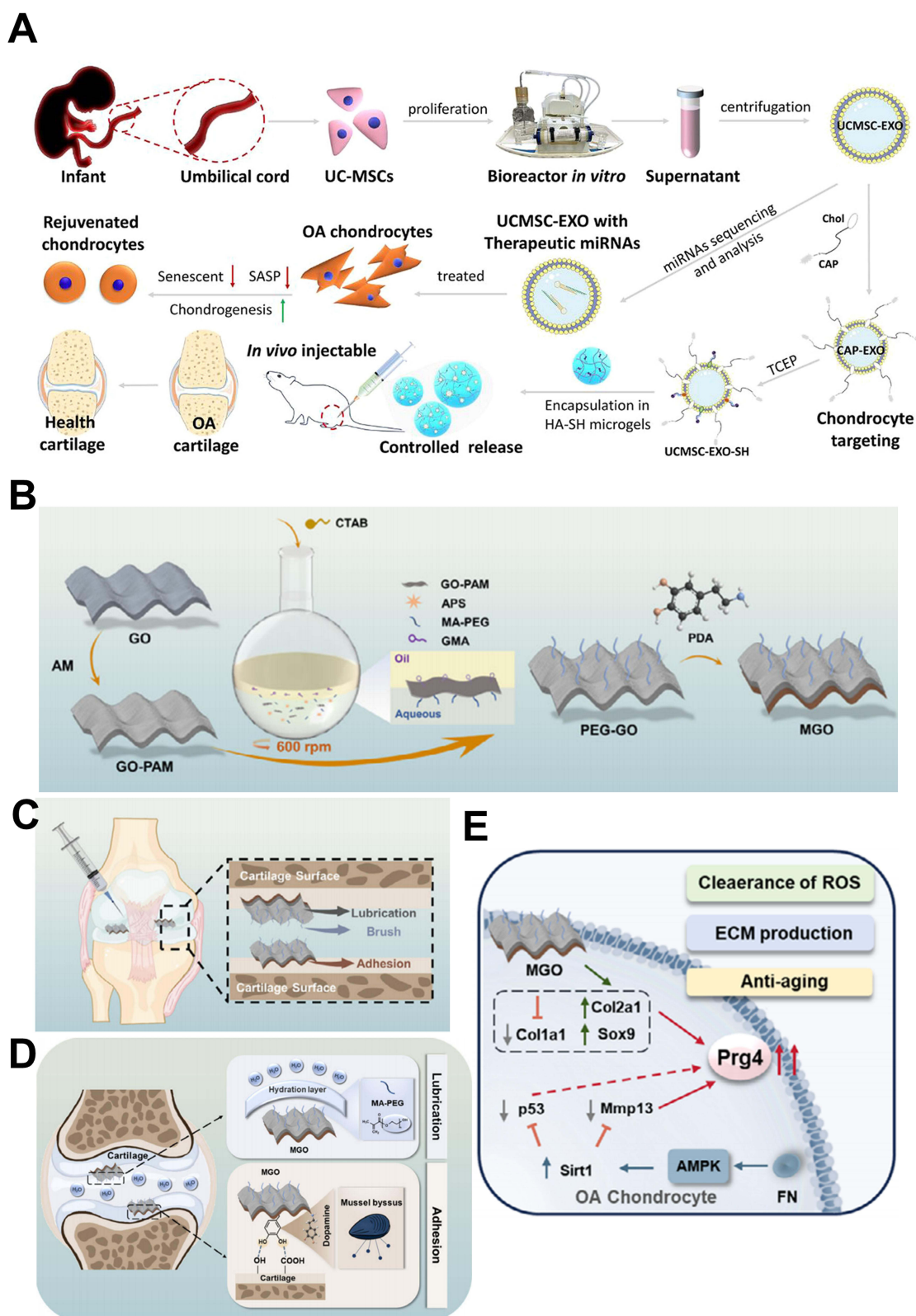


Figure 4 Nanotherapeutic strategies stimulating cartilage regeneration. **(A)** Preparation of the sustained-release of chondrocyte-targeting UCMSC-EXOs containing therapeutic miRNAs to rejuvenate OA chondrocytes *in vivo*. Reproduced from Cao et al¹⁰² Copyright 2023, American Chemical Society. **(B)** Schematic representation of Janus MGO nanoplateform preparation. **(C)** Schematic representation of the dual functions of Janus MGO nanoplateform. **(D)** Schematic representation of the dual-function principle of asymmetric MGO. **(E)** Schematic diagram of the mechanism by which MGO-FN alleviates cellular senescence, inhibits the secretion of inflammatory factors, and promotes matrix regeneration to restore lubrication. Reproduced from Chen et al¹⁰³ Copyright 2026, Wiley.

Beyond exosome delivery alone, recent strategies integrate metabolic modulation with regenerative targeting. In OA cartilage, the CH25H–CYP7B1–ROR α cholesterol axis has been reported to biases chondrocytes toward a SOX9-low, MMP13-high state, favoring matrix degradation over chondrogenic maintenance.¹⁰⁴ Zhao et al¹⁰⁵ suspended C5-24-peptide-labelled lipid nanoparticles (LNPs) in a self-assembling SKPPGTSS hydrogel to reset this cholesterol axis and recruit synovial MSCs for in-situ differentiation in ACLT rats. This approach demonstrates that metabolic reprogramming can remove molecular brakes on regeneration.

To address the poor cartilage-homing of injected MSCs, Wu et al¹⁰⁶ developed a nanoparticle-peptide dual-engineering strategy by electrostatically loading CuO@MSN with Sox9 plasmid (chondrogenesis driver) and Bmp7 protein (anti-hypertrophy factor), then click-conjugating peptide W that binds exposed Col2a1 fragments. The resulting W-CSB-MSCs enhanced hyaline cartilage matrix formation (Col2a1, Acan) while inhibiting hypertrophic differentiation in a surgically induced OA mouse model.¹⁰⁶ This illustrates how nanomaterial engineering can simultaneously improve cell targeting, control differentiation trajectories, and prevent undesirable phenotypic outcomes.

Age-related changes in the cartilage surface microenvironment can initiate a “mechanics-to-inflammation” cascade that accelerates degeneration. Aged cartilage is often associated with reduced lubricin proteoglycan 4 (PRG4), which increases boundary friction. The resulting mechanical stress exacerbates oxidative burden, promoting ROS accumulation and downstream activation of senescence-linked pathways including p53 signaling and iNOS-associated inflammatory responses.¹⁰⁷ Hou et al¹⁰⁸ addressed this mechanics–senescence feedback loop using microfluidic zwitterion-lubricated metformin microspheres (Met@SBHA). The formulation reduced the cartilage friction coefficient while enabling sustained metformin release and AMPK activation for up to 14 days, which was sufficient to improve mitochondrial membrane potential in aged rat knees.¹⁰⁸ This dual-action approach targets both the mechanical and metabolic drivers of chondrocyte senescence.

OA is sustained by a self-reinforcing cycle in which progressive cartilage surface wear compromises boundary lubrication, elevates frictional stress, and further accelerates matrix breakdown. Because most current interventions provide symptomatic relief rather than restoring lubrication or rebuilding surface integrity, their benefits are often transient, underscoring the need for regenerative and lubrication-restoring strategies that can break this cycle. Chen et al developed MGO-FN, an asymmetric nanoplatform that adheres to cartilage, provides lubrication, and releases the anti-aging drug fenofibrate. It effectively fills micro-damage, enabling sustained local treatment. Studies show MGO-FN reduces cartilage degradation, decreases inflammation, and restores lubrication, offering a multi-action therapy to halt OA progression¹⁰³ (Figure 4B–E).

In summary, current regenerative platforms increasingly prioritize restoring a permissive, low-senescence micro-environment so that recruited or delivered cells can survive, differentiate, and produce stable matrix. However, to translate these concepts into durable cartilage restoration, delivery systems must better match the kinetics of cartilage maturation by improving retention and release control while minimizing premature loss of bioactive cues. Future designs should integrate real-time monitoring capabilities to assess repair progression and enable personalized, adaptive therapeutic regimens.

Nanotherapeutic Strategies Targeting Promising Aging-Related Markers

Beyond the core senescence-clearance and autophagy-regulation strategies, emerging nanotherapeutic approaches are increasingly targeting specific aging-related molecular markers that govern cartilage homeostasis. These include the transforming growth factor- β (TGF- β) family, the NAD⁺-dependent deacetylase SIRT6, and the DNA damage response machinery centered on PARP1. These targets represent critical nodes where aging-associated dysregulation converges to drive OA pathology, offering precise intervention points for disease-modifying nanomedicine.

The TGF- β family, particularly TGF- β 1 and TGF- β 3, serves as a master regulator of chondrogenic differentiation, chondrocyte homeostasis, and directed cell migration through canonical SMAD2/3-dependent signaling.¹⁰⁹ However, exogenous TGF- β therapy is hindered by immunogenicity, rapid proteolytic clearance, poorly defined dose-response relationships, and prohibitive costs.^{110,111} Notably, high-dose TGF- β may induce paradoxical synovitis, pannus formation, and cartilage erosion, underscoring the critical need for localized, controlled delivery.¹⁰⁹

Recent advances in nano-delivery engineering have sought to overcome these barriers through scaffold-mediated mechanical retention and cell-specific targeting. Starting from the cartilage surface, Zhou et al co-loaded TGF- β 3 and kartogenin (KGN) into decorin-derived-peptide-decorated, inter-bilayer-cross-linked multilamellar liposomes. Inter-bilayer covalent bridging endows high shear tolerance in synovial fluid, while the decorin-mimetic peptide provides collagen II affinity, preferentially binding microfissured regions where collagen is exposed. This dual design promotes stable cartilage adhesion and sustained, localized release for nearly one month. In a full-thickness rabbit cartilage defect model, the construct improved defect filling and favored hyaline-like cartilage regeneration — a level of structural repair uncommon for freely diffusing nanoparticle formulations.¹¹² Mechanistically, the cross-linked lamellar scaffold concentrates TGF- β 3 signaling at collagen II-positive lesion sites, limiting ectopic exposure and mitigating the hypertrophic tendency often observed with free TGF- β 3 delivery.

In a complementary approach, Kim et al developed a hybrid system through ethanol-mediated fusion of TGF- β 1-overexpressed extracellular vesicles with nicotinamide- and Col2A1-antibody-modified liposomes. The EV membrane protects TGF- β 1 from uptake by synovial macrophages, while the liposomal shell delivers nicotinamide directly to macrophages, enabling dual-cell targeting within a single particle. This construct maintained cartilage homeostasis and prolonged intra-articular retention for up to one month in DMM rats, restricting TGF- β 1 activity primarily to cartilage while reducing macrophage-associated activation.¹¹³ Both platforms achieve month-scale TGF- β retention, with cell-specific targeting toward collagen II or macrophages influencing whether the cytokine primarily promotes matrix synthesis or modulates immune responses. Future studies should focus on optimizing spatial and cell-specific regulation of TGF- β signaling to balance chondrogenic efficacy with immune homeostasis and facilitate clinical translation.

Sirtuins (SIRT6) are a family of NAD⁺-dependent deacetylases that play central roles in regulating cellular metabolism, genomic stability, and aging-associated processes.^{114,115} SIRT6, in particular, has emerged as a key regulatory factor for age-related OA. Evidence indicates that SIRT6 deficiency exacerbates chondrocyte aging and OA progression through multiple mechanisms, including mitochondrial dysfunction, oxidative stress amplification, and inflammatory signaling.^{116,117} Mechanistically, SIRT6 attenuates chondrocyte senescence by deacetylating STAT5 at conserved lysine 163, thereby blocking IL-15/JAK3-driven STAT5 nuclear translocation and dampening downstream pro-senescence signaling.¹¹⁶ Conversely, SIRT6 inhibition promotes a premature senescence phenotype marked by increased MMP-1/MMP-13, elevated p16^{INK4a}, aggravated DNA damage and mitochondrial dysfunction, and reduced expression of cartilage anabolic genes such as COL2A1 and IGF-1.^{118,119}

Despite the therapeutic potential, direct pharmacological targeting of SIRT6 in OA remains largely unexplored from a materials science perspective. The SIRT6-specific activator MDL-800 has exhibited SIRT6-dependent cellular effects in preclinical studies,¹²⁰ yet questions regarding its mechanism of action, optimal dosing, and long-term safety persist. Notably, no depot formulation currently embeds SIRT6 mRNA, the activator MDL-800, or NAD⁺-boosting precursors inside a cartilage-adherent carrier—representing a significant gap in the aging-targeted nanomaterials landscape. Liu et al¹²¹ reported that senescence-responsive miR-33-5p accelerates chondrocyte senescence and OA progression by targeting SIRT6, suggesting that antagomir-based strategies may offer an alternative route to enhance SIRT6 activity. In addition, miR-653-5p is upregulated under senescent conditions and counteracts chondrocyte senescence by promoting matrix synthesis and proliferation while suppressing IL-6/JAK1/STAT3 signaling, thereby attenuating senescence-associated phenotypes.^{117,122} Therefore, the development of nanocarriers capable of delivering SIRT6-targeted miRNA modulators or small-molecule activators specifically to senescent chondrocytes represents a promising therapeutic frontier.

OA joint chondrocytes exhibit high levels of DNA damage, with elevated DNA damage markers identified in both elderly cadaver donors and end-stage OA samples,¹²³ suggesting that DNA damage-induced chondrocyte senescence represents a critical driver of OA progression.^{37,38} Central to the DNA damage response is the NAD⁺-consuming enzyme poly-ADP-ribose polymerase 1 (PARP1). Upon detecting DNA strand breaks, PARP1 catalyzes the transfer of ADP-ribose units from NAD⁺ to target proteins, initiating DNA repair signaling and chromatin remodeling.^{124,125} Persistent DNA damage in aging chondrocytes triggers PARP1 hyperactivation, leading to NAD⁺ depletion and subsequent mitochondrial dysfunction, thereby exacerbating cellular senescence and SASP propagation.^{67,126} Recent evidence has revealed a more nuanced role of PARP1 in OA pathogenesis.¹²⁷ While excessive PARP1 activation can induce cell death

through NAD⁺ depletion, regulated PARP1 activation may confer protective effects by reducing chondrocyte apoptosis and preserving cartilage integrity.^{127,128} This dual nature suggests that modulation of the PARP1-NAD⁺ axis may be required for optimal therapeutic outcomes.

Beyond PARP1, the NAD⁺-degrading enzyme CD38 emerges as a critical regulator of NAD⁺ homeostasis in the aging joint. Inflammation and SASP accumulation promote CD38 expression on synovial macrophages, leading to NAD⁺ depletion and mitochondrial dysfunction through SIRT3 inhibition.¹²⁹ Despite these insights, nanotherapeutic strategies targeting the PARP1-CD38 axis remain unexplored. No current formulation delivers NAD⁺ precursors or CD38 inhibitors with cartilage-targeted, spatiotemporally controlled release. Developing nanoplatforms that simultaneously modulate PARP1 activity and inhibit CD38-mediated NAD⁺ degradation represents a critical unmet need for interrupting the DNA damage-senescence cascade in age-related OA. Table 1 summarized representative nanotherapeutic strategies targeting aging pathogenesis in OA.

Nanotherapeutic Strategies Targeting Metabolism Pathogenesis in OA

In OA, metabolic homeostasis ensures chondrocyte viability via balanced metabolism. Reprogramming shifts energy production to glycolysis, causes mitochondrial dysfunction, disrupts lipid and amino acid metabolism, and drives cartilage degradation and disease progression.¹³⁰ Abnormal metabolism of cartilage is the key process in OA which attracted increasing interests in recent years.¹¹ ROS, which is one of the core characteristics of oxidative stress in OA, limits the self-repair ability of cartilage tissue by increasing catabolism and reducing anabolism, mediating the pathological progression of OA through multiple signaling pathways such as MAPKs, NF-κB and PI3K/Akt.¹³¹ Besides, recent studies highlight several other metabolic abnormalities that contribute to OA pathogenesis, including energy metabolism, chondrocyte survival, iron handling, angiogenesis, as well as mechano-chemical cartilage breakdown.¹³² Notably, emerging metabolic targets have also been identified as associated with OA and show therapeutic potential. Notably, nanotherapeutic strategies such as nanoparticle-based drug delivery systems enable targeted modulation of metabolic pathways in OA by enhancing drug retention, chondrocyte mitochondrial energy metabolism, and restoring metabolic balance.⁹⁴ Therefore, these promising strategies facilitate intra-articular targeting to address pathological metabolic alterations in OA.¹³³

Nanotherapeutic Strategies Targeting Oxidative Stress Caused by ROS

In OA, oxidative stress can disrupt the balance between anabolism and catabolism in joints,^{134,135} which accelerates cartilage degeneration and hinders its repair mechanism.¹³⁶ Research has found that under the pathological condition of OA, the balance between antioxidants and ROS is disrupted,¹³⁷ which leads to oxidative stress and damage in chondrocytes, leading to cartilage degradation. Exogenous antioxidants, particularly superoxide dismutase (SOD), are a mainstream OA treatment.^{138,139} Due to the inherent characteristics of SOD, that is, insufficient retention in disease sites and rapid inactivation of natural SOD, the pharmacokinetics, biodistribution and solubility of SOD can be significantly improved by nano-delivery.¹⁴⁰ Recent research highlights that nano-enzyme complexes with SOD-like activity offer superior catalytic antioxidant effects, chondroprotection properties, and enhanced in vivo stability and retention.^{141–143} In this regard, Gui et al prepared a porous polymer vesicle with encapsulated SOD as antioxidant nanoparticles. The vesicle is composed of polyethylene glycol-polybutadiene copolymer (PEG-PBD) and polyethylene glycol-polypropylene oxide (PEG-PPO), which maintains good SOD activity, reduces its degradation, and enables ROS to enter the polymer, thus reducing the oxidative stress and damage of ROS to chondrocytes to treat OA.¹⁴⁴ Beyond the approach of directly neutralizing ROS with enzyme-based antioxidants, a recent novel strategy uses small interfering RNA (siRNA) delivery to modulate gene expression. Besides, Wu et al developed multifunctional nanoparticle platform TP/siMMP-13. TEMPO neutralizes ROS by mimicking SOD, while siMMP-13 silences catabolic gene expression, thereby suppressing cartilage degradation. Constructed from self-assembled 2,2,6,6-Tetramethylpiperidoxyl-polyethylene glycol-poly (lactic-co-glycolic acid) (TEMPO-PEG-PLGA) and cationic PEG-PLGA-OA9 polymers, it enables efficient intra-articular siRNA delivery to tackle oxidative stress and matrix degradation¹⁴⁵ (Figure 5A).

