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REVIEW

Nanomaterial-Based Drug Delivery Systems Targeting Functional Cells for Osteoarthritis Treatment: Mechanisms, Challenges and Future Prospects

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Abstract: Osteoarthritis (OA) represents a chronic joint disease characterized by articular cartilage degeneration, synovial inflammation, and subchondral bone erosions. Functional cells in OA mainly include macrophages, synoviocytes, chondrocytes, and mesenchymal stem cells. These cells can secrete cytokines and non-coding RNAs and exosomes and interact with each other to coregulate the progression of OA. Some nanomaterial-based drug delivery systems (DDSs) surface ligands can alleviate OA by targeting receptors on the surface of functional cells. Meanwhile, other nanomaterial-based DDSs, whose surfaces are masked by the cell membranes or extracellular vesicles of these functional cells, treat OA by targeting and attacking the diseased site. When ligand-modified nanomaterials target specific functional cells to treat OA, the functional cells are attacked. Functional cells become attackers, similar to arrows, when their cell membranes or extracellular vesicles are modified into nanomaterials to deliver drugs for OA treatment. An increasing number of studies have been conducted on nanomaterial-based DDS-targeted functional cells for the treatment of OA, but none has summarized the corresponding research progress and mechanism of action. In this review, the related references on the treatment of osteoarthritis with nanomaterial-based DDSs targeting functional cells have been included, and how a variety of functional cells can be engineered into nanomaterial-based DDSs serving as targets or arrows to treat OA has been summarised for the first time, providing a new idea and method for the targeted treatment of OA.

Keywords: nanomaterial-based drug delivery systems, osteoarthritis, macrophages, chondrocytes, synoviocytes, mesenchymal stem cells

Introduction

Osteoarthritis (OA) is the most common degenerative joint disease, and its pathologic changes include synovial inflammation, cartilage destruction, subchondral bone sclerosis, and so on.[1] The major risk factors for OA include age, gender, joint trauma, and genetic factors,[2] and its pathogenesis remains unclear. Functional cells, such as macrophages, synoviocytes, chondrocytes, and mesenchymal stem cells (MSCs), play an imperative role in the pathogenesis of OA.[3–5] These cells can secrete cytokines, growth factors, noncoding RNAs and exosomes, and interfere with each other to collectively regulate the progression of OA.[6,7] Given the complexity of OA and the limitations of therapeutic approaches, providing effective treatments to patients with OA remains a challenge.

The treatment methods for OA mainly comprise medications, surgery, exercise therapy, and lifestyle modification.[8] Pharmacological treatment remains the most commonly used clinical tool for OA, and its administration includes systemic administration and intra-articular local injection.[9] Nonsteroidal antiinflammatory drugs (NSAIDs) and analgesics are commonly administered orally and can provide some relief from symptoms and pain. However, the long-term use of these drugs can cause systemic adverse effects and gastrointestinal damage.[10] By contrast, local intra-articular drug

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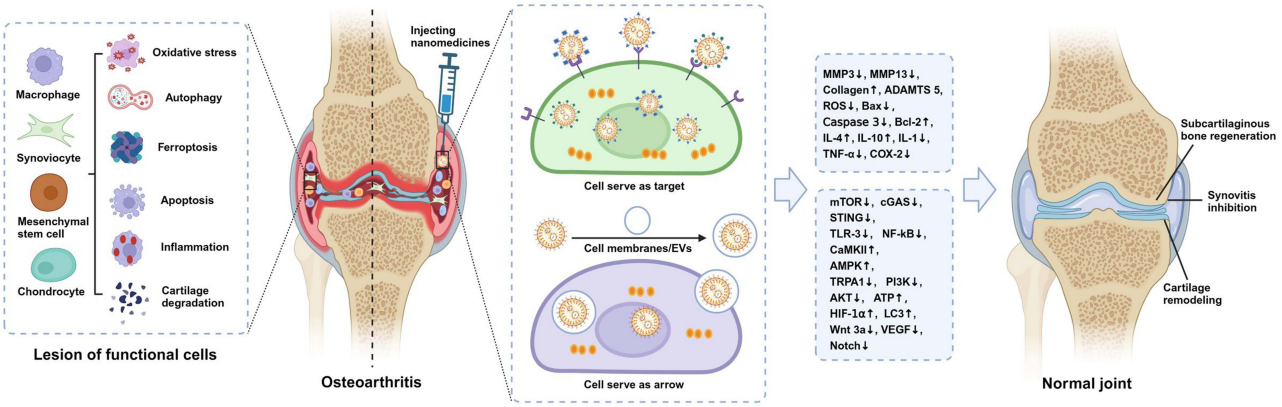
Graphical Abstract



delivery can inject drugs directly into the lesion site, which increases the initial drug concentration in the joint cavity.[11] However, drugs injected in this manner are readily phagocytosed by macrophages or cleared by the lymphatic blood system, and the amount of drug that is actually transported to the inflammation site and penetrates the cartilage is low.

To improve the effectiveness of drug delivery for OA treatment, scholars have adopted nanomaterial-based drug delivery systems (DDSs), including nanoparticles (NPs), hydrogels, liposomes, etc. These systems effectively improve the retention time of delivered drugs in the joints and demonstrates good biocompatibility.[12,13] The DDS for OA has achieved abundant research results, and various types of nanomaterials have been developed to meet drug delivery requirements.[14] Given the degenerative cartilage tissue damage and uneven distribution of inflammation caused by OA, targeted drug delivery to inflamed tissues or lesions can increase drug efficacy and considerably reduce off-target toxicity.[15] Some nanomaterial-based DDSs can target and modulate functional cells through ligand modification to alleviate OA,[16,17] and other nanomaterial-based DDSs, whose surfaces are masked by the cell membranes or extracellular vesicles (EVs) of these functional cells, treat OA by targeting and attacking the lesion site.[18,19] When ligand-modified nanomaterials target specific functional cells to treat OA, the functional cells are attacked. These cells become attackers, similar to arrows, when their cell membranes or EVs are modified into nanomaterials to deliver drugs for OA treatment.

The research on nanomaterial-based DDS-targeted functional cell therapy for OA has been increasing yearly, but no one has generalized and summarized the research progress. This review focuses on the role of functional cells in the treatment of OA with engineered nanomaterial-based DDSs and discusses the prospects and challenges of these nanomaterial-based DDSs associated with OA functional cells in the treatment of OA, which provides a new idea for the development of nanomaterial-based DDSs targeting OA functional cells.

Pathophysiology and Therapeutic Targets of OA

Pathophysiology of OA

OA refers to a common chronic degenerative joint disease with a complex pathophysiologic mechanism closely related to synovial inflammation, cartilage degeneration, subchondral bone sclerosis, bone redundancy formation, and mechanical stress imbalance of joint structures.[20]

An increasing number of studies have revealed that the pathogenesis of OA may initiate with synovial inflammation. The activation of immune cells and release of inflammatory mediators can be observed in the synovium of patients with OA.[21] Activation of immune cells, such as macrophages and T cells, causes their secretion of inflammatory factors, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). These inflammatory factors stimulate synovial cell proliferation and promote synovial neovascularization, which result in an increased synovial inflammation.[22] Synovial inflammation leads to increased synovial exudate and fluid accumulation in the joint cavity, which leads to joint swelling

and pain. In addition, synovitis results in the release of more degradative enzymes and inflammatory factors, which further damage articular cartilage and bone tissue.[23]

Articular cartilage comprises chondrocytes and matrix. Its main components include collagen fibers and proteoglycans, which help maintain the elasticity of cartilage and cushion pressure.[24] In the pathological process of OA, synovitis-derived inflammatory factors lead to chondrocyte dysfunction and the overexpressions of matrix metalloproteinases (MMPs).[25] In addition, the abnormal perception of mechanical stress by chondrocytes can lead to an imbalance in intracellular signaling pathways and the overexpressions of inflammatory factors and catabolic enzymes. This condition leads to the degradation of collagen and proteoglycan in the cartilage and ultimately destroys the structural integrity of the cartilage.[26]

Damaged to the articular cartilage results in a high stress in the subchondral bone. Accordingly, the subchondral bone remodels with a high bone density.[27] This remodeling can cause the microfractures of the subchondral bone to stimulate the differentiation of MSCs into osteoblasts and promote osteophyte formation.[28] Osteophyte is an essential pathological feature of OA, and its formation is associated with several factors. On the one hand, mechanical stress and inflammatory factors can stimulate the activity of osteoblasts and promote bone formation. On the other hand, growth factors derived from chondrocytes and synoviocytes, such as transforming growth factor-beta (TGF-β), can promote the formation of osteophyte.[29] These changes not only influence the mechanical stability of joints but also further aggravate the degradation of cartilage through interaction with the cartilage.

In addition, epigenetic regulatory mechanisms, such as DNA methylation, histone modification, and noncoding RNA regulation, affect the progression of OA.[30,31] Therefore, the pathological process of OA results from the interaction of many factors, involving cartilage degeneration, synovitis, subchondral sclerosis, osteophyte formation, and so on. The in-depth study of the pathological mechanism of OA will provide a theoretical basis for the development of targeted treatment strategies.

Therapeutic Targets for OA

Currently, targeted therapeutic strategies for OA are evolving towards precision regulation to design specific OA interventions. Early studies focused on inhibiting single molecules or pathways, but the heterogeneity of OA and the complexity of the multicellular microenvironment make the search for regulatory targets at multiple levels a key issue to be addressed in OA therapy. Targeting functional cells, cytokines, enzymes and signalling pathways is an important mechanism for precision treatment of OA (Figure 1).

Functional Cells

Targeting of functional cells aims to regulate the pathological process in joints by targeting specific cell types. Chondrocytes, synoviocytes, macrophages, and MSCs are the most commonly targeted cells in OA treatment. Chondrocytes are the main constituents of articular cartilage, and their main function is the synthesis of the cartilage matrix.[32] Targeting of chondrocytes can inhibit the expression of matrix-degrading enzymes, promote the regeneration of cartilage matrix, and restore joint function.[33] Synoviocytes contribute to the regulation of the pathological process of synovitis. Targeting of synoviocytes can inhibit inflammation and reduce joint swelling and pain. Macrophages aggravate local inflammation and tissue destruction by releasing pro-inflammatory cytokines in OA. Targeting macrophages can regulate immune response and reduce inflammation level.[34] MSCs are pluripotent stem cells possessing self-renewal and multidirectional differentiation abilities. They can differentiate into osteoblasts, chondrocytes, and adipocytes and participate in bone and cartilage repair. Targeted MSCs can secrete a variety of growth factors and cytokines, inhibit inflammation, and promote cartilage repair.[35]

Many technologies, such as gene therapy, small-molecule drugs, and nanomaterial-based DDSs, have been developed to target functional cells to treat OA. Introducing therapeutic genes into specific functional cells can regulate their biological behavior and repair damaged cartilage. The introduction of anti-inflammatory genes into synoviocytes or macrophages with viral or nonviral vectors can inhibit their inflammation.[36] In addition, small-molecule drugs and biologics inhibit the release of inflammatory factors or the overexpressions of enzymes by binding to cell-surface receptors or specific intracellular signaling pathways.[37] More importantly, given their small size and modifiability,

