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# Recent advances in nano-targeting drug delivery system for rheumatoid arthritis treatment

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## Abstract

Rheumatoid arthritis is a systemic inflammatory disease that can lead to articular cartilage destruction and periarticular bone erosion, which ultimately compromise joint integrity and function. Anti-inflammatory drugs and biological agents are commonly used to treat RA, but they cannot selectively target inflamed joints due to their systemic mechanism, short half-life, and low bioavailability. Therefore, these agents must be used at high doses that are delivered frequently, which increases costs and the risk of side effects. Drug delivery systems, such as nanoparticles, liposomes and micelles can significantly prolong drug half-life in the body and targeting delivery them into the joints. In this review, we introduce the pathogenesis and clinical diagnosis of rheumatoid arthritis comprehensively, and summarize the recent advances in targeted therapeutic strategies especially nano-targeting systems for rheumatoid arthritis.

**Keywords:** Rheumatoid arthritis; inflammation; nanoparticles; targeting drug delivery; liposomes

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that is typically characterized by persistent synovitis [1] and that manifests as symmetric polyarthritis of large

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and small joints, which may lead to joint and periarticular structural damage [2]. Although the etiology of RA is unclear, genetic and environmental factors appear to play key roles in the disease [3]. RA affects 0.5-1.0% of the population worldwide [4]; it affects women more often than men, and its prevalence is highest among individuals 35-50 years old [5].

Anti-inflammatory drugs and biological agents are commonly used to treat RA, but they cannot selectively target inflamed joints due to their systemic mechanism, short half-life, and low bioavailability. Therefore, these agents must be used at high doses that must be delivered frequently, which increases risk of serious side effects in healthy joint tissues [6]. Recent research has focused on the development of nanoparticle drug delivery systems that actively or passively target inflamed joints [7] while also improving the release of insoluble drugs, thereby maximizing bioavailability and therapeutic efficacy. Such drug delivery systems can significantly prolong drug half-life in the body and promote drug accumulation in the joints [8]. In this review, we focus on the pathogenesis, pathophysiology and clinical diagnosis of RA, as well as on nanocarriers and other targeted methods that are already used, or that may be used in the future, to treat the disease.

## 2. The pathogenesis and physiological characteristics of RA

Although the pathogenesis of RA remains unclear, studies suggest that the interaction of genetic and environmental factors leads to innate and adaptive immune responses that promote development of the disease [9]. External stimuli may also activate innate immune responses by binding to Toll-like receptors (TLRs) [10], which activate macrophages, dendritic cells, mast cells, neutrophils, T cells, B cells, and fibroblasts [11]. Macrophages drive RA by stimulating neovascularization, clearing apoptotic immune cells, and promoting fibroblast proliferation and protease secretion. Activated macrophages also promote inflammation in RA by releasing pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6, as well as reactive oxygen intermediates and prostaglandins [12]. Strong activation of macrophages also upregulates TLR2, TLR3, TLR4 and TLR7 as well as enzymes, cytokines, and other inflammatory factors that promote synovial inflammation and cartilage destruction (Figure 1) [13, 14].

Activation of innate immunity causes dendritic cells promote the pathogenesis of RA by

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taking up self-antigens and presenting them to T cells, leading to their activation or inhibition [15]. Neutrophils interact with fibroblast-like synoviocytes in the synovium to promote inflammatory and antigen-presenting phenotypes [16], while protein-protein interactions between the receptor activator of nuclear factor (NF)-κB ligand (RANKL) and its receptor, RANK, contribute to osteoclast differentiation in bone remodeling [17]. The RANKL/RANK pathway also promotes inflammation by activating transcription factors and signaling molecules such as NF-κB, JNK, AKT/PKB, ERK, Src Kinase, and p38 mitogen-activated protein (MAP) kinase [18]. TNF receptor-associated factors (TRAFs) 1-7 also induce hyperimmune responses that contribute to RA; these factors bind to the TNF receptor, IL-1 receptors and TLRs [19]. TRAF6 activates NF-κB to turn on genes encoding various inflammatory factors that drive synovitis and destruction of cartilage and bone [20].

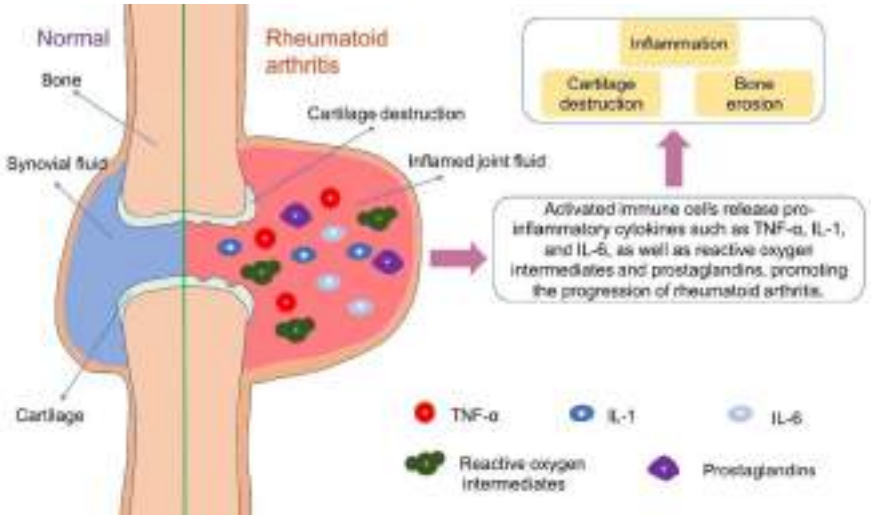


**Figure 1.** Comparison of normal joints and rheumatoid arthritis joints. IL, interleukin; TNF, tumor necrosis factor.

Similar to tumor tissues, RA tissues are affected by extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration (ELVIS), angiogenesis, hypoxia and acidosis. The leaky vasculature of inflamed joints enables the penetration of nanodrugs, which are subsequently internalized by activated synovial cells [21]. The high metabolic demand and rapid growth of synovial membrane in inflamed synovial tissues leads to hypoxia in inflamed joints, causing hypoxia-inducible and vascular endothelial growth factors to induce angiogenesis and promote cell growth [22]. Angiogenesis is essential for

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synovial tissue proliferation and pannus formation. Joint synovial tissues show upregulation of angiogenesis-stimulating factors and downregulation of angiogenesis inhibitors, leading to synovial micro-angiogenesis [23]. Gal-9 induces angiogenesis via signaling pathways involving JNK, Erk1/2, and p38 [24]. Survivin, a member of a family of apoptosis inhibitors that block caspase activity [25], upregulates angiogenesis-related proteins and activates the NOTCH pathway to suppress apoptosis [26]. Endothelial cells and synovial vessels in inflamed joints contain elevated concentrations of semaphorins, which may contribute to angiogenesis [27]. The pH value of interstitial tissues in inflamed joints ranges between 6.0 and 7.0, and acidic pH enhances the inflammatory response of neutrophils [28]. These characteristics of RA can be exploited to treat the disease in a targeted way.