In contrast to polymer-based siRNA delivery, the polymeric nanosystem enhanced cartilage penetration and retention.¹⁴⁸ For instance, Mei et al further developed multifunctional polymeric nanocapsules PDA@CBP-PTH,

Table I Representative Nanotherapeutic Strategies Targeting Aging Pathogenesis in OA

Representative Nanomaterial	Delivery Modality	Loading Drug	Additional Intervention	OA Model	Target Cells/Pathways	Mechanism	Potential Effects and Outcomes	Limitations	Ref.
ESC-sEVs	Embryonic stem-cell-derived small extracellular vesicles	Endogenous EV cargo (miRNAs/proteins), no exogenous drug loaded	–	ACLT rat model	Aging chondrocytes, FOXO1A autophagy axis, SASP	Improving the aging phenotype, promoting ECM synthesis in aging chondrocytes and non-early OA cartilage, relieving oxidative stress, reversing aging-related phenotypes, reducing SASP factor production, and alleviating cartilage damage	Reduces senescent chondrocyte numbers and decreases SASP factor expression in human late-stage bone and joint transplantation cultures	Requires repeated IA injections and lacks long-term safety evaluation and large-animal validation	[86]
FGF18 mRNA-LNP	Lipid nanoparticles	FGF18 mRNA	–	DMM mouse model	Chondrocytes; FOXO3a–autophagy axis	Activating the FOXO3a-autophagy pathway, restoring autophagy, and reversing inflammation-induced chondrocyte senescence	Reduces pain sensitivity, improves gait, attenuates subchondral bone sclerosis, and decreases osteophyte formation	Requires high mRNA expression levels and faces challenges in immunogenicity control and translation efficiency	[87]
FoxO3-NETT@SMs	Nanoengineered injectable hydrogel microspheres	Chondrocyte-targeting CRISPR/Cas9 Foxo3 gene-activation editor	–	DMM rat model	Chondrocytes; Foxo3–PINK1/Parkin–mitophagy pathway	Restoring mitophagy through the PINK1/Parkin pathway, rebalancing mitochondrial function, reducing ROS accumulation, and inhibiting apoptosis	Improves mitochondrial function, enhances cartilage regeneration, reduces inflammation, and alleviates OA progression	Requires further evaluation of gene-editing efficiency and long-term safety	[88]
NAD@NPs@HM	Lactoferrin-modified, positively charged NAD-loaded nanoliposomes	NAD	–	Aged mouse model	M1 macrophages	Promoting repolarization of synovial macrophages from the M1 phenotype to the M2 phenotype and alleviating synovitis	Extends drug release, improves joint lubrication, enhances gait performance, and alleviates age-related OA progression	Lacks detailed mechanistic clarification and requires further validation	[70]
pPNP+TIIA@PFS	Nanofiber hydrogel	TIIA	–	ACLT rat model	BMSCs, Klotho, ROS, MMP13, ZIP8	Transferring the Klotho expression plasmid and TIIA, increasing intra-articular Klotho protein levels, downregulating ZIP8 and MMP13 expression, and reducing osteophyte formation	Induces BMSC differentiation into chondrocytes, accelerates cartilage defect repair, and promotes new cartilage formation	Lacks optimization of the hydrogel-to-pPNP ratio	[61]
A-Lipo/PAHM	Hyaluronic acid hydrogel microspheres	ABT-263 and SDF-1 α	–	ACLT mouse model	Chondrocytes, BMDMs	Inducing apoptosis of senescent chondrocytes and BMDMs, maintaining normal chondrocyte phenotype, and preserving stem cell chondrogenic differentiation capacity	Recruits endogenous stem cells, reverses cartilage aging, and promotes cartilage repair and remodeling	Requires repeated IA injections and increases infection risk due to limited joint residence	[54]
B2M-CuS-NP	Small copper sulfide nanoparticles functionalized with anti-beta-2-microglobulin antibodies	–	–	DMM mouse model	Chondrocytes, Col-2	Inducing apoptosis of senescent chondrocytes, selectively eliminating aging cells, and promoting GAG and Col-2 synthesis	Eliminates senescent chondrocytes and enhances cartilage regeneration	Shows Cu accumulation in the liver and kidney and requires long-term safety and translational validation	[57]

CSP@AS-IV	Copper silicate nanoparticles modified with polyethylene glycol and loaded with AS-IV	AS-IV	–	ACLT rat model	MMP13, Col-2	Inhibiting MMP13 expression and upregulating Col-2 expression, shifting cartilage metabolism toward anabolic synthesis	Reduces subchondral bone sclerosis, alleviates arthritis symptoms, decreases swelling, and enhances chondrocyte repair	Requires repeated IA injections and presents limited cartilage penetration and insufficient long-term safety validation	[62]
E@Au-Ag	EGCG decorated Au-Ag nano-jars	EGCG	Light stimuli (808 nm NIR irradiation)	ACLT rat model	Chondrocytes, MMP13, p-caspase-3	Increasing Col-2 expression, reducing MMP13 and p-caspase-3 expression, promoting chondrocyte proliferation, and enhancing cartilage migration	Improves cartilage integrity, thickens cartilage layers, and repairs cartilage damage	Requires external NIR irradiation and shows limited intra-articular retention	[64]
MND	Molybdenum nanodots	–	Light stimuli (808 nm NIR irradiation)	DMM mouse model	Chondrocytes, ROS	Reversing mitochondrial dysfunction, counteracting ROS-induced chondrocyte aging, and enhancing chondrocyte biological function	Promotes osteogenic differentiation and enhances subchondral bone repair	Requires external NIR irradiation and lacks long-term Mo accumulation safety evaluation	[65]
BS@MD	Intra-articular injection	BTZ	–	ACLT mouse model	DPP4; SASP	Anti-DPP4 targeting of sCDs plus macrophage-membrane cytokine “nanosponge”; pH-responsive release of BTZ/Sab for senolysis and SASP suppression	Enhances joint retention, reduces cartilage degradation and inflammation, promotes cartilage homeostasis	Four-week biocompatibility window only; longer-term translation untested	[60]
WPD-sEVs_siMDM2	Intra-articular injection	siMDM2	–	ACLT mouse model	Senescent chondrocytes; MDM2–P53 pathway	Silencing MDM2 to restoring P53 signaling and reducing chondrocyte senescence	Slows cartilage degeneration and reduces OARSi scores; improves COL2 and SOX9 levels	Murine-dominant evidence; large-animal and long-term safety validation needed	[59]
KPP@PLEL	Dual responsive nanohydrogel system	KGN	Thermal stimuli (body temperature)	ACLT rat model and DMM mouse model	BMSCs; chondrocytes; MMP-13; CBFβ–RUNX1; inflammatory cytokines	Prolonging joint retention through in situ gelation, enhancing cartilage penetration via cationic PAMAM, and promoting BMSC chondrogenesis through MMP-13–triggered KGN release via the CBFβ–RUNX1 pathway while suppressing inflammation	Enhances cartilage penetration, prolongs retention, reduces synovial inflammation, promotes cartilage regeneration, and slows OA progression	Requires large-animal validation and long-term biodegradation and safety evaluation of PAMAM and dosing optimization	[95]
CS/GA/NFs	Silk fibroin nanofiber–reinforced thiolated chitosan injectable hydrogel	Glucosamine sulfate	Thermal stimuli (37 °C)	Osteochondral defect rat model	BMSCs; chondroprogenitors	Reinforcing the chitosan network with nanofibers, supporting BMSC recruitment and proliferation, and promoting chondrogenesis through glucosamine-mediated signaling	Increases compressive strength, enhances defect filling, promotes BMSC proliferation and migration, increases GAG deposition, and improves cartilage repair	Relies on short-term small-animal models and shows mechanical properties below native human cartilage and lacks long-term validation	[96]
CAP-EXO-HA	Intra-articular injection	UCMSC-EXOs	–	ACLT rat model	OA chondrocytes; senescence-related p53 pathway	Releasing UCMSC-EXOs via two-phase HA microgel retention	Enhances cartilage regeneration, reduces fibrosis, and improves repair outcomes	Shows rat-only evidence; large-animal durability and safety untested	[102]
LNPs@S/T	Intra-articular injection	siCH25H	–	ACLT rat model	Chondrocytes; CH25H-mediated cholesterol metabolism; endogenous SMSCs	Silencing CH25H and promoting endogenous SMSC recruitment and chondrogenesis	Enhances cartilage repair, reduces OARSi scores, alleviates pain, and improves cartilage matrix integrity	Requires optimization of hydrogel system; long-term safety and translation unverified	[105]

(Continued)

Table I (Continued).

Representative Nanomaterial	Delivery Modality	Loading Drug	Additional Intervention	OA Model	Target Cells/Pathways	Mechanism	Potential Effects and Outcomes	Limitations	Ref.
W-CSB MSCs	Dual modification of nanoparticles with NPs and targeted peptides	Sox9 plasmid DNA and recombinant BMP7 protein	–	DMM mouse model	MSCs	Enhancing chondrogenic marker expression, reducing hypertrophic marker expression, and prolonging MSC residence in cartilage via peptide-mediated targeting	Balances cartilage regeneration and hypertrophy and enhances cartilage repair	Depends on peptide–cartilage binding efficiency and requires long-term validation of engineered MSC safety	[106]
Met@SBHA	Hydrogel microspheres	Metformin	–	Aged mouse model	Chondrocytes, iNOS/ ONOO ⁻ /P53	Reducing the iNOS/P53 axis activity and maintaining chondrocyte metabolic homeostasis	Enhances joint lubrication and alleviates cartilage aging	Relies mainly on mice and primary cell data and lacks long-term human validation	[108]
MGO-FN	Janus graphene oxide nanoplatfrom	Fenofibrate	–	OA rat model	OA chondrocytes; SIRT1-AMPK axis; PPAR- α ; MMP13; PRG4	Enabling localized FN release, activating PPAR- α /SIRT1 signaling, reducing ROS and MMP13, and upregulating PRG4 and Col2a1 to restore cartilage homeostasis	Reduces cartilage degradation and osteophyte formation, restores PRG4 expression, enhances ECM regeneration, and delays OA progression in vivo	Requires IA injection and further long-term safety validation	[103]
ICMV	Peptide functionalized interconnected multilayer vesicles	TGF- β 3 and KGN	–	Full-thickness cartilage defect rabbit model	MSCs	Co-delivering TGF- β 3 and kartogenin, promoting MSC migration, and inducing chondrogenic differentiation	Promotes transparent cartilage formation and supports subchondral bone remodeling	Requires long-term clinical validation and safety assessment	[112]
Mixed nanoparticles	Hybridization between EVs and LNP	NAM and EV bioactive cargo	–	DMM rat model	MMP13, NF- κ B, IL-6, Col2A1	Reducing MMP13 expression, downregulating NF- κ B and IL-6 signaling, and upregulating Col2A1 expression to protect cartilage	Maintains cartilage homeostasis and enhances cartilage protection	Involves manufacturing complexity and shows batch variability in EV production	[113]

Abbreviations: pPNP, Nanoparticles carrying plasmid DNA; PFS, Stem cell homing peptide; Alg, Sodium alginate; MH, Metformin hydrochloride; B2M, β 2-microglobulin; CSP, Polyethylene glycol modified copper silicate nanoparticles; MSC, Mesenchymal stem cell; EVs, Extracellular vesicles; TGF- β 1, Transforming growth factor- β 1; Col2A1, Type II collagen alpha 1 chain; TLR-2, Toll like receptor 2; NF- κ B, Nuclear factor kappa B; IL-6, Interleukin-6; FOXO1A, Fork head box protein O1A; TET1, Ten-eleven translocation 1; p21, Cyclin-dependent kinase inhibitor 1A; p16, Cyclin-dependent kinase inhibitor 2A; SMSCs, Mesenchymal stem cells derived from synovium; Klotho, Anti-aging molecule; MMP13, Matrix metalloproteinase 13; ZIP8:Zrt/Irt like protein 8; GAG, Glycosaminoglycans; SASP, Aging related secretory phenotype; BMSCs, Bone marrow mesenchymal stem cells; IL-1 β , Interleukin-1 β ; iNOS, Inducible nitric oxide synthase; MMP-9, Matrix metalloproteinase-9; p53, Tumor protein p53; Bcl2, B-cell lymphoma/leukemia -2 protein; BMDMs, Bone marrow-derived macrophages; Col-2, Type II collagen; p-caspase-3, Activated caspase 3; LNP, Lipid nanoparticles; EGCG, Epigallocatechin gallate; ONOO⁻, peroxynitrite; IA, intra-articular; NAD, nicotinamide adenine dinucleotide; AS-IV, astragaloside IV; FGF18, fibroblast growth factor 18; FoxO3, forkhead box O3; TI1A, tanshinone IIA; KGN, kartogenin; ABT-263, navitoclax; SDF-1 α , stromal cell-derived factor 1 alpha; Sox9, SRY-box transcription factor 9; BMP7, bone morphogenetic protein 7; TGF- β 3, transforming growth factor beta 3; ACLT, anterior cruciate ligament transection; DMM, destabilization of the medial meniscus; OA, osteoarthritis; FOXO3a, forkhead box O3a; PINK1, PTEN-induced kinase 1; BMSCs, bone marrow-derived mesenchymal stem cells; Klotho, klotho protein; ROS, reactive oxygen species; MMP13, matrix metalloproteinase 13; ZIP8, Zrt- and Irt-like protein 8; CBF β -RUNX1, core-binding factor beta-runt-related transcription factor 1; PPAR- α , peroxisome proliferator-activated receptor alpha; SIRT1-AMPK, sirtuin 1-AMP-activated protein kinase; MSCs, mesenchymal stem cells; HIF-1, hypoxia-inducible factor 1; iNOS, inducible nitric oxide synthase; p53, tumor protein p53; ECM, extracellular matrix; NIR, near-infrared; PAMAM, polyamidoamine dendrimer; CH25H, cholesterol 25-hydroxylase.

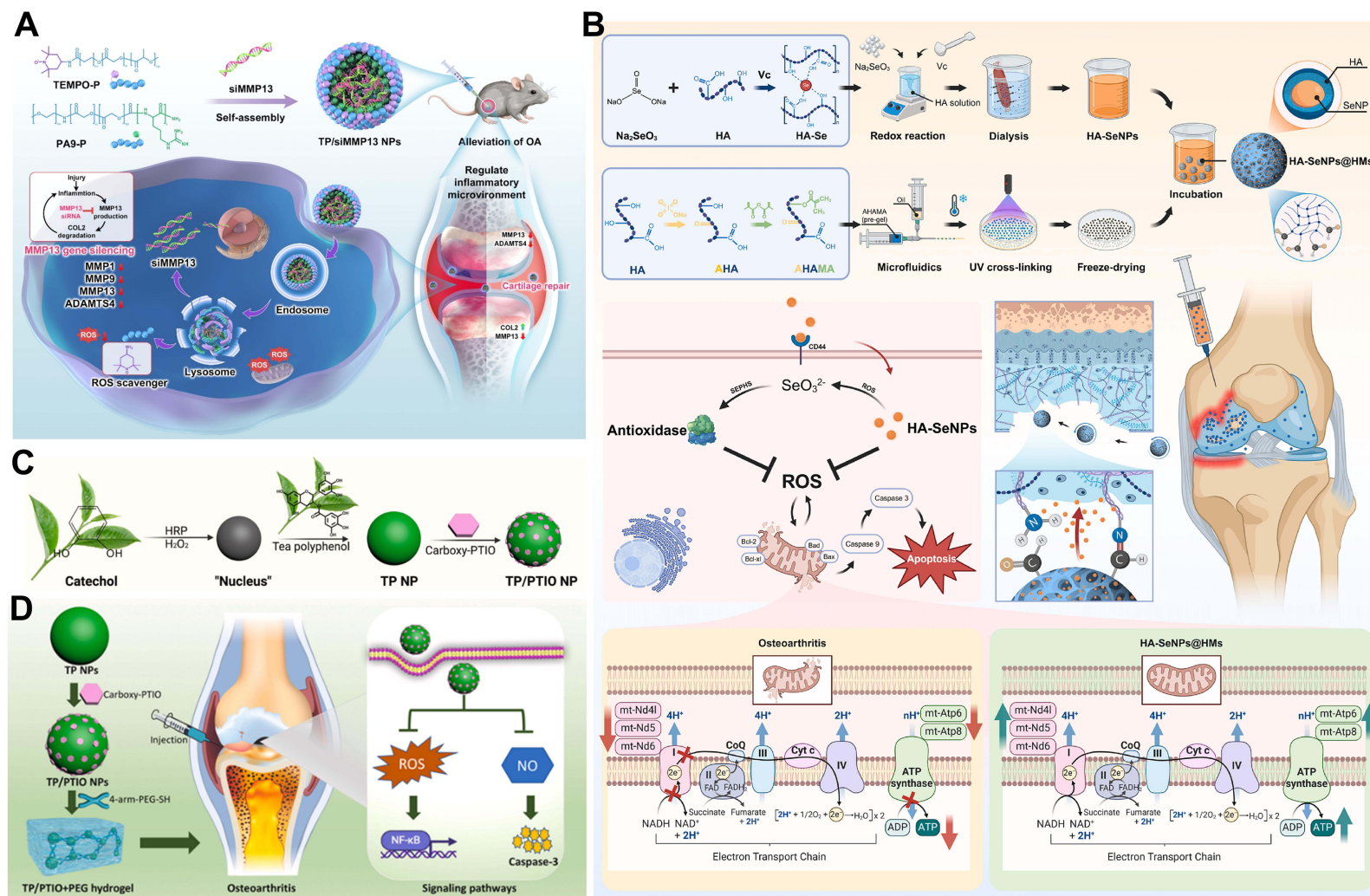


Figure 5 Nanotherapeutic strategies targeting oxidative stress caused by ROS. **(A)** Schematic illustration of the design of polymeric nanoparticles (TP/siMMP-13) for targeted osteoarthritis therapy through redox modulation and gene silencing. Reproduced from Wu et al.¹⁴⁵ Copyright 2026, Elsevier. **(B)** Schematic illustration of the synthesis and function of HA-SeNPs@AHAMA-HMs. Upon injection into the knee joint, HA-SeNPs@AHAMA-HMs exhibit cascade targeting functionality. The AHAMA-HMs selectively adhere to the surface of damaged cartilage through the formation of Schiff base bonds between aldehyde groups in their molecular framework and exposed amino groups on the cartilage surface, achieving micron-scale targeting. Subsequently, HA-SeNPs released from AHAMA-HMs bind to the highly expressed CD44 receptors on OA chondrocyte membranes via their HA shell, enabling nano-scale targeting. Once taken up by OA chondrocytes, HA-SeNPs establish a multifaceted antioxidant defense system by directly scavenging ROS and generating selenite to promote antioxidative selenoprotein synthesis. This effectively alleviates oxidative stress, optimizes mitochondrial function, and ultimately slows the progression of OA. Reproduced from Liu et al.¹⁴⁶ Copyright 2025, Elsevier. **(C)** Synthesis of TP/PTIO NPs. **(D)** Acid-responsive tea polyphenol nanoparticle-based hydrogel platform for osteoarthritis therapy through ROS/NF-κB and iNOS/NO/Caspase-3 signaling. Reproduced from Ding et al.¹⁴⁷ Copyright 2024, Elsevier.

demonstrating superior ROS-scavenging capacity and significantly enhanced the anabolic activity of subchondral bone, contributing to improved joint microenvironment homeostasis in OA.¹⁴⁸ Small-molecule antioxidants help balance ROS but face biocompatibility issues, and converting them into macromolecular nanoscavengers often reduces activity. Recent study by Wang et al developed degradable nanoscavengers via dopamine and 4-formylphenylboronic acid polymerization, addressing the reduced efficacy of conventional macromolecular antioxidants. These degrade in acidic/ROS conditions, exposing groups to enhance antioxidation beyond monomers, and alleviated oxidative stress and inflammation.¹⁴⁹ Additionally, selenium deficiency worsens OA by disrupting cartilage redox balance. To overcome the poor targeting of traditional supplements, Liu et al created a cascade-targeting system using selenium nanoparticles modified with hyaluronic acid (HA-SeNPs). These were loaded into special hydrogel microspheres that adhere to damaged cartilage. The system then targets OA cells via CD44 receptors, delivering selenium to combat oxidative stress and protect mitochondrial function¹⁴⁶ (Figure 5B).

