四川大学学报（医学版） 2026，57（2）：347－366
J Sichuan Univ（Med Sci）

在线全文

Nanoparticle Delivery Systems in Rheumatoid Arthritis: More Than Vehicles

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This work was supported by the National Key R&D Program of China (No. 2022YFC2406600, No. 2022YFC2406604) and the National Natural Science Foundation of China (No. 82272400).

[**Abstract**] Rheumatoid arthritis (RA) is one of the most prevalent systemic autoimmune inflammatory diseases worldwide, causing chronic, progressively worsening arthritis that may ultimately lead to disability. Despite the availability of numerous therapeutic agents, limitations exhibit, including poor aqueous solubility, suboptimal stability, inadequate permeability, short half-lives, and multi-organ toxicity during long-term or high-dose administration. Nanoparticle-based drug delivery offers a robust strategy to mitigate these deficiencies while maximizing therapeutic efficacy through controlled-release mechanisms and rational administration route design. This review systematically summarizes recent advancements in nanoparticle drug delivery strategies for RA treatment from the perspective of three distinct mechanisms. It details the design rationales, therapeutic principles, and effects of various delivery systems, with particular emphasis on their interactions with the disease microenvironment and the entire body.

[**Key words**] Nanoparticle Drug delivery Rheumatoid arthritis Controlled release Review

类风湿关节炎中的纳米颗粒递送系统：不仅仅是载体*

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【**摘要**】 作为全球范围内最常见的系统性自身免疫炎症性疾病之一，类风湿关节炎（rheumatoid arthritis, RA）可导致慢性、进行性加重的关节炎，最终可能导致残疾。尽管已有多种治疗药物可供选择，但这些药物仍存在一些局限性，包括水溶性差、稳定性不佳、渗透性不足、半衰期短，以及长期或大剂量给药时产生的多器官毒性。基于纳米颗粒的药物递送是一种强有力的策略，能够通过控制释放药物和合理的给药途径来改善这些缺陷，并最大限度地提高治疗效果。本综述从三种不同的作用机制角度，系统总结了纳米颗粒药物递送策略在RA治疗中的最新进展，并详细阐述了各类递送系统的设计原理、治疗机制和疗效，特别强调了递送系统与疾病微环境以及整个机体的相互作用。

【**关键词**】 纳米颗粒 药物递送 类风湿关节炎 控制释放 综述

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune inflammatory diseases, with a prevalence ranging from 0.25% to 1% worldwide[1]. RA is characterized by persistent synovitis, bone erosion, and cartilage damage in the joints, while extra-articular manifestations such as subcutaneous nodules, hematological abnormalities, and interstitial lung disease occur in about 40% of RA patients[2-3]. If not treated adequately, RA may lead to progressive disability, premature death, and high socioeconomic costs[4-5].

RA progression is generally divided into three stages: the autoimmune response and non-specific inflammation stage, the chronic inflammation stage, and the tissue damage stage mediated by cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α)[6-9]. The pathological process of RA primarily involves synovial hyperplasia and pannus formation, with other joint components, including cartilage, subchondral bone, tendon, tendon sheaths, capsule, and ligaments, typically affected during the course of the disease[10]. Therefore, the main aim and strategy for RA management are relatively clear. Generally, the objectives of clinical treatment are to

* 国家重点研发计划（No. 2022YFC2406600、No. 2022YFC2406604）和国家自然科学基金面上项目（No. 82272400）资助

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出版日期：2026-03-20

① decrease pain, inflammation, and edema; ② prevent bone deformity; ③ prevent joint destruction and improve joint function; and ④ alleviate systemic symptoms[11-12].

Disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids (GCs), and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in clinical RA treatment[13]. Timely intervention has a disproportionate long-term impact, and prompt initiation of DMARD therapy within a few weeks or months of disease onset has been proven crucial to improving prognosis and long-term outcomes in RA[14]. DMARDs are classified into three categories: ① conventional synthetic DMARDs, such as methotrexate; ② biological DMARDs, such as TNF inhibitors; and ③ targeted synthetic DMARDs, such as JAK inhibitors[3]. Among these, methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine are most commonly used, especially methotrexate, which is traditionally regarded as the first-line therapy and the anchor drug[15]. In addition to DMARDs, GCs are also fundamental in the management of RA, commonly used as bridging therapy when DMARD therapy is initiated, and in some patients, as long-term maintenance therapy[3, 16]. Studies have shown that GCs can improve disease activity and functional status in RA patients[17-18].

Although widely used in clinical treatment, the drugs mentioned above have significant shortcomings. Methotrexate has low bioavailability and a short half-life when administered orally or intravenously, due to its poor water solubility and permeability. Long-term systemic use or dose escalation of methotrexate can result in adverse effects such as stomatitis, mucosal ulcers, and alopecia, or more severe hepatic, pulmonary, renal, and bone marrow abnormalities[19-21]. GCs have a well-known risk profile of side effects, especially with prolonged exposure to high doses[3]. Notably, even low- to medium-dose GCs are associated with adverse effects[22]. The main adverse events of GCs include cardiovascular diseases, infections, gastrointestinal diseases, psychological disorders, endocrine pathologies, dermatological issues, musculoskeletal disorders, and ophthalmological diseases[23]. Despite the slightly divergent positions of the ACR and EULAR on the use of glucocorticoids for RA treatment[24-25], the short-term anti-inflammatory effect and side effects of GCs limit their use in terms of dosage and duration. Representing the newest class of drugs, JAK inhibitors act by inhibiting a family of protein kinases, thereby blocking the production of multiple cytokines implicated in the pathogenesis of RA[3]. However, side effects may also occur, including increased risk of reactivation of herpes zoster infection, venous thromboembolism, serious heart-related events, cancer, blood clots, and mortality[26-28], which restrict the application of JAK inhibitors. Thus, the limitations of current therapeutic agents for RA include high doses, severe side effects, long-term use, and unsatisfactory therapeutic effects[11]. Novel treatment strategies are needed to address the limitations of existing drugs.

With the development of biomaterials, drug delivery strategies have been substantially improved and applied for disease treatment[29]. Appropriate "packing" can not only enhance the pharmacokinetics, solubility, and bioavailability of drugs, but also reduce their side effects by controlling the release rate[30-31]. Accurate targeted delivery, using RA as an example, can specifically affect the cells that mediate or amplify most permanent tissue destruction while sparing other cells that do not contribute to joint damage[32-33].

Among bidirectional strategies for drug delivery, nanoparticle-based delivery has emerged as an outstanding option[34-35], and has been applied in research and even in the treatment of some diseases, especially cancer. For example, Abraxane, a paclitaxel albumin-binding nanoparticle, has been approved by the FDA to treat metastatic breast cancer[29]. In recent years, research on nanomedicine in RA has increased rapidly and advanced significantly[36]. The pathological features in the affected joints of RA patients, such as the acidic environment, elevated reactive oxygen species (ROS) levels, and increased matrix metalloproteinase (MMP) activity, provide responsive signals for drug release in nanodelivery systems. Meanwhile, the complex pathogenic network of RA, formed by cells such as macrophages, T cells, B cells, fibroblast-like synoviocytes (FLSs), and the cytokines they secrete, collectively offers a rich array of targets for targeted drug delivery systems. However, most existing reviews focus on the characteristics of nanoparticles themselves, such as material properties, manufacturing, and release methods, rather than the mechanisms of action of the entire drug-nanoparticle

delivery systems and the changes they bring to the local microenvironment.

In this review, we summarize the latest drug delivery strategies based on nanoparticles in RA treatment. Notably, we emphasize the therapeutic mechanisms of the entire drug-nanoparticle delivery systems, their interactions with the tissue microenvironment, and the therapeutic effects they produce, aiming to bridge the gap between basic and clinical science.

