REVIEW

Nanomedicines for the treatment of rheumatoid arthritis: State of art and potential therapeutic strategies

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Abstract
Increasing understanding of the pathogenesis of rheumatoid arthritis (RA) has remarkably promoted the development of effective therapeutic regimens of RA. Nevertheless, the inadequate response to current therapies in a proportion of patients, the systemic toxicity accompanied by long-term administration or distribution in non-targeted sites and the comprised efficacy caused by undesirable bioavailability, are still unsettled problems lying across the full remission of RA. So far, these existing limitations have inspired comprehensive academic researches on nanomedicines for RA treatment. A variety of versatile nanocarriers with controllable physicochemical properties, tailorable drug release pattern or active targeting ability were fabricated to enhance the drug delivery efficiency in RA treatment. This review aims to provide an up-to-date progress regarding to RA treatment using nanomedicines in the last 5 years and concisely discuss the potential application of several newly emerged therapeutic strategies such as inducing the antigen-specific tolerance, pro-resolving therapy or regulating the immunometabolism for RA treatments.

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1. Introduction

As a complicated autoimmune disease, rheumatoid arthritis (RA) often causes invasive inflammatory infiltration and serious articular destruction, as well as extensive comorbidities in the cardiovascular system, gastrointestinal and pulmonary tissues, severely reducing the life quality and lifetime of RA patients. RA affects approximately 1% of the global population and 0.28% of population in China. It is generally considered that RA is principally induced by the cross-talking of environmental factors and genetic predisposition. Genome-wide studies identify that genes encoding major histocompatibility complex II (MHC II) molecules which are involved in the T cell recognition of autoantigens are closely related with RA onset and development. The interaction of aberrant T cells and B cells, as the prelude of this autoimmune disorder, activates both innate and adaptive immune response and breaks the balance between host tolerance and immune homeostasis. Along with the altered immune reactivity, environmental stimulus such as smoking, dust inhalation and microbiota infection might also contribute to the progression of RA. Although RA is a systemic disease affecting a variety of organs and lymphoid tissues, the synovium in inflamed joints is the center of inflammation. Owing to the rapid proliferation and activation of inflammatory cells such as T cells, B cells, macrophages, vascular endothelial cells (VEC), fibroblast-like synoviocytes (FLS), etc., the synovium tissue abnormally expands with neovascularization, hyperproliferative intimal lining and a prominent amount of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), prostaglandins etc., invasive proteases such as matrix metalloproteinases (MMPs), and autoantibody such as rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPAs). In addition to massive inflammation infiltration, the destructive FLS and osteoclast, as well as MMPs would lead to the damage of cartilage and bone tissues.

Current clinical treatments, including non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids (GCs) and biological agents, mainly focus on alleviating the symptoms of RA via immunosuppression or inhibition of certain inflammatory mediators. NSAIDs such as ibuprofen could effectively relieve pain and swelling by the inhibition of cyclooxygenase (COX). However, they cannot modify the underlying disease process and are associated with serious gastrointestinal damage. GCs such as dexamethasone (Dex) exhibit powerful anti-inflammatory efficacy and can rapidly decrease the inflammatory infiltration, but their adverse effects limit the long-term or high-dose usage. DMARDs including methotrexate (MTX) are considered to be effective in slowing down the RA progress. It is highly recommended to use the combination with multiple DMARDs or GCs in clinical applications to achieve better anti-inflammatory effect and avoid the side effects caused by dose escalation. Biological agents including cytokine antagonists, B cell depleting agents, T cell co-stimulation modulators, and kinase inhibitors show great improvement in controlling RA activity due to their specificity and selectivity. Humira (monoclonal antibody against TNF-α) is one of the world’s top 10 best selling drugs during the past 3 years, which shows the high efficacy in the treatment of rheumatic diseases. However, a significant number of patients show reduced responsiveness after multiple administrations. The traditional Chinese medicines extracted from natural plants, including curcumin, resveratrol, ferulic acid and triptolide have also been demonstrated effective for the treatment of inflammatory diseases including arthritis. The advantages and disadvantages of clinical drugs have been summarized in Table 1.

