

Review Article

Nanoparticle-Based Drug Delivery System—A Target Strategy for Osteoarthritis Treatment

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Osteoarthritis (OA) is a bone and joint disease with pathological characteristics such as articular cartilage degeneration injury and synovial and subchondral bone reactive hyperplasia. Once cartilage is damaged, it is difficult to repair it by itself. Current clinical practice is mainly limited to symptomatic treatment, not changing the degenerative process of osteoarthritis. The important goal of nanomedicine is targeted delivery. Nanoparticles (NPs) can provide many unique potential functions for the targeted treatment of arthritis. This review summarizes the research progress of nanomaterials as a drug delivery system in the treatment of osteoarthritis from three aspects: (1) the etiology of OA and the current research status of applying nanoparticles to treat OA, (2) the construction of osteoarthritis models, and (3) the classification of nanoparticle-based drug delivery systems.

1. Introduction

With the increase in life expectancy, obesity rates and sports injuries, the incidence of arthritis is rising steadily [1]. These reasons have promoted the research of tissue engineering materials in orthopedics or joint surgery. Osteoarthritis, also known as degenerative arthritis, senile arthritis, and hypertrophic arthritis, is a bone and joint disease with main pathological characteristics such as articular cartilage degeneration injury, joint edge and subchondral bone reactive hyperplasia, and synovial hyperplasia [2, 3]. Cartilage lacks nourishing pathways (such as blood vessels, nerves, and lymph), consisting of only a single type of cell with low proliferative activity (chondrocytes) [4]. Therefore, once damaged, it is extremely difficult to repair it by itself. The current traditional methods for the treatment of cartilage defects mainly include autologous cartilage transplantation, microfracture (bone marrow stimulation), and autologous chondrocyte transplantation [5]. Although these methods have certain curative effects, they have defects such as large damage to the donor site, inconsistent characteristics of the repaired area and surrounding cartilage, and poor interface healing. Current clinical practice is mainly limited to symptomatic treatment

(pain relief and artificial joint replacement), not involving the underlying molecular cause of OA. This treatment does not change the degenerative process of osteoarthritis. Figure 1 shows the diagram of normal and cartilage osteoarthritis joints.

Nanomaterials refer to materials whose structure is at the nanometer scale in at least one dimension, or is composed of nanostructured units with special properties. It has been extensively studied in the field of tissue engineering, including as a cell growth scaffold to promote bone tissue regeneration and as a transplant material for repairing peripheral nerves [6, 7]. Nanomaterials can perform biological imaging through spectral and fluorescent signals to promote disease diagnosis [8]. At the same time, nanomaterials can also be used as biosensors to effectively monitor disease progression [9]. This review mainly focuses on the targeted delivery function of nanomaterials in the field of OA. Nanomaterials can provide many unique potential functions for the targeted treatment of arthritis, and they include the following: (1) maintaining the concentration of the drug in the target area to maximize the effect of the drug, (2) carrying more drug molecules and increasing the solubility of some hydrophobic drugs, and (3) loading target molecules

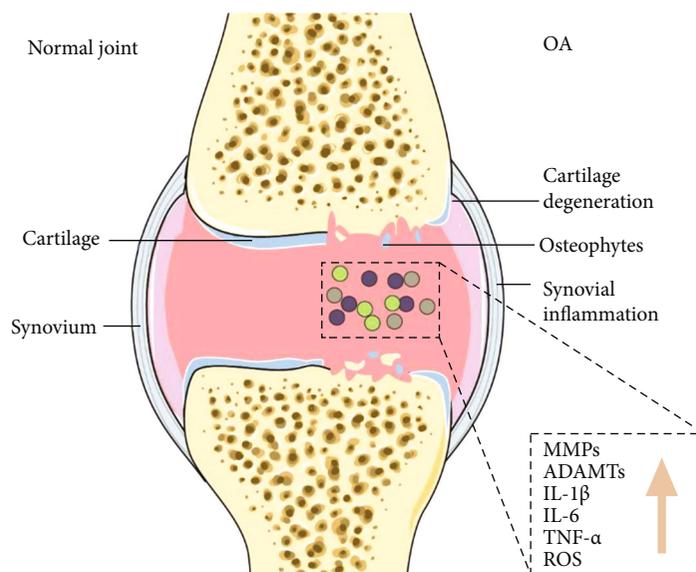


FIGURE 1: Diagram of normal and cartilage osteoarthritis joints.

to nanoparticles through surface modification for targeted delivery [10, 11].

This article summarizes the research progress of nanomaterials as a drug delivery system in the treatment of osteoarthritis from the following aspects: the etiology of OA, the current research status of applying nanoparticles to treat OA, the construction of OA models, and the classification of nanoparticle-based drug delivery systems. In Table 1, we summarize the latest research progress of applying nanoparticles to treat OA.

2. The Etiology of OA and the Current Research Status of Applying Nanoparticles to Treat OA

2.1. Injury. Osteoarthritis that develops after joint injury is considered as posttraumatic osteoarthritis (PTOA) [42]. Both anterior cruciate ligament injury (ACL) and meniscus injury can lead to a high risk of PTOA [43]. At the same time, the load change of the injured joint will promote the development of PTOA. ACL defect or joint reconstruction will change the biomechanical distribution of the tibiofemoral joint contact area, increasing the load on the cartilage area that was previously unloaded and reducing the load on the cartilage area that should have received a higher load during the weight-bearing process, eventually causing the articular cartilage to rupture [44–46]. Studies have shown that quadriceps weakness after knee injury is one of the causes of PTOA [47]. When the quadriceps muscles are weak, as in the case of anterior cruciate ligament injury and reconstruction, they cannot fully absorb the impact energy [48]. This will put more load on the articular cartilage, which will eventually lead to joint degeneration. Intra-articular fractures are also one of the causes of PTOA [49]. Acute mechanical damage and chronic abnormalities of joint load after intra-articular fractures may cause articular cartilage rupture.