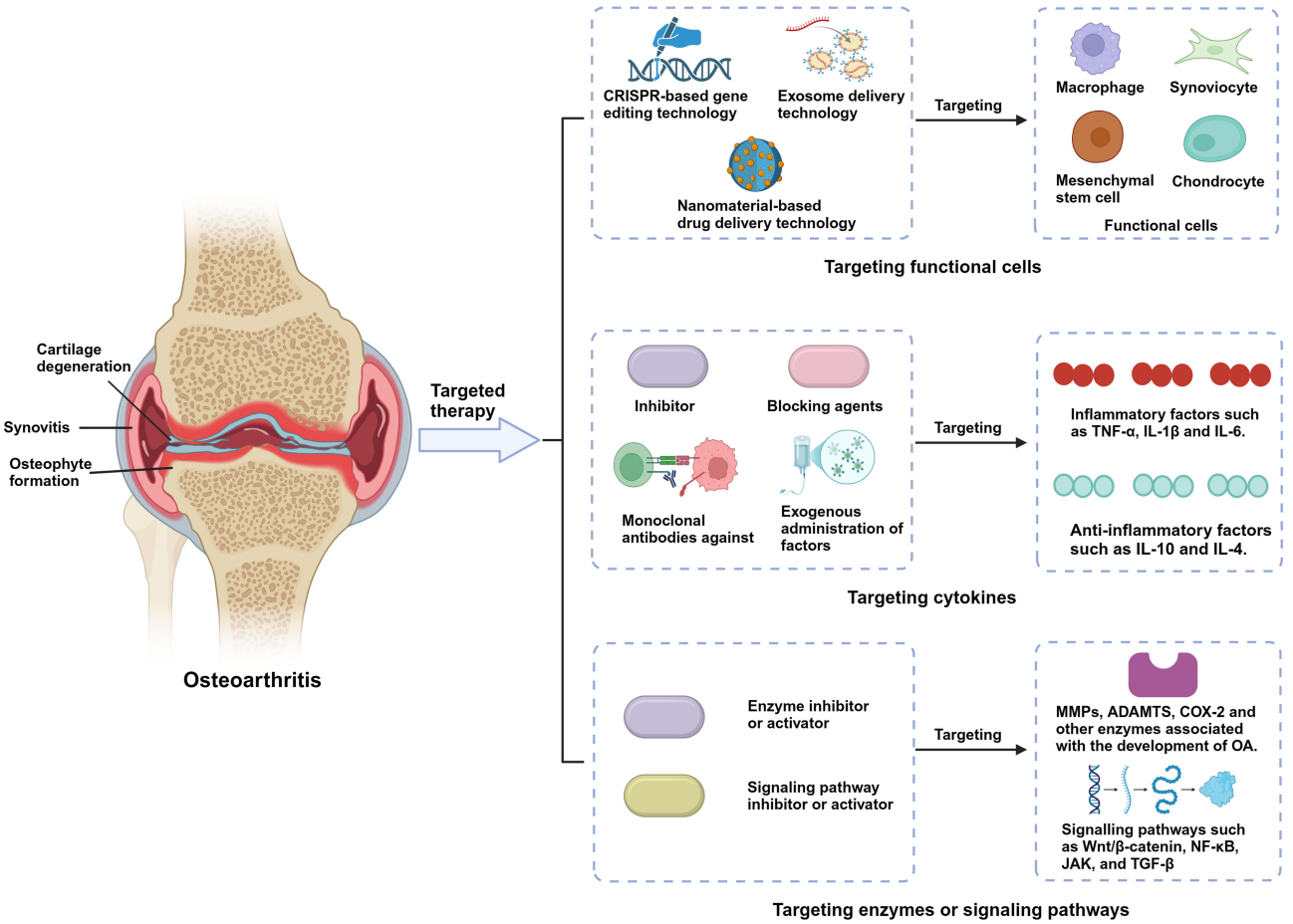


Figure 1 Therapeutic targets for OA. Therapeutic targets for OA can be divided into three main categories. First, macrophages, synoviocytes, mesenchymal stem cells and chondrocytes can be targeted by CRISPR-based gene editing technology, exosome delivery technology and nanomaterial-based drug delivery technology. Secondly, inflammatory factors such as TNF-α, IL-1β and IL-6 and anti-inflammatory factors such as IL-10 and IL-4 can be targeted by inhibitor, blocking agents, monoclonal antibodies against and exogenous administration of factors. Thirdly, inhibitors or activators of enzymes and signalling pathways can target various enzymes and signalling pathways associated with the onset and development of OA.

nanomaterial-based DDSs can deliver drugs or genes to functional cells. Using specific surface modifications (eg, antibodies or ligands), nanomaterial-based DDSs can selectively target cells at the site of OA lesions to enhance local therapeutic effects.[38]

Targeted functional cell therapy for OA shows great promise. Compared with traditional treatment methods, functional cell therapy has the advantages of strong targeting, remarkable efficacy, and limited side effects. With the continuous progress of technology, the isolation, culture, and expansion technology of functional cells will be improved, the gene modification technology will be safer and more effective, and the combined treatment program will become more diversified. The development of these technologies will provide more effective means for the treatment of OA. However, a strategy for achieving efficient cell targeting and effective drug delivery remains a major challenge. Further clinical trials are needed to validate the safety, efficacy, and long-term effectiveness of these approaches.

Cytokines

Targeted cytokine therapy for OA is a therapeutic strategy for the targeted modulation of immune responses and inflammatory mediators. Cytokines play a key role in the pathogenesis of OA. These substances are small-molecule proteins secreted by cells and are involved in inflammatory responses, immune regulation, and tissue repair.[39] Given that OA is a degenerative joint disease associated with chronic inflammation, targeting and inhibiting pro-inflammatory cytokines or enhancing anti-inflammatory cytokine activity has become an essential means for OA treatment.[40]

During the pathological process of OA, cells in the articular cartilage, synovium, bone, and other joint structures produce large amounts of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, due to abnormal stress or injury. These cytokines promote cartilage matrix degradation, synovial inflammation, and bone destruction, which lead to increased damage to joint structures.[41] Meanwhile, anti-inflammatory cytokines, such as IL-10 and IL-4, have an inhibitory effect on inflammation and can reduce tissue damage and promote repair.[42] The principle of targeted cytokine therapy is the inhibition of the production and activity of pro-inflammatory factors and promoted production or activity of anti-inflammatory cytokines. On the one hand, the use of inhibitors, blocking agents, or monoclonal antibodies against TNF-α, IL-1, and IL-6 can inhibit their activity and reduce inflammatory responses and cartilage degradation.[43] On the other hand, cartilage degeneration can be alleviated by exogenous administration of factors, such as IL-10 or IL-4.[44] An important challenge in this type of therapy is the effective delivery of anti-inflammatory cytokines to the site of arthropathy and the maintenance of their local activity.

The research on targeted cytokine therapy for OA remains in its infancy. Although numerous drugs targeting pro-inflammatory or anti-inflammatory cytokines exhibit a great potential in the treatment of OA, their efficacy and safety in clinical application still need further verification. In addition, how to combine nanomaterial-based DDSs to deliver these bioactive molecules accurately to the lesion area and enhance their stability and durability is an important research direction in the future.

Signaling Pathways and Enzymes

Targeting of OA-related pathways or enzymes is an effective therapeutic strategy. The occurrence and development of OA involve not only a number of complex signaling pathways, such as Wnt/β-catenin, nuclear factor-kappa B (NF-κB), janus kinase (JAK), and transforming growth factor beta (TGF-β),[45,46] but also cartilage matrix-degrading enzymes and inflammatory mediators, including MMPs, phospholipase A2, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), and cyclooxygenase-2 (COX-2).[47] We can use small-molecule inhibitors, monoclonal antibodies, gene therapy, and other methods to target OA-related pathways or enzymes. The JAK inhibitor tofacitinib regulates the JAK1/TNF-α pathway through Mir-149-5p, which reduces chondrocyte hypertrophy and inhibits OA inflammation.[48] Tissue inhibitor of metalloproteinase-1, an inhibitor of MMPs, may inhibit cartilage degradation and alleviate OA.[49] Rofecoxib, an inhibitor of COX-2, has been widely used in clinical treatment and has displayed good effects of inflammation inhibition and pain relief.[50] In addition, gene editing technology may play a crucial role. For example, RNA interference or CRISPR-Cas9 technology can be used to selectively knock out or inhibit the *FGF18* gene, regulate related signaling pathways and alleviate OA.[51]

Targeting signal pathway or enzyme therapy for OA is an innovative treatment with great potential. The pathological process of OA can be delayed by interfering with key pathological signal pathways or enzymes. Although therapeutic strategies targeting signal pathways or enzymes have important effects on basic research, they face certain challenges in clinics. The disease phenotype of patients may be heterogeneous, and targeting a single signal pathway or enzyme may not completely prevent the progress of OA.[24] In addition, long-term inhibition of some signal pathways may cause some side effects, such as immunosuppression and cartilage calcification.[52] Therefore, in the future, the dynamic regulation of each signal pathway and its role at different stages of the disease must be deeply studied to develop more accurate and individualized treatment programs.

The Current Treatment Options for OA

Currently, the main treatment options for OA are aimed at relieving symptoms and slowing disease progression. Although traditional therapies are more commonly used in the clinic, the different treatments have some limitations that limit improvements in efficacy.[53] Traditional pharmacological treatments focus on NSAIDs, which reduce pain and inflammation by inhibiting cyclooxygenase (COX) activity, but long-term use can cause gastrointestinal damage and even cardiovascular risks.[54] To avoid these adverse effects, treatment options for OA have gradually shifted to local drug delivery. For example, intra-articular injections of glucocorticoids rapidly suppress synovial inflammatory exudates and their short-term efficacy is evident, but repeated injections may accelerate joint degeneration.[55] Chondroprotective agents

such as chondroitin sulphate and hyaluronic acid (HA) may slow disease progression by improving joint lubrication, providing a practical basis for the therapeutic concept of targeting the cartilage microenvironment.[56]

In addition, non-pharmacological interventions play an important role in the treatment of OA. Exercise rehabilitation improves joint stability by increasing muscle strength, and weight management directly reduces mechanical loading, and the two work synergistically to slow the progression of early OA.[57,58] However, patient compliance can be poor and the effectiveness of this approach is not clear in patients with moderate to advanced OA. When conservative treatment fails, surgery is the last option. However, arthroscopic debridement does not promote cartilage regeneration despite short-term removal of inflamed synovium and debris.[59] While arthroplasty significantly restores knee function, it is associated with the risk of infection and prosthesis longevity.[60]

All of these traditional treatments have limitations. Currently, achieving precise drug delivery and long-lasting modulation is a key issue that needs to be urgently addressed. For example, systemic drug delivery results in poor drug utilisation due to poor joint targeting, while local injection has the problem of rapid clearance and repeated manipulation.[61] In addition, the dynamic complexity of the inflammatory microenvironment makes it difficult to block OA progression by single-pathway inhibition, and multi-target synergistic intervention is required.[62] In recent years, emerging biologics such as anti-cytokine antibodies and gene therapy have the potential for targeted intervention, but they are costly and have complex technical requirements.[63] Therefore, the rapid development of nanomaterial-based drug delivery systems is expected to solve the problems of existing therapies and provide a new approach for precise and personalised treatment of OA by precisely regulating drug release, improving lesion targeting and reducing systemic toxicity.[64]

Research Progress on Nanomaterial-Based DDSs in OA

Nanomaterial-based DDSs are widely used in the treatment of OA. Nanotechnology has great potential in the treatment of OA, mainly in terms of drug targeting, bioavailability, and duration of action.[65] Compared with traditional drug delivery methods, nanomaterial-based DDSs can deliver drugs to the lesion site more accurately, increase the effective concentration of drugs, and control the drug release time.[66] The lesion site of OA is mainly in the joints, which involve synoviocytes, macrophages, and chondrocytes.[67] Traditional drugs are widely distributed throughout the body, and their accurate delivery to these diseased cells presents difficulty. Nanomaterial-based DDSs have unique size and surface charge, which can accumulate in diseased joints. In addition, ligands on the surface of nanomaterial-based DDSs can bind to receptors on the surface of diseased cells and play an active targeting role. Loading ligands that can specifically recognize and bind to joint tissues or cells on nanomaterials has become the main means to achieving the active targeted delivery of nanomaterial-based DDSs.[68,69] Many biological targeting ligands, such as peptides, nucleic acids, small-molecular compounds and macromolecular compounds, show good stability, high affinity and easy modification.

Polypeptides have low immunogenicity, high affinity and easy biological coupling. Therefore, polypeptide ligands are being increasingly applied in the field of nanotherapy.[70] Collagen is the main component of cartilage matrix, with type II collagen accounting for 90–95% of the collagen network. Therefore, targeting ligands for type II collagen can considerably enhance the close combination between nanocarriers and cartilage. Rothefuh et al[71] screened the isolated bovine cartilage through phage display technology, and WYRGRL peptide showed a strong specificity for type II collagen binding. WYRGRL peptides were modified on the surface of nanomaterials through covalent bonds. The aggregation of these nanomaterials containing targeted peptides in the extracellular matrix was substantially higher than that in nanomaterials with interfering peptides. In addition, as an important component of cartilage tissue, chondrocytes are located in the deep layer of cartilage tissues, and their main function is the production and maintenance of the extracellular matrix. If the specific targeting of chondrocytes can be achieved, nanomaterial-based DDSs can penetrate the cartilage matrix and directly reach its deep tissues for effective treatment. Pi et al[72] identified a chondrocyte affinity peptide (CAP) with the sequence of DWRVIIPPRPSA using phage display technology. The affinity peptide has a high specificity for chondrocytes and shows no species difference. Zhao et al[73] modified the copolymer compound with CAP to realize miRNA delivery. The results showed that CAP modification can enhance the ability of chondrocytes to absorb polymers and attains good targeting efficiency and cartilage permeability.