1 Targeting mechanisms, drug release response signals, types of drugs, and administration routes of nanoparticle drug delivery in RA treatment

1.1 Targeting mechanisms of nanoparticle drug delivery

Nanoparticles with appropriate sizes can accumulate in inflamed joints via the ELVIS effect (extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration), which leverages endothelial gaps in hyperplastic blood vessels within inflamed synovium[37-38]. However, due to the minimal proportion of dilated vessels in inflamed synovium relative to the body's total vasculature, this passive targeting is inefficient, resulting in suboptimal local drug enrichment[39-40]. Therefore, building on the ELVIS effect, nanoparticles are often functionalized with targeting ligands to enhance drug accumulation and therapeutic efficacy at inflamed sites through active targeting[41-42]. For example, to actively target macrophages, a common target in RA treatment, ligands can be attached to nanocarrier surfaces to bind macrophage receptors such as CD44, SR-A, and the folic acid receptor.

1.2 Response signals for triggering drug release from nanoparticle carriers

The ideal scenario for drug delivery requires minimal leakage before reaching the target site and precisely stimuli-triggered payload release at the designated location.

Currently, commonly used release signals originate from specific alterations within the RA inflammatory joint microenvironment, which are endogenous signals. RA-inflamed joints exhibit characteristics such as slight acidity, elevated ROS levels, and high MMP activity. Nanoparticles are designed to trigger specific chemical reactions within this microenvironment to release drugs[43-45]. Other delivery strategies utilize exogenous signals to promote drug release. For example, in ultrasound (US)-targeted microbubble (MB) destruction (UTMD) technology, when US energy is applied to tissue following intravenous injection of MBs, it induces MB oscillation. This enhances vascular and cell membrane permeability through the cavitation effect, facilitating drug entry into tissues and cells[11, 46]. Another example involves the fabrication of drug-loaded carriers using phase-transition gel materials combined with nanoparticles. When exposed to near-infrared (NIR) irradiation externally, the gel undergoes a phase transition to achieve controlled drug release[47].

1.3 Types of drugs delivered by nanoparticles for RA treatment

Theoretically, a wide range of drugs can be delivered by properly engineering the delivery carriers. However, not all drugs require delivery, and the objective of using nanoparticulate delivery must be clarified during the design phase.

Among current drugs for RA treatment, several categories have been successfully incorporated into nanoparticulate delivery systems. Traditional therapeutics such as methotrexate and glucocorticoids (GCs) demonstrate improved water solubility, permeability, bioavailability, and extended half-life with reduced adverse effects through nano-delivery. Emerging biologics such as infliximab, when delivered via nanoparticles, mitigate risks associated with prolonged high-concentration systemic exposure[48]. Specialized agents including siRNA and bone marrow-derived mesenchymal stem cells (BMSCs) benefit from nanocarrier encapsulation, which protects siRNA from degradation and shields implanted BMSCs from ROS/hypoxia-mediated cell death and osteogenic limitation, thereby optimizing therapeutic efficacy[49-50]. Moreover, active components from traditional Chinese medicine (such as resveratrol and triptolide) can overcome poor solubility, poor stability, rapid elimination, and multi-organ toxicity through nano-delivery systems.

1.4 Administration routes of nanoparticle-based drugs for RA treatment

Administration routes vary considerably depending on the delivered therapeutics and the design of the nano-delivery system. Intravenous injection remains the predominant approach, while alternative methods include

intra-articular injection, subcutaneous administration, oral delivery, and transdermal penetration. Among these, non-invasive routes such as oral and transdermal administration enhance patient compliance due to their convenience and ease of use. Emerging microneedle (MN) technology represents a breakthrough in transdermal drug delivery for arthritis, combining painless administration with enhanced localized therapy. The integration of nanoparticles within MNs further improves drug stability, solubility, and bioavailability, ensuring rapid accumulation at the target site.

2 Nanoparticle delivery strategies in RA treatment based on mechanisms of action

In this section, we categorize nanoparticle-based drug delivery strategies for RA treatment according to their mechanisms of action, summarizing recent advances from three perspectives: inflammation inhibition, antioxidation, and macrophage polarization alteration. Representative and distinctive strategies are selected for detailed elaboration.

2.1 Inflammation inhibition

The inflammatory response is the cornerstone of RA, involving a complex network of cells such as macrophages, lymphocytes, and FLSs, as well as the pro-inflammatory cytokines they secrete[51-52]. Various cytokines, such as TNF-α and IL-1, induce synovial hyperplasia and pain, followed by the invasion of degrading enzymes, mostly MMPs, into the cartilage and bone. In addition, TNF-α and IL-1 contribute to bone destruction[10].

Therefore, inflammation inhibition is the primary consideration and an essential part of RA management. Existing nanoparticle delivery systems suppress inflammation in RA by inhibiting related cells such as macrophages and lymphocytes, or certain signaling pathways. Different delivery systems are described below in terms of targeted cells and targeted sites.

2.1.1 Targeting macrophages

The inflammatory microenvironment of joints induces macrophages to polarize into the M1 phenotype. M1 macrophages, which interact with a variety of cells (e.g., T cells, B cells, and FLSs), secrete inflammatory cytokines such as TNF-α, IL-1β, and IL-6, driving responses that cause joint pain, swelling, and bone erosion[53-55]. Suppression of activated macrophages, induction of macrophage apoptosis, inhibition of M1 polarization, or induction of macrophage polarization toward the M2 phenotype is effective for the relief of RA[56]. Targeting macrophages can be achieved through various receptors (such as folate receptors, CD44 receptors) or by being captured by macrophages. Since nanoparticle delivery systems that modulate macrophage polarization often have additional mechanisms of action, they will be described separately in section 2.3, "Macrophage polarization alteration", to avoid redundancy.

HAN *et al.*[57] synthesized a fluorinated polyamidoamine (FP) dendrimer to deliver miR-23b into inflamed joints. Dendrimer polyamidoamine (PAMAM) has been widely used as a gene carrier in cancer treatment rather than in RA, possibly due to its limited transfection efficiency. To address this, a fluorination strategy was employed to modify PAMAM, resulting in FP. Compared with PAMAM nanoparticles, FP demonstrated improved endosomal escape ability and higher transfection efficiency, ensuring better drug delivery effectiveness. Regarding treatment effectiveness, in vitro experiments showed that after transfection into LPS-stimulated macrophages, FP/miR-23b effectively inhibited TAB2/3 and IKKA, blocking the NF-κB signaling pathway. Inflammatory cytokines such as TNF, IL-1β, and IL-6 were not efficiently secreted into the joint cavity to activate the inflammatory response, which could ultimately interrupt the inflammatory loop in RA development. In addition, miR-23b delivery also induced an effective apoptotic response in progressively proliferative macrophages via a mitochondrial-dependent apoptotic pathway. *In vivo* experiments showed that FP/miR-23b nanoparticles injected into experimental RA models exhibited therapeutic efficacy, including inhibition of the inflammatory response, reduced bone and cartilage erosion, suppression of synoviocyte infiltration, and recovery of mobility. Notably, FP/miR-23b achieved better therapeutic effects than PAMAM/miR-23b, both *in vivo* and *in vitro*.

GUO *et al.*[11] constructed a methotrexate-loaded mesoporous silica cell-mimetic composite nanoplatform (MMPRF), which is essentially a modified mesoporous silica nanoparticle (MSN). MSNs are well suited as nanocarriers but have the drawback of premature and rapid drug release. Polydopamine (PDA) was introduced to

improve stability by forming an adhesive layer on the surface of MSNs (MMP), thereby encapsulating and slowly releasing drugs. Extracted red blood cell membranes and functionalized phospholipid DSPE-PEG2000-FA were cloaked on the nanoparticles to prolong the effective circulation time of drugs *in vivo* and to target activated macrophages via folate receptors, respectively. Additionally, UTMD was applied to enhance controlled drug release and promote drug entry into tissues and cells. *In vitro* experiments showed that MMPRF was taken up more by activated macrophages than MMP, indicating a better ability of the cell-mimetic "cloak" to target macrophages. After injection into CIA rats, nanoparticles in the MMPRF + US + MB group accumulated most in the ankle joints compared with the MMP and MMPRF groups. Rats in the MMPRF group had lower TNF-α and IL-1β levels, lower arthritis scores, and greater increases in bone mass. These treatment results were further improved when MMPRF was combined with US and MB.