Encouragingly, recent studies demonstrated that introducing nanoparticles into the hydrogel can improve its mechanical strength, retention time, and ability to deliver antioxidants.¹⁵⁰ Nanoparticles can enhance hydrogel mechanics and enable sustained drug release, making hydrogel-nanoparticle composites a promising ROS-targeted OA treatment. Fan et al developed an injectable, boronate-based hydrogel loaded with icariin-PLGA nanoparticles. The system responds to OA's acidic, high-ROS conditions for sustained drug release, aiming to reduce inflammation and promote cartilage repair, representing an advanced therapeutic strategy.¹⁵¹ Likewise, researchers developed a dual-action system combining tea polyphenol nanoparticles with a NO scavenger (carboxy-PTIO). This synergistic combination eradicates both ROS and NO, improving drug stability and enabling pH-responsive release at inflammation sites¹⁴⁷ (Figure 5C). Hence, this nanotherapeutic strategy shows promise for cartilage repair by reducing oxidative stress, and future research should focus on advanced constructs for better tissue integration.¹⁵²

Beyond particulate carriers, antioxidant scaffolds have been explored to improve cartilage regeneration and resist oxidative stress.^{153,154} A PLLA/LP nanofiber scaffold was developed by grafting polylactic acid onto lignin, a phenolic polymer with antioxidant properties.¹⁵⁵ These were then fabricated into nanofibrous tissue engineering scaffolds using electrospinning. The resulting scaffolds were characterized for mechanical properties and antioxidant activity, aiming to support mesenchymal stem cell chondrogenesis for cartilage repair in an oxidative environment. This strategy enhanced the antioxidant capacity of lignin and promoted BMSCs to secrete GAG and upregulate the expression of COL2A1, ACAN, and SOX9 genes.¹⁵⁶ The utilization of nanofibre scaffolds endows desirable properties, including high surface area, biomimetic replication of native extracellular matrix structures, and tunable mechanical properties.^{157,158} Therefore, this approach holds potential as a material targeting oxidative stress in OA metabolism.

Collectively, these nano-antioxidant systems not only provide amplified, long-lived ROS clearance but also integrate chondro-anabolic or osteo-anabolic cues, shifting the redox balance from injury to repair. By simultaneously scavenging ROS and safeguarding the ECM, nanotherapeutic strategies offer a versatile platform for interrupting the oxidative progression that underlies OA progression.

Nanotherapeutic Strategies Targeting ROS-Induced Changes in Cellular Behavior

Beyond direct oxidative damage, ROS can influence cellular behavior, such as osteoclast differentiation and chondrocyte apoptosis.¹⁵⁹ For instance, ROS promotes osteoclasts by acting as a second messenger in RANKL signaling and amplifying inflammation, thereby activating NF- κ B, MAPK pathways, enhancing differentiation and bone resorption. ROS inhibits osteoblasts differentiation through the GSK3 β / β -catenin pathway, impairing oxidative phosphorylation (OXPHOS) and disrupting protein homeostasis, thereby exacerbating bone metabolic imbalance.^{159,160} Additionally, ROS promotes the polarisation of M1 macrophages, thereby amplifying the inflammatory response and ROS production. Concurrently, it inhibits the polarization of M2 macrophages, exacerbating damage to joint tissues.¹⁶¹ ROS induces chondrocyte apoptosis and pyroptosis by activating CASP1, NLRP3 inflammasome, and NF- κ B/p38 MAPK pathways, while inhibiting ECM synthesis and promoting degradation.¹⁶² These effects form a vicious cycle of ROS accumulation, cell dysfunction, and OA progression. Recent nanomedicine research has revealed ROS-responsive nanosystems targeting ROS-induced changes in cellular behavior holds significant application potential.¹⁶³ Through ROS-cleavable

moieties, the systems scavenge excess ROS and release drugs on-demand, which reverses ROS-induced cell senescence and apoptosis, inhibits inflammation, and suppresses osteoclast activation.^{163,164}

ROS are involved in the regulation of osteoclast differentiation,¹⁶⁵ and this dysregulation contributes to aberrant subchondral bone remodeling and chondrocyte apoptosis.^{159,160} In this regard, nanotherapeutic strategies modulating targeting subchondral bone to balance osteoclasts and osteoblasts represents a promising efficient strategy.¹⁶⁶ The therapeutic potential of polydopamine nanoparticles in mitigating reactive ROS has garnered increasing interest. These nanoparticles exhibit strong ROS-scavenging capacity, effectively reducing damage associated with acute inflammation. In materials science, PEG and its derivatives are widely used for surface modification to enhance stability and biocompatibility.¹⁶⁷ Wu et al developed methoxypolyethylene glycol amine (mPEG-NH₂) modified polydopamine nanoparticles (PDA-PEG NPs). The synthesized PDA-PEG nanoparticles can scavenge ROS both in and out of cells, enhance the antioxidant function of nanoparticles. Mechanistically, these nanoparticles inhibited RANKL-induced I κ B α phosphorylation and degradation, leading to the suppression of NF- κ B and JNK signaling pathways, thereby inhibiting osteoclast differentiation. These findings highlight the potential of PDA-PEG nanoparticles as a therapeutic strategy for conditions characterized by excessive osteoclast activity in OA¹⁶⁸ (Figure 6A). In addition to inhibiting the transcription factors of osteoclast formation, inhibiting the differentiation of endochondral cells into osteoclasts is also a therapeutic approach.¹⁶⁹ Mitochondrial ROS can initiate the differentiation of progenitor cells into osteoclasts. Scavenging ROS can inhibit this differentiation, though most antioxidants cannot effectively enter the cartilage due to steric hindrance.^{170–172} It was found that selenium-doped carbon quantum dots (SCT) can penetrate the dense structure of cartilage and reach chondrocytes, subchondral bone and medulla through intra-articular injection, which can effectively inhibit ROS under oxygen stress.¹⁷³ Zuo et al designed and synthesized highly permeable nano-hydrogel microspheres (SCT-HA), which can prevent SCT from being cleared and metabolized by capillaries and lymphatic vessels in synovium. The embedded selenium atoms neutralize mitochondrial ROS in macrophages, inhibiting osteoclast differentiation and protecting chondrocytes from apoptosis, thereby maintaining cartilage matrix balance. In vivo, the microspheres reduce osteoclastogenesis and H-type vessel invasion, key drivers of abnormal bone remodeling, alleviating subchondral cartilage degeneration¹⁷⁴ (Figure 6B). Therefore, the SCT system demonstrates potential as a nanotherapeutic strategy for OA by regulating chondro-bone metabolism.

In chondrocytes, excessive ROS also disrupt mitochondrial function and cellular metabolism, ultimately promoting apoptosis and accelerating OA progression.¹⁷⁷ Recent advances in mitochondrial-targeted nanotherapies have demonstrated that restoring mitochondrial homeostasis is an effective strategy to counteract ROS-mediated cartilage degeneration.^{17,178} Accumulating evidence suggests that disruption of mitochondrial quality control (MQC) homeostasis plays a critical role in cartilage degradation during the onset and progression of OA.¹⁷⁹ In this regard, Chen et al proposed cerium dioxide-based nanoplateforms, which enhance mitochondrial quality control to maintain chondrocyte stability under oxidative stress. Constructed with cerium dioxide nanozymes and metformin, it scavenges ROS and activates autophagy to clear dysfunctional mitochondria. By reducing cartilage degradation and osteophyte formation, this nanoplateform presents a novel subcellular therapy for aging-related OA diseases¹⁷⁵ (Figure 6C). Concurrently, a genetically engineered chondrocyte-mimetic nanoplateform (HKL-GE CM @MPNPs) comprises a honokiol-loaded mitochondrion-targeting core encapsulated within an IL-1R2-overexpressing chondrocyte membrane. This design blocks IL-1 β signaling via membrane-mediated receptor transfer and restores SIRT3 activity through mitochondrial HKL delivery, thereby protecting against inflammation-induced mitochondrial dysfunction in osteoarthritic chondrocytes¹⁷⁶ (Figure 6D). ROS-responsive nanoparticles further reprogram mitochondrial metabolism and direct macrophage polarization toward an anti-inflammatory phenotype.¹⁸⁰ In addition, Kumar et al combined manganese dioxide (MnO₂) with PEG to develop synthesized nanoparticles PEG-MnO₂, which is easily absorbed by cartilage and alleviates oxidative stress. MnO₂ catalyzes the breakdown of H₂O₂, the main ROS in chondrocytes, while PEG helps maintain nanoparticle stability. The nanoparticles can be used for cartilage penetration and long-term retention in joints, and can be located in cartilage in vivo, making it more targeted for the decomposition of ROS, thus reducing cartilage apoptosis.¹⁸¹ Besides, a targeted hydrogel delivering MnO₂ nanoparticles and NAD⁺ precursor to cartilage was developed recently. The nanoparticles catalyze oxygen generation while releasing NAD⁺, reactivating the mitochondrial respiratory chain. This dual approach reduces oxidative stress, improves NAD⁺/NADH balance, inhibits senescence signals, and protects

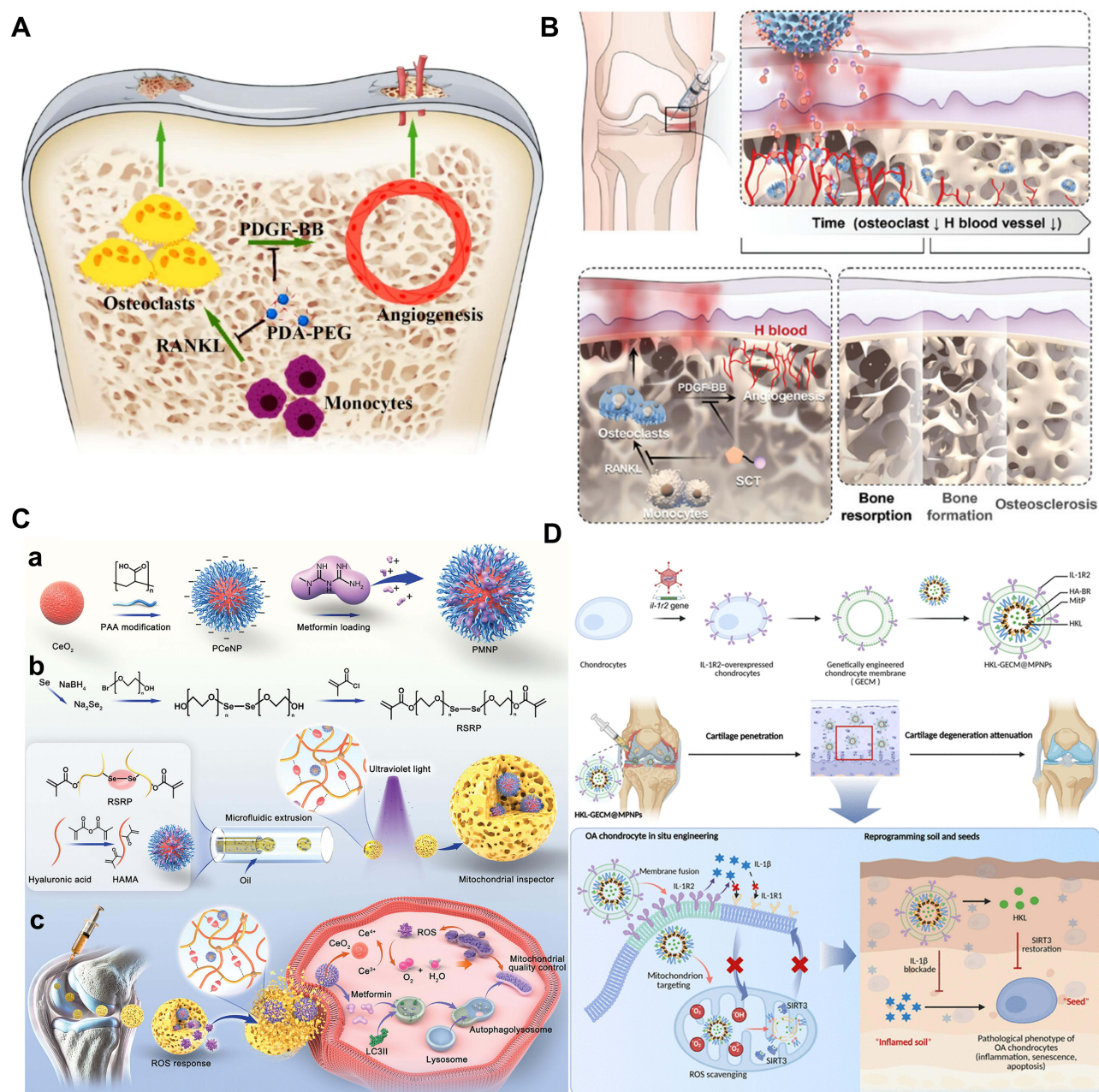


Figure 6 Nanotherapeutic strategies targeting ROS-induced changes in cellular behavior. **(A)** Schematic illustration of PDA-PEG nanoparticles inhibiting osteoclastogenesis and angiogenesis in subchondral bone. Reproduced from Wu et al.¹⁶⁸ Copyright 2022, Springer Nature. **(B)** Schematic diagram illustrating the inhibition of abnormal subchondral bone remodeling by SCT-HA. SCT-HA inhibits the differentiation of monocyte macrophages into osteoclasts and PDGF-BB production to suppress the abnormal invasion of subchondral bone blood vessels in OA. By inhibiting blood vessels, which act as the "executors" of abnormal bone remodeling, SCT-HA also prevents the occurrence of abnormal bone remodeling in subchondral bone. Reproduced from Zuo et al.¹⁷⁴ Copyright 2025, Wiley. **(C)** Schematic diagram of preparation and regulation of the "mitochondrial inspector". (a) electrostatic self-assembly of PMNP. (b) The synthesis of RSRP by incorporation of dynamic diselenide bonds. (c) The injection of "mitochondrial inspector" for treatment of osteoarthritis by mitochondrial quality control. Reproduced from Chen et al.¹⁷⁵ Copyright 2025, Wiley. **(D)** Schematic illustration of the genetically engineered chondrocyte-mimetic HKL-GECM@MPNPs attenuating OA cartilage degeneration. Reproduced from Deng et al.¹⁷⁶ Copyright 2025, American Association for the Advancement of Science.

cartilage, demonstrating a promising strategy to mitigate OA progression.¹⁸² Therefore, ROS-scavenging nanomaterials, which address the stability and bioavailability shortcomings of conventional antioxidants, are emerging as a promising therapeutic approach for OA.

Collectively, these studies establish that mitochondrial-centric, ROS-scavenging nanotherapies not only interrupt osteoclastic subchondral bone remodeling but also revive chondrocyte bioenergetics, thereby blocking the ROS-driven metabolic collapse that underpins cartilage degradation in OA.

Nanotherapeutic Strategies Targeting Energy Metabolism

Compared to healthy chondrocytes, OA chondrocytes showed increased extracellular acidification rate, more lactate production, and lower mitochondrial respiratory rates. These changes were accompanied by decreased cellular adenosine 5'-triphosphate (ATP) production, mitochondrial membrane potential and disrupted mitochondrial morphology.¹⁸³ Given this understanding, recent nanotherapeutic strategies have developed approaches targeting dysregulated energy metabolism, offering unique avenue to restore joint homeostasis.

Building upon the concept of restoring metabolic function, a novel nanotherapy was developed by conjugating mesenchymal stem cells with steroid-loaded gold nanostars (MSC-Au-Steroid). This strategy targets energy metabolism dysregulation in OA, normalizing inflammatory metabolic profiles such as glycolysis and oxidative phosphorylation, improving mitochondrial function, and suppressing ROS via mTOR regulation (Figure 7A). Therefore, MSC-Au-Steroid represents a promising disease-modifying agent targeting metabolic reprogramming.¹⁸⁴

The hypoxic microenvironment of cartilage restricts mitochondrial aerobic respiration, leading to insufficient ATP production and exacerbating energy metabolism defects, which in turn promote cartilage degeneration, subchondral bone sclerosis, and synovitis.^{188,189} In this regard, a hemoglobin-loaded ZIF-8 nanopump (CZIF@Hb) has been engineered to deliver oxygen directly to the avascular cartilage, overcoming its hypoxic microenvironment. Triggered by passive (acidic microenvironment) and active stimuli (ultrasonic driving), CZIF@Hb disassembles with ZIF-8 adsorbs CO₂ and Hb releases O₂. By enhancing oxygen availability, this nanotherapy effectively fuels the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) in OA chondrocytes, thereby boosting mitochondrial ATP production. CZIF@Hb activates a glutamate-mediated metabolic axis to boost energy synthesis, mitigating oxidative damage and synovial inflammation¹⁸⁵ (Figure 7B).

Furthermore, in addition to acid-triggered oxygen delivery, ROS-responsive nanotherapies have demonstrated application potential by leveraging distinct microenvironmental signals to restore energy homeostasis in OA joints.²⁵ The W/KGN@DSeD nanosystem, modified with WYRGL peptide, is a cartilage-targeted and ROS-responsive nanoprodrug for OA therapy. In OA joints, the diselenide bonds in DSeD are cleaved, triggering the controlled release of diclofenac, kartogenin and selenium, which activates the Nrf2 pathway, promotes ECM synthesis for cartilage regeneration, and inhibits inflammation by suppressing PGE2. These components act synergistically to remodel the OA pathological microenvironment, achieving targeted and multimodal therapeutic effects with sustained joint retention and high biocompatibility¹⁸⁶ (Figure 7C).

Building on these stimuli-responsive platforms that modulate energy metabolism, recent work has explored a biohybrid hydrogel system combining naturally-derived vesicles with sustained release. Liang et al developed spirulina platensis-derived extracellular vesicles (SP-EVs) loaded into a pH-responsive rhein hydrogel (Rh Gel@SP-EVs), containing antioxidative and ATP-related compounds. This system enables sustained, intra-articular delivery of SP-EVs to chondrocytes. By improving oxidative stress, restoring mitochondrial membrane potential and ATP levels, and modulating the JAK-STAT3 pathway, Rh Gel@SP-EVs reduce inflammation, restore cellular energy homeostasis, and decelerate cartilage degeneration¹⁸⁷ (Figure 7D).

In summary, these novel nanotherapies target the energy metabolism in OA chondrocytes, achieving precise, spatiotemporal control over therapeutic delivery, and re-establishing metabolic equilibrium. The continued refinement of these intelligent, stimuli-responsive platforms holds significant promise for translating the concept of metabolic reprogramming into durable, disease-modifying clinical outcomes for OA patients.