Cartilage cells will enhance metabolism through mechanoreceptors on the surface of chondrocytes detecting mechanical load [50]. Through the process of mechanical transduction, mechanical signals are converted into chemical signals to regulate the biochemical activity of chondrocytes and induce molecular biosynthesis to maintain tissue integrity [51]. Mechanoreceptors of cell surface include integrins and mechanosensitive ion channels [52]. Integrin is a kind of transmembrane protein that activates intracellular signal transduction by attaching to downstream signal molecules. The activation of mechanoreceptors triggers a cascade of signals within the cell, causing the tissue remodeling process. Excessive mechanical load leads to the imbalance between synthesis and decomposition, causing the consumption of matrix components, and the lack of regeneration ability, resulting in irreversible damage, making it the most obvious trigger of OA [53, 54].

In past tissue engineering research, cartilage cells were loaded on the surface of biomaterials to promote cartilage repair. However, this method cannot solve the problem that resident chondrocytes secrete abnormal extracellular matrix, and it is difficult to maintain the survival rate of transplanted chondrocytes. To solve these problems, researchers invented a kind of cell-free HA nanoscaffold that provided two cytokines, namely, stromal cell-derived factor-1 α (SDF) to increase MSC recruitment and infiltration, and transforming growth factor- β 3 (TGF- β 3; TGF) to promote the formation of cartilage tissue [31]. The ethylene glycol chitosan/fucoidan nanogels (GC/Fu @ KAFK NGs) loaded with KAFK (anti-inflammatory peptide) were prepared by electrostatic interaction and the natural compound genipin. Researchers found that intra-articular injection of this NP not only inhibited the expression of IL-6 and TNF- α but also increased the expression of the chondrogenesis markers type II collagen, proteoglycan, and Sox9 [30]. Based on the camouflage of the natural BMSC membrane, the researchers encapsulated kartogenin (KGN) as a cartilage regeneration

TABLE 1: Research summary of nanoparticle-based drug delivery systems.

Type of NPs	Carrier	Cargo	Outcome	Ref
Liposomes	(HA)-liposomal	Diclofenac, dexamethasone	Effectively relieving the pain of OA and having good biocompatibility	[12]
	SLN system	Integrin $\beta 1$ overexpression pDNA	Reducing chondrocyte apoptosis and enhancing tissue repair	[13]
Micelles	PNIPAM-PMPC	Diclofenac sodium	PNIPAM-PMPC nanospheres are biocompatible and upregulate anabolic genes, while downregulating articular cartilage catabolism genes	[14]
	Polyethylene oxide- (PEO-) and polypropylene oxide- (PPO-) based polymeric micelles	rAAV sox9	Enhancing the deposition of ECM components and cell survival levels, inhibiting inflammation	[15]
	Acid-activatable polymer	Curcumin	Suppression of tumor necrosis factor-alpha (TNF- α) and interleukin 1 β (IL-1 β). Potent antioxidant and anti-inflammatory activities	[16]
Inorganic NPs		MnO ₂ , gold-based nanoformulations, CeO ₂	COL2a1 and ACAN gene expression in chondrocytes was significantly decreased	[17–19]
	MSNs	pSBMA, colchicine	Due to the hydration lubrication mechanism, the wear resistance of the material is enhanced. Reducing nitric oxide, malondialdehyde, COX2, and TNF- α	[20, 21]
	Zeolitic imidazolate framework-8	S-Methylisothiurea hemisulfate salt	Reducing the content of NO and H ₂ O ₂ , thereby inhibiting the production of HIF1 α and M1 macrophages, alleviating mitochondrial function	[22]
	Membrane-disguised Fe ₃ O ₄	Kartogenin	Enabling rapid and high-quality cartilage regeneration	[23]
Polymer NPs	CD-PMPC	Silica	Enhancing penetration of dermal tissue and lubrication, inducing drug release	[24]
	PLGA-PEG	4MAL, kartogenin (KGN)	Prolonging IA drug retention for the treatment of OA. Increasing sulfated glycosaminoglycans	[25–27]
	Electrostatic self-assembly heparin and ϵ -poly-l-lysine	Platelet lysate	Platelet lysate is evenly distributed	[28]
	Hollow dextran/PNIPAM	KAFK	In cartilage explants to suppress inflammation	[29]
	Glycol chitosan/fucoidan nanogels	KAFK	Inhibiting the expression of TNF- α and IL-6. Enhancing the expression of type II collagen, proteoglycan, and Sox9	[30]
	Electro spun cell-free fibrous hyaluronic acid	SDF-1 α , TGF- $\beta 3$	Increasing recruitment and infiltration of MSCs to enhance cartilage tissue formation	[31]
	PLGA	Andrographolide, p66shc siRNA, diacerein	Inhibiting osteoclast function and inflammation	[32–34]
	Poly(D,L-lactic acid)-poly(ethylene glycol)-poly(D,L-lactic acid)	BMP2	Inducing implant differentiation into cartilage and bone but also completely degraded without toxicity	[35]
	LbL polymer microcapsule	MnO ₂	Eliminating hydrogen peroxide H ₂ O ₂ and protecting cells from oxidative stress	[36]
	Exosomes		miR-140, miR-9-5p, miR-100-5p, miR-135b, miR-1405p, and lncRNA KLF3-AS1	Reducing inflammation and promoting cartilage marker production

drug into Fe₃O₄ nanoparticles. As a result, a nanomaterial with excellent biocompatibility and good biosafety is obtained, achieving high-quality and fast cartilage regeneration [23]. Researchers synthesized cerium oxide nanoparticles (CeO₂) with a particle size of about 120 nm and combined them with hyaluronic acid (HA) to construct

nanodelivery drugs. Through in vitro OA model studies, it was found that the delivery system can protect chondrocytes from oxidative stress, and the expression of COL2a1 and ACAN genes in chondrocytes was significantly increased [19]. Janus-based nanotubes (AAT) self-assemble from analogs of synthetic DNA bases (guanine-cytosine motif), which

can transport small RNA molecules to cells and tissues. Researchers encapsulated the nanotube AAT-packaged miR365 antagomir in the yeast cell wall to construct nano-administrative particles. This nanodrug delivery system inhibited the content of miR365 by oral administration to treat PTOA (mice) [55].