Apart from folate receptors, CD44 receptors are also commonly used to target macrophages. CD44 receptor-mediated macrophage-targeted nanoparticles with multiple advantages were designed to address one of the issues affecting delivery efficiency[43]. A considerable portion of nanoparticle delivery systems are internalized into cells through the endocytosis pathway, and escape from the endocytic pathway is the rate-determining step during delivery, as failure to escape results in entrapment and potential degradation in the lysosome[58]. LI *et al.*[43] fabricated a polyelectrolyte nanocarrier (TP/PNPs) composed of the interaction between poly (β-amino ester) (PBAE) and hyaluronic acid (HA). PBAE at weakly acidic pH (i.e., the joint cavity environment of RA) induces the "proton sponge" effect, facilitating endo/lysosomal escape. HA is significant in articular cartilage lubrication, analgesia, anti-inflammation, immunoregulation, and chondroprotection. The combination of PBAE and HA made the nanoparticle not only a vehicle for targeted delivery but also a therapeutic agent to some extent.

To maximize therapeutic efficacy, in addition to improving delivery efficiency, extending drug retention in inflamed synovium is also worth pursuing. QIN *et al.*[59] fabricated an inflammation-responsive, shape-transformable nanoparticle termed Dex-KLVFF-PSA nanoparticles (DKPNPs), composed of amyloid β-derived KLVFF peptide, polysialic acid (PSA), and dexamethasone (Dex or DEX) coupled with an acid-sensitive linker. PSA can specifically bind to sialic acid-binding immunoglobulin-like lectin-E (Siglec-E) expressed on macrophages and facilitate inflammation-targeted delivery[60-61]. Under inflammatory conditions, Dex dissociation triggered by acidic pH or macrophage-induced specific binding with PSA induced the reassembly of DKPNPs from nanoparticles to nanofibers, leading to decreased lymphatic clearance and prolonged efficacy[59]. After injection into AIA rats, DKPNPs showed nearly 20 μg/mL of Dex concentration at 36 hours in arthritic joints, much higher than free Dex and PSA-Dex nanoparticles (PDNPs). Moreover, the T1/2 in the DKPNPs-treated group was 3.78 times higher than that in the PDNPs group in arthritic joints, indicating excellent retention capacity. AIA rats in the DKPNPs group showed superior inhibition of joint and paw swelling, minimal levels of TNF-α and IL-17A, and the development of RA was almost completely suppressed.

In addition to systemic administration, transdermal drug delivery system (TDDS) formulations are a promising approach for long-term RA treatment, as they can avoid the liver first-pass effect, prevent gastrointestinal irritation, and maintain blood concentration for a sustained release effect[62-63].

Overexpressed scavenger receptor A (SR-A) can also be used as a target against macrophage. ZHAO *et al.*[63] developed an SR-A-targeted transdermal formulation: dextran sulfate (DS)-modified DEX-loaded flexible liposome hydrogel (DS-FLs/DEX). DS-FLs/DEX exhibited sustained acid-sensitive drug release and high uptake in macrophages *in vitro*, and ensured improved skin permeation of the encapsulated DEX. DS-FLs/DEX exhibited significantly greater therapeutic efficacy than regular liposome hydrogel (DS-RLs/DEX) in AIA rats, as evidenced by a marked reduction in paw thickness, lower clinical scores, reduced inflammatory cytokine levels, and significantly decreased synovial inflammation and cartilage erosion, possibly due to the higher deformability and permeability of DS-FLs/DEX in arthritic skin.

Dextran-sulfate-PVGLIG-celastrol, named DPC@Cel,

is another example of macrophage-targeted nanomedicine via SR-A[45]. Celastrol was used as the hydrophobic core, and dextran sulfate (DS) served as the hydrophilic block and targeted SR-A. The release of celastrol depended on the hydrolysis and disruption of the bAla-Pro-Val-Gly-Leu-Ile-Gly-bAla-Cys (PVGLIG) peptide by high levels of MMP-2 enzyme in inflammatory joints, making drug release in the joint cavity specific. *In vitro*, DPC@Cel increased the accumulation of celastrol in macrophages and improved the drug release rate in inflammatory joints. AIA rats treated with DPC@Cel showed better therapeutic results in joint swelling, arthritis scores, synovial inflammation, and bone erosion compared with free Cel and CPC@Cel.

Building on this, the research team improved this nanomedicine[64]. Achyranthes polysaccharide was used as the hydrophilic end, and a reactive oxygen species (ROS)-responsive thioketal bond was introduced to synthesize a curcumin-prodrug nanomedicine named Abps-tk-Cur. The previous DPC@Cel was mixed with Abps-tk-Cur to create D&A@Cel. In addition to the proven characteristics of DPC@Cel, the Cel bonds endowed the nanocarrier with ROS responsiveness for more effective specific drug release.

Medicine targeted intestinal macrophages, as well as synovial macrophages, can also regulate inflammatory responses. HU *et al.*[65] synthesized a TNF-α short hairpin RNA (shRNA) oral drug system mediated by non-pathogenic yeast (yeast/TNF-α shRNA). In the gastrointestinal tract, the non-starch polysaccharides on the yeast cell, termed β-D-glucans, can be recognized by macrophages, which are then transported with the circulation of macrophages to exert immunomodulatory activity at joint inflammatory sites and systemically[66]. TNF-α shRNA mediated by yeast significantly reduced the expression of TNF-α, a predominant pro-inflammatory factor, in intestinal macrophages and joint synovium, and upregulated the expression of anti-inflammatory cytokines such as IL-10[65]. At the same time, joint swelling and RA scores were significantly improved in RA rats fed with yeast/TNF-α shRNA, demonstrating its potential as a novel gene therapy strategy.

2.1.2 Targeting lymphocytes

Tregs have strong immunosuppressive properties and maintain immunological homeostasis by controlling peripheral immune tolerance[29]. Accumulating evidence supports the correlation between the number of Tregs and clinical parameters in RA patients[67]. Accordingly, Tregs have become a target in RA treatment[68]. WANG *et al.*[29] optimized a combination of IL-2, TGF-β, and cyclin-dependent kinase inhibitor (IL-2/TGF-β/AS), which could induce Tregs and inhibit the differentiation of Th1 and Th17 cells with high efficiency in vitro. Based on the optimized formula, a chitosan-stabilized nanoparticle drug delivery system (NDDS) was developed. After injection into the knees of CIA mice, the NDDS promoted Treg differentiation and decreased Th17 production, consequently reversing the Treg/Th17 ratio and reducing TNF-α secretion. As a result, the pathological score of CIA mice was remarkably reduced. Meanwhile, inflammatory cell infiltration, synovial hyperplasia, and cartilage tissue damage were minimized.

Although significant progress has been made in the treatment of RA, a subgroup of patients defined as "refractory" or "treatment-resistant" RA do not respond to therapeutic interventions or develop drug resistance shortly after treatment[69-70]. Studies have found that P-glycoprotein (P-gp) is highly expressed on lymphocytes in refractory RA patients, and inhibition or reduction of P-gp overcomes drug resistance and improves disease outcomes[71-72]. Therefore, P-gp is a potential target for the treatment of RA, especially refractory RA. Total glucosides of paeony (TGP) and the P-gp inhibitor nobiletin (N) were coloaded in self-nanoemulsifying drug delivery systems (SNEDDSs) to overcome drug resistance in P-gp-overexpressing lymphocytes[73]. After administration to refractory AIA rats, TGP-N coloaded SNEDDSs overcame drug resistance induced by P-gp via downregulation of the PI3K/AKT and HIF-1α pathways, leading to enhanced overall bioavailability and anti-arthritis effects.