Except the abovementioned conventional medications for RA therapy, gene therapy is gradually entering clinical practice. In 2017, the South Korean Ministry of Food and Drug Safety approved the first gene therapeutic Invossa, which is taking the advantage of retrovirus to deliver transforming growth factor-β (TGF-β) gene into affected joints for arthritis therapy. Meanwhile, a phase I clinical trial of recombinant Adeno-associated virus (AAV) to deliver interferon-β to the joints of RA patients is taking place in the Netherlands. Although notable strides have been made towards genetic medicine in arthritis management, this field is still in its infancy. Thus, we expect that encouraging achievements in genetic medicines for RA therapy will become widely available in the near future.

Before the therapeutic agents reach the inflamed sites and take effect, multiple physiological barriers in vivo must be overcome to...
achieve the desirable therapeutic outcome. Once the drug formulations enter the blood circulation, they will be faced with the phagocytose of reticuloendothelial-system (RES) and the destruction of proteases. In addition, the drug formulations would distribute throughout the body indistinguishably when administered in vivo, resulting in the impaired therapeutic efficacy and elevated risk of side effects. Most importantly, even if the drug reaches the inflamed joints, it will still be cleared rapidly from the articular space. In general, the ideal drug delivery system should overcome the abovementioned barriers in vivo and ultimately maximize the therapeutic efficacy of encapsulated agents.

Nanoscale drug delivery systems provide a promising approach to overcome the drawbacks in current treatments. It has been shown that nanocarriers can increase the solubility of drugs, extend the circulation time of drugs, reduce the clearance of drugs, and deliver drugs to disease sites in a controlled way. More recently, the emerging multifunctional nanocarriers with sophisticated targeted delivery or transformable properties are designed to achieve intelligent drug delivery and promote therapeutic efficacy.

Generally, the integration of efficacious therapeutic agents with effective delivery strategies is an attractive attempt for RA therapy. In this review, we will highlight the recent progress of advanced drug delivery for RA therapy in the last 5 years. In addition, the emerging promising therapeutic strategies and future perspectives of both academic research and clinical translation in terms of RA therapy are also discussed. Our review will probably bring new thoughts for further investigations of effective RA therapy.

### 2. Delivery strategies for different types of agents

The synovial in inflamed joints is abnormally expanded, accompanied by angiogenesis and inflammatory cell infiltration. Thus, the emergence of endothelial gaps in microenvironment of RA allows for the leakage of colloidal nanoparticles into the affected joints, subsequently followed by the sequestration of exogenous nanoparticles mediated by various inflammatory cells. This passive targeting mechanism is similar to the famous enhanced permeability and retention (EPR) effect occurred in tumor tissues due to the analogous leaky vessels presented in disease sites. Unlike EPR in tumors, the retention mechanism in RA mainly relies on the sequestration of local inflammatory cells.

In order to improve the efficacy of current available agents in RA therapy, researchers have developed diverse drug carriers by taking advantages of this passive targeting mechanism. The designing and construction of favorable drug delivery systems should be based on the physicochemical properties of therapeutic agents, as well as their dilemma in vivo. In this section, various drug vehicles for encapsulating and delivering different types of drugs will be summarized and classified in Table 2, which aims to provide general principles and inspiring insights for further explorations.

#### 2.1. Small molecule drug-based delivery systems

At present, the vast majority of drugs used frequently in clinic for RA treatment is small molecule drugs such as DMARDs and GCs, which are the cornerstone of RA management. However, the low solubility, poor pharmacokinetics behavior and non-targeted distribution of small molecule drugs, not only hamper their efficacy, but also give rise to multiple adverse effects. The suitable nanocarriers designed for delivering small molecule drugs should encapsulate the drugs with high drug loading and avoid drug leakage and burst release before reaching the inflamed sites. So far, multifarious delivery strategies aiming at solving these problems principally fall into two parts: conjugation of drugs with macromolecules and encapsulation of drugs within nanocarriers.