**3. Diagnosis of RA**

Common diagnostic methods for RA include magnetic resonance imaging (MRI), ultrasonography, and assays for autoantibodies. MRI can effectively detect changes in inflamed soft tissues, such as synovitis, tenosynovitis and bone marrow edema, through multiplanar tomographic imaging of bone and soft tissue structures in inflamed joints. MRI can evaluate the cartilage damage, bone erosion and tendon tears of peripheral joints. However, the technique is expensive, it takes time, and each MRI scan can cover only a limited area of tissue. Ultrasonography, in contrast, allows real-time, relatively low-cost imaging of synovial proliferation and bone erosion in inflamed joints. Ultrasound has similar sensitivity and accuracy to MRI in the diagnosis of synovitis and tenosynovitis in patients with early rheumatoid arthritis [29]. But ultrasonography can’t detect bone marrow edema. RA can be diagnosed based on the presence of autoantibodies, which are produced in response to abnormal cellular and humoral immune responses. These autoantibodies include rheumatoid factor (RF), which comprises IgG, IgA and IgM, which are also present in healthy people but at higher levels in individuals with RA; and anti-citrullinated protein antibody (ACPA), which promotes bone loss by activating macrophages or by binding to citrullinated vimentin in cell membranes [30]. Its concentration and the diversity of its epitopes increase with levels of pro-inflammatory cytokines. Although RF and ACPA are diagnostic markers of RA, about one third of RA patients are usually negative for RF and

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ACPA. So, simultaneous detection of RA33 antibody, RF and ACPA can improve the diagnostic sensitivity of serological test [31]. In addition, some researchers reported the other four biomarkers, angiotensinogen, serum amylase A-4 protein, vitamin D-binding protein and retinol-binding protein-4 can prevent false negative and improve the accurate of RA diagnose [32].

**4. Drugs used to treat RA**

Drugs used to treat RA include non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids (GCs), biological agents, and RNA interference (RNAi) (Table 1). These drugs can relieve pain, reduce injury, or slow down the progress of the disease efficiently [33, 34].

NSAIDs are suitable for the early stages of RA and can rapidly alleviate symptoms and improve patients' quality of life, but they cannot prevent further joint damage [35]. NSAIDs can also inhibit the production of prostaglandins by blocking the ability of cyclooxygenase-2 to transfer arachidonic acid to the endoperoxide pathway, thereby reducing inflammation associated with RA [36]. Patients' response to NSAIDs varies greatly, especially the elderly patients. Elderly patients with RA have an increased risk of adverse reactions because they tend to take more other drugs besides NSAIDs. In addition, elderly patients have poor compliance with NSAIDs due to physical dysfunction (visual impairment, arthritis, dementia and depression), resulting in poor curative effect [37]. Commonly used NSAIDs are acetylsalicylate (aspirin), naproxen, diclofenac, ibuprofen, and etodolac. Their long-term use is associated with high risk of nausea, abdominal pain, ulcers, gastrointestinal bleeding, heart failure, and high blood pressure [38].

DMARDs, such as methotrexate (MTX), sulfasalazine, hydroxychloroquine, leflunomide and minocycline, can reduce joint swelling, pain, and systemic inflammation [35]. MTX is a folic acid analogue that inhibits nucleotide synthesis and purine metabolism by inhibiting the activity of dihydrofolate reductase. This drug was originally used to treat hematological malignancies and has been shown to be effective for inflammatory arthritis at low doses [34, 39]. Due to its low cost and long-term safety, MTX is currently the most preferred DMARD to treat RA [40]. However, it has been associated with gastrointestinal

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intolerance (nausea, stomatitis, or diarrhea), hepatotoxicity, post-treatment fatigue, headache, dizziness, and rheumatoid nodule formation [41].

GCs, such as dexamethasone, prednisone, prednisolone and betamethasone, are strong anti-inflammatory and immunosuppressive drugs widely used to treat RA [42] due to their ability to control pain, stiffness, and swelling. Nevertheless, GCs are less effective in preventing disease progression [43], and their long-term use increases the risk of cardiovascular disease, gastrointestinal bleeding, hyperglycemia/diabetes, osteoporosis, and infection [44, 45].

Biological agents have recently emerged as a novel therapeutic approach for RA that can effectively alleviate symptoms, slow disease progression, and prevent joint injury. Currently, 12 biological agents are used in clinical practice: five TNF-α inhibitors (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol); inhibitors of IL-6 and its receptor (tocilizumab and sarilumab); a CD80/86-CD inhibitor (abatacept); and an anti-CD20 antibody (rituximab) [34, 46]. However, the use of biological agents has been associated with greater risk of infection, malignancy, cardiovascular injury, immunogenicity, and other adverse events [47].

MicroRNA (miRNA) and small interfering RNA (siRNA) are small RNAs molecule that downregulate protein expression by triggering the degradation of messenger RNAs before their translation into proteins, through a process known as RNA interference (RNAi) [48, 49]. In rat models of arthritis, miR-449 inhibits the production of the inflammatory factor IL-6, while miR-708-5p blocks inflammatory cell infiltration, synovial hyperplasia, and cartilage destruction [50]. While siRNA may show promise for therapeutic RNAi, siRNAs are rapidly degraded in the blood and are inefficiently internalized by cells, limiting their application in the clinic [51, 52].

The efficacy of these drugs may be improved by using them in combination [53, 54]. Nevertheless, the systemic mechanism of these drugs and their poor accumulation in inflamed joints mean that they must be administered often and at high doses, increasing the risk of adverse effects [55].

**Table 1.** Drugs commonly used to treat rheumatoid arthritis.

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| Drug class | Drugs | Adverse effects |
|---|---|---|
| NSAIDs | Acetylsalicylates, naproxen, diclofenac, ibuprofen, etodolac | Nausea, abdominal pain, ulcers, gastrointestinal bleeding, heart failure, high blood pressure |
| DMARDs | Methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, minocycline | Gastrointestinal intolerance (nausea, stomatitis, or diarrhea), hepatic toxicity, post-treatment fatigue, headache, dizziness, rheumatoid nodule formation |
| GCs | Dexamethasone, prednisone, prednisolone, betamethasone | Gastrointestinal bleeding, hyperglycemia/diabetes, osteoporosis, infection |
| Biological agents | Infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, tocilizumab, sarilumab | Infections, malignancies, cardiovascular risk, immunogenicity, risk of exposure in pregnancy |
| RNAi | miRNA, siRNA | Rapid enzymatic degradation in the blood, short half-life in serum, low cellular uptake |

DMARDs, disease-modifying anti-rheumatic drugs; GCs, glucocorticoids; miRNA, microRNA; NSAIDs, non-steroidal anti-inflammatory drugs; RNAi, RNA interference; siRNA, small interfering RNA.

## 5. Targeted drug delivery system

### 5.1. Drug delivery system used to treat RA in the animal model

To overcome the disadvantages of conventional RA drugs, several targeting nanodelivery systems are being developed [56, 57] to control drug release and prolong drug circulation in the blood [58], while reducing systemic toxicity. Nanoparticles, liposomes, and micelles are commonly used in medical applications for drug delivery, diagnostics, and imaging [59] due to their good biodegradability and sustainability [60](Table 2 and Figure 2). Such materials can stabilize drugs, control their release, and enhance their accumulation at inflamed sites [61, 62].