2.1.3 Targeting other cells

Other cells involved in the pathogenesis of RA, besides macrophages and lymphocytes, can also serve as targets for drug delivery.

Synovial fibroblasts (SFs), resident stromal cells in the synovium, play a key role in regulating the progression of RA by producing multiple pathogenic proteins[74]. SFs contribute to inflammatory responses, cartilage erosion, and

bone destruction by releasing cytokines, chemokines, matrix-degrading proteolytic enzymes, and other pathogenic mediators[75-76]. The trafficking, processing, and sorting of these pathogenic proteins are regulated by the Golgi apparatus[75]. DENG *et al*.[75] developed a Golgi-targeting platelet microparticle-mimetic nanoplatform loaded with all-trans retinoic acid (ATRA-Gol-PMMNPs) to selectively downregulate pathogenic factors by causing structural disruption of the Golgi apparatus. In CIA rats, ATRA-Gol-PMMNPs displayed arthritic joint-specific distribution and effectively reduced concentrations of pathogenic factors within joints. Additionally, ATRA-Gol-PMMNPs treatment alleviated inflammation and decreased bone erosion in arthritic joints.

As mentioned above, CD44 receptors were used as targets against macrophages. In fact, CD44 receptors are also overexpressed on other cells such as FLSs, providing delivery systems with the opportunity to simultaneously target different cells for the treatment of RA. FLSs play crucial roles in both the propagation of inflammation and cartilage destruction in joints[77]. A biomimetic SIN-loaded PB nanocomplex (HA@M@PB@SIN) was developed as an example. By embedding HA, the targeting ability of this delivery system to inflammatory macrophages and FLSs in rheumatoid synovial joints was improved[78]. *In vivo* imaging demonstrated that HA@M@PB@SIN resulted in a markedly increased half-life in circulation and higher levels of accumulated drugs at arthritic sites in AIA rats. The nanocomplexes significantly suppressed joint inflammation and protected against bone destruction by inhibiting inflammatory cytokine secretion from synovial macrophages and FLSs, as evidenced by significant reductions in hind paw volume, arthritic score, and milder histopathological manifestations[78].

Another example of CD44 receptors as pan-cell targets is HA-coated teriflunomide-loaded nanostructured lipid carriers (HA-coated TER-NLCs), which can target CD44 receptors on peripheral blood mononuclear cells (PBMCs). From a materials perspective, HA-coated lipid carriers improved TER bioavailability[79] and showed favorable ability to bind to CD44 receptors[80]. After oral administration to AIA rats, HA-coated TER-NLCs achieved the greatest reduction in paw swelling, osteophytic reactivity, loss of cartilage layer, and proinflammatory cytokine (especially TNF-α) levels compared with the positive control group and other treatment groups[80]. A series of studies indicated superior antiarthritic and joint healing effects of CD44-targeted nanoparticle delivery systems.

Triggering receptors expressed on myeloid cells 2 (TREM-2) are involved in inflammation by inducing the production of constitutive inflammatory cytokines. TREM-2 is present on dendritic cells, osteoclasts, microglia, and certain macrophages or neutrophils[81]. Upregulation of TREM-2 in active RA synovium and its subsequent downregulation in inactive RA suggest a role for TREM-2 in RA[82]. Based on this, SIGALOV[83] combined the TREM-2 inhibitory peptide sequence IA9 with the 22-amino-acid peptide sequence of apoA-I helix 6 (PA22) and lipids to form nanosized LPC (IA31-LPC). IA31-LPC enabled targeted delivery of IA31 to cells (e.g., macrophages) via interaction with scavenger receptors. Systemic administration of IA31-LPC significantly decreased synovial tissue sublining TREM-2 expression, reduced the release of plasma and joint proinflammatory cytokines, and markedly suppressed disease progression and joint inflammation. Notably, incorporation of the IA9 sequence into macrophage-specific LPC substantially increased therapeutic efficacy, likely due to targeted delivery to inflammatory sites and prolonged circulatory half-life of the peptide.

2.1.4 Targeting signaling pathways

The stimulator of interferon genes (STING) has attracted increasing attention in various inflammatory diseases. Dysregulation of the STING pathway can upregulate various inflammation-related genes[84]. Given the aberrant activation of STING in various inflammatory diseases, especially autoimmune diseases[85], the role of STING in RA warrants further investigation[86]. Double-stranded DNA (dsDNA) released from damaged or dead cells is a biological feature of RA pathology, and interestingly, the STING pathway senses DNA damage and upregulates the secretion of inflammatory cytokines, such as TNF-α in macrophages[87]. Therefore, scavenging dsDNA may reduce STING activation and alleviate inflammation[86].

Mesoporous polydopamine (PDA) nanoparticles were

developed for delivery of C-176, and the surface of the nanoparticles was decorated with optimized cationic polyethyleneimine (PEI) to achieve high DNA-binding affinity (PEI-PDA@C-176)[86]. PEI-PDA@C-176 nanoparticles demonstrated strong dsDNA scavenging capability, resulting in a greater effect on suppressing dsDNA-induced STING activation and inflammatory cytokine secretion than other control formulations *in vitro*[86]. In a mouse model of dsDNA-induced acute arthritis, PEI-PDA@C-176 mediated faster and greater alleviation of ankle swelling, synovial lining hyperplasia, and cartilage destruction[86]. Another mouse model provided similar evidence: CIA mice treated with PEI-PDA@C-176 showed a greater decrease in clinical score and inflamed knee joint diameter, while synovitis and cartilage destruction were also effectively controlled[86].

Due to the complexity of RA and patient heterogeneity, targeting a single cytokine pathway may not yield a satisfactory response[88]. In inflamed joints, inflammatory cascades, including hypoxia-inducible factor (HIF), nuclear factor κB (NF-κB), and mitogen-activated protein kinases (MAPKs), are activated, leading to the production of proinflammatory mediators[88]. HIF-1α can be activated in hypoxic and inflammatory microenvironments to enhance transcription of genes regulating inflammatory responses[89]. Conversely, RA mice with myeloid-specific HIF-1α deletion showed marked attenuation of RA, resulting from reduced macrophage aggregation, invasiveness, and mobility[90]. NF-κB and MAPKs converge to regulate inflammation, immune responses, and osteoclastogenesis in RA and are also involved in HIF-1α activation[88]. Therefore, the synergistic effect of NF-κB, MAPK, and HIF-1α contributes to maintaining inflammatory responses.

LIU *et al.*[88] proposed HIF-1α small interfering RNA (siRNA)-loaded calcium phosphate nanoparticles encapsulated in apolipoprotein E3-reconstituted high-density lipoprotein (HIF-CaP-rHDL) to downregulate HIF-1α, NF-κB, and MAPK expression for RA therapy. In lipopolysaccharide-activated RAW 264.7 macrophages, HIF-CaP-rHDL showed significant anti-inflammatory effects, along with HIF-1α downregulation and inhibition of NF-κB and MAPK signaling pathways. In CIA mice, inflammatory cytokine secretion was effectively suppressed. Meanwhile, bone erosion, cartilage damage, and osteoclastogenesis were alleviated, indicating a promising therapeutic strategy through suppression of multiple inflammatory pathways.

2.1.5 Targeting proinflammatory cytokines

Proinflammatory cytokines such as TNF-α, IL-1, and IL-6 are involved in the development, activation, growth, and differentiation of macrophages, making them promising targets in RA[91]. Several biologics that block specific cytokines have been approved for the treatment of RA.