##### 2.1.1. Conjugation of drugs with macromolecules

Drug conjugated with macromolecule such as synthetic polymers, natural polysaccharides or proteins via covalent bonding offers a direct and efficient approach to modify the pharmacokinetics performance, promote drug stability and avoid drug leakage or burst release in circulation. Polyethylene glycol (PEG) is one of the widely investigated polymer used for drug conjugation due to its good biocompatibility, long circulation in vivo and controllable properties. For example, Wang and coworkers synthesized various PEG—Dex conjugates with different densities of Dex. The introduction of the acid-cleavable hydrazone bond between PEG and Dex significantly avoided the burst release of Dex in circulation and ensured the selective release in acidic disease sites. The optimized PEG-Dex formulation showed superior therapeutic efficacy. MTX is a first-line treatment for RA patients. Nevertheless, side effects often occurred as MTX is often required for long-term administration. To improve the efficacy of MTX, Chen et al. designed a dextran sulfate—MTX conjugate for targeting the activated macrophages in inflamed sites. This dextran sulfate—MTX conjugates exhibited enhanced cellular uptake and accumulation in arthritic joints owing to the high affinity of

| Classification | Drug         | Advantage                      | Disadvantage                        |
|----------------|--------------|--------------------------------|-------------------------------------|
| NSAIDs         | Indomethacin | Rapidly reduce pain and inflammation by inhibiting COX | Inability to stop joint damage, gastrointestinal bleeding and kidney dysfunction |
|                | Ibuprofen    | Effective in controlling the disease progression | Take effect slowly and hepatic cirrhosis, kidney failure |
|                | Diclofenac sodium | Powerful inhibition of inflammation | Hypertension, osteoporosis and immunosuppression |
| DMARDs         | Methotrexate | Sulphasalazine                  |                                    |
| GCs            | Dexamethasone | Prednisolone                    |                                    |
|                | Betamethasone |                                  |                                    |
| Biological agents | Adalimumab     | High specificity and efficacy    | High cost, low responsiveness and increased risk of infection |
|                | Rituximab     |                                  |                                    |
|                | Anakinra      |                                  |                                    |
The bioavailability of drugs for RA treatment is of great importance. Liposomes have the size, shape, and surface properties of nanocarriers, making them useful in vivo and enabling them to tailor their use. They provide protection for drugs from environmental factors.

2.1.2. Encapsulation of drugs within nanocarriers

The encapsulation of drugs within nanocarriers is a direct and efficient approach to improve the delivery efficiency of drugs in vivo. Liposomes, a well-known nanocarrier, are especially useful for improving drug delivery, as they can protect drugs from the harsh extracellular environment and increase the drug loading yields.

Dextran sulfate to the scavenger receptors overexpressed on activated macrophages, RA often causes the degradation of joint cartilage, leading to the high friction articular cartilages. To improve joint lubrication during the treatment of RA, hyaluronic acid (HA), an important component of lubricant synovial fluids, was conjugated with natural anti-inflammatory agent curcumin (Cur). After being injected into arthritic rats, the HA-Cur conjugates significantly lowered their edema degrees and protected the cartilage caused by joint friction.

Other drug conjugates such as albumin-MTX reported earlier also displayed the successful improvement of anti-inflammatory effects. Despite many benefits of drug conjugates, several issues existed in drug conjugates, such as complicated chemical synthesis and limited drug loading yields.

Table 2 Delivery strategies for different types of agents.

| Category of agents | Agent | Formulation | Ref. |
|--------------------|-------|-------------|------|
| Small molecule     | Dexamethasone | PEG-Dex conjugates | 19 |
|                   | Methotrexate  | Dextran sulfate-MTX conjugates | 20 |
|                   | Methotrexate  | Albumin-MTX conjugates | 21 |
|                   | Methylprednisolone | Cycloextrin-α-methylprednisolone conjugates | 22 |
|                   | Dexamethasone | PEGylation liposomes | 23 |
|                   | Dexamethasone | DC<sub>8</sub>PC and DSPE-PEG liposomes | 24 |
|                   | Dexamethasone | PCL-PEG micelles | 25 |
|                   | Methotrexate  | SA-Dex-OA/MTX micelles | 26 |
|                   | Methotrexate  | MTX-loaded albumin nanoparticles | 28 |
|                   | Methotrexate  | Au/Fe half-shell PLGA nanoparticles | 29 |
| Nucleic acid       | IL-1β siRNA  | Lipidoid-polymer hybrid nanoparticles | 30 |
|                   | p65 siRNA     | PCL-PEI and PCL-PEG micelles | 31 |
|                   | siRNA against BTK | PEG-β-PLGA nanoparticles | 32 |
|                   | TNF-α siRNA   | PEGylated solid-lipid nanoparticles | 33 |
| Peptide/protein    | Core peptide  | PEGylated liposomes | 34 |
|                   | TNF-α antibody | Carbomethyl cellulose microneedle | 35 |
|                   | Etanercept    | HA crosslinked microneedle | 36 |
|                   | TRAIL         | HSA-TRAIL conjugates | 37 |
|                   | Tocilizumab    | Gold nanoparticles | 38 |