Nucleic acid aptamers consist of single-stranded DNA or RNA. They are synthesized artificially by virtue of strict recognition ability and affinity between nucleotides. These small-molecule biomolecules possess a unique tertiary structure and can specifically bind to various targeting targets, such as peptides, small-molecular particles or whole cells.[74,75] Given the easy synthesis and modification of aptamers and their high affinity and specificity for target molecules, nanomaterials modified by aptamers are widely applied in the targeted therapy of OA. Chen et al[76] screened a nucleic acid aptamer CX3, which can specifically bind to fibroblast-like synovial cells. On this basis, CX3-modified liposomes were further constructed, and targeted delivery of dasatinib was used to remove aging synovial cells at the OA site. In vitro cell co-incubation experiments revealed that CX3-modified liposomes have a high specificity for fibroblast-like synovial cells, and they can effectively promote the delivery of nanocarriers to synovial cells. However, the development cost of nucleic acid aptamers is high, and their structural stability is insufficient. Therefore, the related application research remains in the basic stage, and only a few materials have entered clinical studies.

In addition, small-molecular and macromolecular compounds are common biological targeting ligands. Chondroitin sulfate (ChS) is a natural anionic glycosaminoglycan and is also a chronic drug for the treatment of OA. This compound can inhibit the apoptosis of damaged cartilage tissue and repair damaged cartilage.[77] Chitosan (CS), as a small-molecule ligand, can bind to type II collagen, cluster of differentiation 36 (CD36), and other receptors on chondrocytes to achieve targeted localization.[78,79] Bishnoi et al[80] used CS-coupled liposomes to prepare conjugated polymer CS solid-lipid NPs (SLN). After intravenous administration, the experimental group of CS SLN exhibited a considerably higher absorption rate of drugs at the articular cartilage compared with that in the liposome group of unmodified CS. This finding confirmed that CS can target the articular cartilage. The surface of activated M1 macrophages overexpresses the receptors of folic acid (FA) and cluster of differentiation 44 (CD44), which display low expressions in normal cells. Therefore, FA and CD44 can be modified onto the surface of nanomaterials as their corresponding specific macromolecular ligands to construct DDSs that can specifically target and activate macrophages.[81,82] Yang et al[83] used FA-modified HA to wrap carbon monoxide-releasing molecules to construct a nanogel. The FA-modified HA nanogel was marked with CY 5.5, and a strong fluorescence signal was observed in the phagocytosis experiment of activated macrophages. Therefore, small and large molecules used for targeted modification have strong binding capability. However, these ligands, especially monoclonal antibodies, affect their activity due to storage conditions and modification preparation. Thus, the synthesis technology must be further improved in the future to reduce their adverse effects.

Functional Cells Serve as Targets of Nanomaterial-Based DDSs in the Treatment of OA

Targeting Macrophages

Macrophages play a key role in the pathogenesis of OA and directly influence joint degeneration by modulating the inflammatory response. The early stages of OA are usually associated with articular cartilage damage, which activates synovial macrophages.[67] Once activated, M1 macrophages release large amounts of pro-inflammatory cytokines, such as IL-6, IL-1β and TNF-α. These cytokines not only exacerbate cartilage destruction but also stimulate synovial membrane proliferation, which results in persistent chronic inflammation in the joint cavity.[84] However, in addition to their destructive role, macrophages can have beneficial effects. Notably, M2 macrophages promote tissue repair and reduce inflammation.[85]

Therefore, symptoms of OA can be alleviated by modulating the macrophage phenotype, reducing the expressions of inflammatory factors and scavenging reactive oxygen species (ROS) and NO in the body.[86] Activated macrophages have several overexpressed specific receptors on their surface, such as FR2, scavenger receptor class A (SR-A) and CD44.[87,88] Some nanomaterial-based DDSs can selectively deliver drugs to OA-lesion areas through passive targeting effects and actively target macrophages via nanomaterial-based DDSs surface ligands linked to specific receptors (Figure 2). Table 1 shows the nanomaterial-based DDSs targeting macrophages for the treatment of OA.

Nanomaterial-based DDSs employ various mechanisms to target macrophages for the treatment of OA. Ligands on the surface of nanomaterial-based DDSs can bind to specific receptors on the macrophage surface and enhance targeting recognition. Antibodies are common ligands on the surface of nanomaterial-based DDSs and have many applications in

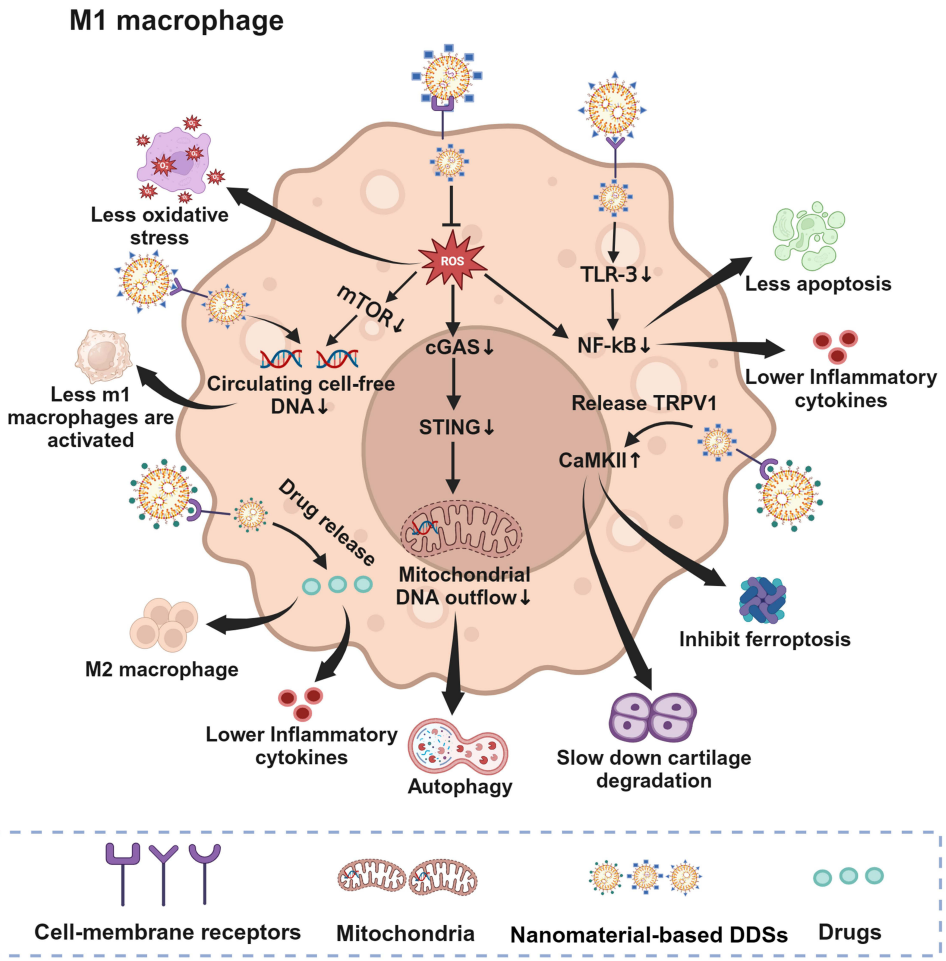


Figure 2 Nanomaterial-based DDSs treat OA by targeting macrophages. Nanomedicines modified with different ligands target macrophages through the corresponding receptors on macrophages to release functional drugs. Different nanomedicines regulate macrophages through different mechanisms. Firstly, nanomedicines reduce circulating cell-free DNA by down-regulating the mTOR signaling pathway. Secondly, nanomedicines inhibit mitochondrial DNA outflow by downre-gulating the cGAS/STING signaling pathway. Thirdly, nanomedicines down-regulate TLR-3, thereby down-regulating the NF-kB signaling pathway. Fourthly, nanomedicines release TRPV1, thereby up-regulating CaMKII. These nanomedicines can ultimately induce M1 macrophages to form M2 macrophages, inhibit apoptosis, ferroptosis and inflammation, promote autophagy and eliminate ROS.

the targeting of macrophages for the treatment of OA.[17,89,94,95] Kou et al[89] prepared opsonized NPs (IgG/Bb@BRPL) by combining IgG, an oxidative stress-responsive bilirubin grafted polylysine biomaterial (BR-PLL), and an anti-inflammatory agent berberine (Bb). IgG/Bb@BRPL specifically targets M1 macrophages in the OA joint cavity by binding IgG to macrophage surface receptors. Bb and BR-PLL can then inhibit the inflammation of M1 macrophages,

Table 1 Nanomaterial-Based DDSs Targeting Macrophages for the Treatment of OA

Target Cell	Nanomaterial	Recognition Mechanism	Targeting Mechanism	Animal Model	Result	Reference
Macrophage	IgG/Bb@BRPL	Biorecognition, IgG and Mi macrophage surface receptor	Active targeting, ligand and receptor	OA rats	Scavenging ROS, inactivating NF-κB signaling pathway, and repolarizing M1 macrophages into M2 macrophages.	[89]
Macrophage	RAPA@MPB-MMP9 NPs	Biorecognition, MMP9-targeted peptides and MMP9	Active targeting, ligand and receptor	CIOA mice	Decreasing the macrophage pyroptosis and promoting mitophagy.	[16]

(*Continued*)

Table 1 (Continued).

Target Cell	Nanomaterial	Recognition Mechanism	Targeting Mechanism	Animal Model	Result	Reference
Macrophage	NP@Poly^{RHAPM}	Biorecognition	ROS-responsive	OA mice	Restoring mitochondrial membrane potential, increasing GSH level, promoting autophagy, and repopulating M1 macrophages into M2 phenotype.	[85]
Macrophage	MSN-PEI	Biorecognition	Passive targeting	CIOA rats	Inhibiting M1 polarization of macrophages and reducing oxidative stress and inflammation.	[90]
Macrophage	NAHA-CaP/siRNA NPs	Biorecognition	Passive targeting	OA mice	Eliminating NO, inhibiting the expression of CA9 in macrophages, inhibiting apoptosis, relieving inflammation and protecting articular cartilage.	[12]
Macrophage	IgG/BRJ	Biorecognition, FcγRs and IgG	Active targeting, ligand and receptor	OA rats	Scavenging ROS, inhibiting NF-κB and mTOR pathways, and regulating macrophage polarization.	[17]
Macrophage	HA-NSc NPs	Biorecognition	Passive targeting	OA rats	Relieving pain, inflammation and joint injury.	[91]
Macrophage	ACP	Biorecognition	pH-responsive	OA mice	Reducing the expression of TNF-α and IL-1β, and inhibiting inflammation and cartilage degradation.	[92]
Macrophage	DEX@PPNP	Biorecognition	Passive targeting	OA mice	Inhibiting the production of ROS and NO, and promoting the repolarization of macrophages.	[93]
Macrophage	G4-TBP NPs-FN	Biorecognition, FN and Integrin on macrophage surface	Active targeting, ligand and receptor	OA mice	Scavenging ROS, promoting M2 polarization of macrophages, thus protecting macrophages from apoptosis.	[87]
Macrophage	DS-TA NPs	Biorecognition, DS-TA and SR-A	Active targeting, ligand and receptor	OA mice	Inhibiting the proliferation of activated macrophages and reducing the expression of pro-inflammatory cytokines.	[88]
Macrophage	MNPs-TRPV1	Biorecognition, MNPs - TRPV1 and TRPV1 channel	Active targeting, ligand and receptor	OA mice	Blocking macrophage inflammation and chondrocyte ferroptosis.	[94]
Macrophage	CAT&SMT@ZIF-8-Ab NPs	Biorecognition, Ab and CD16/32	Active targeting, ligand and receptor	OA mice	Inhibiting NO, improving mitochondrial function, and making macrophages change from pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype.	[95]
Macrophage	GNP	Biorecognition	Passive targeting	OA mice	Modulating the interaction of "microbiota-gut-joint" axis, relieving inflammation and improving cartilage degradation.	[96]
Macrophage	PLEL/ChS-EPL /FGF18	Biorecognition	Passive targeting	OA mice	Relieving the inflammatory reaction of chondrocytes, inhibiting the polarization of macrophage M1, and improving cartilage degeneration and synovitis in OA.	[97]
Macrophage	ICA/TA-NDs	Biorecognition	Passive targeting	OA Rats	Inhibiting inflammation and reducing cartilage damage.	[98]
Macrophage	NHsPP	Biorecognition	Passive targeting	OA mice	Inhibiting inflammation.	[99]
Macrophage	USPBNPs	Biorecognition	Passive targeting	OA rats	Scavenging ROS and repolarizing macrophages to an anti-inflammatory M2 phenotype.	[100]
Macrophage	CLX NPs	Biorecognition	Passive targeting	OA rats	Inhibiting inflammation.	[101]
Macrophage	mPEG-TK-GLX @PVA-MMA	Biorecognition	ROS-responsive	/	Inhibiting inflammation, ROS production and ferroptosis	[102]
Macrophage	METP NPs	Biorecognition	Passive targeting	OA mice	Inhibiting inflammation and reversing the anti-inflammatory phenotype in macrophages	[103]
Macrophage	NIPAM-AMPS	Biorecognition	Passive targeting	/	Inhibiting inflammation	[104]
Macrophage	Cu-EGCG	Biorecognition	Passive targeting	/	Inhibiting inflammation and ROS, and regulating M2 polarization of macrophages.	[105]
Macrophage	PLGA	Biorecognition	Passive targeting	OA rats	Inhibiting inflammation	[106]
Macrophage and Mesenchymal stem cells	F127/COS/KGN$_{DCF}$	Biorecognition	Thermo-responsive	OA rats	Inhibiting synovitis and promoting chondrogenesis.	[107]
Macrophage and Mesenchymal stem cells	DLNPs	Biorecognition	ROS-responsive	/	Inhibiting the proliferation of activated macrophages, inducing apoptosis of macrophages, relieving inflammation, and differentiating BMSCs into chondrocytes.	[108]
Macrophage and chondrocyte	DAMM NPs	Biorecognition	Passive targeting	OA mice	Regulating TLR-3/ NF -κB signaling pathway and inhibiting chondrocyte apoptosis and synovitis.	[109]