As previously mentioned, DMARDs such as sulfasalazine are extensively used as first-line therapy for RA. The development of sulfasalazine-loaded nanoparticles not only enables prolonged drug delivery but also reduces the risk of systemic toxicity[92]. The sulfasalazine-loaded solid lipid nanoparticle (SLN)-based gel (sulfasalazine SLN gel) is a successful example. SLNs offer several advantages, including high stability, biocompatibility, and a favorable drug release profile[93]. MISHRA *et al.*[94] used central composite design to optimize SLNs, resulting in significant improvements in drug release and skin permeability. In vivo studies showed that the optimized sulfasalazine SLN gel significantly inhibited pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6. Additionally, a considerable reduction in paw thickness and arthritic score was observed with the sulfasalazine SLN gel compared to plain gel[94].

Due to its important role in the exacerbation and persistence of joint inflammation, TNF-α has been widely identified as a target in RA[95]. TNF-α inhibitors such as Fc-fusion proteins and mAbs can exert therapeutic effect on RA. A modified hydrophobic ion-pairing complex (INF HIPC) was developed by sequentially introducing bovine lactoferrin (BLF) and HA into the INF solution, which binds human TNF-α and promotes osteoblast proliferation[48]. With good stability, high drug-loading efficiency, and long-term retention, INF HIPC resulted in lower TNF-α levels and less cartilage damage than INF in a transgenic mouse model, whether administered via knee joint or intravenous injection[48]. This carrier-free macromolecular nanoparticle offers new possibilities for delivering antibodies or macromolecules, especially for indications such as RA, where the pathological mechanism

is complex and requires combination therapy[48].

In addition to Fc-fusion proteins and mAbs, siRNA is also a promising strategy for targeting TNF-α. Naked siRNA delivery faces several challenges, including membrane impermeability, enzymatic degradation, and entrapment by the mononuclear phagocyte system. Toxicity is also a significant concern[96]. YU *et al.*[49] developed dendriplexes composed of original cationic amphiphilic phosphorus dendrons (C17P10 dendriplexes), which protected siRNA from nuclease degradation for at least 120 minutes and promoted macrophage uptake. Considering the toxicity, the dendriplexes were safe up to a siRNA concentration of 120 nmol/L[49]. Moreover, they led to potent inhibition of TNF-α expression in activated mouse RAW264.7 macrophage cells *in vitro* and demonstrated significant anti-inflammatory effect in murine arthritis models, as observed by arthritis scoring and histological evaluation[49].

In summary, this section reviewed existing nanoparticle delivery strategies for treating RA by inhibiting inflammation. Delivery targets included: ① cells involved in the inflammatory process, such as macrophages, lymphocytes, SFs, and FLSs; ② signaling pathways, including STING, HIF-1α, NF-κB, and MAPK; and ③ proinflammatory cytokines, including TNF-α, IL-1, and IL-6. These various targeting strategies significantly reduced inflammation and alleviated RA.

2.2 Antioxidation

As noted, inflammation is the cornerstone of RA. However, an equally important factor is oxidative stress[97]. Caused by the accumulation of ROS at the injury site, oxidative stress promotes synovial hyperplasia, neovascularization, and the destruction of bone and cartilage by regulating anti-apoptosis signaling pathways, increasing angiogenic substances, inhibiting cartilage matrix synthesis, and accelerating cartilage matrix degradation[98-99]. Additionally, oxidative stress has "crosstalk" with inflammation. It also acts as a signaling molecule that promotes the accumulation of proinflammatory immune cells such as macrophages and upregulates pathways like HIF-1α/VEGF and Notch, which significantly contribute to synovial hyperplasia and bone destruction[100]. Therefore, antioxidation, or ROS scavenging, is another crucial target for RA treatment, in addition to inflammation inhibition[101].

Different delivery strategies are described below in terms of their function and roles in managing RA.

2.2.1 Antioxidant capacity based on the structure of nanoparticles

CS-CHI@DS, a novel polysaccharide nanoparticle lubricant developed by YANG *et al.*[102], is a representative example of both anti-inflammatory and antioxidant function. The exceptional lubricating properties of CS-CHI nanoparticles are attributed to the synergistic combination of hydration and rolling lubrication mechanisms, due to the hydration layer formed by the negatively charged group (SOO−) from CHI on the surface of CS NPs. After loading the anti-inflammatory drug diclofenac sodium, CS-CHI@DS significantly reduced inflammatory levels in CIA rats, particularly the levels of IL-1β, IL-6, and TNF-α. Meanwhile, the hydroxyl groups on the surface of CS NPs, along with the sulfonic acid and carboxyl groups of CHI, contributed to the antioxidant activities of CS-CHI@DS and facilitated ROS scavenging[103]. The anti-inflammatory and antioxidant effects, as well as lubricating properties, stimulated chondrocyte proliferation and produced excellent cartilage repair in RA[102].

2.2.2 Antioxidant capacity based on the delivered drugs

Some drugs inherently possess anti-inflammatory and antioxidant capabilities, and the use of nanoparticle delivery systems can enhance their functions and improve therapeutic efficacy. Apocynin (APO) is a widely recognized bioactive phenolic compound derived from plants, known for its anti-inflammatory and antioxidant properties. AMAN *et al.*[12] applied it to a nanoscale delivery system and fabricated APO-loaded CPT/CS hybrid NPs. As the newest generation of delivery systems, hybrid NPs integrate lipid-based and polymeric nanocarriers to harness the advantages of both, enabling the incorporation of hydrophilic and hydrophobic drugs while enhancing drug stability and efficacy. Compared to ordinary APO NPs, APO-loaded CPT/CS hybrid NPs exhibited superior skin penetration and drug absorption[12]. Drug administration in CFA-induced RA rats demonstrated that the anti-inflammatory activity of APO is significantly enhanced in these hybrid NPs, and the levels of oxidative stress-related biomarkers were significantly reduced, leading to excellent therapeutic effects in RA.

2.2.3 Oxidative stress alleviation in the microenvironment or other organs

Stem cell-based therapies, especially BMSCs, have emerged as a promising solution for RA management and offer important advantages over traditional treatments[104]. In the RA microenvironment, uncontrolled accumulation of ROS, combined with hypoxia, leads to severe damage of transplanted stem cells and significantly undermines therapeutic outcomes[50]. A feasible solution is to develop an ideal cell delivery system that can both scavenge ROS and generate oxygen synergistically to enhance the efficiency of stem cell therapy at the prosthetic interface within the RA microenvironment.

ZHAO *et al.*[50] synthesized a hydrogel fortified with nanozymes (pTi@Gel-NPs) to transform the adverse RA microenvironment and improve osseointegration at the prosthetic interface. The engineered hydrogel had dual functionalities: it effectively scavenged overproduced endogenous ROS and simultaneously generated dissolved oxygen in a synergistic manner. Owing sop these capabilities, the hydrogel served as an injectable carrier for BMSCs, shielding the implanted cells from ROS and hypoxia-induced death, as well as osteogenic limitation.

In addition to improving the local microenvironment of arthritis for therapeutic purposes, the therapeutic efficacy of certain drugs can also be optimized by reducing oxidative stress in other organs. Particular medications, such as triptolide (TP), demonstrate unique effects in treating RA, but poor aqueous solubility and multi-organ toxicity have greatly limited their application[105]. Fortunately, by being loaded into specifically designed nanoparticle delivery carriers, these issues can be effectively addressed. As one of the most effective antioxidants, vitamin C exerts a significant protective effect by preserving the antioxidant capacity of hydroxyl oxidase and by reducing reactive oxygen species and tissue oxidative damage[106]. Utilizing a vitamin C derivative (L-ascorbate palmitate, VP) to fabricate nanoparticles (TP-VP NPs) as delivery carriers represents an innovative approach. After delivery into CIA mice, the system not only exerted the synergistic anti-inflammatory effects of TP and VP, but also ameliorated oxidative stress in the liver and restored antioxidant enzyme levels to normal[107]. The TP-VP NPs provide new possibilities for medications whose application has been limited due to side effects.