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**Table 2.** Drug-loaded nanoparticle drug delivery vehicles with the potential to treat RA.

| Drug | Carrier type | Brief description | Route of administration | Animal model |
|---|---|---|---|---|
| Dex | Liposomes | Prolonged half-life | Intravenous injection | AIA rats[62] |
| Dex | Liposomes | Enhanced targeting effect | Intravenous injection | AIA rats[63] |
| Tofacitinib citrate | Liposomes | Enhanced distribution in inflamed sites | Intravenous injection | AIA rats[64] |
| Berberine | Liposomes | Reduced inflammatory response | Intravenous injection | AIA rats[65] |
| MTX | Gold NPs | Improved efficacy and reduced toxicities | Intravenous injection | AIA rats[66] |
| Indomethacin | Micelles | Improved anti-inflammatory activity | Intravenous injection | AIA rats[67] |
| Dex/palmitate | Micelles | Enhanced targeting effect | Intravenous injection | AIA rats[68] |
| Tacrolimus | Micelles | Enhanced targeting effect | Intravenous injection | AIA rats[69] |
| MicroRNA124/MTX | Micelles | Enhanced synergy | Intravenous injection | AIA ats[70] |
| Dex/p65 siRNA | Micelles | Co-delivery of siRNA and Dex into macrophage | Intravenous injection | CIA mice[71] |
| Dex/palmitate | PLGA NPs | Improve pharmacokinetics and reduce cell damage | Intravenous injection | CIA mice[72] |
| siRNA | PLGA NPs | Retarded progression of inflammation | Intravenous injection | CIA mice[73] |
| β-Sitosterol | Solid lipid NPs | Inhibiting NF- κ B signaling pathway | Intravenous injection | AIA rats[74] |
| Prednisolone | Solid lipid NPs | Specifically bind to CD44 on the inflammatory cell | Intravenous injection | CIA mice[75] |
| Embelin | Chitosan NPs | Prolonged retention time and improved targeting | Intravenous injection | AIA rats[76] |
| Eugenol | Chitosan NPs | Enhanced anti-arthritic activity | Intravenous injection | CIA mice[77] |
| Zinc gluconate | Chitosan NPs | Enhanced targeting effect | Intravenous injection | CIA mice[78] |
| Carvacrol | Albumin NPs | Exerted potent suppressive effect | Intravenous injection | AIA rats[79] |
| Celastrol | Albumin NPs | Reduced celastrol dose with effective therapy | Intravenous injection | AIA rats[80] |
| Methotrexate | Albumin NPs | Enhanced retention and reduced Carvacrol dose | Intravenous injection | CIA mice[81] |
| Prednisolone/curcumin | Albumin NPs | Co-delivery of prednisolone and curcumin to | Intravenous injection | AIA rats[82] |

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| | | | | |
|---|---|---|---|---|
| | | inflamed site | | |
| Hydroxychloroquine | Biomimetic NPs | Increased half-life and targeting to inflamed joints | Intravenous injection | CIA mice[83] |
| Dex | Injectable hydrogel | Enhanced therapeutic efficacy | Intra-articular injection | CIA mice[84] |
| Indomethacin/MTX/MMP-9 siRNA | Injectable hydrogel | Synergistic treatment of multiple drug | Intra-articular injection | AIA rats[85] |

AIA, adjuvant-induced arthritis; CIA, collagen-induced arthritis; NPs, nanoparticles; Dex, dexamethasone; MTX, methotrexate; PLGA, poly (lactic-*co*-glycolic acid).

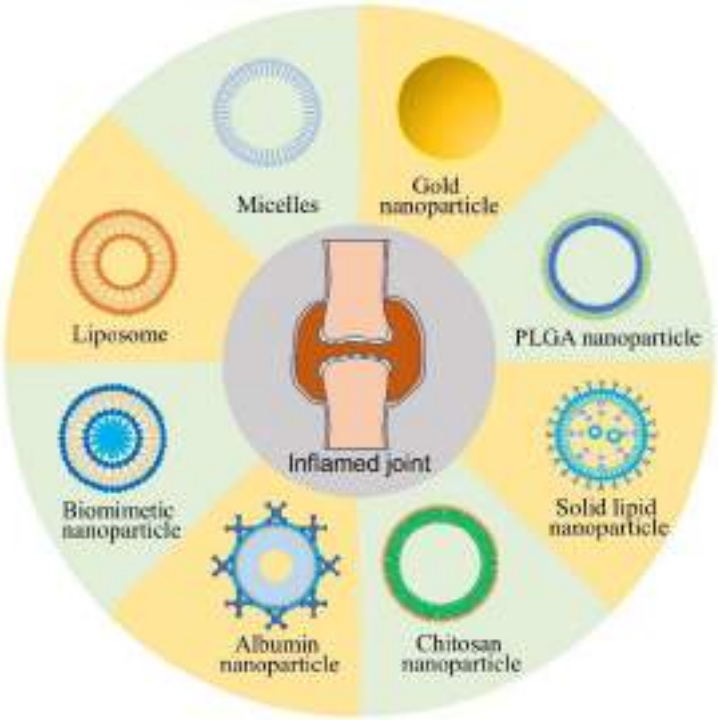


**Figure 2.** Nanoparticles commonly used in targeted delivery systems. PLGA, Poly (lactic-co-glycolic acid).

### *5.1.1 Liposomes*

Liposomes consist of phospholipids and cholesterol can form a lipid bilayer with an aqueous core, and the particle size is usually in the range of 25 nm - 2.5 μm [86]. Liposomes can encapsulate both hydrophobic and hydrophilic drugs, and have good biocompatibility and biodegradability. But the ability of liposome for encapsulating hydrophobic drugs is not ideal and easily leak drugs [87]. However, traditional liposomes clear rapidly by the reticuloendothelial system. Modifying liposomes with polyethylene glycol (PEG) can effectively reduce the adsorption of plasma proteins and subsequent clearance by the reticuloendothelial system, thus prolonging the circulation of drugs in the blood and improving its distribution in inflamed joints [88]. Intravenously administering

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dexamethasone-loaded polymerized stealth liposomes to arthritic rats significantly prolonged drug circulation in the blood and enhanced drug accumulation in inflamed joints [62]. This treatment significantly reduced levels of TNF-α and IL-1β at the lesion site as well as the degree of joint swelling, indicating inhibition of RA progression.

The peptide ART-2 (CKPFDRALC) showed preferential homing to arthritic joints of rats and strong binding to endothelial cells. To improve the targeting efficiency of liposome for inflames joints, another study designed ART-2 peptide modified liposomes. This dexamethasone-loaded liposome with ART-2 modification could accumulated in the inflame joint more than dexamethasone-loaded liposome without ART-2 modification, and relieve the RA more efficiently [63]. Besides hydrophobic drugs, liposomes could also be used to encapsulate hydrophilic drugs efficiently. Hydrophilic drugs can be encapsulated within the the aqueous core of liposome. Liposomes loaded with tofacitinib citrate (TOF), a water-soluble anti-inflammatory drug had been prepared. This liposome could be internalized selectively by inflammatory cells in a rat model of arthritis, and the drug accumulated in arthritic paws [64]. Packing TOF in this way significantly improved its therapeutic efficacy, downregulated inflammatory cytokines in joint tissues, and relieved RA symptoms. In another study, PEGylated liposomes loaded with water-soluble berberine accumulated selectively in inflamed joints of rats with adjuvant-induced arthritis (AIA). Berberine potently activated miR-23a, downregulating inflammatory kinases such as ASK1 and GSK-3β as well as mediators of Wnt1 signaling, ultimately mitigating bone erosion [65]. The safety and efficacy of liposomal bupivacaine (LB) have been confirmed in surgery, but its pharmacokinetic parameters and safety in Chinese population have not been evaluated. A phase I study confirmed that LB was well tolerated and safe among individuals in Chinese descent [89].