Nanotherapeutic Strategies Targeting Novel Sites in Metabolism

Beyond classical antioxidant or anti-inflammatory strategies, nanotherapy is now targeting emerging metabolic nodes that govern chondrocyte survival, iron homeostasis, angiogenesis, and mechano-chemical cartilage breakdown. Leveraging superior colloidal stability, injectability, and cell uptake,⁵⁵ nanotherapies are being engineered to modulate mTORC1

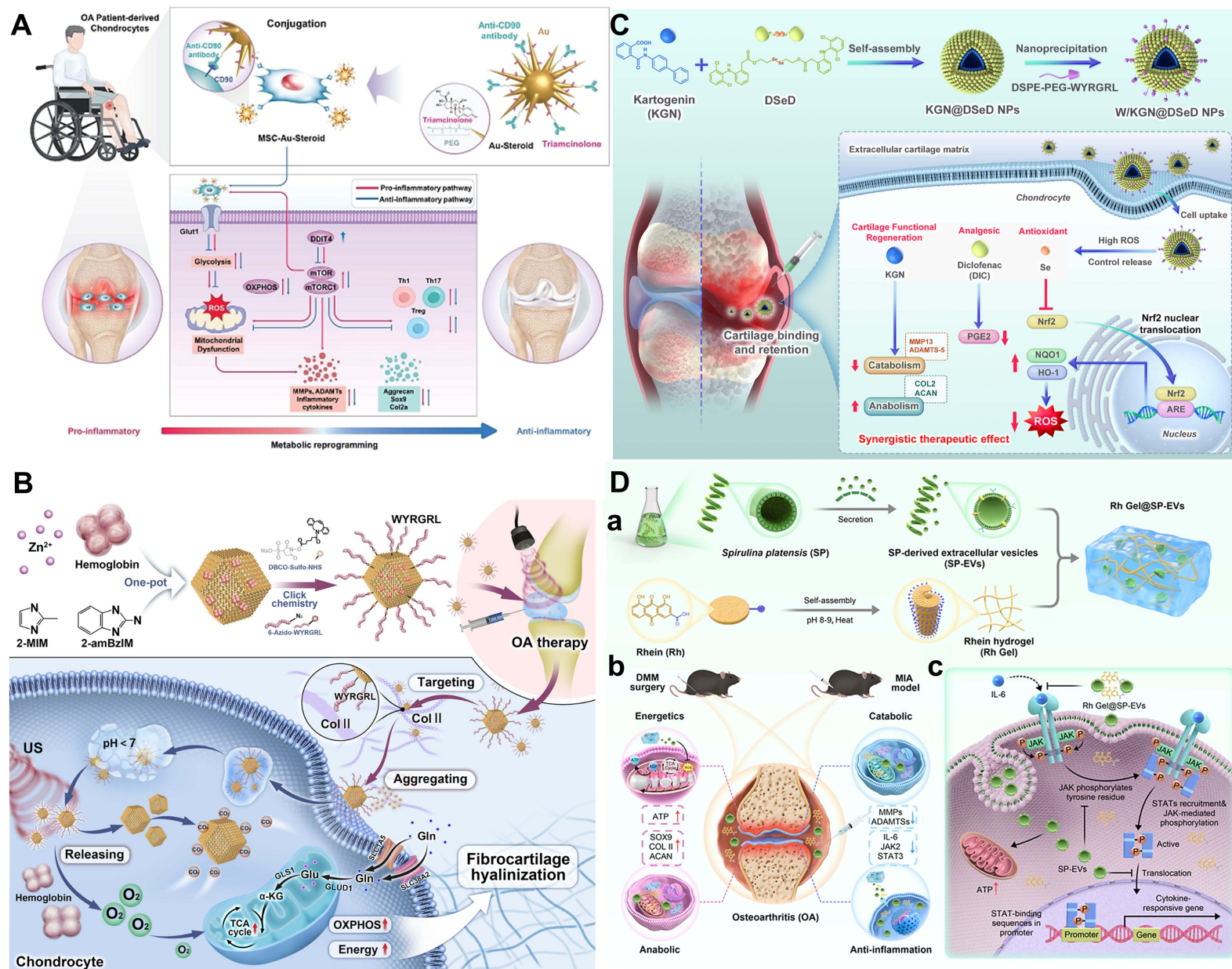


Figure 7 Nanotherapeutic strategies targeting energy metabolism. **(A)** Nano-Steroid-Conjugated MSCs Target CD90⁺ chondrocytes via metabolic reprogramming for accelerated cartilage regeneration in osteoarthritis (OA). Reproduced from Lee et al¹⁸⁴ Copyright 2026, Iyspring International Publisher. **(B)** Oxygen nanopump (CZIF@Hb), composed of ZIF-8 and oxygenated Hb, was synthesized using a click chemistry approach. Upon intra-articular injection, CZIF@Hb specifically attached to and penetrated the chondrocyte membrane, releasing ZIF-8 and Hb in response to external ultrasound (US) stimulation and internal acidic conditions. This process effectively rebalanced the concentrations of O₂ and CO₂ within the microenvironment. Notably, the supplemental O₂ and α-KG generated via the glutamine metabolic pathway enhanced TCA cycle activity and OXPHOS, thereby promoting hyaline cartilage formation and concomitantly alleviating OA. Reproduced from Xia et al¹⁸⁵ Copyright 2025, American Chemical Society. **(C)** Schematic diagram of diselenide-linked self-assembly nanoprodru for mitigating the inflammatory effect, facilitating cartilage functional regeneration, and potentially reversing disease progression in OA treatment. Reproduced from Li et al¹⁸⁶ Copyright 2025, American Chemical Society. **(D)** Self-assembled microalgae extracellular vesicles/herb-based hydrogel for the treatment of OA; (a) Rhein (Rh) molecules can self-assemble into nanofibers via non-covalent interactions, which can further form a 3D bioactive Rhein hydrogel (Rh Gel) with the ability to encapsulate *Spirulina platensis*-derived extracellular vesicles (SP-EVs); Eventually, the designed Rh Gel@SP-EVs integrate the therapeutic effects of both Rh and microalgae EVs; (b) In destabilization of the medial meniscus (DMM) surgery or monoiodoacetate (MIA)-induced mouse models, Rh Gel@SP-EVs effectively alleviate the OA progression by increasing ATP production, inhibiting catabolic metabolism, promoting anabolic metabolism, and suppressing inflammatory responses; (c) Rh Gel@SP-EVs exhibit excellent anti-inflammatory effects via the IL-6/JAK2/STAT3 signaling pathway, exerting regulatory effects on cytokine production and contributing to OA regression. Reproduced from Liang et al¹⁸⁷ Copyright 2025, American Chemical Society.

signaling, ferroptosis pathways, VEGF receptors, and small-molecule chondro-inducers, offering multi-target collaborative strategies for OA management.

The mammalian target of rapamycin complex 1 (mTORC1) is abnormally activated in OA, which promotes chondrocyte hypertrophy, ECM degradation, and disrupts autophagy-apoptosis balance, inducing subchondral bone sclerosis and synovitis.^{190,191} Inhibiting mTORC1 protects cartilage, reduces inflammation, and alleviates OA progression by restoring chondrocyte homeostasis.¹⁹² Rapamycin shows promise by targeting mTORC1 to mitigate OA progression, but its clinical application is hindered by poor water solubility, instability, and rapid clearance from joints. To overcome these limitations, Ma et al developed rapamycin-loaded PLGA nanoparticles (RNPs) with 85% entrapment efficiency. These RNPs achieved sustained intra-articular release, promoted chondrogenic differentiation, prevented chondrocyte senescence, and mitigated cartilage destruction, osteophyte formation, and synovitis in DMM mice.¹⁹³

Ferroptosis, driven by excess iron and oxidative lipid damage, has emerged as a key form of regulated cell death responsible for chondrocyte loss in OA.¹⁹⁴ Notably, downregulation of glutathione peroxidase 4 (Gpx4) in osteoarthritic cartilage heightens chondrocyte vulnerability to oxidative stress and drives ECM degradation, thus linking ferroptosis to OA progression.¹⁹⁴ To counter ferroptotic death, Li et al couple citric acid stabilized gold nanorods (Cit-AuNRs) with transient receptor potential vanillin 1 (TRPV1) monoclonal antibody (Cit-AuNRs@anti-TRPV1), and use AuNRs to intelligently target TRPV1 positive inflammatory macrophages and iron-laden chondrocytes to increase Gpx4 expression and inhibit chondrocyte iron prolapse to protect cartilage.¹⁹⁵

VEGF is upregulated in OA joints, with VEGFR2 mediating cartilage degeneration by promoting catabolic and hypertrophic gene expression and VEGFR1 driving pain transmission. Hence, inhibiting VEGFR1/2 relieves OA pain by blocking VEGFR1-mediated nociceptive signaling in DRG and spinal cord, and inhibits cartilage damage via VEGFR2 suppression, revealing VEGF's novel role in OA neuropathic pain.¹⁹⁶ In this regard, Ma et al developed a nanoparticle formulation of pazopanib (Nano-PAZII) that markedly alleviated cartilage damage and joint pain in preclinical OA models.¹⁹⁷ Mechanistically, the improved nanoparticle can inhibit the phosphorylation activation of VEGFR2 in cartilage and VEGFR1 in synovium, reduce the expression of catabolic enzymes and inflammatory proteins in cartilage, and inhibit the development of knee OA and joint pain by nerve growth factor (NGF)/tropomyosin receptor kinase A (TrkA) signal pathway in knee joint and DRG sensory neurons.¹⁹⁷

In addition to the emerging targets mentioned above, numerous other novel metabolic targets for OA are being explored and identified. Promising nanomaterials, with their high specific surface area and facile surface modification, can serve as carriers to enhance drug accumulation and retention. Additionally, they can be applied in OA therapy by leveraging their unique properties, including catalytic activity, thermal conversion, and mechanical characteristics.¹⁹⁸ Conjugation to cartilage-homing carriers empowers small-molecule chondro-inducers to overcome the challenge of rapid clearance from intra-articular spaces, enabling deep penetration into the dense cartilage matrix.¹⁹⁹ To address their poor water solubility, inability to penetrate the dense avascular cartilage matrix, and rapid clearance from the joint, Xiong et al modified formononetin (FMN) by PEG and coupled cartilage-targeting peptides to prepare a specific cartilage-targeting nano-drug FMN-poly (ethylene glycol) (PCFMN)¹⁷¹. PCFMN can pass through cartilage and increase the duration of FMN, reduce inflammatory factors, reduce the upregulation of VEGF, reduce the expression of MMP-13, and significantly increase COL2a1 to protect cartilage.¹⁷¹ Similarly, He et al developed a multi-arm avidin (mAv) nano-construct that dramatically enhances intra-cartilage delivery efficiency. Their earlier work established the ability of mAv to penetrate dense cartilage and transport small-molecule drugs into negatively charged avascular tissues,^{200,201} and subsequently optimized the multi-arm avidin nano-construct for controlled intra-cartilage drug release.²⁰² Subsequently, He et al conjugated kartogenin (KGN) to mAv to create a cartilage-targeted therapeutic system MAV-KGN. Importantly, a single intra-cartilage administration of MAV-KGN markedly suppressed cytokine-induced OA-related catabolism and protected cartilage structure in vivo, representing a major advancement in cartilage-penetrating nanotherapies.²⁰³ In addition to targeting cartilage, recent studies have identified nanotherapeutic approaches targeting other parts of the OA joint such as synovium and subchondral bone. For instance, Ma et al developed MM@MT nanoparticles (MM@MT NPs) that regulate synovial mitochondrial metabolism for OA nanotherapy. Mechanistically, the system restores mitochondrial membrane potential and dynamics, enhance TCA cycle and OXPHOS, and boost antioxidant capacity, balancing ATP and ROS. By reprogramming synovial metabolism, MM@MT NPs remodel

mitochondrial homeostasis, enabling symptomatic and etiological OA treatment.²⁰⁴ p16^{INK4a} expression is elevated in the synovium of OA patients. Park et al used PLGA nanoparticles to deliver p16^{INK4a} siRNA enabled targeted therapy to the synovium. This treatment reduced inflammatory cytokines in synoviocytes and catabolic factors in chondrocytes, alleviating pain and cartilage damage.²⁰⁵ Moreover, a dual-functional black phosphorus nanosheet (BPNS) therapy proposed by Lu et al targets both cartilage degradation and subchondral bone remodeling in OA. BPNSs scavenge ROS, restore chondrocyte homeostasis, and promote osteogenesis, showing excellent biocompatibility.²⁰⁶ Although current research on subchondral bone nanomaterials remains limited, it offers novel therapeutic options for future OA treatment.¹⁶⁶

In recent years, the development of stimulus-responsive intelligent nanoplateforms has emerged as a dynamic research direction in precision medicine, particularly for addressing the complex pathological microenvironment of OA.²⁰⁷ These systems are designed to exploit specific physiological cues — including localized pH shifts, elevated ROS, and dysregulated enzyme activities— to achieve controlled therapeutic intervention and enhanced imaging contrast.¹⁶⁶ The microenvironment-triggered systems not only prolong drug release but also improve tissue and cellular specificity, allowing more accurate modulation of catabolic mediators such as MMP-13.²⁰⁸ For example, pH-responsive nanotherapies act via acid-sensitive bond hydrolysis and chemical group protonation, triggering nanoparticle cracking to release bioactives.²⁰⁹ Yi et al developed pH-responsive lipid nanoparticles loaded with Urolithin A (LNPs@UA) as a smart nanoplateform targeting OA. By responding to the acidic synovial environment, LNPs@UA effectively deliver UA to inflamed joints, thereby reducing oxidative stress and inflammation, promoting M2 macrophage polarization, and protecting mitochondrial function.²¹⁰ The abundant ROS in the OA microenvironment, alongside pH changes, offers a key design principle for smart nanocarriers, as illustrated by ROS-responsive systems like the MgO-SiO₂ nano-capsules developed by Zheng et al²¹¹ Likewise, NO-responsive nanosensors developed by Jin et al can detect inflammation-associated NO elevations and selectively activate in diseased regions. Notably, MMP-13 expression is significantly upregulated as OA progresses, leading to further ECM degradation and exacerbation of the disease. This detrimental activity establishes MMP-13 as a critical biomarker and an attractive target for designing smart drug delivery systems for OA therapy.²¹² In this regard, an innovative smart nanoplateform (ERMs@siM13) targets early OA by responding to overexpressed MMP13. It features an MMP13-cleavable PEG shell with cRGD ligands and Cy5 fluorescence quenched by BHQ3. PEG detaches upon encountering MMP13, exposing cRGD to enhance chondrocyte uptake, delivering siM13 to silence MMP13. Concurrently, Cy5 fluorescence is restored, enabling real-time imaging of disease severity.²¹³ By integrating responsive motifs into material design, such systems enable spatiotemporally controlled diagnostic and therapeutic functions specifically within diseased tissues, thereby improving targeting accuracy while minimizing off-target effects.¹⁶⁶ This pathological characteristic-driven strategy holds significant promise for advancing the precision and efficacy of OA management.

Together, these findings underscore that nanotherapy-enabled metabolic reprogramming can simultaneously correct chondrocyte metabolism, protect matrix integrity and alleviate pain, opening new avenues for single-dose, multi-target disease-modifying therapy in OA. Table 2 summarized representative nanotherapeutic strategies targeting metabolism pathogenesis in OA.

Nanotherapeutic Strategies Targeting Inflammation Pathogenesis in OA

OA is now widely recognized as a low-grade inflammatory disease that affects the entire joints, which is characterized by cartilage breakdown and synovial inflammation.^{214,215} As a key marker and driving factor in the OA progression, inflammation plays a central role in its pathophysiology through its clear association with immune cells.¹² Immune cells play a crucial role in OA mainly such as macrophages, T cells, and NK cells.^{190,216} In this regard, macrophages, as central immune regulators, coordinate anabolic and catabolic activities across diverse cell populations, thereby driving disease progression.²¹⁷ In addition to immune cells, inflammatory cytokines are among the critical mediators of OA pathophysiology.²¹⁸ Thus, nanotherapeutic strategies targeting macrophages polarization, immune cells function and inflammatory cytokines production become potential therapeutic options for the treatment of OA. For instance, further optimization of this capability can be achieved through precise control over their physicochemical attributes as well as incorporation into hydrogel networks, which enhances biocompatibility, minimizes nanoparticle aggregation, and

Table 2 Representative Nanotherapeutic Strategies Targeting Metabolism Pathogenesis in OA

Representative Nanomaterial	Delivery Modality	Loading Drug	Additional Intervention	OA Model	Target Cells/ Pathways	Mechanism	Potential Effects and Outcomes	Limitations	Ref.
SOD-NPs	Superoxide dismutase vesicles	SOD	–	DMM mouse model	Chondrocytes, ROS	Maintaining good SOD activity, reducing its degradation, allowing ROS to enter the polymer; reducing ROS oxidative stress and damaging to chondrocytes	Attenuates oxidative stress and cartilage matrix catabolism.	Restricted cartilage penetration, no large-animal validation, single enzyme cargo	[144]
PDA@CBP-PTH	Micro multifunctional polymer nanocapsules	PTH 1–34	–	ACLT rat model and DMM rat model	IL-6, MMP-13, iNOS, Col-2	Inhibiting the expression of inflammatory factors IL-6 and MMP-13 in cartilage, reducing the expression of iNOS in cartilage and subchondral bone, increasing the expression of Col-2 in cartilage and OCN in subchondral bone	Preserves cartilage structure and reduces subchondral bone damage.	Requires repeated intra-articular dosing, further validation in other OA models and larger animals, with uncertain long-term safety and joint distribution.	[148]
HA-SeNPs @AHAMA-HMs	Hyaluronic acid modified selenium nanoparticles	HA-SeNPs	–	DMM rat model	Chondrocytes, ROS	Clearing ROS, reducing oxidative stress in chondrocytes, improving mitochondrial function, inhibiting chondrocyte apoptosis	Delays cartilage degeneration and mitigates joint structural deterioration.	Requires injection, CD44-dependent, limited validation, selenium safety concerns.	[146]
ICA NPs-HG	Injectable self-healing hydrogel loaded PLGA nanoparticle	ICA	–	MIA-induced rat model	Chondrocytes; ROS; IL-1 β ; TNF- α ; MMP-13; collagen II; oxidative stress-related pathways	Forming a ROS/pH-responsive borate-crosslinked self-healing network, scavenging ROS synergistically with ICA-borate interactions, enabling ROS-triggered ICA release, and suppressing inflammatory cytokines and MMP-13 while preserving cartilage matrix integrity	Reduces cartilage degeneration and prolongs intra-articular therapeutic retention.	Shows rapid degradation, repeated injections, no large-animal validation	[151]
TP/siMMP-13	Local NP delivery	TEMPO	–	DMM mouse model	Chondrocytes; ROS; MMP-13; ROS-NF- κ B signaling axis	Scavenging ROS via TEMPO redox cycling with SOD/CAT-like activity, enabling siMMP-13 delivery and MMP-13 knockdown, thereby reducing inflammatory signaling and ECM degradation	Improves cartilage integrity and lowers OARSI scores.	Shows short retention, repeated dosing, limited validation	[145]
PLLA/LP	PLA-lignin nanofibers	Lignin	–	Rat cartilage defect model	BMSCs, COL2a1, ACAN, SOX9	Enhancing the antioxidant capacity of lignin, promoting the secretion of GAG by bone marrow mesenchymal cells, and upregulating the expression levels of COL2a1, ACAN, and SOX9 genes	Enhances cartilage regeneration and extracellular matrix formation.	Shows rat-only data, no targeting, limited validation	[156]
PDA-PEG NPs	Methoxypolyethylene glycol amine modified polydopamine nanoparticles	–	–	ACLT mouse model	Osteoclasts, NF- κ B, MAPK, PDGF-BB	Inhibiting NF- κ B and MAPK signaling pathways, inhibiting osteoclastogenesis, downregulating PDGF-BB	Attenuates subchondral bone degeneration and slows cartilage deterioration.	Shows limited IA validation, bone-focused, limited translation	[168]
SCT@AHAMA	Highly permeable micro/nano hydrogel microspheres	–	–	ACLT mouse model	Mononuclear macrophages, osteoclasts, chondrocytes, ROS	Clearing ROS from mononuclear macrophage mitochondria, inhibiting osteoclast differentiation and function, blocking early apoptosis of chondrocytes, and maintaining cartilage matrix synthesis and degradation	Alleviates cartilage degeneration and suppresses subchondral bone remodeling.	Shows murine-only data, unclear long-term biosafety	[174]

(Continued)

Table 2 (Continued).