PEG, polyethylene glycol; DC<sub>8</sub>PC, 1,2-bis(10,12-tricosadiynoyl)-sn-glycero-3-phosphocholine; PCL-PEG, poly(ethylene glycol)-poly(e-caprolactone); SA, sialic acid; OA, octadecanoic acid; PCL-PEI, poly(e-caprolactone)-polyetherimide; HA, hyaluronic acid; Cur, curcumin; PLGA, poly(lactic-co-glycolic acid); TRAIL, tumor necrosis factor (TNF)-related apoptosis-inducing ligand; HSA, human serum albumin.

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2.1.2. Encapsulation of drugs within nanocarriers

The encapsulation of drugs within nanocarriers is a direct and useful approach to provide the protection of drugs from environments and tailor their in vivo performance by manipulating the size, shape, and surface properties of nanocarriers.

Liposomes are a well-known nanocarrier in improving the bioavailability of drugs for RA treatment. Liposomes have sparked great interest in drug delivery for a long time, for it sparked great interests in drug delivery for a long time, for it improved anti-inflammatory effects. Despite many advantages, conventional liposomes still faced challenges such as poor stability and drug leakage in vivo. Recently, Wang et al. designed a polymerized liposome composed of 1,2-bis(10,12-tricosadiynoyl)-sn-glycero-3-phosphocholine (DC<sub>8</sub>PC) and DSPE-PEG, in which DC<sub>8</sub>PC molecules were cross-linked in the bilayer of the liposomes upon UV irradiation and the PEG present at the surface of the liposome provided a stealth layer. The polymerized stealth liposome was highly stable and showed long circulation time in vivo. After being administrated into arthritic rats, the Dex-loaded polymerized stealth liposomes significantly suppressed the proinflammatory level in joint tissues and reduced the swelling of inflamed joints.

Most of small molecule drugs used in RA therapy are hydrophobic. Thus, micelles with hydrophobic core are frequently adopted for solubilizing and delivering hydrophobic drugs. In addition to solubilizing hydrophobic drugs in aqueous solution, self-assembled micelles could keep stable as long as the concentration of micelles is higher than the critical micellization concentration (CMC). Wang et al. demonstrated the Dex-loaded poly(ethylene glycol)-poly(e-caprolactone) (PCL-PEG) micelles could potently reduce the joint swelling and bone erosion of arthritic rats at a low Dex dose without causing any side effect. In order to achieve anti-inflammatory effect and bone repair simultaneously, Xu et al. developed a sialic acid-dextran-octadecanoic acid (SA-Dex-OA/MTX) micelle to deliver MTX. This MTX-loaded micelle greatly improved the drug accumulation in arthritic joints via interaction between SA and vascular endothelial cells, finally displaying favorable therapeutic effects and minor side effects.