#### *5.1.2 Gold nanoparticles*

Gold nanoparticles (AuNPs), with particle sizes ranging from 1 to 100 nm, are widely used in diagnostics, therapy, and biological imaging [90]. AuNPs had excellent stability and biocompatibility, customizable shape and dimension, easily functionalized surface, high drug loading capacity, and low toxicity. However, AuNPs tend to accumulate in the kidney, liver, and spleen after enter the body, and possibly leading to incomplete metabolism in the body

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[91]. AuNPs has strong affinity to thiol and amine group, which allow binding with targeting agents that possess these group. In addition, AuNPs has good binding ability to vascular endothelial growth factor (VEGF) and shows natural antiangiogenic effects in inflamed synovium. Intra-articular injections of AuNPs with various dimensions to CIA mice showed an obvious antioxidant action significantly increasing the catalase activity without causing any side effect on hematological indices. AuNPs with 50 nm showed superior effect in inhibiting synovial angiogenesis than 13 nm and achieve better antioxidant and therapy in the early stage of arthritis [92]. In another study, an MTX delivery system consisting of gold nanorods with a mesoporous silica shell (FAGMs) was study for controlling the release of MTX. The release rate of MTX from FAGMs in vitro increased markedly under 808 nm laser irradiation and achieving superior effect in inhibiting RA progression in AIA rats, while reducing the systemic toxicity of MTX [66]. These indicating FAGMs could be promising for the treatment of RA. In addition, clinical trials have tested the coupling of human proinsulin peptide (C19-A3) with AuNP (C19-A3-AuNP) for the treatment of type 1 diabetes. In a phase I clinical trial, the safety of intradermal administration of C19-A3-AuNP through microneedles was explored [93]. The results showed that patients with type 1 diabetes had a good tolerance to C19-A3-AuNP, and no signs of systemic allergy were observed.

***5.1.3 Polymer micelles***

Polymeric micelles are core-shell structures with a particle size of 10-100 nm that form through self-assembly of amphiphilic block copolymers in aqueous solutions [94]. Polymer micelles can effectively avoid clearance by the kidney and reticuloendothelial system, and they can target inflamed tissues through the ELVIS effect [95]. Micelles form when the polymer concentration in the solution is higher than the critical micelle concentration, and they dissociate into monomers when the polymer concentration is below the critical micelle concentration. Micelles with lower critical micelle concentration are therefore more stable in circulation [96].

Copolymer micelles loaded with indomethacin, a non-steroidal anti-inflammatory drug that can effectively control inflammation [67], significantly relieve inflammatory symptoms and reduced arthritic index and paw diameter in AIA rats. Similarly, micelles loaded with dexamethasone palmitate can also accumulate at inflamed sites and reduce joint inflammation

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[68]. In another study, maltodextrin-α-tocopherol nano-micelles loaded with tacrolimus (TAC@MD-α-TOC) was prepared for RA therapy. This micelle showed stronger anti-rheumatic effects than the free drug. *In vitro* and *in vivo* experiments showed that TAC@MD-α-TOC was more effective than free drug at promoting the viability of Vero cells and reducing the levels of IL-6 and TNF-α in serum and synovial fluid [69]. Monotherapy with MTX usually leads to irreversible joint injury because of its slow onset and long duration. MicroRNA-124 (miR-124) had direct bone protective activity against RA. Hybrid micelles containing both MTX conjugated polymer and miR-124 can targeting accumulate in the inflamed joints of AIA rats and enhance the synergistic effects of MTX and miR-124 effectively [70]. P65 is a member of the NF-κB family. Wang et al. utilized a polymer micelle to co-delivering Dex and p65 siRNA for treating RA [71]. The results showed that the micelle can co-deliver Dex and p65 siRNA to arthritis site successfully. This co-loaded micelle can inhibit the NF-κB signaling in macrophages of CIA mice and return activated macrophages in arthritic synovial membrane to an anti-inflammatory state efficiently. In the treatment of RA, micelle co-loaded with Dex and p65 siRNA also showed more excellent efficiency than other groups. In addition, a phase II study on the efficacy and safety of docetaxel-PM for treating recurrent or metastatic squamous cell carcinoma of the head and neck was conducted in 2015. And this docetaxel-PM is now on the market.

#### *5.1.4 PLGA nanoparticles*

Poly (lactic-*co*-glycolic acid) (PLGA) is a non-toxic, biodegradable polymer often used as a drug delivery carrier. PLGA nanoparticles can regulate drug release and their surface can be easily modified. They are commonly used to protect biological agents, such as proteins and nucleic acids, from rapid metabolism and clearance *in vivo* [97]. The drug release from PLGA particles depends on the molecular weight of the polymer. Polymers with higher molecular weight have longer polymer chains, so it takes longer degradation time and lead to slower drug release rate [98]. For example, loading apremilast, a small-molecule drug designed for oral delivery, into PLGA nanoparticles significantly prolonged its half-life and mean residence time *in vivo* [99]. Luteinium-177, a radionuclide with a half-life of 6.71 d that can be used for radiation treatment of joints with advanced arthritis due to its β maximum emission energy (0.497 MeV, 78%). Hyaluronic acid (HA) is a polymer can specifically bind

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to CD44 overexpressed on inflamed synovial cells. In a study, PLGA modified with Luteinium-177 and HA was prepared for encapsulating MTX (177Lu-DOTA-HA-PLGA(MTX)). This 177Lu-DOTA-HA-PLGA(MTX) nanoparticles could bind strongly to inflamed synovial cells, internalized efficiently by them [100]. In addition, some research had report that encapsulating dexamethasone palmitate into PLGA-PEG nanoparticles can improved the drug's pharmacokinetic profile and reduced its tendency to damage cells and aggregate in the liver, kidneys, and lungs [72]. Bruton's tyrosine kinase (BTK) in macrophages and B cells is an important target for RA therapy. However, high dosage of BTK inhibitors was needed for effective BTK inhibition limits its clinical application. Zhao et al. developed cationic lipid-assisted PEG-b-PLGA nanoparticles (CLAN) loaded with BTK siRNA (CLANsiBTK) [73]. In the CIA mice model, CLANsiBTK can significantly alleviate the arthritis symptoms, downregulate the expression of inflammatory cytokines (TNF-α, IL-1β and IFN-γ), and reduce the damage to the paw joints.

#### *5.1.5 Solid lipid nanoparticles (SLNs)*

SLNs are a lipid-based drug delivery system with a particle size of 10-1000 nm that can specifically target inflamed tissues and control drug release [101]. SLNs show low immunogenicity in the human body and can easily infiltrate biological tissues, while carrying large amounts of lipophilic compounds. However, the ability of solid lipid nanoparticles to encapsulate hydrophilic drugs is poor. And, the drug release curve changes, polymorphic transformation and particle aggregation will occur during storage [102]. Zhang et al. had loaded β-sitosterol into SLNs to improve its water solubility and bioavailability in AIA rats. The developed nanoparticles (β-sitosterol-SLNs) exhibited good anti-arthritic effects by inhibiting NF-κB and activating the heme oxygenase-1/NF-erythroid 2-related factor 2 pathway [74]. To improve the targeting for inflamed tissue, prednisolone-loaded SLNs coated with HA was prepared. This HA modified SLN could accumulate in the inflamed joints of CIA mice and reduced joint swelling, bone erosion, and levels of inflammatory cytokines in serum [75].