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promote their polarization into M2 macrophages, and ultimately play a therapeutic role in OA. In addition, peptides can be used as ligands on the surface of NPs to target macrophages for the treatment of OA. Qi et al[16] prepared MMP9-targeting peptide-modified mesoporous Prussian blue NPs (MPB NPs) for targeted delivery to synovial macrophages. By loading rapamycin (RAPA), the RAPA@MPB-MMP9 NPs inhibited macrophage pyroptosis and mammalian target of rapamycin (mTOR) complex 1 pathway activation, which attenuated inflammation. Small molecules are also common ligands on the surface of NPs that can target macrophages. She et al[88] observed that dextran sulfate-triamcinolone acetonide conjugate NPs can selectively target SR-A on activated macrophages and mediate the internalization of NPs, which considerably inhibited the viability of activated M1 macrophages and ultimately reduced the expressions of inflammatory factors.

Nanomaterial-based DDSs can also be surface modified to increase their specific biocompatibility and targeting. Shi et al[90] revealed that polyethylenimine (PEI)-functionalized diselenide-bridged mesoporous silica NPs (MSN-PEI) can target the joint lumen and aggregated at the site of OA inflammation upon entry into the body due to the presence of MSN-PEI surface charges interacting with cells. Subsequently, MSN-PEI inhibited inflammation and suppressed macrophage activation by reducing the binding of cfDNA to toll-like receptor (TLR9). Yan et al[12] reported that after the "two-in-one" nanocarrier (NAHA-CaP/siCA9 NPs) were passively targeted to the inflammatory sites in the joint cavity, the NP-loaded CA9 siRNA (siCA9) regulated the intracellular and extracellular pH balance, inhibited the inflammatory response of M1 macrophages, and promoted the repolarization of macrophages toward the M2 phenotype by binding to the CA9 mRNA overexpressed by OA macrophages.

Nanomaterial-based DDSs can be engineered to respond to the inflammatory microenvironment. They can undergo structural changes or release drugs in response to acidity, oxidative stress, or specific enzymes. This responsive targeting mechanism allows nanomaterial-based DDSs to aggregate and release therapeutic drugs specifically at the inflammation site, which increases the local drug concentration and enhances the therapeutic effect. Li et al[85] indicated that after ROS-responsive biodegradable NPs were introduced into the body via intravenous injection, the thioketal bonds of the NPs were broken in M1 macrophages with high ROS levels, which led to the dissociation of the NPs, release of the loaded drug, and a therapeutic effect. Similarly, Zhen et al[102] showed that NPs (mPEG-TK-GLX@PVA-MMA) were ROS responsive and slowly released GLX351322 (GLX), which inhibited inflammation, ROS production, and ferroptosis in OA macrophages. Kang et al[92] revealed that under acidic conditions, acid-activatable curcumin polymer microspheres rapidly dissociated due to the rapid hydrophobic/hydrophilic transition of protonated amine groups and responsively released curcumin, which exerted antioxidant, anti-inflammatory and anti-arthritic effects.

Therefore, nanomaterial-based DDSs can be used to treat OA through the precise delivery of drugs or genetic materials into OA macrophages through multiple targeting mechanisms. In addition, the retention time and specificity of nanomaterial-based DDSs in joints can be improved by optimizing their size, shape and surface functionalization, thus further enhancing their efficacy. Although nanomaterial-based DDSs still needs to be improved, their application in the treatment of OA targeting macrophages is very promising.

Targeting Synoviocytes

Under normal physiological conditions, synoviocytes are responsible for maintaining a healthy environment in the joint cavity. In the development of OA, synoviocytes proliferate and release inflammatory factors, which in turn promote the production of MMPs and accelerate cartilage degradation.[110] Moreover, synovial hyperplasia leads to tissue hypertrophy, which restricts joint motion and exacerbates pain. Although synoviocytes may be involved in the repair mechanism in the early stages, their dysfunction and apoptosis increase with disease progression, which ultimately leads to joint dysfunction.[111] Synoviocytes are both drivers of pathological changes and important indicators of disease progression in OA. Therefore, specific regulation and intervention of synoviocytes is the key to the treatment of OA. We can develop targeted drugs or treatments by identifying specific molecular markers or receptors related to synoviocytes, which inhibit the abnormal proliferation and inflammation of synoviocytes.

Nanomaterial-based DDSs can target synoviocytes to treat OA through surface modification and interaction with cell surface receptors. HA in CS/HA NPs can target synoviocytes through electrostatic interaction and binding with CD44 receptor on the surface of synoviocytes.[69] Similarly, Deng et al[112] and Zhou et al[113] observed that HA in HA/CS-cytokine

response modifier A and CS/HA/plasmid-DNA encoding IL-1 receptor antagonist gene can target CD44 receptor on the surface of synoviocytes, which inhibits synovitis and cartilage degradation. In addition, huntingtin-associated protein 1 peptide can be used as a ligand to bind to specific receptors on the surface of synoviocytes. Thus, the nanocomposite 4-arm-poly(ethylene glycol) (PEG)-maleimide/poly (lactic-co-glycolic) acid (PLGA) NP microgels can target synoviocytes. The microgels can remain in the joint cavity for a long time without causing articular cartilage degeneration or synovial thickening and thus have a good effect on relieving synovitis.[68]

Nanomaterial-based DDSs can also be used as drug delivery carriers to deliver various therapeutic drugs or therapeutic genes to the synovial tissue and play a therapeutic role. PLGA NPs can encapsulate diacetylsalicylic acid (DIA) and reduce inflammation by releasing DIA continuously.[114] Similarly, PLGA NPs can encapsulate p16INK4a siRNA to form p16INK4a siRNA-loaded PLGA NPs (p16 si_NP). p16 si_NP mostly enters synoviocytes and some chondrocytes, which ultimately inhibits synovial inflammation, cartilage degradation, and pain in mice.[115] Table 2 shows the nanomaterial-based DDSs targeting synoviocytes for the treatment of OA.

Nanomaterial-based DDSs target synoviocytes to inhibit synovitis, slow down cartilage degeneration, and ultimately treat OA. Ren et al[116] reported that ceria NPs targeted synoviocytes and alleviated synoviocyte senescence by scavenging ROS and inactivating the NF-κB pathway. Histidine functionalized generation 5 polyamidoamine dendrimer delivered miR-224-5p into synoviocytes and protected them from degradation. Subsequently, they exerted anti-inflammatory, anti-apoptotic,

Table 2 Nanomaterial-Based DDSs Targeting Synoviocytes for the Treatment of OA

Target Cell	Nanomaterial	Recognition Mechanism	Targeting Mechanism	Animal Model	Result	Reference
Synoviocytes	CeNP	Biorecognition	Passive targeting	OA rats	Scavenging ROS, inhibiting NF-κB signaling pathway, reducing aging and protecting cartilage from degeneration.	[116]
Synoviocytes	SP-NEs	Biorecognition	Passive targeting	OA rats	SP-NEs regulates TRPA1 through AMPK-mTOR signaling pathway, and relieves synovitis.	[117]
Synoviocytes	DIA/PLGA NPs	Biorecognition	Passive targeting	OA rats	Inhibiting synovitis and cartilage degeneration.	[114]
Synoviocytes	HA/CS-CrmA	HA and CD44	Active targeting, ligand and receptor	OA rats	Inhibiting synovitis and cartilage degeneration.	[113]
Synoviocytes	EGC-NPs	Casein and synovial cell surface receptor	Active targeting, ligand and receptor	OA rats	Inhibiting synovitis and cartilage degeneration.	[118]
Synoviocytes	HA/CS/pCrmA	HA and CD44	Active targeting, ligand and receptor	/	Inhibiting synovitis and cartilage degeneration.	[69]
Synoviocytes	MSN-CC-PEI	Biorecognition	Passive targeting	OA mice	Inhibiting synovitis and cartilage degeneration.	[119]
Synoviocytes	CS/HA/pIL-1Ra	HA and CD44	Active targeting, ligand and receptor	/	Inhibiting synovitis and cartilage degeneration.	[112]
Synoviocytes	PH-NPPs	Biorecognition	Passive targeting	OA mice	Inhibiting synovitis and cartilage degeneration.	[120]
Synoviocytes and chondrocyte	CP/DNA	HA and CD44	Active targeting, ligand and receptor	OA rabbits	It is a safe and efficient non-viral vector and can be used to deliver genes to chondrocytes and synovial cells.	[121]
Synoviocytes and chondrocyte	G5-AHP/miR-224-5p	Biorecognition	Passive targeting	OA mice	Inhibiting cartilage degradation and synovitis.	[122]
Synoviocytes and chondrocyte	p16INK4a-siRNA	Biorecognition	Passive targeting	OA mice	Inhibiting synovitis and cartilage degeneration.	[115]
Synoviocytes and chondrocyte	PEG-4MAL/PLGA NPs	HAP-1 peptide and synovial cell surface receptor; WYR peptide and chondrocyte surface receptor	Active targeting, ligand and receptor	OA rats	Inhibiting synovitis and cartilage degeneration.	[68]

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antineovascularization and autophagy-promoting effects.[122] Sanse Powder essential oil nanoemulsion targets synoviocytes, inhibits transient receptor potential ankyrin 1 (TRPA1) through the AMP-activated protein kinase (AMPK)-mTOR signaling pathway, and alleviates OA synovitis.[117] Therefore, targeting synoviocytes to modulate multiple cytokines and signaling pathways to inhibit synovial inflammation and slow down cartilage degeneration may be a potential therapeutic strategy for OA (Figure 3).

Targeting MSCs

MSCs play an important role in OA. On the one hand, MSCs can undergo self-renewal and multidirectional differentiation and differentiate into chondrocytes, osteoblasts, etc., which promote the repair of damaged joint tissues.[123] However, during the pathogenesis of OA, changes in the joint microenvironment, release of inflammatory factors, and increased oxidative stress may affect the function of MSCs. On the other hand, MSCs can also regulate the local immune response and inflammatory state of joints by secreting various bioactive factors, such as growth and anti-inflammatory factors.[124] Nanomaterial-based DDSs targeting MSCs shows great potential in the treatment of OA. Nanomaterial-based DDSs not only enhance the viability of the stem cells but also provide sustained drug release, which further enhances the therapeutic effect. Table 3 shows the nanomaterial-based DDSs targeting MSCs for the treatment of OA.