Albumin is the most abundant plasma protein in vivo. It is the major protein responsible for the colloid osmotic pressure in blood. Nanoparticles made from albumin have attracted considerable attention as a drug carrier due to their excellent in vivo circulation. More recently, Liu et al. found that the
expression of secreted protein acidic and rich in cysteine (SPARC) significantly increased in RA synovium. Considering the intrinsic high affinity of SPARC to albumin, they investigated the therapeu-
tic effect of MTX-loaded albumin nanoparticles in a collagen-
induced arthritis model (CIA) and confirmed the large accumu-
lation and long joint retention of MTX-loaded albumin nano-
particles in inflamed joints, as well as a better therapeutic index
compared with free MTX. Besides abovementioned soft nano-
carriers, inorganic nanoparticles such as silicon nanoparticles and
metallic nanoparticles were also used for versatile drug delivery
due to their unique physicochemical properties such as excep-
tional optical absorption or controllable physicochemical proper-
ties. For example, Kim and co-workers fabricated an Au/Fe half-shell poly(lactic-co-glycolic acid) (PLGA) nano-
particle modified by arginine-glycine-aspartic acid (RGD), which
could be used for multimodal imaging and magnetic targeted
chemo-photothermal treatment at the same time in RA therapy.

2.2. Nucleic acid-based delivery systems

Gene therapy has hold great potential in the treatment of inflam-
matory arthritis. After many ups and downs, great development of
gene therapy in clinical trials have been made. Although a number of
clinical trials of gene therapeutics are ongoing, there are very
limited clinically available genetic agents. Due to the unique
characteristics of nucleic acid such as high molecular weight,
negative charge and instability, the application of gene therapeu-
tics such as siRNA, mRNA, microRNA and plasmid DNA has
been hindered by a series of biological barriers, including enzy-
matic degradation, inability to transport across cell membrane,
elicitation of immune response, as well as endosomal degrada-
tion. It is nearly infeasible to directly use naked nucleic acids for
clinical applications. As a result, there has been great interest in
developing delivery vehicles to overcome these biological bar-
riers. In order to efficiently transport gene therapeutics to the sites
diseases, the gene delivery must not only be able to complex
with nucleic acid, but also must meet the following requirements:
1) protect the nucleic acid from the degradation of nuclease; 2)
facilitate the sufficient cellular uptake of nucleic acid; 3) release
nucleic acid in cytoplasm in time from endosome. Currently, the
most used non-viral delivery vehicles for nucleic acid delivery are
cationic lipids and polymers. Song et al. designed a polymer-
lipid hybrid nanoparticle (FS14-NP) composed of F127 and
25

2.3. Peptide/protein agent-based delivery systems

Peptide/protein therapeutics have drawn extensive attention due to
their advantages over small molecule drugs such as high efficacy,
low toxicity, and specificity. Despite their unique properties, the
clinical application of these macromolecules has been greatly hampered by their instability, low bioavailability and
immunogenicity. Therefore, seeking for new strategies to enable
the effective delivery of peptide/proteins is full of thorns. Peptide/
protein agents often have a relatively large molecular weight and
unique spatial structure. The drug vehicles used for delivering
peptide/protein agents should possess enough space to accom-
modate such kind of agents. And peptide/protein agents are easily
degraded by the widespread proteases in vivo. Therefore, the drug
 carriers should be responsible for offering the proper protection
for the peptide/protein agents.

Bioactive peptides, which were used for the treatment of chronic inflammatory diseases, are very limited. Among them,
melittin, derived from bee venom, shows good anti-inflammatory
effect on AIA rat model via the inhibition of NF-κB pathway. However, no further investigation aiming at improving the
bioavailability of melittin using drug delivery systems has been
reported. Besides, Vanniasinghe et al. found that immunosup-
pressive peptide (core peptide, CP) loaded liposomes were effective in ameliorating arthritis. The suppression of inflamma-
tion might be attributed to the peptide-induced inhibition of T-cell
activation, which consequently resulted in a more sustained long-
term effect compared to prednisolone-loaded liposomes.