#### *5.1.6 Chitosan nanoparticles*

Chitosan, a polysaccharide that arises through the deacetylation of chitin, is widely used in the preparation of microns and nanoparticles [103]. Chitosan nanoparticles have good

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biodegradability, low immunogenicity and high cell permeability, which make them suitable nanocarriers for targeted drug delivery [104]. For example, chitosan nanoparticles can improve the efficacy of the anti-inflammatory drug embelin, which is poorly absorbed in the body, where it is rapidly metabolized and cleared. Loading embelin into chitosan nanoparticles downregulated malondialdehyde and nitroxide as well as TNF-α, IL-6, and IL-1β in serum in AIA rats, while reducing oxidative stress [76]. In a study with CIA rats, loading eugenol into chitosan nanoparticles significantly improved the drug's ability to reduce the expression of monocyte chemoattractant protein-1 and transforming growth factor-β and to alleviate joint synovial hyperplasia and cartilage injury [77]. Similarly, loading zinc gluconate into chitosan nanoparticles improved the compound's ability to inhibit the infiltration of inflammatory cells in ankle joints; downregulate TNF-α, IL-6 and inducible nitric oxide synthase (iNOS); and upregulate SOD1 [78].

#### *5.1.7 Albumin nanoparticles*

Albumin is the most abundant protein in plasma, accounting for approximately 60% of total protein in the blood [105]. It is considered an ideal candidate for drug delivery due to a strong ability to bind hydrophobic and hydrophilic drugs, relatively long half-life in blood (19 days), biodegradability, and lack of immunogenicity [106]. Albumin, which has a molecular weight of 66.5 kDa, can be obtained from various sources, such as egg white (ovalbumin), bovine serum (BSA), and human serum (HSA) [107]. Albumin can prolong the circulation of nanoparticles in the blood by forming protein crowns [108]. For example, coating albumin onto the surface of liposomes or embedding it directly into phospholipids of the liposomes allowed the nanostructures to evade phagocytosis, prolonging their circulation [109]. In a study with AIA rats, loading carvacrol into BSA nanoparticles significantly improved the anti-inflammatory agent's ability to mitigate swelling and reduce the release of the inflammatory cytokines NO and IL-17 in arthritic rats [79]. To improve the targeting of BSA nanoparticles, Gong et al. had prepared a palmitic acid modified BSA nanoparticle (PAB NPs) and loaded celastrol in it. This PAB NPs could bind to scavenger receptor-A (SR-A) efficiently and showed 9-10 times more macrophages than normal BSA NPs. PAB NPs could delivery anti-inflammatory drugs celastrol (CLT) to inflamed tissues more effectively than BSA NPs and alleviate RA symptoms at a lower dose [80]. Loading MTX into HSA

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nanoparticles labeled with chlorin e6 improved the drug's accumulation and retention in inflamed joints of CIA rats, such that the encapsulated drug slowed RA progression as effectively as a 50% higher dose of free drug [81]. In a study with AIA rats, loading prednisolone and curcumin into HSA nanoparticles led to lower levels of pro-inflammatory cytokines in activated macrophages, higher levels of the anti-inflammatory cytokine IL-10, greater drug accumulation in inflamed joints and stronger therapeutic efficacy than nanoparticles loaded with single drugs or free drugs alone or a simple mixed of two drugs [82]. Abraxane (paclitaxel combined with albumin) was approved by FDA for sale in 2005. In 2021, FDA approved Fyarro (Sirolimus albumin-bound nanoparticles, nab- sirolimus, ABI-009) to be marketed for intravenous infusion in the treatment of locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumors.

All the above researchers used exogenous albumin to prepare nanoparticles *in vitro*. However, after nanoparticle entered the body, they can also cause immunogenic reaction. Therefore, some researchers intend to use the endogenous albumin in the body to prepare albumin bounded nanoparticle for targeting therapy. Albumin binding domain (ABD, 46 amino acids) was reported to have strong affinity for serum albumin, among which ABD035 variant shows superior affinity toward albumin of various sources (such as human, mouse, rat, cow and monkey). Zhang et al. designed a redox-responsive paclitaxel micelle system modified by ABD035 peptide [110]. After intravenous injection, the micellar system combined with endogenous albumin in blood, and then delivered paclitacel to the tumor cell by gp60 and SPARC receptor. The inflammatory tissue had similar characterizations with tumor tissue, such as abundant albumin receptor, incomplete vascular structure, etc. So, developing nanoparticle can bind to endogenous albumin maybe a good strategy for targeting RA therapy.

#### *5.1.8 Biomimetic nanoparticles*

Biomimetic nanoparticles have attracted particular attention in recent years because of their ability to evade clearance by the reticuloendothelial system [111]. The biomembranes was usually extracted by the following method. Cells were placed in hypotonic liquid for cell disruption and lysis, and then purified and collected by discontinuous gradient centrifugation

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at 4 ℃. Protease inhibitor should be added in the whole extraction process to protect the activity of protein [112]. Such nanoplatforms are prepared by encapsulating nanoparticles into cell membranes extracted from red blood cells, macrophages, neutrophils, and platelets [113] through co-extrusion, extrusion/sonication, freeze-thaw/sonication, extrusion/sonication and other methods [114, 115]. These nanoplatforms show great biocompatibility, effective drug delivery, prolonged circulation time in blood, and minimal adverse immune responses[116, 117]. For example, spherical, prolate-spheroidal, and oblate-spheroidal PLGA nanoparticles coated with erythrocyte membrane effectively evaded clearance by macrophages [118]. Wrapping hydroxychloroquine-loaded nanoparticles with membranes from umbilical vein endothelial cells expressing TNF-related apoptosis-inducing ligand generated nanoparticles that delivered hydroxychloroquine to inflamed joints in CIA mice, while also inducing M1 macrophage apoptosis by upregulating death receptor-5 [83]. The result was effective inhibition of RA progression. In CIA mice, coating nanoparticles with neutrophil membranes and then administering these nanostructures together with immunoregulatory molecules promoted tissue repair, downregulated pro-inflammatory cytokines, and inhibited synovitis [119].

***5.1.9 Injectable hydrogel***

Hydrogel is a highly hydrated three-dimensional network of hydrophilic polymers, whose bionic structure is similar with the extracellular matrix of natural biological tissues and has good biocompatibility. Injectable hydrogel should have more comfortable, less pain, and fewer side effects than non-injectable hydrogels. It is difficult to obtain a desirable injectable hydrogel by using a single material. Incorporating nanofiller into a polymer matrix can achieve desirable injectable gel with higher biocompatibility and biodegradability, easier changed properties, and better ability to deliver hydrophilic or hydrophobic macromolecules in a sustained manner. Injectable hydrogel with loosely inter-connected polymer chain has higher burst release and more rapid clearance of drug [120]. Wang et al. have developed a temperature-sensitive hydrogel (DLTH) base on chitosan-glycerol-borax for intra-articular delivery of dexamethasone [84]. In CIA mice model, intra-articular injection of DLTH load with dexamethasone showed good anti-inflammatory and analgesic effects. Similarly, in situ hydrogels were also designed to co-deliver indomethacin, methotrexate and MMP-9 siRNA

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for synergistic and comprehensive treatment of RA [85]. This in situ hydrogels can down-regulated the expressions of inflammatory factors (TNF-α, IL-6) and MMP-9 in plasma and knee joint fluid significantly after intra-articular injection.

### 5.2. Targeted RA treatment in the animal model

#### *5.2.1 Passive targeting*

Synovial thickening during the development of RA induces hypoxia and angiogenesis, leading to vascular leakage at the site of inflammation. Since the ELVIS effect in RA is similar to the EPR effect in tumor tissues [21], which has been exploited by many cancer therapies, passive targeting strategies against RA have been developed based on the ELVIS effect [121]. Nanoparticles with a size of 20-200 nm can penetrate the synovial tissue through the intercellular space between endothelial cells and accumulate at inflamed sites, significantly reducing drug side effects (Figure. 3). In contrast, nanoparticles smaller than 10 nm are easily cleared by renal filtration, while those larger than 200 nm are removed by phagocytes in the reticuloendothelial system [122, 123].