Representative Nanomaterial	Delivery Modality	Loading Drug	Additional Intervention	OA Model	Target Cells/ Pathways	Mechanism	Potential Effects and Outcomes	Limitations	Ref.
MnO ₂ NPs	Manganese dioxide nanoparticles	–	–	IL-1 β -induced bovine cartilage explant model	ROS, IL-1 β , iNOS, MMP-1, MMP-13	Clearing ROS, downregulating IL-1 β , inhibiting iNOS expression in chondrocytes, and inhibiting MMP1 and MMP-13	Improves chondrocyte survival and preserves extracellular matrix.	Nos therapeutic validation in an in vivo OA model; long-term safety and dose window not established	[181]
CeNPs	Cerium oxide nanoparticles	Metformin	–	DMM rat model	Mitochondrion	Improving the mitochondrial oxidative stress microenvironment, activating autophagy by binding with metformin, and clearing mitochondria with persistent dysfunction	Maintains chondrocyte homeostasis and delays OA progression.	Complex fabrication; long-term cerium retention/toxicity and biodegradation need further evaluation	[175]
HA-PLL/PNIPAm	Cartilage-mitochondria cascade-targeted micro/nano composite hydrogel	NMN	Thermal stimuli ($\approx 32^{\circ}\text{C}$ LCST; in situ gelation upon warming to body temperature)	SD rat model	SOD, CAT, GPx, NAD, NADH, SASP	Enhancing the activity of antioxidant enzymes including SOD, CAT, and GPx, increasing the ratio of NAD to NADH, inhibiting the release of SASP factor, maintaining mitochondrial metabolic homeostasis, and inhibiting the degradation of cartilage matrix	Delays cartilage aging and reduces matrix degradation.	Falls in vivo protocol/details not available from abstract; hydrogel degradation and oxygen-release safety need long-term assessment	[182]
HKL-GECM @MPNPs	Genetically engineered chondrocyte-mimetic nanopatform	Honokiol		DMM mouse model and human OA cartilage explant	IL-1 β , SIRT3, Col-2, ACAN, MMP-13	Blocking IL-1 β , upregulating SIRT3 expression, increasing Col-2 and ACAN levels, reducing MMP-13 expression and secretion	Reduces cartilage degeneration and improves cartilage repair.	Complex biofabrication and scale-up; potential batch variability/immunogenicity of cell-membrane coating	[176]
HBPTG@OD	Nanocarriers engineered to respond to the osteoarthritic microenvironment	4-octyl itaconate and dexamethasone	–	DMM mouse model	M1 macrophages, iNOS, ROS	Clearing mitochondrial ROS, inhibiting iNOS expression, and reprogramming mitochondrial metabolism of M1 macrophages effectively repolarizes M1 macrophages into M2 phenotype	Delays OA progression and reduces joint inflammation.	Dual-drugs nanoparticle system; potential off-target uptake (glucan/TPP targeting) and long-term safety need further study	[180]
CZIF@Hb	Intra-articular injection	Hb	Ultrasound stimuli (1.0 MHz, 1.0 W/cm ² , 5 min)	DMM mouse model	Chondrocytes; SLC1A5/SLC38A2-GLUT1-GLS axis; glutamine metabolism	Enhancing oxygen delivery and mitochondrial metabolism; activating glutamine metabolic axis	Promotes hyaline cartilage formation and attenuates OA progression	Requires repeated IA injection and ultrasound; murine-only validation	[185]
MSC-Au-Steroid	Intraperitoneal injection	Au-Steroid	–	MIA-induced OA mouse model	Chondrocytes; immune cells	Upregulating DDIT4 to inhibit mTORC1, preserving mitochondrial integrity and reducing ROS; suppressing Th1/Th17 while inducing Treg-mediated immune tolerance	Preserves proteoglycan, reduces synovitis and osteophytes, lowers OARSI scores, and partially restores subchondral bone structure.	Shows murine-only evidence; needs long-term Au biodistribution/clearance and translational validation.	[184]

W/KGN@DSeD NPs	Intra-articular injection	DSeD prodrug	–	DMM mouse model	Chondrocytes; ROS-Nrf2	Cleaving diselenide bonds under ROS to release DIC, KGN, and Se; activating Nrf2 antioxidative signaling; enhancing cartilage targeting via collagen II binding	Prolongs intra-articular retention, preserves cartilage matrix, reduces osteophyte formation, alleviates pain, and attenuates OA progression	Requires repeated IA administration; murine-only validation; long-term safety and large-animal translation not established	[186]
RNPs	Rapamycin-PLGA nanoparticles	Rapamycin	–	DMM mouse model	MMP-13, Col-2, SOX9	Reducing the expression of MMP-13, a marker of chondrocyte catabolism, and increasing the expression of Col-2 and SOX9, markers of chondrocyte synthesis	Reduces cartilage degeneration, synovial inflammation, and joint pain.	Maies still require repeat injections; potential systemic immunosuppression risk from rapamycin needs monitoring	[193]
Cit-AuNRs @Anti-TRPV1	Citrate-stabilized gold nanorods were functionalized by conjugation with a TRPV1 monoclonal antibody.	–	Light stimuli (880 nm laser)	DMM mouse model	TRPV1, GPX4, Ncoa4, Cox2, 4HNE	Inhibiting chondrocyte degeneration, activating TRPV1, increasing GPX4 expression, and decreasing Ncoa4, Cox2, and 4HNE expression	Protects cartilage and slows joint degeneration.	Requires external irradiation; photothermal safety and long-term gold persistence/clearance remain concerns	[195]
Nano-PAZII	Nanoparticle-based sustained delivery of the VEGFR inhibitor pazopanib	Pazopanib	–	MIA-induced mouse model	Chondrocytes, VEGFR1, VEGFR2, IL-1 β	Blocking VEGFR1, inhibiting VEGFR2, inhibiting the NGF/TrkA signaling pathway, and blocking IL-1 β in chondrocytes	Relieves joint pain and attenuates cartilage degeneration.	VEGFRs blockade may have vascular/off-target risks; efficacy and safety need confirmation in large-animal/long-term studies	[197]
PCFMN	Nanosized amphiphilic polymer-drug conjugate	Formononetin	–	ACLT rat model	IL-6, TNF- α , IL-1 β , MMP-3, MMP-13	Inhibiting IL-6 and TNF- α , reducing the expression of IL-1 β , MMP-3, MMP-13, weakening oxidative stress, and promoting Col2a1	Improves cartilage integrity and reduces inflammatory damage.	Shows variable targeting, unclear dosing and safety	[171]
MAV-KGN	Charge-based cartilage targeting formulation of KGN by using a multi-arm cationic nano-construct of Avidin	KGN	–	OSM and IL-1 α -induced bovine cartilage explant model	MiR-146a, NRF2, FLNA, CBF β , RUNX1	Enhancing the inhibitory effect of KGN on miR-146a, upregulating NRF2 protein levels, reducing oxidative stress, and promoting FLNA, CBF β , and RUNX1	Reduces cartilage matrix loss and cell death.	Primaries ex vivo evidence; in vivo efficacy, durability, and immunogenicity need further evaluation	[203]
MgO@SiO ₂	Intra-articular injection	–	–	MIA-induced OA rat model	Chondrocytes; ROS; proinflammatory mediators	Extending intra-articular Mg ²⁺ release; suppressing ROS generation; downregulating IL-6, MMP-13, and COX-2 in cartilage	Alleviates cartilage degeneration and destruction, preserves articular surface integrity, reduces OARSI scores, and decreases cartilage ROS levels	Shows aggregation risk, short follow-up, limited translation	[211]

Abbreviations: SOD, Superoxide dismutase; CBP, Collagen-binding polypeptide; PTH, Parathyroid hormone; HA, Hyaluronic acid; PDA, Polydopamine; SCT, Conjugated carbon quantum dots with triphenylphosphine; AHAMA, Hyaluronic acid containing aldehydes and methacrylic anhydride; HKL, Honokiol; GEEM, Geotechnical engineering environmental control module; MPNPs, Magnetic polystyrene nanoparticles; HBPTG, Reactive oxygen species responsive nanocarriers; Cit-AuNRs, Citrate modified gold nanorods; Anti-TRPV1, TRPV1 antibody; Nano-PAZII, Nanoparticle based pazopanib formulation; PCFMN, Cartilage targeted polyethylene glycol mangiferin nanomedicine; MAV, Multi arm cationic avidin nanocarrier; KGN, Kartogenin (cartilage promoting and cartilage protective drug); HA-PLL, Hyaluronic acid–poly-L-lysine; PNIPAm, Poly(N-isopropylacrylamide); GAG, Glycosaminoglycan; COL2a1, Type II collagen alpha 1 chain gene; ACAN, Agglomerated proteoglycan gene; SOX9, SRY-related high-mobility group box 9; NF- κ B, Nuclear factor kappa B; MAPK, Mitogen activated protein kinase; PDGF-BB, Platelet derived growth factor BB; NAD, Nicotinamide adenine dinucleotide; NADH, Reduced nicotinamide adenine dinucleotide; IL-1 β , Interleukin-1 β ; SIRT3, Deacetylase 3; TRPV1, Key ion channels for pain and temperature perception; VEGFR1, Vascular endothelial growth factor receptor 1; VEGFR2, Vascular endothelial growth factor receptor 2; MMP-13, Matrix metalloproteinase 13; miR-146a, Key regulatory molecules in microRNAs; NRF2, Nuclear factor - related factor 2; SB, Subchondral bone; CAT, Catalase; GPx, Glutathione peroxidase; CBF β , Core binding factor β ; RUNX1, Runt-related transcription factor 1; IL-6, Interleukin-6; iNOS, Inducible nitric oxide synthase; Col-2, Type II collagen; OCN, Osteocalcin; BMSCs, Bone marrow mesenchymal stem cells; TNF- α , Tumor necrosis factor- α ; MMP-1, Matrix metalloproteinase 1; ECM, Extracellular matrix; SASP, Senescence-associated secretory phenotype; NGF, Nerve growth factor; TrkA, Tropomyosin receptor kinase A; MMP-3, Matrix metalloproteinase-3; GPX4, Glutathione peroxidase 4; Ncoa4, Nuclear receptor co activator 4; Cox2, Cyclooxygenase 2; 4HNE, 4-hydroxynonenal; PLGA, poly(lactic-co-glycolic acid); NP, nanoparticle; PLA, polylactic acid; OA, osteoarthritis; HA-SeNPs, hyaluronic acid-modified selenium nanoparticles; ICA, icariin; TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl; PDA-PEG NPs, polydopamine–polyethylene glycol nanoparticles; NMN, nicotinamide mononucleotide; DMM, destabilization of the medial meniscus; ACLT, anterior cruciate ligament transection; FLNA, filamin A; MIA, monosodium iodoacetate; ROS, reactive oxygen species; siMMP-13, small interfering RNA targeting matrix metalloproteinase 13; OARSI, Osteoarthritis Research Society International; CD44, cluster of differentiation 44; Nos, nitric oxide synthase; TPP, triphenylphosphonium.

facilitates injectability, thus supporting their tailored design for targeted therapeutic uses.^{219–221} This section highlights recent nanomedicine approaches that specifically target immunoinflammation in OA.

Nanotherapeutic Strategies Reprogramming Macrophage Polarization

Emerging evidence underscoring the critical role of the polarization process of macrophages towards the M1 and M2 phenotypes, which drives synovitis, matrix degradation, and impaired tissue repair.²²² Modulating this polarization represents a promising therapeutic strategy, and recent advances in nanotherapeutic offer innovative solutions.²¹⁹ Nanomaterials with tunable physicochemical properties can effectively reprogram macrophages toward an M2-dominant phenotype both *in vitro* and *in vivo*. This shift reduces M1-associated inflammatory mediators while enhancing M2-linked anti-inflammatory factors, thereby attenuating synovitis, protecting cartilage, and slowing OA progression.²²⁰ Mechanistically, these effects are achieved via modulation of transcription factors, key intracellular, signaling pathways and environmental signals.²²³ By leveraging such pathway-specific immunomodulation, nanomaterials not only suppress the inflammatory microenvironment but also foster a regenerative milieu, positioning nanotherapeutic strategies as targeted and effective strategies for OA management.^{219,220}

Accordingly, nanotherapeutic approaches to directly eliminate M1 macrophages or inhibit M1 polarization, thus reducing the secretion of harmful cytokines may be potential treatments for OA. In this regard, Li et al developed GelMA@FPPD, folate-functionalized micelles encapsulating dexamethasone for M1 macrophage targeting via folate receptor β in OA (Figure 8A). This *in situ* targeting system leads to inhibition of cytokine storm, induction of M1 apoptosis, and downregulation of cytokines such as IL-1 β and TNF- α . By mitigating synovial inflammation and protecting articular cartilage, GelMA@FPPD significantly attenuates OA progression *in vivo*.²²⁴ Besides, BRD4 is an epigenetic regulator that is highly expressed in OA cartilage and synovium, where it regulates macrophage polarization related signaling to promote inflammatory progression.²²⁵ Xu et al developed apoptosis-stimulated phosphatidylserine nanoliposomes loaded with the BRD4 inhibitor JQ1 (JQ1@PSLs), which specifically target synovial macrophages, inhibit M1 polarization, and thereby alleviate synovial inflammation and cartilage degradation in OA.²²⁶

Pro-inflammatory molecules, such as excess ROS and cell-free DNA (cfDNA), are major influencing factors in OA, which require regulation through effective clearance mechanisms. A high level of cfDNA in the articular cavity would recruit and activate immune cells, ultimately promoting the onset and progression of OA.²²⁹ Besides, ROS drives OA via chondrocyte damage, synovitis aggravation and chondrocyte aging, forming vicious pathological cycles.²³⁰ Based on this, Shi et al created polyethylenimine (PEI)-functionalized diselenide-bridged mesoporous silica nanoparticles (MSN-PEI) with possessing high nucleic acid binding and antioxidative properties. MSN-PEI reduced cfDNA levels and oxidative stress in the joint cavity and suppressed M1 macrophage polarization during OA progression.²³¹ In contrast to MSN-PEI, which relies on PEI-mediated cfDNA binding and diselenide-based ROS responsiveness, Singh et al developed a multifunctional “push-and-pull” nanotherapeutic system integrating drug delivery with dual scavenging of ROS and cfDNA within a single mesoporous ceria platform, modulating macrophage polarization, and targeting cartilage to effectively alleviate OA in rat models.²²⁷ The mesoporous ceria (mCNP) core provides broad-spectrum ROS elimination, while the polycationic PAMAM-G3 shell binds cfDNA and boosts cartilage retention. Additionally, mesopores allow pH-responsive dexamethasone release for anti-inflammatory “push” alongside ROS/cfDNA “pull”. This integrated system suppresses macrophage activation, protects chondrocytes, enhances joint retention and penetration, and improves OA therapy²²⁷ (Figure 8B).

Multiple intracellular signaling pathways, including PI3K/Akt/mTOR, MAPK, NF- κ B, JAK/STAT and hypoxia-dependent signaling, govern polarization between pro-inflammatory M1 and reparative M2 phenotypes.^{190,232} In regulating NF- κ B pathway, drug-loaded nanocarriers has gained increasing traction due to its combined antioxidant, metabolic-regulatory, and signal-modulatory properties.^{233,234} In particular, Zhang et al designed core-shell quercetin nanoformulations with improved aqueous stability and prolonged synovial retention, enabling sustained intra-articular activity. Their system effectively scavenged excessive ROS, reduced expression of IL-1 β and TNF- α , and reprogrammed synovial macrophages from M1 to M2, thereby reconstructing a pro-repair microenvironment rather than merely suppressing inflammation²³⁵ (Figure 9A–C). Sun et al further introduced G2-OH₂₄ phosphorus dendrimers co-delivering catalase (CAT) and quercetin. The co-delivery nanosystem strengthens intracellular antioxidant defense via upregulation of