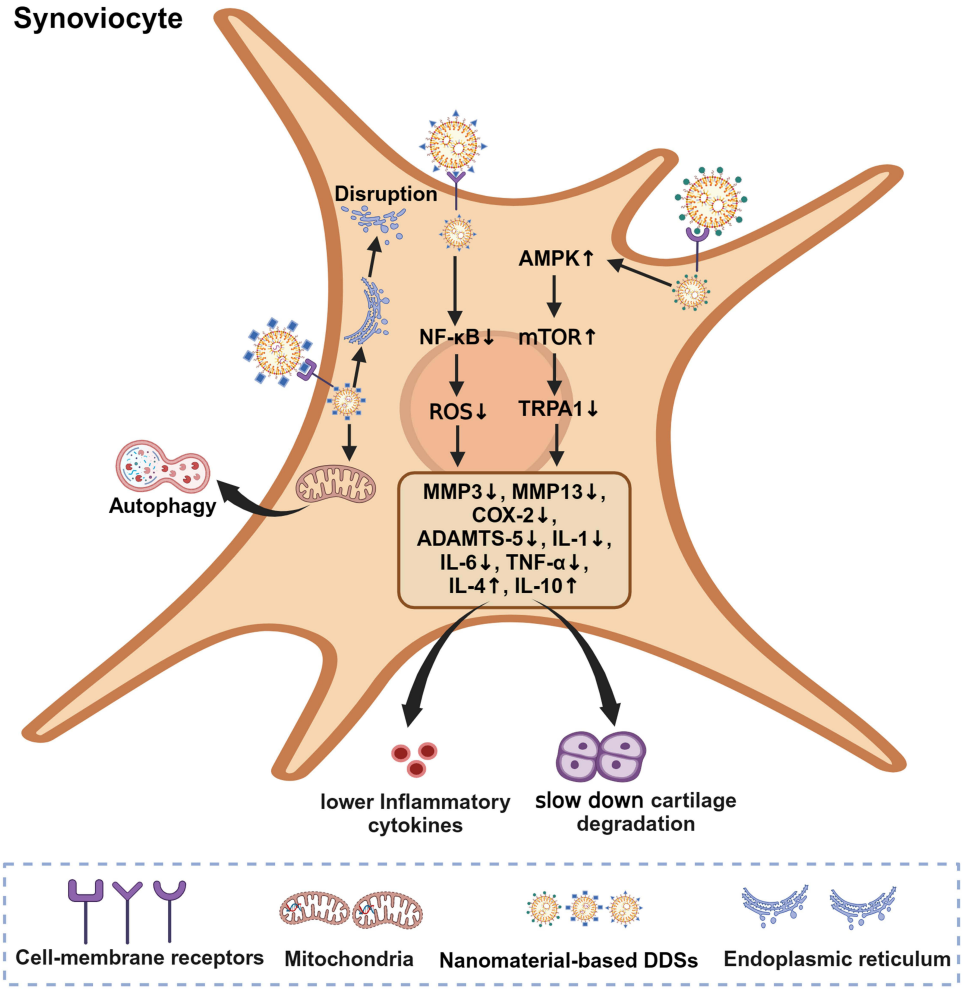

Figure 3 Nanomaterial-based DDSs treat OA by targeting synoviocytes. Nanomedicines modified with different ligands target synoviocytes through the corresponding receptors on synoviocytes to release functional drugs. Different nanomedicines regulate synoviocytes through different mechanisms. On the one hand, nanomedicines down-regulate the NF-kB signaling pathway, thereby reducing the production of ROS. On the other hand, nanomedicines up-regulate the AMPK/mTOR signaling pathway, thereby inhibiting TRPA1. These nanomedicines can down-regulate cartilage degradation factors and inflammatory factors such as MMP3, MMP-13, ADAMTS 5, COX-2, IL-1, IL-6 and TNF-α, and up-regulate cartilage synthesis factors and anti-inflammatory factors such as collegen, IL-4 and IL-10, and finally inhibit inflammation, promote autophagy and delay cartilage degradation.

Table 3 Nanomaterial-Based DDSs Targeting Mesenchymal Stem Cells for the Treatment of OA

Target Cell	Nanomaterial	Recognition Mechanism	Targeting Mechanism	Animal Model	Result	Reference
Mesenchymal stem cells	METP NPs	TPP and mitochondria	Active targeting, ligand and receptor; intracellular microenvironment-responsive	OA mice	Restoring the function of mitochondria and MSC.	[125]
Mesenchymal stem cells	WPV-CuO NPs	WPV and Type II collagen; WPV and MSC	Active targeting, ligand and receptor	OA rats	Inhibiting PI3K/AKT/mTOR pathway and promoting chondrogenesis.	[126]
Mesenchymal stem cells	CuO@MSN-Sox9/BMP7 NPs	WYRGRLCCCC and Col2a1	Active targeting, ligand and receptor	OA mice	Promoting cartilage repair.	[127]
Mesenchymal stem cells	ChoS (HA/CS) NPs	Biorecognition	Passive targeting	/	Promoting cartilage regeneration.	[128]
Mesenchymal stem cells	C-TMN	CD90 and C-TMN surface antibody; COL2 and C-TMN surface antibody	Active targeting, ligand and receptor	OA rats	Reducing the progression of OA.	[129]
Mesenchymal stem cells	PLGA-PEG-HA	HA and CD44	Active targeting, ligand and receptor; electrostatic attraction	/	Promoting the interaction between KGN and MSC.	[130]
Mesenchymal stem cells	PPG-KGN	Biorecognition	Electrostatic attraction	OA rats	Promoting cartilage formation and repair.	[131]
Mesenchymal stem cells	PEG-PAMAM	KGN and MSCs receptor	Active targeting, ligand and receptor	OA rats	Promoting MSCs to differentiate into chondrocytes.	[132]
Mesenchymal stem cells	KGN@PLGA/PDA-PEG-E7	E7 peptide and MSCs receptor	Active targeting, ligand and receptor; PH-responsive	OA rats	Promoting MSCs to differentiate into chondrocytes.	[133]
Mesenchymal stem cells	MNPs-KGN	KGN, PLA and MSCs receptor	Active targeting, ligand and receptor; magnetic field action	OA rats	Promoting MSCs to differentiate into chondrocytes.	[134]
Mesenchymal stem cells	CHI-KGN NPs	Chitosan, KGN and MSCs receptor	Active targeting, ligand and receptor	OA rats	Promoting MSCs to differentiate into chondrocytes.	[135]
Mesenchymal stem cells	NPs-clo	Chitosan, HA and MSCs receptor	Active targeting, ligand and receptor	/	Promoting MSCs to differentiate into chondrocytes and relieving cartilage degeneration.	[136]
Mesenchymal stem cells and chondrocyte and	HNPs/HMP	HNPs, HMPs and MSCs receptor	Active targeting, ligand and receptor	OA rabbit	Scavenging ROS and promoting cartilage regeneration.	[137]
Mesenchymal stem cells and chondrocytes	pPNP + TIIA@PFS	PFS peptide and BMSC surface receptor; pPNP and chondrocyte surface receptor	Active targeting, ligand and receptor; electrostatic attraction	OA rats	Reducing osteophyte formation and articular cartilage degeneration.	[138]

A variety of nanomaterial-based DDSs have demonstrated unique advantages in targeting MSCs for the treatment of OA. These nanomaterial-based DDSs include PLGA NPs, polydopamine (PDA)-modified NPs, and CS (CHI)-bonded NPs with kartogenin (KGN).[139] PLGA NPs can be used as KGN carrier and prepared through emulsification–solvent evaporation method. The PDA modified on its surface can scavenge ROS and reduce oxidative stress.[133] PDA can also improve the hydrophilicity and biocompatibility of NPs and increase their stability and circulation time in vivo. The NPs formed by the combination of CHI and KGN can promote the differentiation of MSCs into chondrocytes and enhance their ability for cartilage regeneration.[135] In addition, magnetic NPs, such as iron oxide NPs, can deliver KGN through surface modification and external magnetic field, which can improve the concentration and residence time of drugs in joints.[129] These nanomaterial-based DDSs can target MSCs through magnetic field, electrostatic attraction, pH response, and mutual recognition between surface ligands and MSC surface receptors and play a therapeutic role (Figure 4).

The mechanism of nanomaterial-based DDSs targeting MSCs in the treatment of OA mainly includes the following aspects. First, nanomaterial-based DDSs can accurately deliver therapeutic drugs to MSCs and regulate their biological

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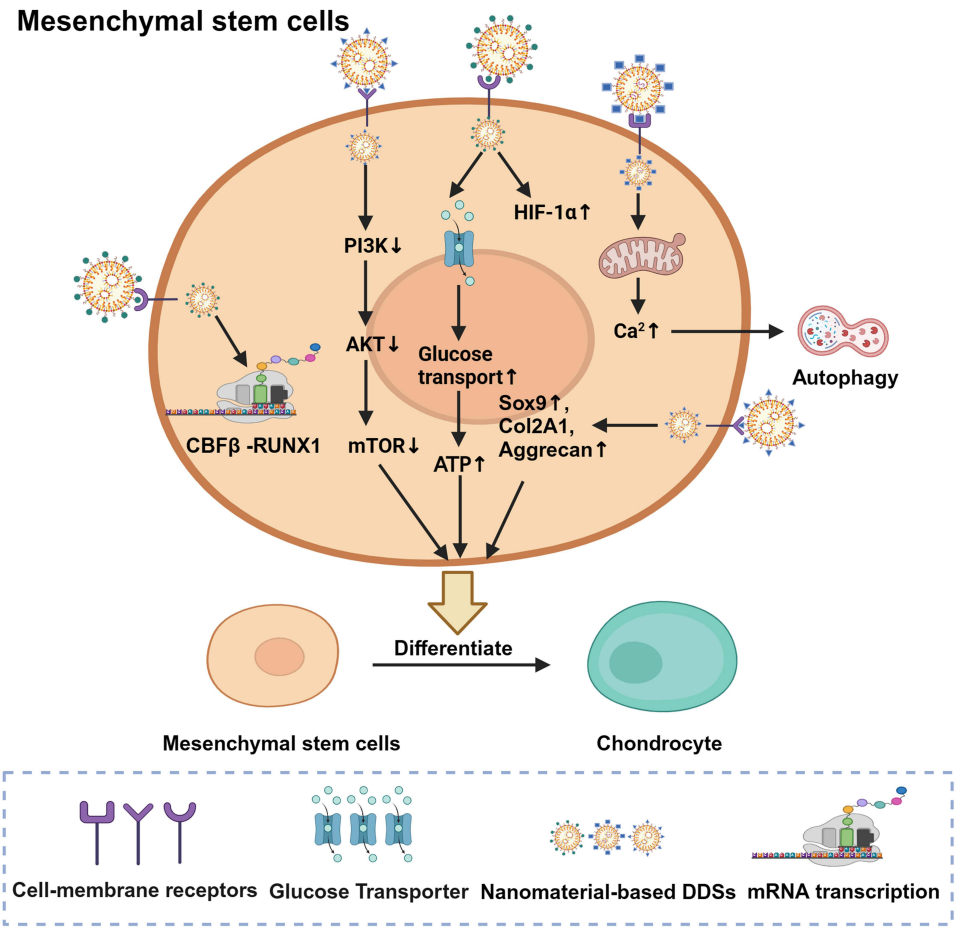

Figure 4 Nanomaterial-based DDSs treat OA by targeting MSCs. Nanomedicines modified with different ligands target MSCs through the corresponding receptors on MSCs to release functional drugs. Different nanomedicines regulate MSCs through different mechanisms. Firstly, nanomedicines up-regulate the PI3K/AKT/mTOR signaling pathway. Secondly, nanomedicines promote glucose transport, thereby releasing more ATP. Thirdly, nanomedicines up-regulate HIF-1α. Fourthly, nanomedicines accelerate the release of Ca^{2+} from mitochondria, thereby promoting autophagy. Fifthly, nanomedicines promote the transcription of CBFβ -RUNX1. Sixthly, nanomedicines up-regulate Sox9, COL2A1 and Aggrecan. These nanomedicines eventually stimulate MCSs to differentiate into chondrocytes.

functions, such as proliferation, differentiation, and migration. Nanomaterial-based DDSs can also deliver KGN to MSCs, induce MSCs to differentiate into chondrocytes, and repair damaged cartilage tissues.[131] Second, nanomaterial-based DDSs can improve the microenvironment of MSCs, reduce inflammation, and inhibit apoptosis. Antioxidants carried by nanomaterial-based DDSs can eliminate ROS, reduce the damage of oxidative stress to MSCs, and maintain the normal function of MSCs.[138] In addition, nanomaterial-based DDSs can reduce inflammation and promote the repair and regeneration of joint tissue by regulating the immune function of MSCs.

Therefore, nanomaterial-based DDSs targeting MSCs is a promising treatment strategy for OA and has great potential for clinical application. By thoroughly studying the characteristics and mechanism of nanomaterial-based DDSs and optimising the treatment plan, more effective treatment methods can be provided for OA patients.