2.2. Inflammation. OA is also a disease caused by underlying immune response leading to bone remodeling and cartilage degradation. Typical symptoms include swelling, pain, and stiffness [56]. By initiating the inflammatory process and inducing cartilage decomposition, the early changes in the cartilage surface are manifested as fibers extending distally, forming deep cracks, leading to cartilage delamination, forming calcified cartilage [57]. The thinning of articular cartilage is closely associated with dilation of basal calcified cartilage, which in turn leads to increased mechanical stress and further production of degrading factors [58]. Major signaling molecules involved in OA immune response are usually divided into the anti-inflammatory and inflammatory groups. The inflammatory cytokines include TNF- α , IL-1 β , IL-6, IL-8, and IL-17, and the anti-inflammatory cytokines include IL-13, IL-4, IL-10, and IL-1Ra [42, 49, 59]. Cytokines can participate in the pathological process of cartilage degeneration by mediating multiple signaling pathways, mainly including the mitogen-activated protein kinase (MAPK) signaling pathway [60], the AMPK signaling pathway [61], and the Wnt/ β -catenin signaling pathways [62]. They can also promote the synthesis of PGE₂ and induce the production of chondrocytes to synthesize metalloproteinases (ADAMTS) [63], HIF2 α , NOS2, MMPs, and COX2, thereby promoting the inflammatory process and inhibiting the proliferation of chondrocytes [64, 65].

Therefore, implanting anti-inflammatory factors or enzymes into the joint cavity and maintaining the drug concentration is another research direction for OA treatment. Hollow dextran/PNIPAM nanoparticles loaded with KAFK effectively deliver therapeutic peptides to inhibit inflammation. These heat-responsive nanoparticles may be an effective drug delivery system that can deliver anti-inflammatory therapeutic peptides in an OA environment [29]. The researchers encapsulated three hydrophobic anti-inflammatory drugs (tenoxicam, dexamethasone, and celecoxib) into core-shell terpolymer nanoparticles. Experiments have shown that these loaded nanoparticles have the activity of acting as inflammatory mediator production regulators in vitro [66]. MnO₂ nanoparticles, with excellent biocompatibility, can be used as artificial nanoenzymes to effectively eliminate reactive oxygen. Hollow MnO₂ (H-MnO₂) was synthesized by the Stober method and modified with NH₂-PEG-NH₂, reducing the inflammatory response of OA [17].

2.3. Obesity. Obesity is a state of excessive accumulation of fat in the body, which is believed to be directly related to some metabolic diseases such as high blood pressure, dyslipidemia, diabetes, and osteoarthritis [67–69]. Obesity plays an important role in the occurrence and development of weight-bearing and non-weight-bearing joint osteoarthritis. Increased joint load and systemic metabolic changes may

be important factors in the occurrence of obesity-related osteoarthritis. Moderate mechanical load can maintain the dynamic balance and integrity of articular cartilage. Compared with normal BMI people, tibiofemoral cartilage of high BMI people withstand more compressive stress during short-term running tasks [70]. The proteoglycan content in obese subjects is reduced, indicating that the cartilage is in a “pre-osteoarthritis” state. Osteoarthritis caused by obesity is defined as a “metabolic osteoarthritis” phenotype [71]. Metabolic osteoarthritis is associated with increased fat deposits that release inflammatory cytokines/adipokines, leading to systemic inflammation, cartilage loss, and osteophyte formation [72].

In order to solve the abrasion caused by mechanical erosion, viscoelastic supplements based on hyaluronic acid (HA) have been widely used to treat knee joint injuries. However, current HA formulation cannot provide effective healing and recovery. Researchers have developed a nanofiber-HA membrane system to protect arthritic cartilage tissue from degeneration. The material has a unique scaffold structure that can provide a 3D microenvironment like natural ECM, and deliver biologically active signals that can activate chondrocyte proliferation and functional collagen I synthesis. Researchers injected the ankle joint to fill the joint cavity and found that this hybrid nanofiber membrane has a better therapeutic effect than the commercially available Hyalgan and Synvisc gels at a lower concentration, providing a simple and feasible alternative to OA treatment [73].

2.4. Age. Age is one of the main factors of osteoarthritis. There are literatures showing that the prevalence of knee arthritis increases almost linearly after the age of 40 [74]. The incidence of osteoarthritis increase with age, which may be due to the accumulation of various risk factors and the result of biological changes [75]. Osteoarthritis is characterized by the imbalance between catabolic and anabolic activities in the joints. Aging chondrocytes do not respond well to growth factor stimulation and cannot maintain the homeostasis of articular cartilage, leading to the occurrence of OA [76].

How to improve the response of aging chondrocytes to growth factors has received extensive attention. Platelet lysate (PL) is a cost-effective mixture of growth factors. Electrostatic self-assembly heparin (Hep) and ϵ -poly-L-lysine (EPL) nanoparticles (NPs) were engineered to enhance the sustained release ability of PL. This nanodrug delivery material retained the initial gelling ability and showed long-term PL release ability, ameliorating cartilage degeneration in the late stage of OA [28]. Researchers have prepared a cationic lipid nanoparticle (SLN) system that can efficiently deliver plasmid DNA (pDNA) into cells. This study reported that the overexpression of pDNA carrying integrin β 1 was transported into rat chondrocytes via liposomes, reducing IL-1 β -stimulated chondrocyte apoptosis and enhancing tissue repair [13]. Researchers developed a thermosensitive bifunctional nanosphere polymer (PNIPAM-PMPC) through emulsion polymerization. The nanospheres can enhance lubrication by forming a hydration layer around the base

of the zwitterion head, and deliver local drug by wrapping diclofenac sodium (an anti-inflammatory drug) [14, 77].