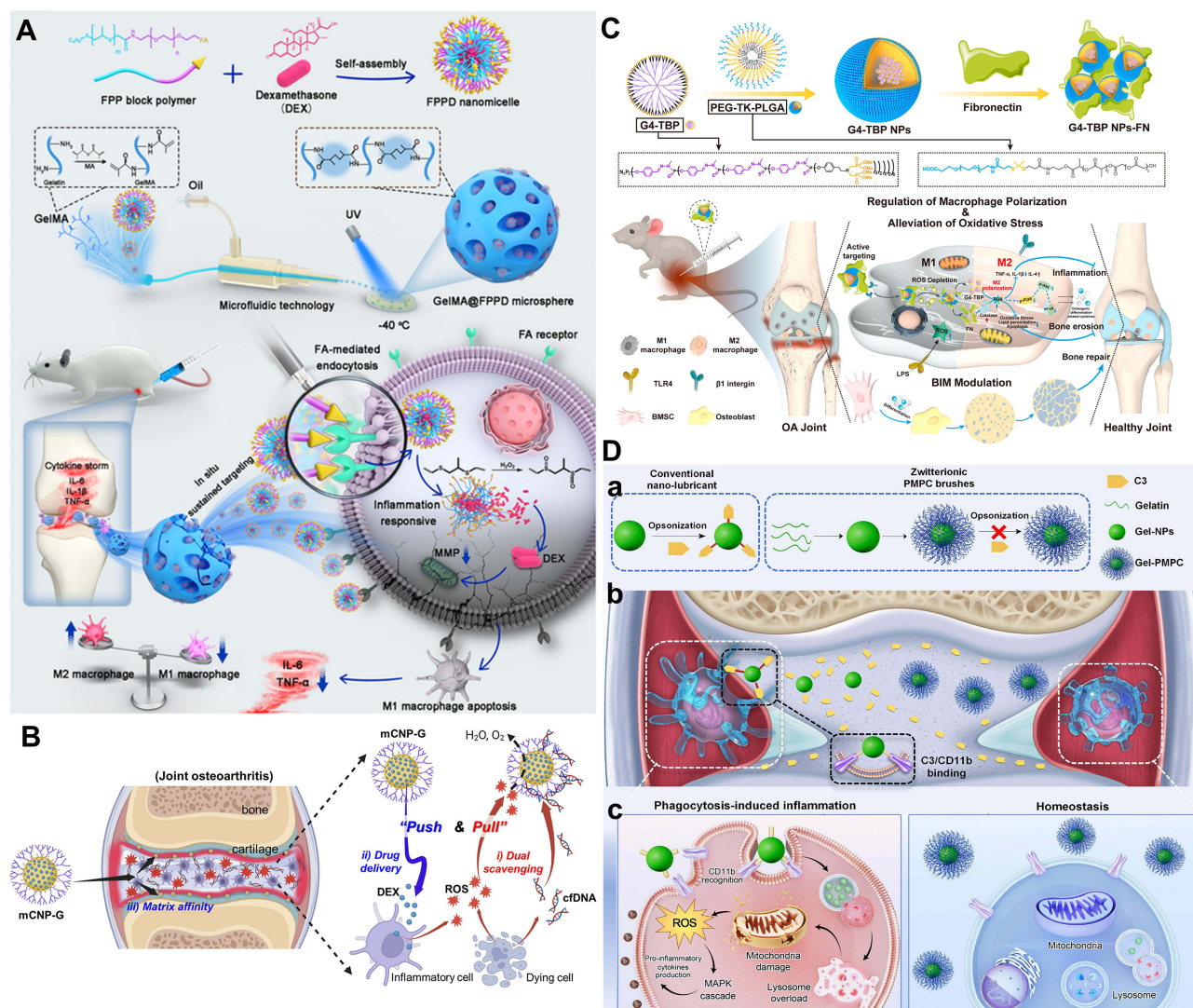


Figure 8 Nanotherapeutic strategies reprogramming macrophage activation and polarization. **(A)** Schematic diagram of nanomicelle-hydrogel microspheres (GelMA@FPPD) that sustainably target and regulate M1 macrophage, inhibit "cytokine storm", and alleviate OA. Reproduced from Li et al²²⁴ Copyright 2023, American Association for the Advancement of Science. **(B)** Schematic representation of the multifunctional therapeutic roles of mCNP-G through a "push-and-pull" action, involving (i) dual scavenging of ROS and cfDNA and (ii) delivery of an anti-inflammatory drug, as well as through (iii) high affinity for the cartilage matrix, enabling prolonged retention and tissue penetration. Reproduced from Singh et al²²⁷ Copyright 2025, American Chemical Society. **(C)** Preparation of G4-TBP NPs-FN for the combination treatment of OA via macrophage polarization, oxidative stress alleviation, and stem cell osteogenic differentiation. Reproduced from Zhan et al²²³ Copyright 2024, American Chemical Society. **(D)** Gel-PMPC evades synovial macrophage phagocytosis by inhibiting C3 adsorption. (a) C3 opsonization on conventional nano-lubricants initiates synovial macrophage phagocytosis within joint cavity, while Gel-PMPC can inhibit C3 opsonization on its surface. (b) Gel-PMPC evades synovial macrophage phagocytosis mediated by binding of C3 (on NPs) to CD11b (on synovial macrophages). (c) Excessive uptake of NPs by synovial macrophages leads to the harmful release of cytokines, inflammation, and progressive tissue injury, while Gel-PMPC maintains macrophage homeostasis by evading macrophage phagocytosis. Reproduced from Cai et al²²⁸ Copyright 2025, Wiley.

SOD and glutathione, while downregulating hypoxia-inducible factor (HIF-1α) and glycolysis-related proteins, promoting durable M2-skewed macrophage profiles and mitigating cartilage matrix loss in vivo.²³⁶ Building on these findings, Huang et al developed immunoglobulin G-conjugated bilirubin/JPH203 self-assembled nanoparticle (IgG/BRJ), which targets M1 macrophages and disassembles under oxidative stress. Released bilirubin and JPH203 scavenge ROS and inhibit inflammatory pathways, repolarizing macrophages to an M2 state²³⁷ (Figure 9D). Collectively, these studies highlight nanosystems as versatile immunoregulatory scaffolds that reshape synovial immune homeostasis through integrated metabolic and transcriptional reprogramming. However, its intrinsic hydrophobicity, rapid clearance, and

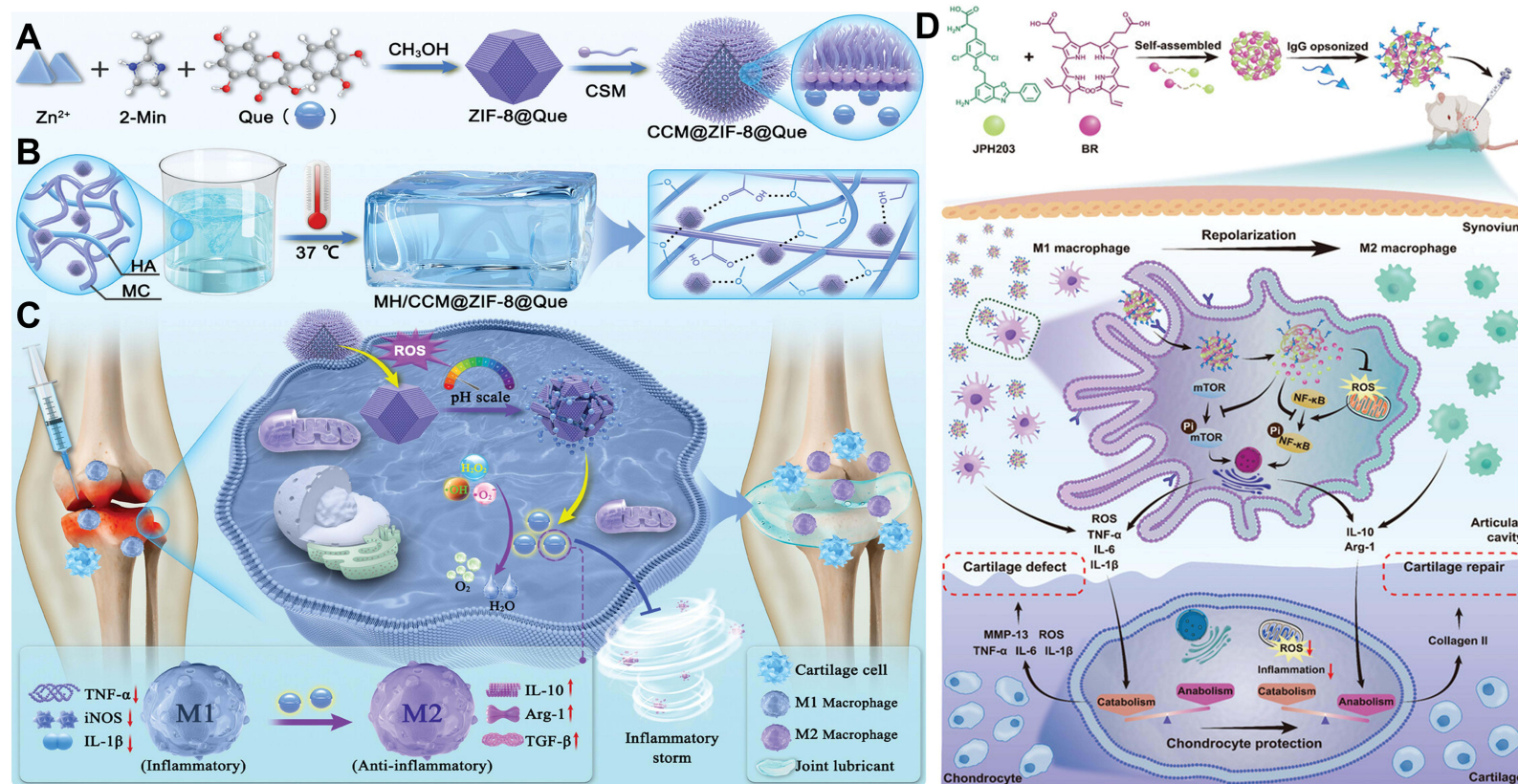


Figure 9 Drug loaded nanocarriers treat OA by modulating intracellular pathways and reprogramming macrophage polarization. **(A)** The preparation schematic diagram of CCM@ZIF-8@Que nanoparticles. **(B)** The structure diagram of MH/CSM@ZIF-8@Que hydrogel. **(C)** The mechanism of MH/CSM@ZIF-8@Que hydrogel promoting OA therapy. Reproduced from Zhang et al.²³⁵ Copyright 2025, Wiley. **(D)** Schematic illustration of the preparation and mechanism of opsonized bilirubin/JPH203 nanoparticles (IgG/BR) for osteoarthritis therapy. Reproduced from Huang et al.²³⁷ Copyright 2024, Wiley.

limited cartilage penetration necessitate optimized delivery platforms to achieve clinically actionable bioavailability and sustained therapeutic efficacy.

The hypoxic conditions within the joint can trigger an increase in HIF-1 α expression, influencing the equilibrium of macrophage polarization. Modulating this hypoxic microenvironment emerges as a crucial strategy for enhancing OA interventions.¹⁶⁰ In this regard, Zhou et al synthesized encapsulated S-methylisothiurea hemisulfate salt (SMT) and CAT ZIF-8 NPs to restrain HIF-1 α and recover macrophage mitochondrial dysfunction. The system relieves hypoxia by catalyzing H₂O₂ to O₂ and inhibiting NO production, suppresses HIF-1 α , restores mitochondrial function, reprograms metabolism, and shifts synovial macrophages from M1 to M2.²³⁸ Chen et al developed opsonization-based macrophage-targeting IgG/Fe-CV nanoparticles incorporating Chrysin and V-9302.²³⁹ This nanosystem targets M1 macrophages via IgG opsonization, inhibits HIF-1 α and GLUT1 to block aerobic glycolysis, suppresses glutamine uptake, thereby reprogramming M1 to M2 polarization, relieves hypoxia, and alleviates OA inflammation and cartilage damage.²³⁹

To enhance the specificity of nanomedicines targeting active inflammation in nanotherapeutic strategies, targeting ligands like folic acid, cartilage-targeting peptides, chitosan and hyaluronic acid,^{240,241} or biomimetic cell membrane coatings from macrophage, neutrophil and other immune cells, have been decorated on the surface of nanoparticles. Additionally, anti-inflammatory receptors and chemokine receptors on the membrane surface enable targeted inflammation, thereby mediating macrophage recruitment and reprogramming.²⁴² Protein-engineered nanoparticles can enhance the stability and therapeutic efficacy of intra-articular drug delivery.²⁴³ Due to M1/M2 synovial macrophages imbalance in OA pathophysiology, inhibiting aerobic glycolysis to promote the shift from M1 type to M2 type is a therapeutic strategy for OA. Macrophage-targeting IgG/Fe-CV nanoparticles were developed, which inhibited aerobic glycolysis and glutamine uptake in M1 macrophages, promoting their repolarization to the anti-inflammatory M2 phenotype.²³⁹ Besides, nanoparticles coated with fibronectin (FN) renders them to specifically target tumor cells to enhance the drug delivery efficiency.¹⁶⁶ To further enhance targeting specificity and immune microenvironment regulation in OA, Zhan et al developed ROS-responsive HOOC-PEG-TK-PLGA nanoparticles loaded with G4-TBP and subsequently modified their surface with FN. The G4-TBP NPs-FN nanosystem targets macrophage reprogramming via FN's RGD binding to macrophage β 1 integrin for specific uptake. ROS-responsive dissociation releases G4-TBP and FN, which scavenge ROS, alleviate hypoxia, inhibit NF- κ B/PI3K/Akt pathways, suppress M1 markers, and protect macrophages from apoptosis, thus driving M2 polarization efficiently²²³ (Figure 8C). Recently, nanozyme provides novel strategies for OA treatment by scavenging ROS and improving intra-articular delivery and retention.²⁴⁴ An injectable hydrogel containing ϵ -PLE/MnCoO nanoparticles with catalase-mimicking nanozyme activity designed by Wang et al alleviates OA by scavenging ROS, polarizing M1 to M2 macrophages, reducing inflammation, and promoting cartilage repair.²⁴⁵

Cell membrane-camouflaged biomimetic nanovesicles merge cell membrane properties with drug delivery to overcome poor bone targeting. These nanoparticles enhance biocompatibility, prolong circulation, and improve targeted delivery. Functionalized membrane modifications enable more precise therapy, making them ideal for treating bone-related conditions.²⁴⁶ In this regard, Cai et al developed a biomimetic nanoparticle formulation coated with macrophage cell membrane-derived functional proteins, enabling the particles to avoid recognition and phagocytosis by pro-inflammatory M1 macrophages. This immune-shielded delivery system prevented excessive macrophage activation, reduced overproduction of TNF- α and IL-6, and stabilized the synovial immune microenvironment by limiting feed-forward inflammatory amplification. In OA rat models, the biomimetic nanoparticles significantly alleviated synovitis and cartilage degeneration, illustrating that restraining inflammatory activation at the macrophage-ECM interface is a viable strategy for halting OA progression²²⁸ (Figure 8D). Additionally, dual-engineered macrophage-membrane nanoplatfrom (BS@MD) enables NF- κ B/BCL-2 blockade, while membrane receptors broadly neutralize SASP and promote M1 to M2 macrophage transition.⁶⁰ Moreover, Fu et al designed neutrophil membrane-coated nanoparticles loaded with siIL33 (NM-NP-siIL33). Based on the ability of IL-33 to induce chondrocyte senescence through p38 MAPK-mediated autophagy inhibition, NM-NP-siIL33 delivered siIL33 to OA tissues, thereby reducing cartilage degradation.²⁴⁷ In summary, protein-engineered and biomimetic nanoparticles offer a versatile platform for targeted OA therapy. By modulating the synovial immune microenvironment through metabolic reprogramming, ROS scavenging, or immune evasion, these systems effectively suppress inflammation and protect against cartilage degradation.

Recent studies have highlighted that the therapeutic effects of MSCs in OA are largely mediated through their secreted extracellular vesicles (EVs), which regulate synovial macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotype, thereby alleviating joint inflammation and cartilage degradation.²⁴⁸ For instance, hUCMSC-derived EVs have been shown to reduce m6A modification of NLRP3 mRNA by delivering miR-1208, which binds METTL3 and suppresses NLRP3 inflammasome activation. This pathway leads to decreased release of pro-inflammatory cytokines and reduced cartilage ECM degradation, thereby attenuating OA progression in vivo.²⁴⁹ Li et al discovered that extracellular vesicles from human umbilical cord mesenchymal stem cells (hUCMSC-EVs) may promote M2 macrophage polarization, exhibiting anti-inflammatory effects and immunomodulatory potential in OA progression by delivering key proteins and modulating miRNAs through the PI3K-Akt signaling pathway, thereby alleviating inflammation and cartilage degradation.²⁵⁰ EVs derived from BMSCs can alleviate cartilage damage, reduce osteophyte formation, and alleviate arthritis by inhibiting M1 macrophage production and promoting M2 macrophage production.²⁵¹ This shift from M1 to M2 macrophage predominance, documented in multiple independent studies including BMSC-EV animal models and MSC-EV immunomodulatory reviews, underpins the chondroprotective effect in OA.^{252,253}

Meanwhile, hydrogel-nanosheet combination therapies show great potential for OA treatment, exhibiting multi-target effects such as anti-inflammation, antioxidation, and cartilage regeneration, while also possessing high biocompatibility and minimally invasive delivery characteristics.²⁵⁴ For instance, Zhang et al developed an injectable hydrogel platform loaded with calcium boride nanosheets (CBN), CBN@GelDA hydrogel. It could continuously release H₂ in situ than CBN alone, inhibiting scavenger excessive ROS to repolarize macrophages from M1 to M2 as well as reducing inflammatory expression, thus alleviating OA progression.²⁵⁵ Additionally, Zhao et al designed an injectable chitosan-based hydrogel (L-MNS-CMDA) loaded with MnO₂ nanosheets. It offers mechanical support, tissue adhesion, scavenges H₂O₂ to relieve oxidative stress, and shifts macrophages from pro-inflammatory M1 to regenerative M2 phenotype, creating an immune-friendly environment. Consequently, it reduces early inflammation and significantly enhances cartilage regeneration and joint function in rat model, demonstrating strong clinical potential.²⁵⁶ Hence, hydrogel-nanosheet systems represent a promising and multifunctional strategy for OA therapy, enabling synergistic anti-inflammatory, antioxidant, and chondroprotective effects.²⁵⁷

In conclusion, the application of nanotherapeutic strategies in regulating macrophage polarization represents a promising and rapidly evolving approach for OA treatment. By modulating the synovial immune microenvironment via altering material properties such as surface modification of nanoparticles and hydrogel-nanosheet combination, these nanosystems effectively suppress inflammation and protect against cartilage degradation.

Nanotherapeutic Strategies Modulating Immune Cell Functions

Dysregulated activation of immune cells in the pathogenesis of OA causes spanning polarized phenotypes, metabolic reprogramming, and inflammatory cell death, promoting synovitis, cartilage degradation, and joint destruction.²⁵⁸ Modulating these multifaceted immune cell functions represents a promising therapeutic frontier, and recent advances in nanotherapeutics offer increasingly superior strategies to achieve this goal.²¹⁹ By leveraging biomimetic designs, metabolic interventions, and precision targeting, these nanotherapeutic strategies aim to convert pro-inflammatory immune cells from drivers of tissue destruction into promoters of resolution and repair.

M2 macrophages can secrete anti-inflammatory factors. However, they also present low-expression of some pro-inflammatory cytokines and induce cartilage damage by expressing some MMPs.²⁵⁹ On-demand M2 mimics have therefore been engineered. Ma et al developed artificial M2 macrophages (AM2M) composed of macrophage membrane as “shell” and inflammatory response nanogel as “yolk”. The nanogel was prepared by physical interaction between gelatin and chondroitin sulfate (ChS) through ionic and hydrogen bonds. ChS was used to simulate the beneficial secretion of M2 macrophages in OA therapy to improve the treatment of OA. Artificial M2 macrophages can reside in inflamed areas for a long time, downregulate inflammation, and are continuously released to repair cartilage when there is low inflammatory activity.²⁶⁰ Consistently, Tong et al exploited the same ChS-based NPs for the bioencapsulation of FGF18, which not only suppressed IL-1 β -induced chondrocyte inflammation, but also promoted M2 macrophage polarization while inhibiting M1 activation, further emphasizing the therapeutic value of ChS-based immunomodulatory delivery systems in OA²⁶¹ (Figure 10A). Considering the potential uptake by macrophages and lack of targeting in the

circulation by conventional drug delivery, Xue et al fused erythrocyte membranes and neutrophil membranes on a hollow copper sulfide surface to provide a promising platform (D-CuS@NR NPs) for inflammation-associated diseases. This biomimetic nanoparticle possesses excellent photothermal conversion capacity and controlled drug release behavior.²⁶²

Metabolic dysregulation drives low-grade inflammation in OA by coordinating inflammatory and redox pathways in macrophages.²¹⁶ The metabolism-inflammation crosstalk in chondrocytes also highlights metabolic modulators as promising therapeutic targets for OA.²⁶⁶ Based on the fact that lipid-metabolic rewiring can switch macrophage fate, Deng et al developed a self-assembling nanoparticle (LCF-CSBN) targeting M1 macrophages via CD44, releasing licoferone to reprogram Golgi-associated lipid metabolism, driving pro-inflammatory M1 macrophages toward an anti-inflammatory M2 phenotype. The study demonstrated that reprogramming sphingolipid and arachidonic acid metabolism can promote macrophage transition, highlighting metabolic remodeling as another viable strategy for restoring synovial homeostasis in OA²⁶³ (Figure 10B). Meanwhile, OA synovial macrophages undergo gasdermin D-dependent pyroptosis, inhibiting mitophagy, triggering mtDNA release, and activating the inflammatory pathway.²⁶⁷ Moving beyond polymeric platforms, nanogel-based strategy KZIF@HA has recently been engineered to finely tune macrophage phenotypes through microenvironment-responsive ion flux and metabolic remodeling, providing a next-generation strategy for achieving precise and durable immune homeostasis in OA therapy.²⁶⁸ Qi et al engineered MMP9-targeted RAPA@MPB-MMP9 NPs, integrating ROS-scavenging MPB NPs, mTORC1 inhibitor rapamycin and macrophage-targeting peptides. These NPs suppressed synovial macrophage pyroptosis, promoted mitophagy, inhibited cGAS-STING pathway, alleviated FLS senescence, and protected cartilage in CIOA mice with good biosafety.²⁶⁷

Additionally, recent research has proved the crucial contribution of NK cells in OA progression, including identify and eliminate senescent chondrocytes and synovial cells within the joint.^{269,270} Zhang et al developed photoactivatable exosomolytics which recruit NK cells upon light activation, enhance their grip on senescent cells, and activate the cGAS-STING pathway, effectively clearing senescent cells in OA mice, suppressing inflammation, and remodeling the immune microenvironment²⁶⁴ (Figure 10C and D). Besides, T cells participate in the adaptive immune response to OA, driving inflammation and cartilage destruction through pro-inflammatory subsets. Treg function leads to immune imbalance, collectively propelling disease progression.²⁷¹ A new strategy includes immunomodulatory nanoparticles loaded with collagen II and rapamycin. In OA mice, these nanoparticle induced antigen-specific anti-inflammatory Treg cells, shifted cytokine balance towards anti-inflammation, and reduced joint inflammation, ultimately protecting cartilage and alleviating pain. The approach presents a promising targeted strategy²⁶⁵ (Figure 10E).