Targeting Chondrocytes

Chondrocytes are the only cell type found in articular cartilage. In the OA microenvironment, inflammatory factors, ROS, and MMPs can induce abnormal chondrocyte function, which further disrupts cartilage homeostasis and accelerates cartilage degradation.[140] The damaged chondrocytes in turn secrete inflammatory mediators that further exacerbate the local inflammatory response, which creates a vicious cycle that accelerates the progression of OA.[141] Therefore, selective chondrocyte-targeted modulation may be a promising therapeutic approach for OA. Table 4 provides the nanomaterial-

Table 4 Nanomaterial-Based DDSs Targeting Chondrocytes for the Treatment of OA

Target Cell	Nanomaterial	Recognition Mechanism	Targeting Mechanism	Animal Model	Result	Reference
Chondrocyte	RNPs	Biorecognition	Passive targeting	OA mice	Promoting cartilage formation and differentiation.	[139]
Chondrocyte	HA-CUR@CS NPs	Biorecognition	Passive targeting	OA mice	Inhibiting inflammation and chondrocyte apoptosis.	[142]
Chondrocyte	MT@PLGA-COLBP	COLBP and collagen II	Active targeting, ligand and receptor	OA mice	Scavenging ROS and improving cartilage metabolism.	[15]
Chondrocyte	PCA NPs	Biorecognition	Passive targeting	OA rats	Reducing inflammation, oxidative stress, matrix degradation and ferroptosis of chondrocytes.	[143]
Chondrocyte	SeNPs	Biorecognition	Passive targeting	OA mice	Inhibiting NF-κB p65 and p38/MAPK signaling pathways, and relieving inflammation.	[144]
Chondrocyte	OHA/HA-ADH@SeNPs	Biorecognition	Passive targeting	OA rats	Scavenging ROS and inhibiting apoptosis	[145]
Chondrocyte	siFoxM1-ACBP-NP	Rho	ROS-responsive	OA mice	Inhibiting chondrocyte aging and cartilage degradation.	[146]
Chondrocyte	Ta-NH_2NPs	Biorecognition	Passive targeting	OA rats	Scavenging ROS.	[147]
Chondrocyte	B2M-CuS NPs	B2M and aged chondrocytes	Passive targeting	OA mice	Removing aged chondrocytes and promoting cartilage regeneration.	[148]
Chondrocyte	GelMA-DSF/NPs	Biorecognition	Electrostatic action	OA rats	Inhibiting inflammation	[149]
Chondrocyte	PGA-Mn	Biorecognition	Electrostatic action	OA rats	Scavenging ROS and reducing inflammation.	[150]
Chondrocyte	CH-CS NPs	CS and CD44	Active targeting, ligand and receptor	/	It is an efficient targeting gene delivery vector for chondrocytes.	[151]
Chondrocyte	O3NPs@MHPCH	D-mannose and chondrocyte surface receptor	Active targeting, ligand and receptor; electrostatic action	OA mice	Relieving inflammation and promoting cartilage proliferation.	[152]
Chondrocyte	HA-NPs	HA and CD44	Active targeting, ligand and receptor	OA mice	Inhibiting cartilage catabolism and protecting articular cartilage.	[153]
Chondrocyte	HA/CNP	HA and CD44	Active targeting, ligand and receptor	OA Rats	Inhibition of inflammation and chondrocyte apoptosis in OA by regulating NF-κB signaling pathway.	[154]
Chondrocyte	LPCAT3-siRNA nanoparticles	Biorecognition	Electrostatic action	OA mice	Inhibiting matrix degradation and inflammation.	[155]
Chondrocyte	Curcumin nanoparticles	Biorecognition	Passive targeting	OA mice	Reducing cartilage erosion and synovitis.	[156]
Chondrocyte	p47phox si_NPs	Biorecognition	Passive targeting	OA rats	Reducing the production of ROS and alleviating the death of chondrocytes.	[157]
Chondrocyte	CNPs	Biorecognition	Passive targeting	/	Scavenging ROS and protecting articular cartilage.	[158]
Chondrocyte	PLGA NPs	Biorecognition	Passive targeting	OA rats	Inhibiting apoptosis and promoting autophagy.	[159]
Chondrocyte	Rebamipide/NPs	Biorecognition	Passive targeting	OA rats	Inhibiting inflammation and relieving joint degeneration.	[160]
Chondrocyte	HA-Lipo-DIC/DEX	Biorecognition	Passive targeting	OA mice	Relieving pain.	[161]
Chondrocyte	PLGA NPs4HCO3	HA and CD44	Active targeting, ligand and receptor	OA mice	Relieving OA.	[162]
Chondrocyte	Cit-AuNRs@Anti-TRPV1	Cit - AuNRs@Anti - TRPV1 and TRPV1	Active targeting, ligand and receptor; near Infrared Responsive	OA mice	Protecting chondrocytes from ferroptosis and reducing the progress of OA.	[163]
Chondrocyte	Hyt@tgel	Biorecognition	Passive targeting	/	Scavenging ROS and inhibiting inflammation.	[164]
Chondrocyte	p66shc si_NPs	Biorecognition	Passive targeting	OA rats	Reducing cartilage damage induced by mitochondrial dysfunction.	[165]
Chondrocyte	K-CS NPs	Biorecognition	Passive targeting	/	Inhibiting inflammation and pain.	[166]
Chondrocyte	TGFα-NPs	Biorecognition	Passive targeting	OA mice	Maintaining the anabolism of articular cartilage.	[167]
Chondrocyte	Cur-NPs	Biorecognition	Passive targeting	/	Inhibiting chondrocyte ferroptosis.	[168]

(*Continued*)

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Table 4 (Continued).

Target Cell	Nanomaterial	Recognition Mechanism	Targeting Mechanism	Animal Model	Result	Reference
Chondrocyte	Pio@C-HA-DOs	WYRGRL peptide and Collagen II	Active targeting, ligand and receptor	OA rats	Reducing ROS level, restoring mitochondrial membrane potential and protecting articular cartilage.	[169]
Chondrocyte	ZASC	Biorecognition	Passive targeting	OA rats	Promoting proliferation, anti-inflammation and anti-apoptosis.	[170]
Chondrocyte	HA/BM/PRP	Biorecognition	Passive targeting	OA rats	Promoting chondrocyte proliferation and protecting chondrocytes from oxidative stress.	[171]
Chondrocyte	PN-KGN	Biorecognition	Passive targeting	OA rats	Reducing matrix degradation and protecting articular cartilage.	[172]
Chondrocyte	FNPs	Biorecognition	Passive targeting	/	Inhibiting inflammation.	[173]
Chondrocyte	AcPEI-NPs	Biorecognition	Passive targeting	/	Inhibiting matrix degradation and protecting articular cartilage.	[174]
Chondrocyte	CBD-PLGA-NPs	Biorecognition	Passive targeting	/	Inhibiting matrix degradation and protecting articular cartilage.	[175]
Chondrocyte	BQ-123-CHI, R-954-HA	Biorecognition	Passive targeting	/	Inhibiting inflammation and cartilage catabolism.	[176]
Chondrocyte	pep-PEI/siRNA nanoparticles	CAP and Chondrocyte surface receptor	Active targeting, ligand and receptor	/	Inhibiting matrix degradation and protecting articular cartilage.	[177]
Chondrocyte	CSL@HMSNs-Cs	Biorecognition	Passive targeting	OA rats	Inhibiting inflammation and cartilage degradation.	[178]
Chondrocyte	geraniol@nanogel	Biorecognition	PH/redox-responsive	OA mice	Regulating oxidative stress and inflammation	[179]
Chondrocyte	Cartilage-penetrating nanocarriers	IGF–1 and IGF–1 receptor	Active targeting, ligand and receptor	OA rats	Improving delivery and efficacy of growth factor treatment of OA.	[180]
Chondrocyte	CeO_2	Biorecognition	Passive targeting	/	Inhibiting oxidative stress and protecting articular cartilage.	[181]
Chondrocyte	Injectable Regenerated Silk Fibroin Micro/Nanosphere	Biorecognition	PH-sensitive; ROS-sensitive	OA mice	Inhibiting apoptosis, relieving oxidative stress and improving neuropathic hyperalgesia.	[182]
Chondrocyte	GC/Fu@KAFAK NGs	Biorecognition	Passive targeting	OA rats	Relieving inflammation and protecting articular cartilage.	[183]
Chondrocyte	AuNps	Biorecognition	Passive targeting	/	Stimulating chondrocyte proliferation and enhancing extracellular matrix production.	[184]
Chondrocyte	PLGA-PEG-PLGA NPs	Biorecognition	Passive targeting	OA rats	Inhibiting inflammation and protecting articular cartilage.	[185]
Chondrocyte	CAP-Lipos-CKIP-1	CAP and chondrocyte surface receptor	Active targeting, ligand and receptor	OA mice	Inhibiting inflammation and degradation of extracellular matrix.	[186]
Chondrocyte	PNIPAM-PMPC	Biorecognition	Passive targeting	/	Enhancing lubrication and local drug delivery.	[187]
Chondrocyte	Chondrocyte-specific aptamer-decorated PEGylated polyamidoamine nanoparticles	tgg2 and FGFR1	Active targeting, ligand and receptor	OA mice	Optimization of transport kinetics of miR-141/200c to chondrocytes.	[188]
Chondrocyte	Qu@ZIF-8	Biorecognition	Passive targeting	OA mice	Protecting chondrocytes from inflammation and apoptosis by activating autophagy and inhibiting PI3k/Akt signaling pathway.	[189]
Chondrocyte	BBR-CNs	Biorecognition	Passive targeting	OA rats	Inhibiting apoptosis and protecting articular cartilage.	[190]
Chondrocyte	NIPAm-co-AMPS-AAc-BAC	Biorecognition	Passive targeting	OA rats	Promoting intra-articular delivery of therapeutic drugs and inhibiting inflammation.	[191]
Chondrocyte	MnO2NPs	Biorecognition	Passive targeting	OA rats	Inhibiting inflammation and oxidative stress.	[192]
Chondrocyte	PDA@CBP-PTH	Biorecognition	Passive targeting	OA rats	Scavenging ROS, enhancing the synthesis and metabolism of subchondral bone.	[193]

(*Continued*)

Table 4 (Continued).

Target Cell	Nanomaterial	Recognition Mechanism	Targeting Mechanism	Animal Model	Result	Reference
Chondrocyte	MSN-OL	Biorecognition	Passive targeting	OA rats	Scavenging ROS and inhibiting apoptosis.	[194]
Chondrocyte	Supramolecular nanoparticle loaded with bilirubin	Biorecognition	Passive targeting	OA rats	Regulating oxidative stress and inflammation.	[195]
Chondrocyte	$Gd_2(CO_3)_3$@PDA nanoparticles	DW peptide and chondrocyte surface receptor	Active targeting, ligand and receptor	OA mice	Anti-apoptosis and anti-inflammation.	[196]
Chondrocyte	p5RHH-siRNA NP	HA and CD44	Active targeting, ligand and receptor	/	Maintaining cartilage homeostasis.	[197]
Chondrocyte	PLA/PEGDA-EDT@rGO-PPGF	Biorecognition	Passive targeting	OA mice	Anti-inflammatory and anti-oxidation.	[198]
Chondrocyte	IA-ZIF-8@HMs	Biorecognition	Passive targeting	OA rats	Inhibiting inflammation and oxidative stress.	[199]
Chondrocyte	PDA-Pd-NPs	Biorecognition	Passive targeting	OA rats	Inhibiting inflammation and oxidative stress.	[200]
Chondrocyte	p5RHH-NF-κB siRNA NP	Biorecognition	Passive targeting	OA mice	Regulating autophagy and maintaining cartilage homeostasis.	[201]
Chondrocyte	AG@MSNs-PAA	Biorecognition	Passive targeting	OA rats	Inhibiting inflammation and protecting articular cartilage.	[202]
Chondrocyte	Q-NP	Biorecognition	Passive targeting	/	Eliminating aging chondrocytes and inhibiting apoptosis.	[203]
Chondrocyte	PCFMN	WYRGRL and collagen II	Active targeting, ligand and receptor	OA rats	Inhibiting inflammation and cartilage catabolism.	[66]
Chondrocyte	p5RHH-siRNA	Biorecognition	Passive targeting	OA mice	Protecting articular cartilage.	[204]
Chondrocyte	CHS-CA-NR	CHS and chondrocyte surface receptor	Active targeting, ligand and receptor	OA rats	Inhibiting inflammation and oxidative stress, improving cartilage matrix biosynthesis.	[205]
Chondrocyte	SA-g-GluNPs	Biorecognition	Passive targeting	/	Inhibiting inflammation and oxidative stress.	[206]
Chondrocyte	PEI/ION	Biorecognition	Magnetic-targeting	OA rabbits	Promoting cartilage repair.	[207]
Chondrocyte	O-HTCC-SOD	Biorecognition	Passive targeting	OA rats	Scavenging ROS and protecting articular cartilage.	[208]

based DDSs targeting chondrocytes for the treatment of OA. Figure 5 shows the mechanism of action of nanomaterial-based DDSs targeting chondrocytes for the treatment of OA.