2.5. Genetic Factors. Epidemiological studies have confirmed that genetic factors play a major role in the pathogenesis of osteoarthritis. Studies based on the family history also confirmed that OA has hereditary susceptibility [78, 79]. The main mechanisms leading to OA were chemical modification of DNA, such as methylation, posttranslational modification of histones, and regulation of noncoding RNA.

- (1) DNA methylation is a type of chemical modification of DNA that can alter the performance of genes without changing the DNA sequence. It refers to the covalent attachment of the methyl group to the 5th carbon position of cytosine in the genomic CpG dinucleotide under the action of DNA methyltransferase. Studies have shown that DNA methylation can cause changes in chromatin structure, DNA conformation, DNA stability, and the way DNA interacts with proteins, thereby controlling the gene expression. The analysis of the whole genome showed that the methylation of genes related to OA have changed, including genes encoding transcription factors, such as SOX9; genes encoding ECM protein and matrix degrading protease, including COL2a1, ACAN, and MMP13; and participating genes that signal growth factors and cytokines, such as GDF5 and BMP7 [80]. Some emerging trends indicate that methylation patterns may differ between different OA joints and stages of the disease [81]. For example, different methylation patterns may occur between knee cartilage and hip cartilage, and between mild and severe cartilage from the same joint [82, 83]
- (2) Gene expression is a complex process regulated by multiple factors. Histones are an important part of the basic structure of chromosomes-nucleosomes, and their N-terminal amino acid residues can undergo acetylation, methylation, phosphorylation, and ubiquitination [84]
- (3) Noncoding RNA (ncRNA) refers to RNA that does not encode protein. These include rRNA, tRNA, snRNA, snoRNA, microRNA, and other RNAs [85]. The common feature of these RNAs is that they can be transcribed from the genome, performing their biological functions at the RNA level without being translated into proteins [86]. For example, miR-140 can inhibit the expression of harmful genes ADAMTS5, MMP13, and IGFBP5 in OA [87]

Upregulating gene expression in target organs by delivering specific signaling molecules is a kind of method to treat OA caused by inheritance. Exosomes contain specific information about the source cell, with ability to deliver molecules targeting organs or tissues. The application of exosomes and their derivatives by intra-articular injection open up new possibilities for the treatment of OA. Studies

have shown that exosomes derived from primary chondrocytes that overexpress miR-95-5p promoted cartilage development and cartilage matrix expression by directly targeting histone deacetylase [88]. Exosomal miR-8485 may regulate the expression of GSK-3 to suppress the production of glycogen synthase kinase, targeting the binding antagonist of DACT1 to activate the Wnt/ β -catenin pathway and promote cartilage differentiation [89]. In Figure 2, we show the common predisposing factors of osteoarthritis.

3. Method of Constructing an OA Animal Model

Animal models are essential in studying the etiology of the disease and the effectiveness of various treatment tools. The ideal model should include the following features: (1) all joint tissues (as the human body) are affected; (2) early stages of the disease are included; (3) animal models can simulate human disease; (4) animal species are easy to handle and raise; (5) the results can be evaluated in different biochemical, genetic, and imaging biomarkers, and should be transferable to the specificity of human medical therapeutics and pathology. It is recommended to consider the following points when selecting the OA model: the stage of OA that needs to be studied, the expansion of the lesion (focal or systemic), the therapeutic effect, and the target tissue to be studied (cartilage, membrane, bones, or synovial fluid) [90].

OA models can be divided into induced models (surgery or injection) and spontaneous models (natural development and genetic models). Spontaneous models can be used to study the pathogenesis of OA, with high economic costs and long time to achieve goals [91, 92]. On the contrary, the induction model achieves a reproducible and early OA model, but it prevents researchers from studying the possible pathogenesis of diseases. Small mammals (mice, rats), rabbits, and guinea pigs are the most common models for studying the pathogenesis and pathophysiology of OA.

3.1. Spontaneous Models (Age, Obesity, and Genetic Factor). The main feature of spontaneous models is slow evolution, with a very long research cycle and high economic costs. However, they have an excellent correlation with natural processes from a pathophysiological point of view. Spontaneous models can be further subdivided into two subgroups: naturally occurring models or models produced by individual genetic manipulation.

3.1.1. Age. OA tends to occur in the elderly. The animal model of spontaneous osteoarthritis is close to the progression of human OA, as a valuable tool for studying the pathogenesis of osteoarthritis. When a Hartly guinea pig about 3 months old weighs 700 g, OA may appear on the medial tibial plateau of the knee joint. By the age of 18 months, the guinea pig's medial tibial plateau had severe OA pathological changes and there was no meniscus covering on the surface [93, 94]. OA is manifested by cartilage degradation, mainly histological changes in the cartilage in the weight-bearing area, which is similar to the occurrence and development of human osteoarthritis. The distribution

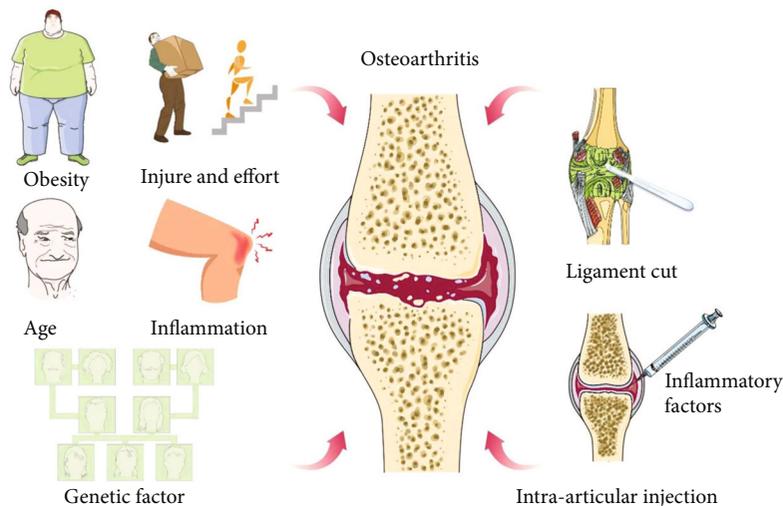


FIGURE 2: The etiology of osteoarthritis and the model construction method.