To improve the passive targeting ability of nanoparticles of suitable size, their surface has been modified with PEG, which shields surface charge, inhibits the adsorption of serum proteins and helps evade detection by circulating macrophages [124, 125]. For example, allowing hydrophilic short-chain methoxy PEG to self-assemble with gambogic acid, a natural drug that inhibits inflammation by downregulating IL-1β and TNF-α, improves the drug's ability to reduce paw inflammation in CIA mice [126]. The free drug, in contrast, shows low water solubility, poor pharmacokinetics, and hemolytic toxicity. Similarly, modifying liposomes of 100 nm diameter and slightly negative charge with 10% $PEG_{5000}$ improved their *in vivo* circulation time and ability to target inflamed joints in CIA mice, allowing encapsulated dexamethasone to work much better than the free drug [127]. Similarly, liposomes prepared with hydrogenated phosphatidylinositol can avoid the clearance of reticuloendothelial systems and prolong the blood circulation time. Doxorubicin loaded in the hydrogenated phosphatidylinositol liposome can be detected within 72 hours after the injection. The circulation time of hydrogenated phosphatidylinositol liposome is significantly longer than ordinary liposome [128]. In addition, nanoparticles coated with poly

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(ethylene oxide)-block-poly (γ-methylprednisolone) had nearly neutral surface charges also can avoid the non-specific binding of macromolecules to the nanoparticles and escape from the clearance of reticuloendothelial systems successfully [129].

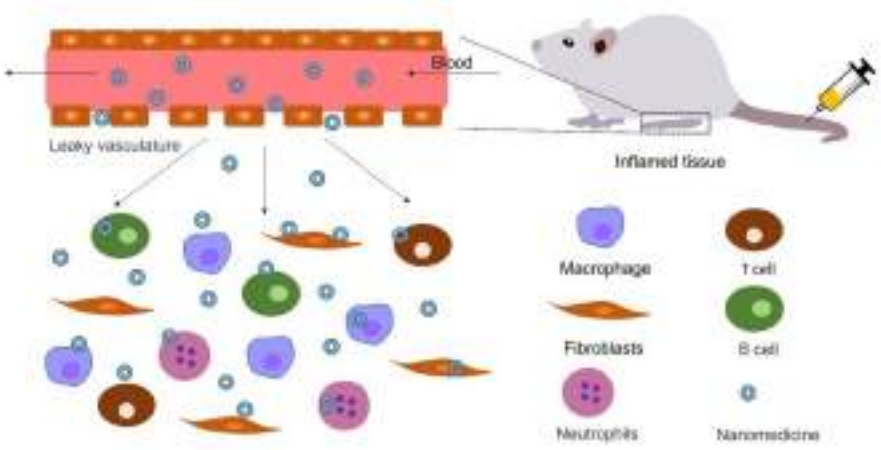


**Figure 3.** Schematic illustration of the extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration (ELVIS) effect.

### *5.2.2. Active targeting*

Active targeting mainly involves modifying the nanocarrier surface with appropriate ligands that bind to receptors expressed on the surface of target cells at inflamed sites (Table 3) [130]. RA involves vascular regeneration and inflammation, and these processes involve B cells, T cells, macrophages and other immune cells [11]. The processes are driven by growth factors, pro-inflammatory cytokines, chemokines, cell adhesion molecules, proteases, and the hypoxia-vascular endothelial growth factor angiopoietin. Activated macrophages are abundant at sites of inflammation, where they produce large amounts of pro-inflammatory IL-6, IL-1β, and TNF-α [131]. The surface of activated macrophages contains abundant folate receptor-β, vasoactive intestinal peptide receptor, scavenger receptor class A, TLRs, transforming growth factor-β receptor, CD44, CD64, and other receptors (Figure. 4), while the surface of endothelial cells contains abundant $\alpha_v\beta_3$-integrin, E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 [132, 133]. If drug-loaded nanoparticles can selectively bind to these receptors, they can target their cargo to inflamed tissue. This assumes, of course, that the nanoparticles can evade clearance by the

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reticuloendothelial system and penetrate inflamed vascular endothelium (Figure. 5) [55].

**Table 3.** Drug-loaded nanoparticles targeting receptors highly expressed in rheumatoid arthritis tissue.

| Targeted receptor | Drug | Carrier | Animal model |
|---|---|---|---|
| Folate receptor | MTX | Chitosan nanoparticles | CIA mice[134] |
| Folate receptor | MTX | Liposomes | CIA mice[135] |
| Folate receptor | Myeloid cell leukemia-1 siRNA/Dex | Micelles | CIA mice[136] |
| Scavenger receptor | MTX | Double layered hydroxide nanocomposites | AIA rats[137] |
| Scavenger receptor | Celastrol | Micelles | AIA rats[138] |
| CD44 | Dex | Polymeric nanoparticles | AIA rats[139] |
| CD44 | MTX/teriflunomide | Hydroxyapatite nanoparticles | CIA mice[140] |
| CD44 | Tripterine | Bilosomes | CAIA rats[141] |
| Mannose receptor | *p*-Coumaric acid | Liposomes | AIA rats[142] |
| Mannose receptor | Morin | Liposomes | AIA rats[143] |

AIA, adjuvant-induced arthritis; CAIA, collagen antibody-induced arthritis; CIA, collagen-induced arthritis;

MTX, Methotrexate; Dex, Dexamethasone

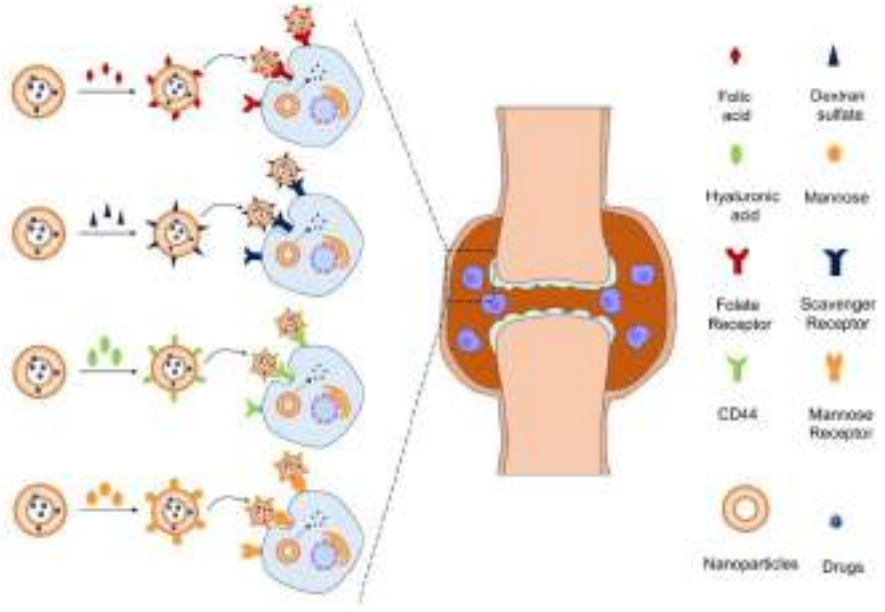


**Figure 4.** Active targeting of cells in inflamed joints through specific binding between ligand-modified nanoparticles and targeted receptors.