Therapeutic proteins such as monoclonal antibodies or fusion
proteins have become a dominant therapeutic modality in auto-
immune diseases in the worldwide scale. In 2018, the top-10
best-selling drugs have a total sale of 79.7 billion dollars.
Among them, three protein drugs were used in combating RA in
clinical applications. In an attempt to inhibit NF-κB signaling efficiently, Wang et al. fabricated a polymeric hybrid
micelle consisted of poly(ε-caprolactone)–polyetherimide (PCL–PEI) and poly(ε-caprolactone)–poly(ethylene glycol) (PCL–PEG) to co-deliver Dex and p65 siRNA which could
silence the expression of p65 subunit in NF-κB family. The dual
drug-loaded hybrid micelle was able to switch macrophages from
the M1 to M2 state and effectively reduce the inflammatory level
synergistically. It was reported that Bruton’s tyrosine kinase
(BTK) is a critical mediator in facilitating B cell activation and
macrophages polarization. Thus, it is considered as a potential
therapeutic target for RA. Zhao and co-workers employed
cationic lipid-assisted PEG-b-PLGA nanoparticles (CLANs) to
encapsulate siRNA against BTK. In a CIA model, the intravenous
administration of CLANs/siRNA dramatically reduced joint
inflammation without causing any toxicity. Aldayel et al. reported a pH-induced sheddable PEGylated nanocarrier by incor-
porating TNF-α siRNA into solid-lipid nanoparticles. The lipid
nanoparticles showed a high siRNA encapsulation efficiency
(>90%) and a minimum burst release of siRNA (<5%). The
systemic injection of this formulation significantly reduced the
the thickness and bone damage in a CIA mice model.

Generally, gene therapeutics provide considerable potential
because of their capability of inducing the specific knockdown or
expression of a broad range of genetic targets. However, the un-
desirable delivery efficiency of gene therapeutics remains to be a
challenging issue. Hence, safe and effective delivery approaches
are still in demand for the application of gene therapeutics in RA
therapy.
bioequivalence to the conventional administration. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a type II transmembrane protein in TNF family. Once binding to death receptors, TRAIL would lead to the programmed death of abnormal cells. Due to its apoptotic and anti-proliferative effect on inflammatory cells, TRAIL has been considered as a potential candidate in RA treatment. Human serum albumin (HSA–TRAIL) conjugates with the diameter of ~15.4 nm displayed enhanced therapeutic efficacy compared to free TRAIL. The enhanced therapeutic efficacy might be attributed to the extended systemic circulation and efficient targeting delivery in inflamed sites endowed by HSA37. Tocilizumab (TCZ), a monoclonal antibody against IL-6 signaling, could rapidly suppress inflammation and prevent the joint destruction in RA patients. Lee et al.38 developed HA modified gold nanoparticles to encapsulate TCZ for improving the therapeutic efficacy of TCZ. The TCZ-loaded gold nanoparticles exerted the synergistic therapeutic effect in CIA mice model by simultaneously targeting vascular endothelial growth factor (VEGF) and IL-6R.

So far, only a few nanomedicines entered the clinical trials. A prednisone-loaded liposomal formulation with improved safety and efficacy has been confirmed in a phase II clinical study53. Apart from that, several clinical studies using adeno-associated virus or retrovirus to deliver gene therapeutics for RA therapy are undergoing16.

Although significant achievements have been made, the translation of nanomedicines in clinic and marketplace is still challenging. Several problems lying in the way of nanomedicines translation should be addressed before novel nanomedicines being investigated in clinical trials. For example, inappropriate use of nanomaterials with potential toxicity or immunogenicity, low reproducibility of formulation with complicated preparation technique and insufficient study of in vivo safety, hinder the current nanomedicines from bench to besides. Therefore, we propose that investigators try to use the FDA-approved pharmaceutic excipients to fabricate the drug formulations and avoid the usage of too much toxic chemical reagents. And detailed pre-clinical evaluation in terms of in vivo pharmacokinetics and underlying safety risk should be systemically investigated before beginning the clinical trial.

3. Functional delivery strategies in RA treatment

As outlined above, the drug-loaded nanocarriers exhibited obvious advantages such as enhanced therapeutic efficacy and reduced side effects in RA therapy compared with conventional treatments. Meanwhile, researchers are continuously seeking for superior approaches to further improve the delivery efficacy and decrease the risk of side effects. Now, more intelligent drug delivery systems with multifunctionalities such as selective accumulation, intelligent drug release and active targeting to a certain cell type are under intense investigation according to the special pathological characteristics in RA.