of glycosaminoglycans in cartilage is abnormal. Studies have found that the production of NO in guinea pig knee cartilage cells is positively correlated with age and the progression of OA, suggesting that it may be an important factor leading to mitochondrial dysfunction and calcification of OA chondrocytes [63, 95]. It can be observed that 12-20-week-old STR/ort mice have knee joint OA lesions [96]. The histological changes are mainly manifested as severe degeneration of the medial articular cartilage, similar to human OA, and calcification of the subchondral layer. This kind of mice also showed a marked increase in the release of local and systemic inflammatory factors, such as RAGE, AGE, IL-1, and IL-6 [97].

3.1.2. Obesity. Obesity can cause a variety of musculoskeletal system diseases, especially OA. The entire joint tissue, especially the synovial tissue, is affected by a high-fat diet. Obesity has been confirmed to be associated with the development of posttraumatic arthritis through a variety of mechanisms [98]. The mouse obesity model is usually induced by a high-fat diet. Louer et al. fed C57BL/6 mice with normal food (13% fat) and a high-fat diet (60% fat) from 4 weeks of age. After 16 weeks of age, the medial meniscus (destabilization of the medial meniscus (DMM)) was removed. The results showed that the serum levels of systemic inflammatory factors and proinflammatory factors increased in the high-fat group, including IL-12p70, IL-6, TNF- α , and several other chemokines [99]. STR/ort mice are more prone to osteoarthritis and hyperlipidemia. Studies confirmed that STR/ort mice have same symptoms as human hyperlipidemia patients, such as high serum total cholesterol, high serum triglycerides, hyperinsulinemia, and insulin resistance. It is a good model for studying abnormal lipid metabolism and OA.

3.1.3. Genetic Factor. With the rapid development of transgenic technology, transgenic animal models provide new options for osteoarthritis research. Animal studies have found that in the process of OA, knocking out apoptosis-

related genes will ultimately lead to the occurrence of OA. However, conventional gene knockout methods can easily cause embryonic death or severe bone deformation. In order to overcome this defect, conditionally inducible gene knockout technology is widely used, such as Bgn-Fbn double gene knockout mice [100, 101]. Biglycan and fibromodulin are two small molecular proteoglycans coexpressed in tissues such as tendon, cartilage, and bone. The double gene knockout mice can present heterotopic ossification and OA lesions similar to STR/ort mice. The genetically modified mice lack the expression of bone morphogenetic protein (BMP) receptor protein specifically in joints, resulting in the occurrence of multijoint OA lesions at an early stage. Genetically modified mouse OA models usually include mice lacking expression of type II collagen, mice lacking expression of type IX collagen, MMP13 transgenic mice, and aggrecan knockout mice [102–104].

Animal models of spontaneous OA formation have similar pathogenic characteristics to human OA: the initial stage and the progression of the disease are more moderate, which is better than operation animal models. It is worth noting that due to the slow development of the disease, the early diagnosis of OA is difficult, and researchers need to pay attention to the pathological changes.

3.2. Induced Models (Surgery or Injection)

3.2.1. Surgical Induction Models. The biomechanical changes of weight-bearing joints caused by instability are an important reason for OA, which can lead to the degeneration of articular cartilage cells, degrading the extracellular matrix. Surgery or man-made trauma causes the joints to lose stability and the stress changes on the joint contact surface, inducing the occurrence of OA. This modeling method usually shows the formation process of OA after trauma.

(1) *Anterior Cruciate Ligament Transection (ALCT)*. This is the most commonly used method for establishing OA models in recent years. After the anterior cruciate ligament

is cut, the number of cartilage cells in the superficial zone decreases, swells, and becomes fibrotic [105, 106]. The degradation products of denatured type II collagen are significantly increased in the fibrotic area. It was reported that after cutting the anterior cruciate ligament of the canine knee joint, the synovial membrane of the canine joint was thickened, the cartilage surface was eroded and osteophytes formed [107]. This phenomenon is the same as the pathological changes of natural joint instability caused by the rupture of the anterior cruciate ligament. This kind of model is simple to operate with less traumatic. It can fully reflect the pathological process of cartilage degeneration. However, this method takes a long time to successfully model—at least 6 weeks. Some researchers fix the contralateral limb after the rabbit anterior cruciate ligament is removed, so that the surgical limb is overloaded, and the time to make the OA model is shorter [108].

(2) *Meniscal Destabilization*. The researchers removed part of the meniscus of the rabbit knee joint, causing the instability of the joint. The meniscus resection alone can reduce the damage caused by the operation, but the modeling time is correspondingly prolonged. 12 weeks after removal of the lateral meniscus of the miniature pig's knees, the number of chondrocytes and the proteoglycan content decreased, the number of cells arranged in clusters increased, the thickness of cartilage became thinner, the surface of cartilage became fibrotic, and the femoral intercondylar notch osteophytes formed [109, 110].

(3) *Hulth Model*. Under sterile conditions, a longitudinal cut is made on the inside of the knee joint, the cruciate ligament and medial collateral ligament are cut off, and the medial meniscus is completely resected without damaging the articular cartilage surface. After the operation, the injured limb was not fixed and moved freely. After experimental animals underwent the Hulth method surgery, due to joint instability, increased friction on the articular surface, and the lack of cushioning effect of the meniscus, osteoarthritis can easily occur [111].