In the design and development of nanomaterial-based DDSs, targeting is the key to improving therapeutic efficacy. Through surface modification and ligand attachment, nanomaterial-based DDSs can specifically recognize chondrocytes. Researchers often use specific antibodies or targeting peptides to increase the affinity of nanomaterial-based DDSs for chondrocytes, a process that not only improves drug targeting but also reduces damage to surrounding healthy tissues. Liang et al[15] designed a melatonin-loaded nano-delivery system (MT@PLGA-COLBP) whose surface cartilage-targeting peptide (COLBP) can specifically bind to type II collagen on the surface of chondrocytes, which allows the NPs to accumulate and target chondrocytes in the joints. Subsequently, MT@PLGA-COLBP released melatonin, which exerted a protective effect on chondrocytes by inhibiting the TLR2/4-myeloid differentiation primary response 88 (MyD88)-NF-κB signaling pathway and scavenging ROS. Similarly, Xiong et al[66] observed that formononetin (FMN)-PEG (denoted as PCFMN), consisting of PEG, cartilage targeting peptide (CollBP), and FMN, can be used for the treatment of OA. CollBP bound to collagen II, which made PCFMN cartilage-targeted. PEG increased the solubility of the drug. FMN showed anti-inflammatory and antioxidant effects, which protected chondrocytes from oxidative stress damage and activated the Nrf2-dependent antioxidant pathway. Chen et al[169] also developed a WYRGRL-modified HA-based cartilage-targeted nanomicelles (C-HA-DOs). The system consisted of HA, WYRGRL peptide, and dodecylamine. The WYRGRL peptide can specifically bind to collagen II on the surface of chondrocytes to target them. After the NPs entered the cells, Pio@C-HA-DOs protected chondrocytes from oxidative

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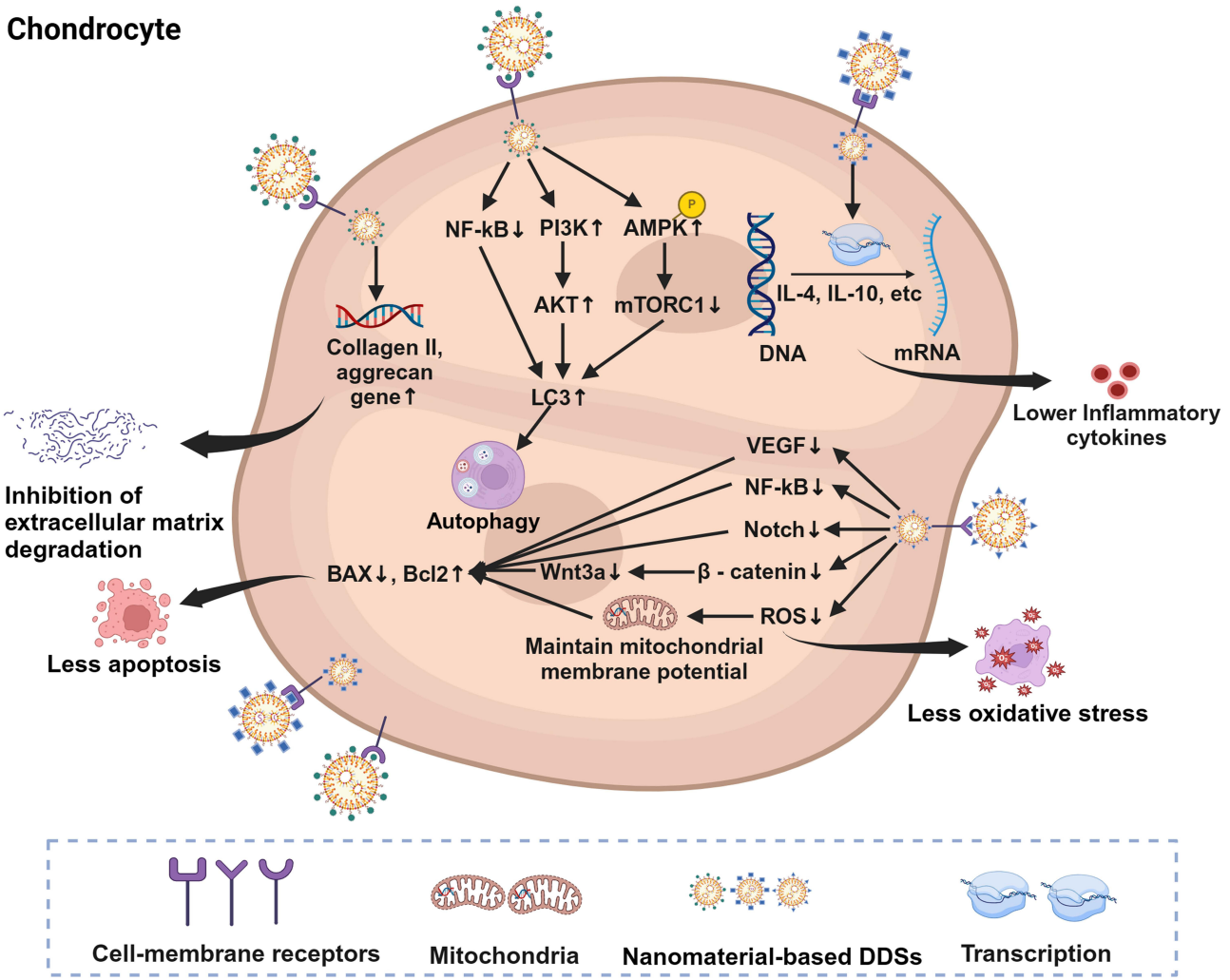

Figure 5 Nanomaterial-based DDSs treat OA by targeting chondrocytes. Nanomedicines modified with different ligands target chondrocytes through the corresponding receptors on chondrocytes to release functional drugs. Different nanomedicines regulate chondrocytes through different mechanisms. Nanomedicines down-regulate signaling pathways such as NF-kB, VEGF, Notch, β-catenin and Wnt3a, and up-regulate signaling pathways such as PI3K/AKT and AMPK. Nanomedicines also up-regulate cartilage degradation, apoptosis, inflammation and autophagy related genes, such as collagen, aggrecan, Bcl-2, IL-4, IL-10, and LC3, thereby inhibiting inflammation, apoptosis, extracellular matrix degradation and oxidative stress, and promoting autophagy.

stress damage by decreasing the intracellular ROS levels and restoring the mitochondrial membrane potential. In addition, the physicochemical properties of nanomaterial-based DDSs, such as size, shape, and surface charge, influence their distribution and targeting ability in vivo.[147,149] Some nanomaterial-based DDSs can also respond to physiological signals in vivo, such as pH and redox potential, to realize intelligent drug release and further improve treatment precision.[146,182]

Nanomaterial-based DDSs can slowly release drugs after entering chondrocytes through endocytosis, which in turn regulates the physiological activities and biological function of chondrocytes. Nanomaterial-based DDSs can effectively deliver anti-inflammatory drugs and promote the regeneration of repair factors, which alleviates symptoms and promotes cartilage repair in OA. PLGA NPs can encapsulate and continuously release drugs, such as rapamycin, which effectively alleviates the symptoms of OA.[139] Some nanomaterial-based DDSs can promote the proliferation and differentiation of chondrocytes, which improves the repair ability of cartilage tissue. CS NPs can improve chondrocyte activity, promote cartilage matrix synthesis, and reduce chondrocyte apoptosis.[142] In addition, nanomaterial-based DDSs can inhibit the inflammatory response and oxidative stress in chondrocytes, which reduces the progression of OA.[152] Therefore, Nanomaterial-based DDSs targeting chondrocytes also have great prospects for application in OA treatment.

Functional Cells Serve as Arrows of Nanomaterial-Based DDSs in the Treatment of OA

Although nanomaterial-based DDSs have achieved great research progress in targeting functional cells to treat OA, some shortcomings remain. Exogenous nanomaterial-based DDSs cannot avoid phagocytosis by reticuloendothelial cells and have poor long-term stability and safety.[209] However, endogenous bionanomimetic membranes display many advantages in nanomaterial-based DDSs, such as low immunogenicity, capability to interact with natural autologous components, long duration of action, and low toxicity and side effects.[210] EVs can also communicate between cells and transport cytokines, small-molecule metabolites, or enzymes to different cells.[211] Therefore, during treatment of OA using nanomaterial-based DDSs, in addition to targeting functional cells, such as macrophages, synoviocytes, MSCs, and chondrocytes, cell membranes or EVs can be used as arrows to target primitive cells (Table 5). Figure 6 briefly illustrates the arrows of nanomaterial-based DDSs for the treatment of OA.

Nanomaterial-Based DDSs Apply Cell Membranes as Arrows

Nanomaterials modified by the cell membrane retain antigens and the cell membrane structure and thus possess the unique functions of protocells, such as active targeting, long-term blood circulation, and immune escape.[221] These characteristics render this type of materials with a great potential for the treatment of OA. A variety of biomembrane nanocarriers have been developed, and they mainly include macrophage, MSC, and chondrocyte membranes.[18,213]

Table 5 Functional Cells Serve as Arrows in the Treatment of OA by Nanomaterial-Based DDSs

Cell Membrane/EV	Nanomaterial	Arrow	Animal Model	Result	Reference
Cell membrane	M2H@RPK	M2 Macrophage membrane	OA rats	Reducing pro-inflammatory cytokines, inhibiting synovitis and relieving joint injury.	[18]
Cell membrane	MVPs	M1 Macrophage membrane	OA mice	Regulating YAP1/TXNIP signaling axis, inhibiting the synovial glycolysis and the infiltration of M1-polarized macrophages, and finally ameliorating OA.	[34]
Cell membrane	DS/TPP-MMSP	Macrophage membrane	OA mice	Scavenging mitochondrial ROS, inhibiting NO synthase, reprogramming mitochondrial metabolism of M1 macrophages, and restoring aerobic respiration.	[212]
Cell membrane	KGN-MNPs	MSCs membrane	OA rats	Promoting cartilage regeneration.	[213]
Cell membrane	NGs	MSCs membrane	OA mice	Inhibiting inflammation.	[214]
Cell membrane	CTP-MSC	MSCs membrane	OA mice	Inhibiting the degradation of extracellular matrix and promoting chondrogenesis.	[215]
Cell membrane	Magcells	MSCs membrane	OA rats	Promoting chondrogenesis.	[216]
Cell membrane	EMNP	MSCs membrane	OA rats	Increasing both cellular uptake and penetration depth in the target cells and tissues under inflammatory microenvironments to protect the injured cartilage.	[217]
Cell membrane	CM-NPs-Ada	Chondrocyte membrane	OA rats	Preventing cartilage degeneration and protecting articular cartilage.	[210]
Cell membrane	DEX@HMCeNs@M	Cell membrane of apoptotic chondrocytes	OA mice	Scavenging ROS, inhibiting inflammation, restoring mitochondrial damage and reducing chondrocyte apoptosis.	[218]
Extracellular Vesicles	T-CD90@NP	CD90 MCSs-derived microvesicles	OA rats	Inhibiting apoptosis, promoting chondrocyte proliferation and relieving inflammation.	[19]
Extracellular Vesicles	MPM	MSCs Exosomes Delivery Microcarriers	OA rats	Promoting cartilage repair.	[219]
Extracellular Vesicles	S-EXO	Synovial-derived exosomes	OA mice	Enhancing the antioxidant capacity of chondrocytes and protecting articular cartilage.	[220]