In this section, we provide a detailed overview of various nanoparticle delivery strategies for treating RA through antioxidation mechanisms, including: ① antioxidant capacity based on the structure of nanoparticles; ② antioxidant capacity based on the delivered drugs; and ③ alleviation of oxidative stress in the microenvironment or other organs. Additionally, we are pleased to note that certain nanoparticle delivery systems not only exhibit antioxidant effects but also demonstrate anti-inflammatory properties. Achieving multiple therapeutic outcomes through a single nanodelivery platform is both innovative and efficient. Further examples of such multifunctional systems will be presented in subsequent chapters.

2.3 Macrophage polarization alteration

Among macrophage-targeted nanoparticle delivery systems, some function by altering the polarization state of macrophages. Macrophages are generally classified into pro-inflammatory M1 and anti-inflammatory M2 phenotypes. Excessive production of inflammatory cytokines by M1 macrophages perpetuates and exacerbates inflammation in joints affected by RA[108]. In contrast, M2 macrophages secrete anti-inflammatory factors, exert anti-inflammatory effects, and recruit a substantial number of Tregs, one of the most potent anti-inflammatory immune cell populations[109-110]. Therefore, altering macrophage polarization – either by inhibiting M1 macrophage formation or promoting the conversion of M1 to M2 macrophages – is a promising strategy for RA treatment.

In RA patients, ROS, inflammatory pathways, and macrophage polarization form a positive feedback loop through mutual reinforcement. Accumulation of ROS activates inflammatory pathways such as NF-κB/MAPK, leading to the production of pro-inflammatory cytokines and promoting M1 macrophage polarization. In turn, M1 macrophages generate more ROS and pro-inflammatory cytokines, further activating inflammatory pathways. Moreover, macrophages are involved not only in inflammation but also in osteoclast activation.

Since current nanodelivery systems designed to modulate macrophage polarization for RA treatment often involve additional mechanisms, we dedicate a separate

section to elaborate on delivery strategies for macrophage polarization alteration and multifunctional platforms centered on this mechanism.

2.3.1 Macrophage polarization alteration and inflammation inhibition

As mentioned earlier, siRNA delivery is a promising strategy for treating RA, provided the siRNA is protected by an appropriate delivery vehicle and its toxicity is minimized. GUO *et al.*[111] used tannic acid (TA)-based metal-organic framework (MOF)-coated nanoparticles (TFSB) as a delivery vehicle for TNF-α siRNA. In addition to delivering siRNA and enabling its rapid endo/lysosome escape through the proton-sponge effect to effectively downregulate cytokines, the TA in the nanoparticle also possessed antioxidant activity[111]. Thus, beyond its delivery function, the nanoparticle itself had intrinsic radical scavenging capability, enabling the elimination of a broad spectrum of reactive oxygen and nitrogen species. This repolarized M1 macrophages into the M2 phenotype, synergizing with TNF-α siRNA to enhance RA therapy. In mouse experiments, the TNF-α siRNA-TFSB system demonstrated a triple effect: macrophage repolarization, anti-inflammation, and MMP-2 downregulation, effectively alleviating joint inflammation and bone destruction[111].

Germacrone (GER) is a bioactive compound derived from Rhizoma curcuma that can inhibit the NF-κB signaling pathway in RA, thereby slowing disease progression[112]. However, like many plant-derived drugs, GER requires effective delivery systems to overcome its poor stability, low solubility, and rapid clearance *in vivo*[113]. TAN *et al.*[114] used folic acid-modified nanocarriers to target macrophages for GER delivery. *In vitro* experiments showed that FA-NPs/GER promoted the polarization of M1 macrophages toward the M2 phenotype. In AIA rats, the formulation significantly reduced pro-inflammatory cytokine levels, markedly decreased paw swelling, and attenuated inflammatory cell infiltration[114]. Encapsulation of GER within nanocarriers enabled sustained and controlled release, resulting in enhanced therapeutic efficacy while maintaining a favorable safety profile.

IL-10 is an anti-inflammatory and immunosuppressive cytokine primarily produced by activated M2 macrophages. Studies have shown that encapsulating IL-10 plasmid DNA (IL-10 pDNA) in uncoagulated alginate nanoparticles can effectively repolarize macrophages from the M1 type to the M2 type, making it a potential therapeutic agent for RA[115]. Building on the effects of IL-10 pDNA, ZHENG *et al.*[116] co-loaded it with Dex sodium phosphate (DSP), a common drug for treating RA, into a carrier made of human serum albumin (HSA), resulting in a gene and chemical drug co-delivery system constructed from biomimetic natural materials (pDNA/DSP-NPs). The synergistic treatment with IL-10 pDNA and DSP exhibited significant therapeutic efficacy in CIA rats compared with other treatment groups, including those receiving only IL-10 pDNA or DSP delivery systems.

Neutrophils are also a reliable source for biomimetic materials. As the most abundant cell type in the synovial fluid of patients with active RA, neutrophils migrate to sites of inflammation through a regulated multi-step process involving various cell adhesion molecules, chemokines, and chemokine receptors[117]. Due to the inherent pro-inflammatory capabilities of neutrophils, which preclude their direct use as drug carriers, researchers have developed biomimetic drug delivery systems with inflammation-targeting properties by utilizing neutrophil membranes containing key molecules[118]. The peptide-anchored neutrophil membrane-coated biomimetic nanoparticle (R4F-NM@F127) is a notable example of targeted drug delivery in RA. By coating nanoparticles with neutrophil membranes, these systems inherit the membrane proteins and associated functions of neutrophils, enabling the nanoparticles to be directed to inflamed synovial tissue via the chemotactic effects of IL-8 abundant in the synovial fluid[119]. After being loaded with celastrol, the delivery system significantly inhibited M1 macrophage polarization and enhanced M2 macrophage polarization *in vitro*, and exhibited marked anti-inflammatory efficacy in CIA mice[119].

Interestingly, not only can macrophages in inflamed joints serve as therapeutic targets, but circulating monocytes also show targeting potential due to their inflammatory chemotactic properties and ability to penetrate endothelial barriers[120]. FENG *et al.* [121]fabricated a dextran sulfate-functionalized zeolitic imidazolate framework nanoparticle loaded with Dex (Dex@ZDNP), which can be specifically

taken up by circulating monocytes and transported to arthritic joints. Subsequently, monocytes that phagocytosed Dex@ZDNP polarized into an anti-inflammatory phenotype under the influence of Dex and combated RA through the secretion of a spectrum of anti-inflammatory cytokines. This strategy effectively reprogrammed monocytes into "living drug depots", enabling them to function as "guided missiles" that precisely homed to inflammatory sites, thereby achieving efficient and intelligent RA therapy.

2.3.2 Macrophage polarization alteration and antioxidation

Current research has revealed that the HIF-1α and NF-κB pathways initiate a complex and interconnected inflammatory signaling cascade in RA. As a result, inhibiting a single pathway alone may not achieve optimal effects, highlighting the need for combination therapy[44]. Dex reduces capillary permeability and suppresses NF-κB transcription, leading to a reduction of pro-inflammatory cytokines and chemokines. Artesunate (ART), a potent natural molecular therapeutic agent, inhibits HIF-1α expression, which facilitates synergistic bidirectional suppression of the HIF-1α/NF-κB cascade with DEX and promotes M2 macrophage polarization. Consequently, ROS-responsive DEX/HA-TK-ART micelles were developed. After distributing to inflamed joints, the micelles were taken up by M1 macrophages through CD44 receptor-mediated endocytosis and, subsequently, triggered by ROS to co-release ART and DEX, which synergistically inhibited the expression of NF-κB p65 and HIF-1α, promoted IκB-α degradation, and depleted ROS, thereby promoting the polarization of M2 macrophages.