(4) *Models for Generating Focal Defects*. In the OA model obtained through intra-articular surgery, joint instability is a factor that promotes the progress of OA. At the same time, in this type of OA model, the presence of synovial inflammation leads to joint degeneration, which will affect the therapeutic effect of treatment measures for cartilage protection and repair. An articular focal defect is a good model for observing the pathology development. Researchers used sharp tools to scratch the articular cartilage in the weight-bearing area of the joint, but they did not damage the subchondral bone. This method would lead to pathological changes in the bone and joint. The joint focal defect method is an ideal model for observing the early manifestations and treatment effects of OA. It is particularly sensitive in observing the therapeutic effects of cartilage protection and repair [112, 113].

3.2.2. *Intra-Articular Injection*. Toxic or inflammatory compounds were injected directly into the joint cavity of the

knee joint to induce disease by destroying the extracellular matrix or articular cartilage cells. This method is simple to operate, reproducible, and has a short cycle. It is suitable for OA pathology and antiosteoarthritis drug research. Commonly used injections to induce osteoarthritis include papain, collagenase, and monosodium iodoacetate. Researchers have found that collagenase can cause cartilage destruction and joint tissue inflammation in rabbit knee joints in the early stage and articular cartilage degradation in the late stage [114]. The glycolysis inhibitor monosodium iodoacetate (MIA) was injected into the knee joints of Wistar rats. Within 1 week, chondrocytes became degenerated and necrotic, and full-thickness changes of cartilage could also appear in the tibia and femoral condyles. MIA injection-induced osteoarthritis is currently the most commonly used pharmaceutical preparation [115]. Vitamin A, hyaluronidase, cartilage fragments or foreign bodies, adrenal cortex hormones, etc. injected into the joint cavity of animals can also cause articular cartilage degeneration and form an OA model [116, 117].

3.2.3. *Joint Brake Modeling Method*. The composition, structure, and function of articular cartilage can be maintained only by ensuring the normal movement and function of the joints. Fixing limbs to break the joints can induce articular cartilage atrophy, resulting in cartilage thinning, edema, and decreased proteoglycan content [118]. Because these cartilage changes are similar to the pathological changes of human OA, this model is especially used for the study of cartilage degeneration. However, the use of this model has gradually decreased in the research on the differences in the basic morphology of cartilage. In the cartilage of OA, chondrocytes proliferate focally in cell clusters or cell nests, which are usually active at the later stage of OA. In the fixed-joint model, chondrocytes have no such changes. However, cell clusters often become necrotic, especially when the splint is firmly fixed without any movement. This change in cartilage may be caused by the lack of nutrients in cartilage cells. Moreover, if the immobilized limbs are allowed to move in a small range, the range of cartilage degeneration will be significantly reduced [119, 120]. In Table 2, we compare the characteristics of several osteoarthritis models.

4. Classification of Nanoparticle-Based Drug Delivery System

Nanomaterials have a close relationship with biological bodies in terms of size. For example, the ribonucleic acid protein complex, one of the elements of life, has a linearity between 15 and 20 nm. Nanobiomedical materials are the intersection of nanomaterials and biomedical materials. Nanoparticles and other materials are combined to make various composite materials. With the further deepening of research, nanomaterials have begun to penetrate into many disciplines, showing great potential application value. In recent years, the exuberant development of nanotechnology in drug delivery systems has spawned new methods for treating OA. This section describes the current development and new applications of NP-based drug delivery for the treatment of OA,

TABLE 2: Classification and characteristics of osteoarthritis animal models.

	Spontaneous models	Surgical induction models	Intra-articular injection models
Principle of the experiment	The cause of OA is related to certain genetic mutations OA spontaneously occurs with age Genetically modified animals constructed using transgenic or gene knockout technologies can also spontaneously form OA	Using surgery to cause disease in the joint cavity to produce OA	Injecting toxic or inflammatory compounds directly into the joint cavity of the joint to induce disease by destroying extracellular matrix or articular cartilage cells
Types of commonly used models	Male Hartly guinea pig, STR/ort mice, Bgn-Fbn double gene knockout mice, Cre-Gdf5/Bmpr1a floxP mice	The Hulth method, anterior cruciate ligament transection (ACLT), partial or full meniscus resection, medial meniscus tear, joint mark method	Types of drugs: chemicals, enzymes, and hormones Common injection drugs: MIA, collagenase, papain, etc. (1) The molding speed is fast (2) The pathological changes of cartilage in the end-stage OA can be observed in a short time (3) Less traumatic and easy to operate
Advantage	Animal models of spontaneous OA have similar pathogenic characteristics to humans	Using aseptic technique to induce, the results are highly reproducible and the modeling experiments are shorter	
Disadvantage	Early diagnosis of OA is difficult. The research time is long. The model may be restricted by environmental factors, ethical conditions, and high economic cost	(1) The trauma is large, and postoperative infection is prone to occur (2) Traumatic arthritis and synovial inflammation may occur during the operation, which may affect the experimental results	It is difficult to have a certain standard for drug dosage. Different animals have different doses of drugs injected. Therefore, a poor grasp of the drug dosage will cause errors in experiments

including liposomes, micelles, polymeric nanoparticles, exosomes, and inorganic nanoparticles [121].

4.1. Exosome. Exosomes are membrane vesicles with a diameter from 30 to 150 nm, reflecting complex molecular processes that occur in parent cells. Exosomes, as endogenous drugs, have diagnostic, drug delivery, and targeted therapy capabilities by transporting nucleic acids (DNA, mRNA, microRNA, and lncRNA), biologically active lipids, and proteins [122]. Exosomes do not require the same harsh storage conditions as seed cells, but can perform functions similar to seed cells. Therefore, it is more suitable for treatment and delivering active substances [123, 124].