By forming biomimetic cell membrane, participating metabolic progression, and ablating hyperactive M1 cells, or replacing them with self-regulated M2 surrogates, nanotherapeutic strategies convert immune cells function from cartilage destruction to joint protection. The convergence of multiple systems provides a multifunctional immunomodulatory approach capable of long-term suppression of synovial inflammation without immune compromise.

Nanotherapeutic Strategies Neutralizing Pro-Inflammatory Cytokines

Pro-inflammatory cytokines, particularly IL-1 β , TNF, and IL-6, are key drivers of OA pathology.²⁷² Produced by chondrocytes, synovial macrophages, and osteoblasts, these cytokines orchestrate a destructive cascade: upregulating MMPs and prostaglandins, suppressing collagen synthesis, and driving cartilage degradation alongside subchondral bone resorption.⁹¹ Conventional systemic biologics targeting these cytokines face significant limitations, including immunosuppression, infection risk, and poor joint penetration.⁹⁴ Nanotherapeutic strategies including nanogels,^{92,273} exosomes²⁷⁴ and functionalized nanoparticles²⁷⁵ now function as intra-articular cytokine traps, sequestering pro-inflammatory mediators, blocking inflammatory cascades, and protecting cartilage ECM while enhancing local drug efficacy through targeted delivery.⁹⁴

Recent advances have focused on composite nanosystems that integrate multiple functionalities into a single platform, simultaneously reducing cytokine burden, modulating immune cell activity, and enabling controlled drug release.²⁷⁶ Building upon the success of ozone therapy in OA,²⁷⁷ Wu et al⁹² fabricated an injectable thermo-responsive hydrogel loaded with an ozone-rich nanocomposite and D-mannose (O₃NPs@MHPCH). This system decreases IL-1 β , IL-6, TNF- α , and iNOS levels while alleviating synovial inflammation, cartilage destruction, and subchondral bone remodeling. Meanwhile, Yang et al²⁴⁰ developed CPHs, a peptide dendrimer nanogel loaded with CORM-401 and coated with FA-

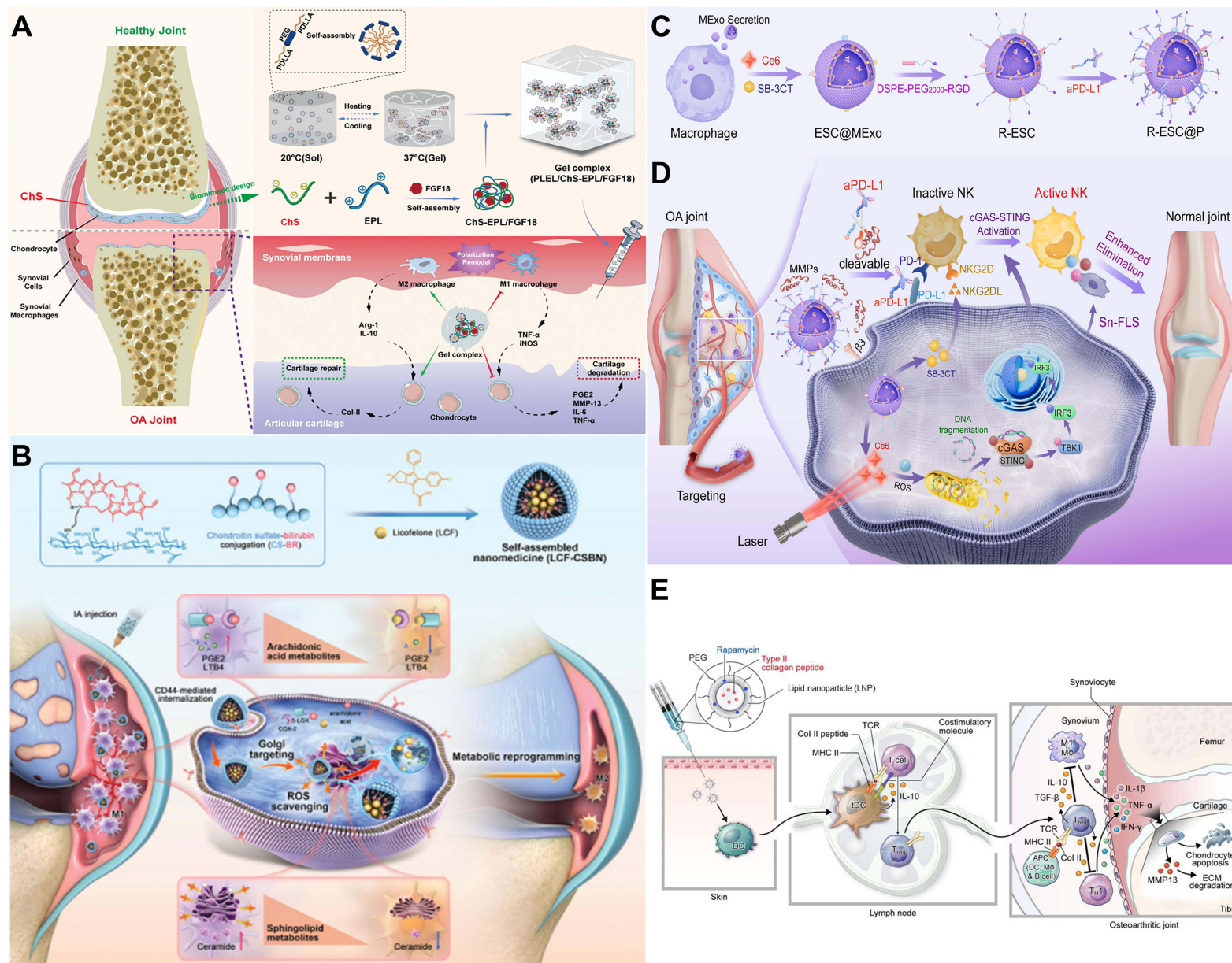


Figure 10 Nanotherapeutic strategies modulating immune cell functions. **(A)** Schematic diagram demonstrating the construction and use of a bionic thermosensitive sustainable delivery system for remodeling the anti-inflammatory and immunomodulatory microenvironment in OA. Reproduced from Tong et al.²⁶¹ Copyright 2024, Wiley. **(B)** Schematic representation of LCF-CSBN targeting the Golgi apparatus in M1 macrophages and promoting M1 macrophages to M2 phenotype by reprogramming sphingolipid and arachidonic acid metabolism. Reproduced from Deng et al.²⁶³ Copyright 2025, Wiley. **(C and D)** Photoactivatable exosensolytics activate natural killer cells for delaying osteoarthritis via activation of cGAS/STING pathways. **(C)** Schematic illustration of the design and biological function of exosensolytics (R-ESC@P). **(D)** Following intravenous injection, exosensolytics exhibit a remarkable ability to home in the synovitis site of OA joints, responding to elevated inflammatory factors in the OA microenvironment. Upon reaching the synovium, the aPD-L1 antibody is released through the cleavage of matrix metalloproteinase-9 (MMP-9), which is overexpressed in the OA synovial microenvironment. The remaining exosensolytics selectively accumulate in Sn-FLS by targeting integrin $\alpha\beta3$, enabling real-time visualization of OA joints through in vivo imaging. Subsequent activation of photodynamic therapy (PDT) induces the recruitment of NK cells to the synovium. Exosensolytics enhance the gripping effect of NK cells on Sn-FLS by blocking the aPD-L1-PD-L1 immune checkpoint pathway, thereby preventing immune evasion of senescent cells. Additionally, the release of SB-3CT further activates NK cells by inhibiting the shedding of soluble NKG2D ligands, such as MICA and ULBP1, which are critical for NK cell recognition and targeting of senescent cells. Through these mechanisms, exosensolytics promote a cGAS-mediated inflammatory response in NK cells, enhancing their ability to eliminate senescent cells for delaying OA. Reproduced from Zhang et al.²⁶⁴ Copyright 2025, American Chemical Society. **(E)** Intradermal injection of LNP-Col II-R to OA mice would induce Col II-specific Tregs. The Tregs in the synovium would inhibit M1 macrophages and TH1 cells, both of which express inflammatory cytokines (eg, TNF- α , IFN- γ , and IL-1 β) and inhibit chondrocyte apoptosis and matrix destruction in the OA articular cartilage. Reproduced from Sohn et al.²⁶⁵ Copyright 2022, American Association for the Advancement of Science.

HA, targeting activated macrophages to deplete ROS and trigger CO release, effectively suppressing pro-inflammatory cytokines and cartilage degradation through integrated oxidative stress and inflammatory modulation.

Immunoregulatory MSC-derived exosomes have emerged as potent cytokine modulators with intrinsic anti-inflammatory properties.²⁷⁸ Deer antler adipose-derived stem cell exosomes (ASC-Exos) enriched in miR-140 effectively suppress IL-6 and TNF- α secretion from OA chondrocytes while simultaneously inhibiting MMP13-mediated collagen degradation through the miR-140/MMP13 axis.²⁷⁹ Similarly, embryonic MSC-derived exosomes preserve chondrocyte phenotype by promoting collagen II synthesis and suppressing ADAMTS5 expression, creating a dual mechanism that both neutralizes inflammatory signals and prevents matrix breakdown.²⁷⁸ However, clinical translation of exosome-based therapies remains challenged by uncontrolled cargo release, uneven in situ distribution, and limited persistence.^{280–282} To address these limitations, innovative strategies integrate immunoregulatory exosomes with 3D bioprinted hydrogel scaffolds (3D-BPH-Exos), enhancing stability and enabling targeted delivery to chondrocytes and cartilage tissue.²⁷⁴ This approach reduces IL-1 β , TNF- α , and IFN- γ release while preventing chondrocyte apoptosis, offering improved therapeutic outcomes through sustained, localized cytokine neutralization.²⁷⁴

Collectively, these nano-platforms break the inflammatory cycle in OA by neutralizing pro-inflammatory cytokines from exosome-based modulation to smart hydrogel-enabled sustained release. Future designs should combine biologics with multi-responsive hydrogels for personalized, long-acting therapy capable of adapting to the evolving inflammatory microenvironment. Table 3 summarizes representative nanotherapeutic strategies targeting inflammation pathogenesis in OA.

Conclusion and Perspectives

OA represents a paradigm shift from passive “wear-and-tear” degeneration to an active, multifactorial joint failure syndrome orchestrated by the pathological triad of cellular senescence, metabolic dysregulation, and chronic inflammation.^{130,283} Conventional therapies remain largely palliative, offering symptomatic relief and often accompanied by significant adverse effects,^{284,285} necessitating disease-modifying interventions that target these interconnected mechanisms.^{286–288} Nanotherapeutic strategies have emerged as a transformative model, leveraging tailorable surface chemistry, cartilage-penetrating dimensions, and stimuli-responsive cargo release to achieve spatiotemporally controlled drug delivery within the joint microenvironment.^{286,289–291} Besides, nanomaterials can be engineered to actively modulate key cellular processes, including inflammation, autophagy, and apoptosis, thereby supporting chondrocyte survival and matrix preservation. Expanding material interfaces with multiple immune cell populations may further refine local immune regulation. As delineated in this review, nano-enabled platforms demonstrate multimodal efficacy: senolytic delivery coupled with mitochondrial repair and autophagy activation rejuvenates the aging chondrocyte population,^{8,292} ROS-scavenging nanozymes and metabolic modulators restore redox homeostasis and bioenergetic balance,²⁹³ immunoregulatory nanoparticles reprogram synovial macrophages from pro-inflammatory M1 to reparative M2 phenotypes, thereby disrupting the inflammatory feed-forward loop.^{221,223} The convergence of these models positions nanomedicine not merely as a delivery vehicle, but as an active modulator of joint pathobiology. A systematic comparison of representative nanotherapeutic strategies for OA drug delivery is presented in Table 4, focusing on their delivery mechanisms, effects, and practical feasibility, and providing a clear overview of current strategies and design features.

Recent integration of nanotherapeutics with 3D and 4D printing represents a significant frontier in structural repair.^{294,295} 3D-printed scaffolds with customizable architecture and tunable mechanical properties offer superior recapitulation of native extracellular matrix, while nanocarrier incorporation enables spatially controlled drug release.^{296–298} 4D printing further introduces dynamic responsiveness to environmental triggers, creating microenvironment-adaptive interventions.²⁹⁹ Despite these advances, clinical translation requires coordinated progress across several areas. First, enhancing targeting precision and biosafety remains essential. Rational surface engineering and physico-chemical optimization should achieve high cartilage specificity while minimizing off-target distribution and long-term toxicity. Second, predictive preclinical models are urgently needed. Joint organoid systems and advanced animal models that better recapitulate human OA pathology would provide more accurate evaluation of nanoparticle efficacy, biodistribution, and safety. Third, metabolic and immunological insights should inform nanoformulation design. Multi-targeted

Table 3 Representative Nanotherapeutic Strategies Targeting Inflammation Pathogenesis in OA

Representative Materials	Delivery Modality	Loading Drug	Additional Intervention	OA model	Target Cells/ Pathways	Mechanism	Potential Effects and Outcomes	Limitations	Ref.
GelMA@FPPD	M1 macrophage-targeted micro/nano drug delivery system	Dexamethasone	H-nuclear magnetic resonance	MIA-induced rat model	M1 macrophages, IL-1, IL-6, TNF- α	Promoting M1 macrophage apoptosis, inhibiting M1 polarization, downregulating TNF- α , IL-1, and IL-6	Inhibits the vicious cycle of cytokine storm, protects inflamed joint cartilage, and alleviates OA	Lacks of other OA subtype models, long-term experimental data, and clinical translation studies, failure to thoroughly elucidate molecular mechanisms, failure to explore the efficacy of combination therapy, and failure to clarify the optimal dosing regimen and long-term cumulative toxicity	[224]
MSN-PEI	Polyethylenimine functionalized diselenide-bridged mesoporous silica nanoparticles	–	–	DMM mouse model and CIOA rat model	M1 macrophages, cfDNA	Inhibiting M1 polarization of macrophages, alleviating oxidative stress, and suppressing inflammation caused by cfDNA	Inhibits inflammation and oxidative stress in the joint cavity, alleviates the onset and progression of OA	Lacks of data from primate experiments and human clinical trials, short experimental cycles, lacks of exploration of drug combination therapy, failure to cover multiple subtypes of OA, and failure to consider the impact of joint physiological microenvironment	[231]
mCNP-G	Polycationic-functionalized mesoporous ceria nanoparticle	Dexamethasone sodium phosphate	–	CFA-induced rat model	TNF- α , MMP-13, iNOS, IL-6, IL1 β , COX2, COL2A1, SOX-9	Reducing TNF- α release, downregulating MMP-13 expression, iNOS, IL6, IL1 β , and COX2, upregulating COL2A1 and SOX-9, and inhibiting macrophage inflammatory signaling	Relieves symptoms of OA and tissue damage, restores cartilage structure, and prevents subchondral bone destruction	Lacks of weight-bearing joint and large animal experimental data, short experimental period, unoptimized dosing regimen, and failure to cover multiple subtypes of OA	[227]
JQ1@PSLs	Phosphatidylserine-containing nanoliposomes	JQ1	–	ACLT mouse model	M1 macrophages, BRD4, TRPA1	Inhibiting BRD4 in macrophages, suppressing TRPA1 expression, and inhibiting M1 macrophage polarization	Relieves synovitis and joint pain, slows down cartilage degradation, and reprograms inflammatory macrophages	Lacks of large-scale animal models and human clinical trial data, failure to cover primary OA subtypes, and lack of optimized dosing regimens	[226]
MH/CCM@ZIF-8@Que	Injectable nanocomposite hydrogel	Quercetin	–	MIA-induced rat model	Synovial macrophages, ROS, IL-1 β , TNF- α	Clearing ROS, reducing the expression of IL-1 β and TNF- α , and reprogramming synovial macrophages from M1 to M2	Reduces synovial joint inflammation, inhibits cartilage degeneration, and promotes the repair of OA	Lacks of data from large animal experiments and human clinical trials, coverage of multiple OA subtypes, shallow interpretation of molecular mechanisms, and insufficient consideration of the impact of joint physiological microenvironment on hydrogel action	[235]
G2-OH24 /CAT@Que	Phosphorus dendrimers	Catalase, quercetin	–	MIA-induced mouse model	BMSCs, macrophages, HIF-1 α , MMP, ROS	Inhibiting the expression of HIF-1 α , enhancing MMP, clearing ROS, restoring mitochondrial function, promoting M2 polarization of macrophages, promoting chondrogenic growth and osteogenic differentiation of BMSCs	Relieves oxidative stress, inhibits synovitis, restores metabolic and synthetic balance of inflamed articular cartilage matrix	Lacks of large-scale animal experiments and comprehensive human clinical trial data, failure to cover multiple subtypes of OA, and insufficient exploration of downstream molecular signaling pathways	[236]