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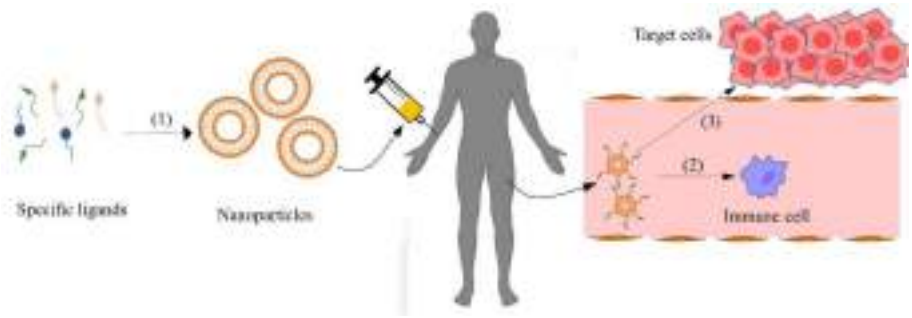


**Figure 5.** Active targeting of inflamed tissues by (1) drug-loaded nanoparticles modified with specific ligands that can evade (2) reticuloendothelial clearance and penetrate (3) inflamed vascular endothelium.

*5.2.2.1 Folate receptors*

Folate receptors are glycopolypeptides with high affinity for folic acid that can be found in four isoforms (FR-α, FR-β, FR-γ and FR-δ) differentially expressed in different tissues [144]. FR-β is widely expressed on the surface of activated synovial macrophages in RA patients, making it a potential target for disease treatment [145]. For instance, encapsulating MTX into hydrophobically modified ethylene glycol chitosan nanoparticles conjugated to folic acid showed significantly reduced pro-inflammatory cytokine expression, paw thickness, and arthritic score in CIA mice compared with nanoparticles without folic acid conjugation [134]. In another study, folic acid was coupled with $PEG_{100}$ monostearate to prepare liposomes co-loaded with MTX and catalase. The obtained liposomes showed enhanced cellular uptake through folate-mediated endocytosis and strong toxicity against activated RAW264.7 cells, as well as increased accumulation in inflamed joints and therapeutic efficacy in CIA mice, while causing minimal toxicity to major organs [135]. Myoloid cell leukemia-1 (Mcl-1) is overexpressed in macrophages of arthritic joints. Inhibiting MCL-1 can induce apoptosis of macrophages and thus alleviate inflammation. Li et al. developed folate-modified polymeric micelle co-loading MCL-1 siRNA and DEX for RA therapy [136]. In CIA mice model, this DEX/siRNA co-loaded polymeric micelle can significantly reduce the MCL-1 mRNA level in macrophage and significantly reduce levels of the inflammatory factors, such as TNF-α and IL-1β.

*5.2.2.2 Scavenger receptors*

Scavenger receptors belong to a superfamily of structurally heterogeneous proteins, including transmembrane proteins and soluble secretory extracellular domains, can

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effectively regulate the uptake of oxidized and acetylated low-density lipoprotein [146]. Scavenger receptor class A (SR-A) is expressed mainly on the surface of mature macrophages and has been associated with atherogenesis [147]. This receptor has been targeted for RA treatment: MTX-loaded layered double hydroxide nanocomposites were modified with dextran sulfate (LDH-MTX-DS), a hydrophilic block that specifically binds to SR-A [148]. LDH-MTX-DS released MTX faster at pH 5.5 than at pH 7.4 and actively targeted scavenger receptors on the surface of activated RAW 264.7 cells, leading to significantly stronger therapeutic effects than free MTX in AIA rats [137]. In another study, a micelle modified with dextran sulfate was also prepared for celastrol delivery. This micelle can effectively accumulate and release celastrol in RAW264.7 cells by binding to the SR-A, then significantly improved the therapeutic effect of celastrol in vivo without causing obvious systemic toxicity [138].

*5.2.2.3 CD44*

CD44 is a non-kinase transmembrane glycoprotein that is overexpressed in inflammatory synovial macrophages and fibroblasts [149]. It promotes pathological angiogenesis by regulating the proliferation, migration, and adhesion of endothelial cells. HA is a natural polysaccharide in the extracellular matrix that can specifically bind to the CD44 receptor [54, 150]. Therefore, HA-coated acid-sensitive polymer nanoparticles composed of egg phosphatidylcholine, polyethyleneimine, and poly(cyclohexane-1,4-diyl acetone dimethylene ketal) were loaded with dexamethasone to target activated macrophages overexpressing CD44 [139]. The obtained nanoparticles significantly reduced inflammatory cell infiltration as well as damage to bone and cartilage in the ankles of AIA rats, showing stronger therapeutic efficacy than the free drug [139]. In another study, HA -functionalized hydroxyapatite nanoparticles loaded with MTX and teriflunomide showed high cellular uptake and cytotoxicity *in vitro*, prevented the progression of arthritis and promoted joint regeneration in CIA rats, and led to less hepatotoxicity than commercially available formulations [140]. Bilosomes loaded with tripterine, a natural compound with strong antioxidative, antiangiogenic and antirheumatic properties, were prepared using cationic lipids by the thin film hydration method, then coated with HA to form HA@Tri-BLs [141]. The resulting nanosystem improved the cycle retention time of tripterine and increased its

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systemic and intra-arthritic bioavailability in a collagen antibody-induced arthritis model. The *in vivo* anti-arthritic efficacy of HA@Tri-BLs was also significantly higher than that of uncoated bilosomes due to high drug accumulation in the articular cavity.

*5.2.2.4 Mannose receptors*

Mannose receptors belong to the C-type lectin family and are overexpressed on the surface of macrophages during inflammation, and they mediate endocytosis of glycoproteins [151]. Mannose-conjugated liposomes loaded with *p*-coumaric acid, a compound with anti-inflammatory and osteoclastic effects, prolonged the drug's residence time in joints and downregulated pro-inflammatory TNF-α, IL-1β, IL-6, and IL-23, as well as the transcription factor NFATc1, which triggers osteoclast differentiation [142]. In another study, the mannose-modified liposomes were used to encapsulate morin, a bioflavonoid with anti-inflammatory, antitumor, and anti-oxidant activities. This mannose-modified liposome can be internalized preferentially by macrophages of arthritic rats, and inhibited the inflammatory immune response and osteoclastogenesis better than the dexamethasone palmitate encapsulated mannosylated liposomes, a reference drug as evidenced by clinical and histological analysis [143].

***5.3. Targeting based on environmental stimuli***

The microenvironment of inflamed tissues differs from that of healthy tissue in pH, redox conditions as well as levels of oxygen, reactive oxygen species (ROS), glucose, enzymes, and ATP. These differences can be exploited to trigger drug release from responsive delivery systems, thereby avoiding premature release into the circulation or healthy tissues, which reduces risk of adverse or other off-target effects [152-154].