Exosomes used to treat OA are principally derived from MSCs. Recent studies have shown that exosomal miRNA and lncRNA play a key role in anti-OA. It remains a major challenge to deliver a drug through the dense cartilage matrix. Liang et al. use lysosomal-membrane glycoprotein to fuse chondrocyte active peptide (CAP) on the surface of chondrocyte-derived exosomes. In vivo studies have shown that the delivery of miR-140 based on CAP exosomes significantly reduces the development of OA in a rat model by IA injection [37]. Several recent studies have shown that miRNA may participate in the regulation of several signals such as the SIRT1/p53 pathway, the Wnt/-catenin pathway, and the NF- κ B pathway, thereby regulating the expression of genes involved in the decomposition and anabolism of OA. By delivering miRNA, exosomes can inhibit the production of proteolytic enzymes and proinflammatory cytokines (e.g., IL-1, IL-6, and TNF- α) to affect the treatment of OA [125, 126].

Natural exosomes have their own therapeutic agents and can be used for drug delivery. However, the number of exosomes released by cells is uncertain due to the lack of clinical research. Obtaining a sufficient number of exosomes for in vivo research is a technical challenge. In order to increase the production of exosomes, some studies are exploring the use of three-dimensional spheres or tetrahedrons to transport therapeutic substances. With the elucidation of exosomal mechanism and the maturity of exosomal manufacturing technology, it will create a new field of OA treatment [127].

4.2. Liposome. The liposome is an artificial membrane. When the hydrophilic head of the phospholipid molecule is inserted into the water, the hydrophobic tail of the liposome extends to the air. After agitation, a spherical liposome with a double layer of lipid molecules is formed, with a diameter ranging from 25 to 1000 nm [13]. Liposomes can be used for genetically modified or prepared medicines. The liposomes can fuse with the cell membrane to deliver the medicines into the cell. Liposomes are the first nanodrug carrier approved by the FDA, deemed to be the most ideal drug delivery vehicle. Liposome formulations have been extensively tested as drug delivery vehicles in OA, not only because of their ability to carry hydrophobic and hydrophilic drugs but also because of their excellent biocompatibility.

Adenosine is a key autocrine cytokine for maintaining cartilage homeostasis. The A2A receptor is a kind of receptor for adenosine. Researchers encapsulated adenosine and A2A receptor agonists in liposomes, and then they injected the liposomes to prevent the OA progression of obesity-

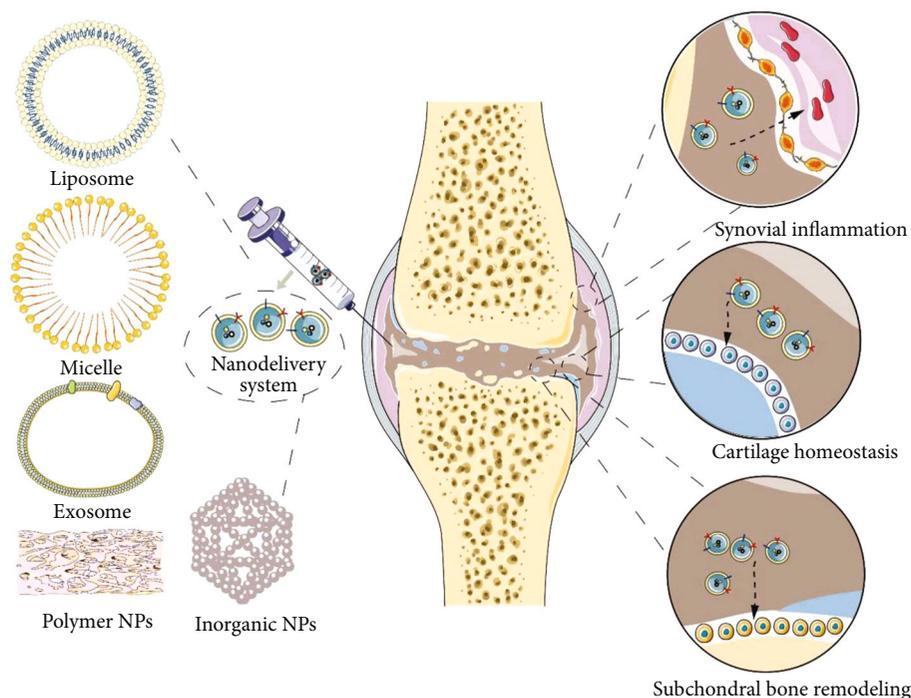


FIGURE 3: Classification and function of a nanoparticle-based drug delivery system.

induced mouse and rat posttraumatic OA [128]. Recent studies have shown that rapamycin encapsulated in liposomes has a notable anti-inflammatory effect in the spontaneous OA model [129].

4.3. Micelle. Micelle refers to the orderly aggregates of molecules that begin to form in large quantities after the surfactant concentration in an aqueous solution reaches the critical micelle concentration (CMC). In micelles, the hydrophobic groups of surfactant molecules aggregate to form the inner core of the micelle, and the hydrophilic polar groups form the outer layer of the micelle. Micelles can also be taken up by cells by binding to ligands, antibodies, or peptides. Because of its low CMC, polymer micelles have a longer cycle time and are more stable, so they are the most widely used in drug delivery systems [130, 131].

A study has reported that overexpression of the SOX9 transcription factor by using polymer micelles as a carrier can readjust the metabolic balance in OA. In the presence of inflammatory factors IL-1 β and TNF- α , micellar-guided rAAV-sox9 increases the level of extracellular cartilage matrix (ECM) deposition and chondrocyte survival [15].

4.4. Inorganic Nanoparticles. Inorganic nanoparticles (INPs) are synthesized from inorganic particles and biodegradable polycations. Typical inorganic nanoparticles include metal, metal oxides, and carbon materials (such as fullerenes, nanotubes, and fibers) and magnetic nanoparticles composed of superparamagnetic iron oxide nanoparticles (SPION). The more commonly used is mesoporous silica nanoparticles (MSN), which have the characteristics of uniform pores, easy functionalization, biocompatibility, high specific surface area, large pore volume, and biodegradability. In order to

improve the gene loading efficiency and cell absorption efficiency of MSN, its surface or inner pore will be coated with a cationic polymer [132, 133].