Ceria oxide nanoparticles (CeO_2 NPs) have been widely studied in diseases associated with high oxidative stress for their ROS scavenging activity[122]. However, a major limitation in their application for RA treatment is the acidic microenvironment, where excessive H^+ secreted by activated osteoclasts hinders the Ce^{4+} to Ce^{3+} conversion, thereby impairing the antioxidant efficacy of CeO_2 NPs[122-123]. To address this, FU *et al.*[110] used a simple acid-base neutralization strategy, employing nanoceria-loaded magnesium aluminum layered double hydroxide (LDH-CeO_2), to enhance the ROS scavenging activity of CeO_2 NPs while simultaneously promoting immune regulation and bone repair. The mild alkalinity of LDH neutralized excess H^+ in the RA microenvironment, triggering an enhanced antioxidant effect of CeO_2, which initiated the repolarization of pro-inflammatory M1 macrophages toward the anti-inflammatory M2 phenotype. This process led to the secretion of abundant anti-inflammatory cytokines, recruitment of Treg cell populations, and suppression of local Th17 cells and plasma cell activity. The Mg^{2+} released from LDH not only enhanced macrophage polarization but also inhibited osteoclast formation and activated osteoblasts, thereby promoting bone repair[124].

While conventional smart delivery systems are based on "stimulus-responsive" and "drug release" mechanisms, WANG *et al.*[124] argued that this approach might lead to abrupt accumulation of delivered drugs, posing challenges for the application of toxic agents such as triptolide. To address this, WANG *et al.*[124] developed a dual dynamically cross-linked hydrogel (SPT@TPL) that demonstrated sensitive microenvironment regulation and microenvironment modulation-independent drug release for nearly 30 days. The innovation of this hydrogel was its ability to rapidly form abundant intermolecular hydrogen bonds for structural repair after boronate ester cleavage. As a result, the ROS regulation process did not trigger a sudden release of triptolide, greatly reducing the risk of its toxic side effects. Furthermore, through ROS-responsive release of the tea polyphenol component and sustained triptolide release, SPT@TPL reprogrammed M1-type macrophages into the M2 phenotype at the lesion site. This dual mechanism suppressed inflammatory cytokine expression while promoting articular cartilage regeneration, with therapeutic efficacy validated in RA rat models.

2.3.3 Multifunctional system

Similar to the aforementioned GER, resveratrol (RSV) is a natural chemoprotective agent that promotes the transformation of macrophages into the M2 phenotype and has anti-inflammatory and antioxidant functions[125]. Due to the adverse side effects of RSV on the kidneys and gastrointestinal tract, a polyethylene glycol/folic acid (PEG/FA)-modified and resveratrol (RSV)-loaded Ag/Ag_2S nanotriangle (Ag/Ag_2S-PEG-FA/RSV NTs) homologous heterostructure was developed[126].

In this nanodelivery system, each component played a distinct role. The Ag/Ag_2S heterostructure scavenged H_2S and inhibited the MAPK/ICAM-1 pathway under near-infrared light irradiation, thereby suppressing the exacerbation of inflammation. Ag catalyzed the decomposition of ROS through its superoxide dismutase- and catalase-like activities, improving photocatalytic efficiency by replenishing oxygen. Meanwhile, RSV inhibited the activation of NF-κB, promoting the transformation of macrophages into the M2 phenotype and reducing inflammatory cytokine levels. In both in vitro and in vivo experiments, the synergy of the material, unique structure, and drug collectively regulated macrophage polarization and exerted anti-inflammatory and antioxidant effects, demonstrating a highly effective therapeutic strategy[126].

Similarly, TAO *et al.*[47] designed a multifunctional delivery strategy based on materials, structures, and drugs to overcome the drawbacks of methotrexate (MTX). Named PDA/MTX@TSG, this delivery system consisted of polydopamine (PDA) nanoparticles, MTX, and a thermosensitive lipogel. The system demonstrated dual degradation mechanisms: it triggered sustained but controllable drug release through both "enzyme erosion" in the MMP-rich RA microenvironment and external NIR irradiation. This process released MTX to directly induce apoptosis of M1 macrophages and suppress inflammatory factors. Furthermore, the lipogel effectively eliminated intracellular ROS and produced oxygen to inhibit HIF-1α expression, thereby improving the unfavorable local microenvironment and enhancing M2 macrophage polarization in RA joints. The team ultimately demonstrated that a single intra-articular injection of PDA/MTX@TSG combined with NIR irradiation in AIA rats elicited a potent synergistic effect in alleviating RA symptoms and promoting joint repair.

LI *et al.*[127] developed a percutaneous multifunctional nano-delivery platform (DES-MSNs) for methotrexate delivery. DES-MSNs consisted of two components: ① cerium nanoparticles (nanoceria) were synthesized and incorporated into mesoporous silica nanoparticles (MSNs), followed by loading methotrexate (MTX) to form functionalized MSNs; ② a deep eutectic solvent (DES) system was synthesized from arginine, citric acid, and water, then incorporated into a hydrogel. After topical administration, the hydrogel enabled noninvasive transdermal delivery of rigid nanoparticles, allowing prolonged penetration and targeted accumulation of functionalized MSNs at subcutaneous inflammatory lesions. Simultaneously, the encapsulated MTX directly mediated therapeutic efficacy, while nanoceria modulated the inflammatory environment through dual mechanisms: scavenging ROS and reprogramming macrophage polarization. This integrated strategy harnessed the synergistic effects of carrier-mediated immunotherapy (via nanoceria) and drug-driven chemotherapy (via MTX), achieving combinatorial therapeutic action against RA[127].

The RA microenvironment is characterized by low pH and high ROS concentrations. Based on this unique pathological environment, researchers have developed pH-sensitive and ROS-responsive nano-delivery platforms[128]. However, due to potential depletion of H^+ or ROS, drug payloads in nanomedicines may not be fully released. To address this limitation, LU *et al.*[129] designed a dual-responsive nanoplatform with both pH and ROS sensitivity. They used cinnamaldehyde, a compound known to alleviate RA progression through its antioxidant and anti-inflammatory properties, as the drug carrier[130]. Building on this, they synthesized a ROS-responsive material by modifying α-cyclodextrin with 4-(hydroxymethyl) phenylboronic acid pinacol ester. These two components were then integrated to create pH/ROS dual-responsive nanoparticles for delivering methylprednisolone (MPS/RGD-CA-HPAP-αCD). Articular destruction was significantly alleviated in CIA mice by promoting M1-to-M2 macrophage polarization and downregulating the NF-κB signaling pathway[129].

Similarly, WANG *et al.*[2] designed pH/ROS dual-responsive nanoparticles (HA-CDs-PEG-β-CD/DEX) for dexamethasone (DEX) delivery, based on the acid- and ROS-responsive degradation properties of HA[131]. When administered to AA rats, HA enhanced drug delivery efficiency to M1 macrophages via the CD44-dependent endocytosis pathway. The carbon dots-β-cyclodextrin (CDs-β-CD) crosslinked with HA subsequently released DEX. This was the first successful demonstration of using

HA degradability to achieve responsive DEX release for improved RA treatment. The system simultaneously delivered drugs to inhibit M1 macrophage polarization and exert anti-inflammatory effects, as well as demonstrated the ROS-responsive and scavenging properties of the nanoparticles[2].

In this section, we described nanoparticle delivery strategies for treating RA by altering macrophage polarization states. Multiple strategies based on this foundation have been developed to create multifunctional delivery platforms capable of achieving therapeutic effects such as anti-inflammatory and antioxidant actions.

3 Discussion

As one of the most common systemic autoimmune inflammatory diseases, RA is generally incurable and requires long-term treatment for most patients, significantly impacting quality of life, work capacity, and socioeconomic costs[3]. For decades, researchers worldwide have persistently explored improved therapeutic approaches, driving the iterative evolution of pharmacological interventions. From glucocorticoids and conventional synthetic DMARDs to biological DMARDs and targeted synthetic DMARDs, the treatment paradigm for RA has progressively shifted from broad-spectrum anti-inflammatory strategies toward precisely targeted immunomodulation.