3.1. Actively targeted delivery systems

In RA pathology, cells involved in RA onset and development would go through a series of alterations such as the up-regulation of specific surface receptors or transformation of phenotype54. As a result, nanocarriers with the special binding affinity to these inflammation-related cells would consequently further promote the targeted drug delivery in inflamed sites. In the past five years, enormous progress has been made in the actively targeted drug delivery in various inflammatory disorders. Herein, nanomedicines engineered with small molecules, polymers, peptides, or proteins to achieve the active targeting are comprehensively summarized in Fig. 2. In the following sections, several representatives of actively targeted strategies in RA therapy were showed and discussed (Table 3)55–84.

![Figure 2](image-url) Schematic illustration of active targeting delivery strategies.
| Type       | Receptor                  | Delivery strategy                  | Drug       | Ref. |
|------------|---------------------------|------------------------------------|------------|-----|
| Small molecule |                           |                                    |            |     |
| FA         | Folate receptor β         | BSA nanoparticles                   | Etoricoxib | 55  |
|            | Dendrimer G5              |                                    | Methotrexate | 56  |
|            | FA-PEG-DSPE liposomes      |                                    | Prednisolone and methotrexate | 57  |
|            | DOPE/CH/DSPE-mPEG liposomes|                                    | Methotrexate | 58  |
|            | Nanogold-core dendrimer   |                                    | Methotrexate | 59  |
|            | FA-PSA-CC micelles        |                                    | Dexamethasone | 60  |
|            | FA-PLGA nanoparticles     |                                    | Dexamethasone | 61  |
|            | FA-PEG-CH-DEAE15 nanoparticles|                                  | siRNA      | 62  |
|            | Mannose receptor          | DSPC/Chol/Man liposomes             | Withaferin-A | 63  |
|            | SA                        | DSPC/Chol/F-DHPE/Man liposomes      | Morin      | 64  |
|            | SA                        | SA-Dex-OA micelles                 | Methotrexate | 26  |
|            | SA                        | SA-cholesterol conjugated liposomes| Dexamethasone palmitate | 65  |
| Galactose  | Galactose-specific C-type lectin |                                  | Triptolide | 66  |
| Polymer    |                           |                                    |            |     |
| DS         | Scavenger receptor        | DS-b-PCL nanoparticles              | Methotrexate | 67  |
|            | HS                        | DS-g-MTX micelles                  | Methotrexate | 20  |
|            | CD44                      | HA—MTX conjugate                   | Methotrexate | 68  |
|            | HA                        | HA—DP  liposomes                   | Prednisolone | 69  |
|            | HA                        | HA/Cur micelles                    | Curcumin   | 27  |
|            | HA                        | HA polymeric nanoparticles          | Dexamethasone | 70  |
|            | HA                        | HA-phospholipid micelles           | Triamcinolone | 71  |
|            | HA                        | HA—gold nanoparticles              | Tocilizumab | 38  |
| Protein    | Anti-CD64 antibody        | Anti-CD64-SPIONs-PLGA nanoparticles| Methotrexate | 72  |
|            | Albumin                   | MTX@HSA nanoparticles               | Methotrexate | 28  |
|            | CD163 monoclonal antibody | Anti-CD163-dexamethasone conjugate  | Dexamethasone | 74  |
| Peptide    | RGD                       | RGD-Lip-PRE liposomes               | Prednisone | 34  |
|            |                           | Au/Fe/Au PLGA nanoparticles         | Methotrexate | 29  |
|            |                           | Au PLGA nanoparticles               | Methotrexate | 75  |
|            | VIP                       | VIP receptor                        | Camptothecin | 78  |
|            |                           | Alginate nanoparticles              | IL-10 DNA | 79  |
| HAP-1      | Synovial                  | HAP-1 liposomes                     | Prednisolone | 34  |
|            | CBP                       | CBP—α-TNF conjugates               | TNF-α antibody | 80  |
|            | ADK                       | Endothelial cells                  | ART-1-IL-27 liposomes | 41  |
| Membrane   | Platelet membrane         | P-selectin and GVPI                | PLGA nanoparticles | 81  |
|            | Neutrophil membrane       | LFA-1                               | PLGA nanoparticles | None | 82  |
|            | Macrophage membrane       | Mac-1                               | PLGA nanoparticles | Tocilizum | 83  |
|            | TRAIL-expressing vein      | TRAIL ligands                       | PLGA nanoparticles | Hydroxychloroquine | 84  |