L-MNS-CMDA	Grafting vinyl and catechol groups onto chitosan macromolecule loaded MnO ₂ hydrogel	–	Magnetic stirring at 1200 rpm/min	Rat knee joint cartilage defect model	Macrophages, rBMSCs, ROS, HIF-1 α , NF- κ B	Clearing ROS, inhibiting M1 macrophage polarization, promoting M2 polarization, inducing rBMSCs cartilage differentiation, upregulating GAG and Col-2 expression	Relieves cellular oxidative stress caused by long-term hypoxia, thereby rebuilding an immune friendly microenvironment to ultimately enhance cartilage regeneration	Lacks of multiple OA subtype models and large animal experimental data, insufficient exploration of downstream molecular signaling pathways, and failure to consider individual patient differences	[256]
IgG/BRJ	Immunoglobulin G-conjugated bilirubin/JPH203 self-assembled nanoparticle	Bilirubin, JPH203	Magnetic stirrer (250 rpm)	ACLT rat model	Macrophages, ROS, NF- κ B, mTOR	Promoting the repolarization of macrophages from pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype, clearing ROS, and inhibiting NF- κ B and mTOR pathways	Promotes macrophage polarization, protects chondrocytes, and facilitates cartilage repair	Lacks of primary OA subtype models and large animal experimental data, and insufficient exploration of downstream molecular mechanisms associated with TCA cycle and macrophage polarization	[237]
ZIF-8 NPs	Zeolitic imidazolate framework-8 nanoparticles	Catalase, S-Methylisothiourea hemisulfate	–	ACLT mouse model	Macrophages, HIF-1 α , COL10A, RUNX2, MMP-13, COL2A1, aggrecan	Inhibiting the expression of HIF-1 α , COL10A, RUNX2, and MMP-13, promoting the gene expression of COL2A1 and aggrecan, and facilitating the transition of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype	Inhibits macrophage CM induced chondrocyte hypertrophy and slows down cartilage degeneration	Lacks of primary OA subtype models and large animal experimental data, insufficient exploration of the association mechanism between MAPK/NF- κ B pathway and metabolic reprogramming, and failure to consider individual differences among patients	[238]
CBN@GelDA	Calcium boride nanosheets loaded hydrogel platform	–	–	MIA-induced rat model	Macrophages, IL-1 β , TNF- α , IL-6, IL-10	Promoting macrophage polarization from M1 to M2, inhibiting the secretion of IL-1 β , TNF- α , and IL-6, and upregulating the expression of IL-10	Removes excessive ROS, alleviates OA, and reduces degeneration of articular cartilage	Lacks of primary OA subtype models and large animal experimental data, and failure to evaluate the long-term accumulation effects of CBN degradation products	[255]
HOOC-PEG-TK-PLGA	NPs of amphiphilic block copolymer poly(ethylene glycol)-thioketal-poly (lactic-co-glycolic acid)	Fourth-generation azabisis (dimethylphosphonate)-modified phosphorus dendrimer, fibronectin	–	MIA-induced mouse model	Macrophages, MMP-13, TNF- α , IL-1 β , ROS	Clearing ROS, promoting macrophage polarization, downregulating MMP-13, TNF- α , and IL-1 β	Inhibits cartilage matrix degradation, promotes cartilage repair through BMSC recruitment and bone differentiation	Lacks of primary OA subtype models and large animal experimental data, insufficient exploration of downstream molecular signaling pathways for the synergistic regulation of BIM and BMSC osteogenic differentiation by FN and G4-TBP, and lacks of optimized dosing regimens	[223]
Gel-PMPC	Zwitterionic poly (2-methacryloyloxyethyl phosphorylcholine) grafted as a brush layer on gelatin NPs	–	ALV light (wavelength 632.8 nm)	ACLT rat model	Macrophages, IL-1 β , IL-6, TNF- α , ROS, MAPK	Inhibiting the secretion of IL-1 β , IL-6, and TNF- α , preventing ROS production, mitochondrial damage, and upregulation of MAPK signaling pathway, and avoiding M1 polarization of macrophages	Avoids phagocytosis of synovial macrophages and prevents the release of harmful cytokines in the OA microenvironment	Lacks of primary OA subtype models and large animal experimental data, and insufficient exploration of the molecular details of PMPC inhibition of C3 adsorption and the quantitative correlation between gelatin core softening and immune escape	[228]
ϵ -PLE/MnCoO	HA and peroxidase-mimetic nanoenzyme-enhanced hydrogel, containing ϵ -polylysine/Mn _{1.8} Co _{1.2} O ₄ nanoparticles	ϵ -polylysine/manganese cobalt oxide	–	Rat medial collateral ligament transection model	Macrophages, MMP-13, TNF- α , IL-1 β , iNOS, Col-2, SOX-9	Eliminating ROS, promoting macrophage polarization, reducing the expression of MMP-13, TNF- α , IL-1 β , and iNOS, and promoting the expression of Col-2 and SOX-9	Reduces oxidative stress and induces differentiation from M1 phenotype to M2 phenotype	Lacks of primary OA subtype models and large animal experimental data, insufficient exploration of molecular mechanisms related to macrophage polarization	[245]

(Continued)

Table 3 (Continued).

Representative Materials	Delivery Modality	Loading Drug	Additional Intervention	OA model	Target Cells/ Pathways	Mechanism	Potential Effects and Outcomes	Limitations	Ref.
hUCMSCs-EVs	Small extracellular vesicles derived from human bone marrow mesenchymal stem cells	–	–	ACLT rat model	Macrophages, chondrocytes, PI3K-Akt signaling pathway	Promoting macrophage M1 polarization, upregulate IL-10 and IL-4, downregulating TNF - α , IL-1 β , and IL-6, inhibiting MMP-13 and TNF - α expression, upregulating SOX9, ACAN, and Col-2	Reduces synovitis and cartilage degeneration, protects cartilage	Lacks of primary OA subtype models and large animal experimental data, and unclear details on the independent functions and synergistic effects of a single miRNA/protein	[250]
RAPA@MPB-MMP9 NPs	Surface modified MMP9 targeted peptide loaded rapamycin mesoporous prussian blue nanoparticles	Rapamycin	–	CIOA mouse model	M1 synovial macrophages, FLS	Clearing ROS, promoting macrophage mitochondrial autophagy, reducing mitochondrial DNA release, decreasing IL-1 β and IL-18 secretion, and reducing MMP3 and MMP13 release	Reduces synovial hyperplasia and inflammatory cell infiltration, improves cartilage integrity, thereby slowing down the progression of OA.	Lacks of primary OA subtype models and large animal experimental data, unclear tissue specificity of MMP9 targeting peptides and direct causal relationship between mtDNA and cGAS STING pathway	[267]
R-ESC@P	Microphage-derived exosomes	Ce6, SB-3CT	Laser irradiation (633 nm, 5 J/cm ²)	DMM mouse model	NK cells, PD-1/PD-L1 pathway	Blocking the PD-1/PD-L1 pathway promotes the secretion of cytokines such as IFN- β by NK cells	Reduces synovial inflammation, protects cartilage integrity, and improves OA	Dependents on laser irradiation activation, limits clinical application, unclear whether it enhances CD8 ⁺ T cell-mediated clearance of senescent cells	[264]
TLNPs	Lipid nanoparticles	Rapamycin, Col-2	Magnetic activation cell sorting and separation of T cells	DMM mouse model	Dendritic cells, M1 macrophages	Inducing secretion of IL-10 and TGF - β , inhibiting M1 macrophage infiltration, reducing the release of IFN - γ , IL-1 β , TNF - α , decreasing MMP13 expression, inhibiting cartilage matrix degradation, and reducing chondrocyte apoptosis	Inhibits chondrocyte apoptosis and cartilage matrix degradation, alleviates OA	Only targets Col-2 specific immune response and limits applicable population, not covering primary OA subtypes, and not optimizing dosing regimen	[265]
D-CuS@NR NPs	Neutrophil-erythrocyte hybrid membrane-coated hollow copper sulfide nanoparticles	Dexamethasone sodium phosphate	NIR laser (1064nm)	ACLT mouse model	M1 macrophages, TNF- α , IL-1 β , IL-6	Inhibiting the secretion of pro-inflammatory cytokines by M1 macrophages, alleviating synovial inflammation, and reducing cartilage matrix degradation	Reduces cartilage matrix degradation, protects cartilage integrity, and alleviates OA	Dependents on 1064 nm NIR laser irradiation to limit clinical application scenarios, not covering primary OA subtypes	[262]
LCF-CSBN	Self-assembling, licofelone-loaded nanoparticle	Licofelone	–	MIA-induced rat model	M1 macrophages	Reducing oxidative stress in the high matrix of M1 macrophages and promoting lipid metabolism rearrangement from M1 macrophages to M2 phenotype	Reprograms synovial M1 macrophages for lipid metabolism in OA, inhibits synovitis and reduces cartilage degradation	Lacks of large animal and human clinical trial data, failure to cover primary OA subtypes, and insufficient precision in macrophage subtype classification	[263]
AM2M	Artificial M2 macrophage with yolk-shell structure	Chondroitin Sulfate	–	Papain-induced mouse model	Synovial macrophages, NF- κ B pathway	Blocking the immune stimulation of macrophages by chondroitin sulfate, reducing ROS and pro-inflammatory cytokine production, promoting cartilage repair while inhibiting inflammation rebound.	Inhibits chondrocyte apoptosis and joint surface erosion, alleviates OA	The mechanism for regulating the release ratio of ChS dual load is unclear and does not cover other subtypes of OA	[260]

PLEL/ChS-EPL/FGF18	Integration of chitosan based nanoparticles into poly (D, L-lactide) - poly (ethylene glycol) - poly (D, L-lactide) hydrogel	Fibroblast growth factor 18	–	ACLT mouse model	Synovial macrophages, NF- κ B pathway	Regulating macrophage polarization, reducing TNF- α and IL-6 release, increasing IL-10 secretion, reducing MMP13 expression, and inhibiting cartilage matrix degradation;	Inhibits the inflammatory response of chondrocytes, alleviates synovitis and cartilage degeneration, and alleviates OA	The specific molecular mechanism of FGF18 regulating macrophage polarization and the direct correlation between chondrocyte macrophage crosstalk are not clear	[261]
KZIF@HA	Self-reinforced MOF-based nanogel	Chondrogenin	–	DMM mouse model	Synovial macrophages, JNK/ERK pathway	Inducing polarization of M2 macrophages, secreting IL-10 to inhibit JNK/ERK pathway, and reducing inflammation	Relieves synovitis, promotes transparent cartilage regeneration, and alleviates OA	The specific molecular targets and long-term cumulative toxicity of Zn ²⁺ induced M2 polarization have not been identified	[268]
O ₃ NPs@MHPCH	Nanocomposite hydrogel loaded with D-mannose	D-Mannose	–	ACLT mouse model	IL-1 β , IL-6, TNF- α , iNOS, Col-2, aggrecan	Reducing VEGF, decreasing IL-1 β , IL-6, TNF- α , iNOS, promoting the expression of Col-2 and aggrecan	Reduces synovial inflammation, cartilage destruction, and subchondral bone remodeling to alleviate OA	The release rate of O ₃ in the body is difficult to accurately regulate and its long-term safety has not been evaluated	[92]
CPHs	Peptide dendrimer nanogel	Carbon monoxide-releasing molecules	–	MIA-induced rat model	P38 MAPK pathway, NF- κ B pathway	Downregulating p38 MAPK, NF- κ B inflammatory pathways, reducing IL-1 β , IL-6, TNF- α secretion	Inhibits the proliferation of activated macrophages and induces apoptosis, effectively inhibits the degradation of articular cartilage and extracellular matrix	The precise regulatory mechanism and long-term exposure safety of CO release have not been clearly defined	[240]

Abbreviations: MSN, Mesoporous silica nanoparticles; PEI, Polyethylenimine; JQ1, BRD4 inhibitor; PSs, Phosphatidylserine-containing nanoliposomes; Que, Quercetin; ZIF-8, Zeolitic imidazolate framework-8; G2-OH24, Co delivery nano system of second-generation hydroxyl terminated bioactive phosphorus trees 24; CAT, Catalase; CBN, Calcium boride nanosheets; O3NPs, O3 is encapsulated in nanoparticles composed of perfluorotributylamine and fluorinated hyaluronic acid; MHPCH, D-mannose undergoes alpha amino coupling with hydroxypropyl chitin via Schiff base; FPPD, Dexamethasone loaded nanomicelles; MH, Double network hydrogel formed by methyl cellulose loaded hyaluronic acid; CCM, Carboxymethyl chitosan modified with methionine; HOOC, Carboxyl group; PEG, Polyethylene glycol; TK, Disulfide bond; PLGA, Poly (lactic-co-glycolic acid); PMPC, Poly (2-methoxyethyl acrylate); ϵ -PLE, ϵ -Polylysine; IgG, Immunoglobulin G; BRJ, Bilirubin/JPH203 nanoparticles; CSBN, Development of self-assembled nanocarriers based on chondroitin sulfate-bilirubin complex; IL-1 β , Interleukin-1 β ; TNF- α , Tumor necrosis factor α ; cfDNA, Circulating free DNA; BRD4, Bromodomain-containing protein 4; TRPA1, Transient receptor potential ankyrin 1; NF- κ B, Nuclear factor kappa B; HIF-1 α , Hypoxia inducible factor-1 α ; IL-6, Interleukin-6; iNOS, Inducible nitric oxide synthase; IL-1, Interleukin-1; MMP-13, Matrix metalloproteinase 13; COX2, Cyclooxygenase 2; COL2A1, Type II collagen alpha 1 chain; SOX-9, SRY related HMG cassette gene 9; BMSCs, Bone marrow mesenchymal stem cells; MMP, Matrix metalloproteinases; mTOR, Mammalian rapamycin target protein; COL10A, X-type collagen alpha 1 chain; RUNX2, Runt related transcription factor 2; IL-10, Interleukin-10; MAPK, Mitogen activated protein kinase; Col-2, Type II collagen; JNK, C-jun n-terminal kinase; ERK, Extracellular signal regulated kinase; DMM, Destabilization of the medial meniscus; MIA, Monosodium iodoacetate; CIOA, Collagen-induced OA; FLS, Fibroblast-like synoviocytes; CFA, Complete freund's adjuvant; ACLT, Anterior cruciate ligament transection; GelMA, Gelatin methacryloyl; CMDA, Chitosan methylacryloyl-dopamine; CM, Chitosan methylacryloyl; MNS, Manganese dioxide nanosheets; MPB, Mesoporous prussian blue; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; MMP9, Matrix metalloproteinase 9; Ce6, Chlorin e6; SB-3CT, Selective MMP-2/MMP-9 inhibitor; EVs, Extracellular vesicles; hUCMSCs, Human umbilical cord mesenchymal stem cells; NK cells, Natural killer cells; ChS, Chondroitin Sulfate; EPL, ϵ -Polylysine; FGF18, Fibroblast Growth Factor 18; KZIF, Zn-based metal-organic framework; JPH203, L-type amino acid transporter 1 inhibitor; mtDNA, Mitochondrial DNA; LCF, Licofelone.

Table 4 Systematic Comparison of Nanotherapeutic Strategies for OA Drug Delivery

Material Types	Specific Features	Advantages	Limitations	Clinical Translation Progress with OA
Nanohydrogels	Regulate intra-articular environment, enhance drug bioavailability, reduce systemic effects, prolong treatment	Biocompatible, biodegradable, sustained, and multi-drug release	Low mechanical strength; prone to water loss and shrinkage	Widely studied, promising in tissue engineering, needs optimization.
Inorganic nanoparticles	Good permeability and targeting; photothermal/photodynamic capabilities; ROS scavenging	Enhanced efficacy and targeting; can deliver multiple drugs; ferroptosis inhibition	Potential liver and kidney toxicity; complex preparation; possible accumulation in subchondral bone	Some in clinical trials show promise for OA; long-term safety data needed
Polymeric nanoparticles	Encapsulate proteins, small molecules, nucleic acids; tunable degradation kinetics	Controlled release; versatile surface modification	Burst release; protein denaturation; acidic degradation products	Established drug delivery platforms; some formulations in clinical use
Liposomes/Lipid nanoparticles	Phospholipid bilayer structure; encapsulate hydrophilic/hydrophobic drugs; fusion with EVs	Excellent biocompatibility; high drug loading; cell membrane fusion capability	Rapid clearance; instability in synovial fluid; batch variability	OA applications in preclinical/clinical stages
Exosomes/Extracellular vesicles	Cell-derived membrane vesicles; natural targeting; low immunogenicity	Excellent biocompatibility; innate cell-targeting; diverse biomolecule delivery	High cost; content heterogeneity; unclear mechanisms; difficult large-scale production	Promising regenerative therapy; preclinical stage in OA; standardization challenges
Polymer vesicles/Polymersomes	Self-assembled bilayer from block copolymers; tunable membrane permeability	Controlled permeability; versatile functionalization	Complex synthesis; limited clinical validation; higher production costs	Preclinical stage; promising for enzyme/protein delivery
MOF-based nanoparticles	Porous crystalline structure; high surface area; stimuli-responsive degradation	High drug loading capacity; tunable pore size; responsive to pH/ROS	Potential metal ion toxicity; long-term biodegradation unclear	Emerging platform; mostly preclinical studies
Dendrimers	Highly branched structure; multivalent surface; precise molecular weight	Monodisperse; controllable size/surface; high drug/nucleic acid loading	Potential cytotoxicity; liver accumulation; complex synthesis	Some clinical trials for other diseases; OA applications emerging
Nanomicelles	Core-shell structure; stimuli-responsive cores; small size	Excellent tissue penetration; responsive drug release; macrophage targeting	Low drug loading for hydrophilic drugs; stability upon dilution; rapid renal clearance	Preclinical stage; promising for M1 macrophage targeting
Biomimetic nanoparticles	Natural cell membrane coating; immune evasion; homing capabilities	Immune evasion; prolonged circulation; inflammation targeting	Complex preparation; membrane variability; storage stability	Emerging platform; preclinical studies show promise
Quantum dots	Zero-dimensional carbon/selenium nanocrystals; strong fluorescence; tunable emission; enzyme-like activity	Deep tissue penetration; ROS scavenging; ferroptosis modulation; imaging-guided therapy	Potential heavy metal toxicity; long-term biodistribution unclear; photobleaching at high power	Limited clinical translation; mostly research tools and preclinical studies
Nanogels	Swollen gel structure; high water content; stimuli-responsive	High drug loading; responsive swelling; injectable; protect cargo	Lower mechanical strength; potential burst release; long-term stability	Preclinical stage; promising for intra-articular delivery
Composite/Hybrid systems	Integration of multiple nanomaterials; synergistic functionalities	Combined advantages; multi-modal therapy; enhanced mechanical properties	Complex preparation; component interactions; regulatory complexity	Early stage; promising for personalized OA therapy

Abbreviations: OA, osteoarthritis; MOF, metal-organic framework; ROS, reactive oxygen species; EVs, extracellular vesicles.

nanotherapies addressing metabolic reprogramming in chondrocytes and immunoregulatory modulation of the intra-articular milieu will likely yield superior outcomes. Fourth, addressing declining chondrocyte density in aged cartilage is fundamental. Future nanomaterials should integrate chondroprotective cues with pro-regenerative signals to stimulate endogenous cell proliferation and enhance transplanted cell survival. Finally, personalized nanomedicine approaches tailored to patient-specific disease phenotypes represent the future of OA management. Stratified therapeutic strategies based on biomarker profiles and disease subtypes will optimize clinical outcomes.

In conclusion, while the path to clinical application is fraught with challenges, the prospects of nanotechnology in OA treatment are encouraging. With continued research and innovation, nanomedical strategies have the potential to revolutionize the management of OA, offering patients more effective and safer treatment options.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82402478) and the Science and Technology Development Project of Jilin Province (Grant 20230508171RC).

Disclosure

No potential conflict of interest was reported by the author(s).

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