The researchers prepared mesoporous silica nanoparticles (MSN) and used them as an encapsulant for colchicine. The free colchicine or encapsulated drug is then embedded in the self-healing hydrogel. Treatment studies of this drug delivery in a rat osteoarthritis model induced by monoiodoacetic acid (MIA) have shown that nanoparticle/hydrogel patches have an effective and safe therapeutic potential for OA [21]. Oxidative stress is caused by the accumulation of reactive oxygen and nitrogen substances (ROS and RNS) in the cell microenvironment. These ROS and RNS can destroy the cell structure, leading to cell apoptosis and senescence. Researchers use the layer-by-layer (LbL) method to manufacture polymer microcapsules that encapsulate manganese dioxide nanoparticles to exert antioxidant effects [36].

4.5. Polymer Nanoparticles. Cationic polymers have become another major type of nonviral gene delivery vehicle due to their ease of synthesis and flexibility. For example, synthetic or natural siRNA nanopolymers are colloidal solid materials that are specifically designed to degrade in the body without producing toxic components. Polymers can be combined with nucleic acids to form multimeric complexes at physiological pH to facilitate gene delivery. Generally, polymer nanoparticles have positively charged units to promote electrostatic binding with nucleic acids [134]. However, by using a degradable linker (such as a disulfide bond or a sulfhydryl-maleimide bond), the covalent linkage of the nucleic acid and the polymer can also be achieved. Representatives in this category are synthetic polymers, such as poly-L-lysine, poly-L-ornithine, linear and branched polyethyleneimine (PEI),

TABLE 3: Classification and characteristics of nanoparticle-based drug delivery system.

Nanocarriers	Classification	Advantage	Disadvantage
Lipid based	Liposome	Operability, stability, low toxicity. Embedding lipophilic and hydrophilic drug	Drug leakage, easily degraded
	Micelle	Improving the solubility of lipophilic drugs, operability, releasing the drug in a controlled manner	Nonencapsulated hydrophilic drugs, CMC dependency, toxicity
PNP	PLA, PLGA, PCL, chitosan, alginate, gelatin, albumin	Combining hydrophilic and hydrophobic drugs, stability, sustained release	Poor drug loading, toxicity
Exosome		Natural source, biocompatibility, targeting	Low yield, uncertain dose
Inorganic NP	CeO ₂ , MnO ₂ , Pt	Simple to prepare	Toxicity, poor targeting ability

diethylaminoethyl-dextran, polyamide-amine dendrimer (PAMAM), and polydimethylaminoethyl methacrylate (PDMAEMA). In addition, natural polymers, such as chitosan (CS), dextran and gelatin, and complex synthetic substances are currently under study [135, 136].

Studies have reported that poly(lactic-co-glycolic acid) (PLGA), loaded with p66shc-siRNA, was injected into the knee joint of rats to inhibit the expression of p66shc and relieve the pain, cartilage damage, and inflammatory cytokine production induced by sodium iodoacetate (MIA) [33]. Researchers designed the nanocomposite 4-arm-poly(ethylene glycol)-maleimide (PEG-4 MAL) microgels. This kind of gel presents the effect of joint tuberculosis peptide and overcomes the adverse effects caused by the gel after rapid clearance. The gel can stay in the joint space for at least 3 weeks without causing any joint-degenerative changes [26]. In Figure 3, we show the classification and functions of five NP-based drug delivery systems.

5. Conclusion and Prospects

Although the NP-based drug delivery system shows significant targeting ability in OA treatment, there are still some shortcomings in clinical application. We have listed the characteristics of different NP-based drug delivery systems in Table 3. PNP particles, such as PLGA, have been widely used because of the diverse forms. However, due to immune rejection, it may cause a new inflammatory response in vivo. Polymer nanoparticles modified by HA, chitosan, or other materials are a new direction to improve the biocompatibility of nanomaterials [137]. On the contrary, as an endogenous substance, exosomes have good biocompatibility, but the purification methods and the extremely low yield hinder its further development. Significantly improving the yield of exosomes is an important direction for future exosome research [123]. Although liposome-based drug delivery systems have been extensively studied, they are not the best choice for hydrophilic drugs. For inorganic nanoparticles, the extremely low targeting and instability limit their further applications.

Current clinical treatments for OA are only to delay the symptom of the disease, relieve pain, and improve motor function [7]. There is still a major challenge in nanoparticle-based drug delivery systems for OA treatment. In addition to

the common problems of treatment drugs in the body (immune response, ethical challenges, and biocompatibility issues), there is a fact that needs to be overcome: “resident chondrocytes cannot secrete matrix with the same characteristics as those formed during development [138].” The ultimate goal of NP-based drug delivery systems is the complete regeneration of the limbs, which requires “forming multiple types of tissues at the same time and assembling these into complex organ systems.” As explained in this review, NP-based drug delivery systems are promising for the treatment of OA [139].

Although this article outlines the developments of NP-based drug delivery systems, there are still many challenges ahead: (1) Various nanomaterials need to be combined to produce an effective therapeutic delivery system. For example, the use of nanoscaffold materials loaded with cytokines can induce chondrocyte production while restoring cartilage defects. (2) Nanomaterials can be studied to deliver drugs to other joint tissues, including fat pads, ligaments, and meniscus, all of which contribute to the research of OA treatment. (3) NP-based drug delivery systems can be engineered by modifying liposome membranes to improve the targeting ability. NP-based drug delivery systems are one of the most promising methods in the field of tissue and organ repair. By improving new strategies and technologies, regenerative tissue engineering will eventually be able to deal with more complex tissue systems, organs, and limbs. The drug delivery system based on NPs may continue to push us to adopt a comprehensive treatment strategy and contribute to the treatment of OA.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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