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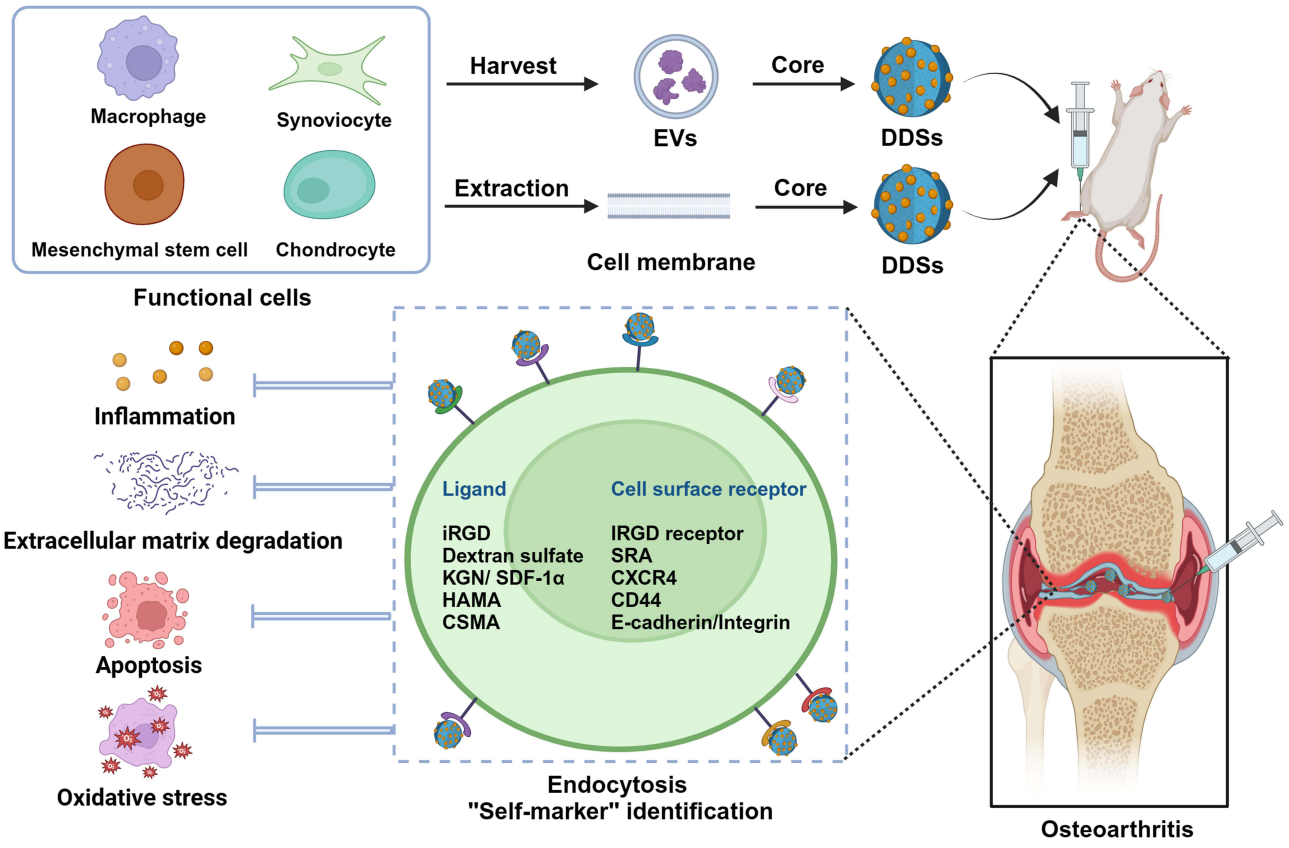

Figure 6 Schematic illustration of cell membranes/EV-disguised nanomaterial-based DDSs. The cell membranes or EVs of functional cells such as macrophages, synoviocytes, MSCs and chondrocytes are extracted and encapsulated in nanomaterial-based DDSs. The nanomaterial-based DDSs are then injected into the knee joint of animals. The nanomaterial-based DDSs use biomolecules such as glycoprotein and integrin on the membrane surface to accurately identify the joint microenvironment, target functional cells and ultimately inhibit inflammation, extracellular matrix degradation, apoptosis and oxidative stress.

During inflammation of the body, a large number of immune cells are activated. In the development of OA, macrophages accumulate in the synovium and joint cavity, where inflammation occurs and induces polarization reaction.[222] Therefore, the biomimetic carriers of macrophage membrane have attracted increasing attention in the field of drug delivery, and the polarization of M2 macrophages shows a great potential in the treatment of OA. Ma et al[223] used mouse macrophage membrane to cover nanogelatin and ChS and crosslinked them to form a nanogel surface to construct artificial M2 macrophages. The results show that, compared to the nanogel without a membrane coverage, the artificial M2 macrophages had evident adhesion and accumulation on the surface of inflammatory cartilage and synovium and an anti-inflammatory effect. Zhou et al[18] used PEI to condense cell-penetrating peptide Kafak and shRNA-LEPR, modified them with HA, and coated M2 macrophage membrane to develop an M2H @ RPK nanotherapeutic system. M2H @ RPK had the highest internalization degree in synoviocytes and can deliver shRNA-LEPR efficiently. Therefore, polarized biomimetic nanocarriers of macrophage membrane can effectively target inflammatory tissues and cells in joints using specific antibodies and chemotaxis on macrophage membrane. In addition, it can also inhibit OA inflammation and delay the progression of OA by promoting macrophage repolarization.

The MSC membrane also serves as one of the carriers commonly used in nanodelivery systems. MSCs have multidirectional differentiation potential and immunomodulatory function, and their cell membranes can retain these characteristics.[215] The application of MSC membrane in nanomaterial-based DDSs can improve their biocompatibility and safety and reduce immune rejection. Zhang et al[217] created MSCs in bone marrow highly expressing CXC chemokine receptor 4 (CXCR4) through genetic engineering technology, which enhanced their ability to migrate to the injured site. Then, the cell membranes of these cells were separated, purified, and coated on fluorescent NPs to prepare NPs with an active targeting capability. These NPs can increase the uptake and penetration depth of damaged

chondrocytes and protect the damaged cartilage. However, the stability and functional integrity of the MSC membrane may be challenged during storage and transportation and thus need further improvement.

Chondrocyte membrane has the physiological function of chondrocytes and can achieve targeted drug delivery. Coating chondrocyte membrane on nanomaterial-based DDSs can improve their uptake and accumulation in chondrocytes. A kind of PLGA NPs coated with chondrocyte membrane can effectively penetrate the cartilage tissue, deliver drugs to chondrocytes, inhibit chondrocyte apoptosis, and promote the synthesis of cartilage matrix.[210] Apoptotic chondrocyte membrane can be recognized and absorbed by macrophages. Coating apoptotic chondrocyte membrane on nanomaterial-based DDSs can enhance the accumulation and retention of nanomaterial-based DDSs at inflammatory sites and improve the therapeutic effect of drugs. The hollow mesoporous cerium oxide nanospheres coated with apoptotic chondrocyte membrane can effectively simulate chondrocyte apoptosis bodies in joints, which enables the targeted delivery of the anti-inflammatory drug dexamethasone and subsequent controlled release triggered by the acidic environment of OA. These nanomaterial-based DDSs can eventually eliminate ROS, relieve inflammation, reduce mitochondrial damage, and inhibit chondrocyte apoptosis.[218]

However, despite the remarkable progress of cell membranes as carriers of nanomaterial-based DDSs in the treatment of OA, several challenges remain. Future studies need to continuously improve the stability and biocompatibility of cell membranes and optimize their modification and functionalization strategies to provide effective means for the treatment of OA.

Nanomaterial-Based DDSs Apply EVs as Arrows

EVs are mainly composed of apoptotic vesicles, microparticles, microvesicles, and exosomes.[224] They can facilitate information transfer between cells by carrying biomolecules, such as proteins, lipids, RNA, etc., and act as carriers to transport bioactive molecules (eg, drugs and signaling molecules) to the target cells.[211] EVs can inherit some endogenous protein ligands from the source cells and actively target specific loci.

MSC-EVs can help nanomaterial-based DDSs to recognize the site of inflammation due to their homing capability. D'Atri et al[214] removed the cytoplasm of MSCs and transformed them into nanosized vesicles. The accumulation of nanovesicles in inflammatory chondrocytes exceeded that in healthy cells. These nanovesicles can target inflammatory cells and show good anti-inflammatory effect, and thus, they are ideal targeted drug-delivery carriers. Colombini et al[225] extracted the exosomes of adipose-derived MSCs to deliver miRNA to the cartilage layer. The penetration test of chondrocyte explants revealed the highest content of exosomes extracted from the collagen-rich cartilage matrix layer. EVs contain a variety of biomolecules that have high targeting and biological safety and can selectively act on recipient cells or deliver biological information to regulate cell functions.

In addition, the common exosomes in EVs, with a diameter of 40–160 nm, mainly originate from the inner buds of cells and surrounded by lipid bilayers.[226,227] Given their immune escape, anti-inflammation, and good capability to target chondrocytes, MSC exosomes are also often used as carriers of nanomaterial-based DDSs to target inflammatory sites. Li et al[19] developed CD90 MSC-derived microvesicles-encapsulated NPs (CD90@NPs) and observed that CD90@NPs can bind to damaged primary chondrocytes. Then, they encapsulated a model glucocorticoid, triamcinolone acetonide, in CD90@NP to form T-CD90@NPs. The injection of T-CD90@NP into the articular cavity can inhibit inflammation and apoptosis and promote cartilage regeneration and repair. Yang et al[219] prepared magnetic polysaccharide microcarriers (MPM) composed of natural polysaccharides, Fe_3O_4@$MgSiO_3$ and an anti-inflammatory drug, diclofenac sodium (DS), and loaded them with exosomes. The MPM showed a good biocompatibility, promoted chondrocyte proliferation, migration, and differentiation, recruited stem cells, and induced macrophage polarization toward M2 phenotypes. MPM-loaded DS and Exo synergistically protected chondrocytes in vitro and effectively attenuated cartilage degradation and promoted chondrogenesis in OA rats in vivo. This finding was comparable to the effect of MSCs. Cao et al[220] prepared a hydrogel microsphere (GM@PDA@S-EXO) enriched with exosomes of SOD3. GM@PDA@S-EXO effectively delivered SOD3 to cartilages, improved the antioxidant capacity of chondrocytes, reduced the level of mitochondrial ROS, and attenuated the progression of OA.

At present, the new method of therapeutic drug delivery by EVs has a great application prospect in the treatment of OA. As a new model of stem-cell therapy, EVs have opened a new avenue to reduce the treatment risk of OA. However,

standardized EV separation technology and quality control means remain lacking, and thus, EV preparation and purification technology must be further explored to ensure their quality and therapeutic effect.

Conclusion and Prospects

With the gradual application of nanomaterial-based DDSs in the treatment of OA, an increasing number of studies have shown that functional cells play an important role as targets or arrows. Nanomaterial-based DDSs targeting functional cells represents a breakthrough frontier in OA therapeutics. The unique advantages of nanomaterials, such as tunable biodistribution, enhanced cellular uptake and stimuli-responsive drug release, make it achieve unprecedented accuracy in modulating chondrocytes, macrophages, synoviocytes and MCSs. This review describes the mechanism of action and research progress of nanomaterial-based DDS-targeted functional cell therapy for OA and discusses how functional cells can be used as the arrow of nanomaterial-based DDSs in the treatment of OA. Nanomaterial-based DDSs use cell membrane and EVs as arrows, which can improve the drug targeting and biocompatibility and reduce side effects.[212,220] Therefore, nanomaterial-based DDSs are expected to become a new means for OA treatment.

Although nanomaterial-based DDSs have obvious curative effects in the treatment of OA, there are still some challenges in clinical application. For example, inconsistent targeting efficiency in heterogeneous OA microenvironment and unresolved long-term biocompatibility concerns. This is mainly due to the clinical complexity of disease progression in patients with OA, and the inability to precisely control the release of drugs in nanomaterial-based DDSs according to the disease conditions of different patients.[209] In addition, the toxicity and elimination of nanomaterial-based DDSs are key challenges limiting clinical translation. Although liposomal and polymeric NPs can be cleared by the reticuloendothelial system, when their particle size is too small, they can easily penetrate vascular endothelium and enter parenchymal organs, resulting in off-target toxicity.[161,165] Notably, nanomaterial-based DDSs mainly rely on renal excretion, hepatic metabolism and phagocytosis by the reticuloendothelial system for in vivo elimination, but the elimination efficiency varies significantly among different materials.[228] For example, dendritic polymers are difficult to filter through glomeruli due to their dense structure and may be retained in the liver, whereas iron oxide NPs can be phagocytosed by macrophages and then excreted via the hepatobiliary system.[229–231] Therefore, there are still many issues that need to be addressed before nanomaterial-based DDSs can be better applied in OA therapy.

In the future, the research on nanomaterial-based DDS-targeted functional cell therapy for OA will continue to deepen. First, with the continuous development of nanotechnology, more novel nanodelivery systems will be developed to provide additional options for OA treatment. Smart NPs can automatically adjust drug release based on changes in the body environment to improve their therapeutic effect.[232] Multifunctional NPs can simultaneously target multiple therapeutic targets to realize synergistic therapy.[233] Second, with the in-depth understanding of OA pathophysiology, more new therapeutic targets will be discovered. Nanomaterial-based DDSs can treat OA by regulating gut flora and inhibiting inflammation. Third, combination therapy is a future development direction.[234] Combining nanomaterial-based DDS-targeted functional cell therapy with traditional therapeutic methods, such as physical and drug therapies, can improve the therapeutic outcomes and reduce side effects. Fourth, integrate nanotechnology with gene-editing tools or design artificial intelligence-driven platforms to develop multi-mode treatments. In future research, we need to strengthen multidisciplinary cooperation and integrate the knowledge and technology of nanotechnology, biology, medicine, and other fields to jointly promote the research and application of nanomaterial-based DDS-targeted functional cell therapy for OA.

Data Sharing Statement

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

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Disclosure

The authors report no conflicts of interest in this work.

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