*5.3.1 pH-responsive drug delivery*

Under normal conditions, the pH of the extracellular medium and blood is usually ~7.4, but it falls to 6.0 in the synovial microenvironment [155]. This pH difference between the inflammatory microenvironment and normal tissues has been exploited to design pH-responsive targeted drug delivery systems based either on ionizable polymers (polyacids or polybases) whose conformation or solubility changes with pH, or on polymer systems with acid-sensitive bonds [155, 156]. For example, pH-sensitive polymeric micelles prepared by

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the self-assembly of PEG-based derivatives and the hydrophobic drug prednisolone through acid-labile hydrazone bonds promoted the accumulation of prednisolone in inflamed joints and showed stronger anti-inflammatory effects *in vivo* than the free drug [157]. Another study reported the preparation of pH-sensitive polymer nanoparticles that delivered siRNA when the surrounding pH was 5.0, allowing them to deliver the drug selectively to sites of inflammation, leading to therapeutic efficacy in AIA rats [52]. A small library of biocompatible amphiphilic polymers has been synthesized based on methoxy poly(ethylene glycol)-poly(cyclohexane-1,4-diyl acetone dimethyleneketal) and methoxy poly(ethylene glycol)-poly((cyclohexane$_{86.7\%}$, 1,5-pentane-diol$_{13.3\%}$)-1,4-diyl acetone dimethylene ketal) for the targeted delivery of superoxide dismutase. The novel polymers released the enzyme in a pH-dependent manner, allowing the enzyme, which is normally rapidly cleared or degraded *in vivo,* to show good anti-oxidant and anti-inflammatory activities in AIA rats [158].

*5.3.2 Redox-responsive drug delivery*

Activated T cells produce 10-100 times more ROS at sites of inflammation than in normal tissues, which trigger an anti-oxidant glutathione (GSH) response in order to prevent further increases in ROS and resulting cellular damage [159]. The increased GSH concentration in inflammatory microenvironments means that disulfide bonds are cleaved there [160, 161]. Reduction-responsive polyprodrug amphiphiles were prepared through "reversible addition fragmentation chain transfer" polymerization of indomethacin-based redox-responsive prodrug monomers bearing disulfide bonds that were GSH-responsive and phenylboronic acid ester bonds that were $H_2O_2$-responsive [162]. The resulting polymers efficiently antagonized the effects of lipopolysaccharide on RAW264.7 macrophages.

*5.3.3 ROS-responsive drug delivery*

ROS such as $H_2O_2$, superoxide ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), peroxynitrite ($ONOO^-$), and hypochlorite ($OCl^-$) play an important role in normal cellular signaling pathways and oxidative metabolism. However, their excessive production in cells or tissues can cause oxidative stress, leading to various diseases, including inflammation, cancer, and atherosclerosis [154, 163, 164]. To target the high ROS levels in RA tissues, 4-phenylboronic acid pinacol ester-conjugated cyclodextrin biomaterials were used to prepare ROS-responsive dexamethasone-loaded nanoparticles [165]. The particles were efficiently internalized by

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activated macrophages, they accumulated in inflamed joints, and they reduced joint swelling and cartilage destruction in CIA mice.

*5.3.4 Enzyme-responsive drug delivery*

Enzymes such as proteases, glycosidases, metalloproteases, lipases, and phospholipases are biocatalysts that play a key role in countless normal processes [166], but their expression may be altered in disease [167]. Such changes can be exploited as triggers for environmentally responsive drug delivery [168]. For example, phospholipase A2 is overexpressed under inflammatory conditions, and it specifically hydrolyzes sn-2 ester bonds in phospholipids [169]. Thus, this enzyme can attack liposomes of the appropriate composition, leading to controlled release of the drug cargo [170], Similarly, high phospholipase A2 levels can release colchicine from phosphatidylcholinase-responsive liposomes that are otherwise stable in the blood circulation [171].

***5.4 Local injection strategies***

Local intra-articular injection is also an important therapeutic strategy for RA. Intra-articular injection has several advantages in RA therapy, including good bioavailability, reduced systemic exposure, and reduced adverse events and costs. The intra-articular injection of corticosteroids is the first-line treatment for RA. Now, researchers have found that intra-articular injection of etanercept is a safer and more promising treatment than corticosteroids [172]. Drugs currently used for intra-articular injection are dissolved in solution. So, the drug will rapidly diffuse into the systemic circulation after intra-articular injection, resulting in rapid removal from the joint cavity and short retention time. So, frequent intra-articular injection is required for good therapeutic effect on RA, and increase the risk of local pain, joint swelling and infection [173]. Therefore, several nanoplatforms have been developed to improve drug accumulation at inflamed sites. For example, injecting tetramethylpyrazine as a nanosuspension with hydrophobic ions prolonged its retention in the articular cavity of rats, leading to greater anti-arthritic efficacy than the free drug [174]. Loading siRNA targeting TNF into lipid-polymer hybrid nanoparticles of lipidoid and PLGA inhibited inflammation in murine experimental arthritis models even at the low siRNA dose of 1 μg [175]. Intra-articular injection of HA-modified liposomes loaded with diclofenac and

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dexamethasone effectively reduced inflammation and paw swelling in mice for four weeks [176].

## 6. Summary and Perspectives

Although great progress has been made in treating RA, the clinical application of traditional therapies is limited due to their high costs and requirements for frequent, long-term dosing. Nanocarriers can actively or passively deliver drugs to inflamed sites, thereby prolonging drug half-life, improving drug accumulation in target tissues, and reducing drug systemic toxicity. Although large numbers of nanocarriers have been developed for RA therapy, little has entered the clinical trials. These nanocarriers facing several challenge: (1) Most of the nanocarrier are unstable in circulation and usually leak the drug before reaching inflamed sites. (2) Nanocarriers captured by reticuloendothelial easily after the intravenous injection. (3) The targeting activity of nanocarriers for inflamed regions was too low. So, developing more safer and efficient nanocarriers is still the most important work at present.

In addition, although nanocarrier can greatly improve the therapeutic effect of RA, it still has some shortcomings. For example, the modification of ligands or targeting molecules is complex and costly. How to simplify the modification and reduce the cost is the key to for clinical transformation. PEG modification is usually used for improving the blood circulation time and RA targeting of nanocarrier. But it can also hinder the interaction between nanoparticles and cells, and inhibit the cellular uptake. In addition, after multiple intravenous injections, the PEG modification nanoparticles remove from the blood circulation rapidly [177]. So, developing simple and easy preparation biological new material that can escape from phagocytosis of the reticuloendothelial system, prolong the cycle time, and target the arthritis site is important for RA therapy.

Recent research has focused on the construction of targeting nanocarriers modified with ligands that can bind to specific receptors on the surface of cells involved in RA. Most of these nanocarriers can target RA by targeting the receptors on vascular endothelial cells, fibroblast-like synoviocytes and macrophages. Actually, except these cells, autoreactive T-cells or B-cells also contribute largely to the inflammatory process. Activated T cells can activate the monocytes, macrophages and synovial fibroblasts. Developing nanocarriers

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targeting these cells is also important.

A recent approach for targeted treatment of RA is to deliver RA-related antibodies and antigens to auto-reactive lymphocytes or dendritic cells with the aim of inducing antigen-specific immune tolerance [178] while maintaining protective immunity [179, 180]. To this end, future work should explore as many RA-related antibodies and antigens as possible. For example, RA-related cell injury and death release so-called cell-free DNA (cfDNA) into the peripheral blood and synovial fluid [181, 182]. Auto-antibodies bind to the cfDNA and the resulting complex activates Toll-like receptors, leading to the secretion of inflammatory cytokines [183]. Thus, using cationic polymers to eliminate cfDNA may be a promising treatment against RA. As a step in this direction, one study showed that cationic dimethylamino group-modified polydopamine nanoparticles bound strongly to cfDNA and efficiently inhibited cfDNA-induced inflammation in an animal model [184]. Reducing the systemic toxicity of these cationic polymeric nanoparticles is an important priority for future work.

At present, RA-related disability and mortality had affected large numbers of people. Despite decades of exploration on nanocarrier for RA, there are widely unknown areas yet to be investigated. Developing more superior nanocarrier for RA therapy is also an important and urgent work.

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## Competing interests

The authors declare that they have no conflict of interest.

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