Although these drugs have been integrated into clinical practice, they have notable limitations, such as low bioavailability, short half-life, and significant adverse effects, which may compromise patient compliance and therapeutic efficacy. In recent years, nanoparticle-based drug delivery systems for RA treatment have developed rapidly. Current strategies mainly focus on alleviating joint synovitis by delivering anti-inflammatory agents to the joints[132].

This review provides a comprehensive overview of the latest nanoparticle-based drug delivery strategies for RA treatment, emphasizing therapeutic effects and their interactions with the disease microenvironment. Focusing on mechanisms of action, we describe various delivery systems that exert therapeutic effects through inflammation inhibition, antioxidation, and alteration of macrophage polarization. Delivery systems with anti-inflammatory mechanisms suppress inflammation and alleviate RA symptoms by precisely targeting inflammation-related cells (such as macrophages, lymphocytes, and synovial fibroblasts), blocking key signaling pathways (e.g., NF-κB, STING, and HIF-1α), and inhibiting pro-inflammatory cytokines (such as TNF-α, IL-1, and IL-6). Delivery systems based on antioxidation mechanisms exert their effects by scavenging ROS and alleviating oxidative stress. Certain delivery systems, such as pTi@Gel-NPs[50], can generate dissolved oxygen, thereby improving the hypoxic microenvironment while exerting antioxidant effects. Antioxidant efficacy can be achieved either by utilizing the inherent chemical structural characteristics of nanoparticles (e.g., surface functional groups such as hydroxyl, sulfonic, and carboxylic groups) to scavenge ROS, or through strategies including nanoparticle encapsulation, amelioration of the local microenvironment, and attenuation of oxidative stress in other organs, thereby enhancing therapeutic outcomes. In macrophage-targeted nanoparticle delivery systems, one category functions by altering the polarization state of macrophages. By inhibiting pro-inflammatory M1 macrophages and inducing anti-inflammatory M2 macrophages, these systems reduce the release of pro-inflammatory cytokines, chemoattractant factors, and metalloproteinases, while promoting angiogenesis, tissue remodeling, and repair, thus achieving the goal of treating RA[133].

Nanotechnology has evolved from original nanomaterials into diverse modifications driven by specific needs over time[134]. Beyond their roles in drug loading, targeted delivery, and local concentration, nanoparticle delivery systems in RA treatment further enable coordinated therapeutic effects via material selection and strategic modifications: ① controlled drug release via stimuli-responsive nanostructures triggered by RA microenvironment features (such as acidic pH, high ROS, and MMP enzyme levels), prolonging local retention[47, 59, 64]; ② enhanced intracellular delivery by promoting endosomal/lysosomal escape[43, 57, 111]; ③ immune evasion using biomimetic structures to extend circulation time and improve inflammatory targeting[11, 116, 119]; ④ ROS scavenging or acid neutralization via antioxidant groups or enzyme-mimetic activity to alleviate RA inflammation[102]; ⑤ cellular modulation, such as macrophage polarization,

through physicochemical effects[2, 111, 129]; ⑥ signal pathway intervention, for instance, inflammatory pathway blockade by adsorbing associated molecules via surface charge or structural affinity[86].

Through rational design and chemical synthesis strategies, versatile delivery platforms can be fabricated to achieve either codelivery of multiple therapeutic agents for synergistic outcomes[44, 116], or functionalized nanoparticle constituents that execute distinct therapeutic modalities beyond their conventional role as carriers[47, 126]. Interestingly, we found that even when delivering the same drug, differences in mechanisms of action occur due to variations in carrier design, which further highlights the additive role of nanocarriers in therapy. For example, as mentioned earlier, both C17P10 dendriplexes and TFSB delivered anti-TNF-α siRNA. However, due to the inherent reactive oxygen and nitrogen species-scavenging capability of the TA-based MOFs in TFSB, it not only exhibited anti-inflammatory effects similar to those of C17P10 dendriplexes but also possessed the additional function of altering macrophage polarization[49, 111].

The superiority of multifunctional delivery systems stems from their capacity to integrate multi-mechanism synergistic therapies on a unified platform, enhancing therapeutic efficacy while mitigating adverse effects associated with excessive accumulation of single agents. Owing to these benefits, multifunctional delivery systems are expected to become a favored choice in clinical settings. However, before deployment in clinical practice, more real-world evidence needs to be accumulated, and various potential application issues must be addressed. These include how to rationally configure the proportions of different drugs in a single system to achieve optimal efficacy with minimal side effects; how to select systems with different mechanisms of action based on the patient's actual condition; and how to balance manufacturing and usage costs against optimal clinical benefit.

Currently, very few nanoparticle delivery systems for the treatment of RA have reached GLP toxicology, scale-up, or early-phase human studies. One of the rare exceptions is the randomized, double-blind, active-controlled, multicenter trial of pegylated liposomal prednisolone sodium phosphate in RA patients conducted by METSELAAR[135]. Beyond the issues already highlighted in the aforementioned multifunctional systems, the following considerations and challenges must be addressed during the clinical translation of nanoparticle delivery systems: ① nanoparticle-induced immunomodulation, such as complement activation, which may compromise the integrity of nanoparticles and potentially diminish the therapeutic efficacy of nano-encapsulated drugs[136-137]; ② long-term safety assessment, particularly the prolonged retention and accumulation in reticuloendothelial systems like the spleen and lymph nodes, and the potential for chronic inflammation or tissue damage this may cause; ③ the critical importance of production process and quality control, where stable and uniform manufacturing and controlling batch-to-batch variability are key steps for industrialization.

The limitations of this review are as follows. First, the inflammatory responses, oxidative stress processes, and interactions among immune cells in RA are continuous, networked, and intricately interconnected. We divided the mechanisms of action into three main sections based on the targeting objectives of the nanoparticle delivery systems described in different literature sources using a classification approach, which involves a certain degree of subjectivity, such as the inability to fully demonstrate the network interactions of each component during the treatment of RA. Second, the functional validation of nanoparticle delivery systems is currently conducted either *in vitro* using cell lines or *in vivo* within experimental animals, lacking data from clinical validation. Third, when elaborating on the multifunctional delivery platforms, constrained by the content of the cited literature and to maintain the coherence of the review, we do not compare the therapeutic differences between multifunctional and single-functional platforms, or the differences in efficacy related to drug loading levels.

In conclusion, this review summarized the latest strategies for drug delivery using nanoparticles to treat RA. Focusing on the effects of therapeutic strategies on the microenvironment and the entire body, we introduced three distinct mechanisms of action. Starting with single-functional delivery systems, we elaborated on their characteristics and efficacy in both *in vitro* and *in vivo* experiments, and then described the synergistic efficacy of

multifunctional platforms. Due to space constraints, we discussed some representative delivery systems. A more comprehensive summary is provided in Supplementary Table 1[2, 11-12, 29, 43-45, 47-50, 57, 59, 63-65, 73, 75, 78, 80, 83, 86, 88, 94, 102, 107, 110-111, 114, 116, 119, 121, 124, 126-127, 130, 138-148], available online at the publisher's website (https://ykxb.scu.edu.cn/). We look forward to the near future when these ingeniously designed therapeutic strategies – achieving maximum therapeutic effects with minimal intervention – can be applied in clinical practice, bringing significantly greater benefits to patients.

* * *

Author Contribution ZHANG Keyi is responsible for conceptualization, data curation, formal analysis, investigation, and writing--original draft. GUO Yixue is responsible for data curation, investigation, and methodology. ZENG Xianghu is responsible for data curation, investigation, and visualization. CAI Bei is responsible for methodology and resources. ZHANG Junlong is responsible for conceptualization, funding acquisition, and writing--review and editing. LI Yi is responsible for conceptualization and writing--review and editing. NIU Qian is responsible for conceptualization, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

Declaration of Conflicting Interests All authors declare no competing interests.

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（2025 – 08 – 19收稿, 2026 – 03 – 10修回）

编辑 吕 熙