FA, folic acid; BSA, bovine serum albumin; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine, DSPE-mPEG, N-(carboxyl methoxypolyethylene glycol)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine; PSA, polysialic acid; PLGA, poly(lactic-co-glycolic acid); CH, chitosan; DEAE, diethylamethylene; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; Chol, cholesterol; Man, mannose; F-DHPE, N-(fluorescein-5-thiocarbamoyl)-1,2-dihexadecanoyl-sn-glycero-phosphoethanolamine, triethylammonium salt; SA, sialic acid; Dex, dexamethasone; OA, octadecanoic acid; GDR, galactosyl-dextran-retinal; TPT, triptolide; DS, dextran sulfate; PCL, poly(ε-caprolactone); MTX, methotrexate; HA, hyaluronic acid; DPPE, dipalmitoyl-sn-glycero-3-phosphoethanolamine, Cur, curcumin; SPIONs, superparamagnetic iron oxide nanoparticles; SPARC, secreted protein acidic and rich in cysteine; HSA, human serum albumin; TAC, tacrolimus; RGD, arginine-glycine-aspartic acid; PRE, prednisone; PLA, polyactic acid; VIP, vasoactive intestinal peptide; CBP, collagen-binding peptide; ART-1, CRNADKFP; TRAIL, tumor necrosis factor (TNF)-related apoptosis-inducing ligand.
Nanomedicines for the treatment of rheumatoid arthritis

3.1.1. Small molecule modification mediated targeted delivery
Folate acid (FA) is known to show high affinity to FA receptors, which are widely expressed on tumor cells and activated synovial macrophages in RA. In a study, a folate-modified dextran-methotrexate conjugate was synthesized to self-assemble into micelles. The MTX-loaded micelles exhibited the improved macrophage uptake mediated by the FA modification and possessed the improved biodistribution in inflammatory regions. In CIA mice, these FA-modified micelles showed stronger retention of arthritis in comparison with free MTX and unmodified micelles. More recently, Sun et al. constructed an FA-conjugated PEG-PLGA nanoparticle for delivering Mcl-1 siRNA to inflamed joints in RA, in which a pH-sensitive linker was introduced into the nanoparticles to facilitate the intracellular release of Mcl-1 siRNA. These nanoparticles treatment led to a significant improvement in the clinical outcomes of paws and reduced the level of pro-inflammatory cytokines.

Sialic acid (SA), a natural monosaccharide, is mainly located on the surface of cell membranes. As the binding ligand of E-selectin receptors, SA has been used to improve the efficiency of targeted delivery in a recent research. Xu et al. fabricated an MTX encapsulated SA-dextran-octadecanoic acid micelle (SA-Dex-OA/MTX) to inhibit the inflammatory response and enhance the bone repair function in the treatment of RA. In vivo studies showed increased accumulation of micelles in inflamed paws due to the presence of SA.

Galactosyl, also known as a ligand binding to selectins, shows good macrophages targeting in CIA mice model. In this study, an amphiphilic galactosyl dextran-retinal (GDR) nanoparticle has been constructed, in which dextran was conjugated with all-trans retinal via an acid-sensitive hydrazone linker, followed by the modification of galactosyl on the hydrophilic part to finally acquire macrophages-targeting ability. Results showed that GDR nanoparticles preferentially accumulated in inflammatory tissues. When anti-inflammatory compound triptolide was incorporated, treatments using the nanoparticles resulted in a remarkable decrease in inflammation infiltration. While toxic effect caused by triptolide was attenuated owing to this targeting strategy. In addition to these abovementioned molecules, other small molecular ligands such as mannose and sialyl lewis are also emerging as promising targeting ligands in arthritis treatments previously. The receptors of these ligands are highly expressed on the monocytes or monocyte-derived cells in the synovial tissues of arthritic joints.

3.1.2. Polymer-based targeted delivery
HA is one of frequently used polymers for inflammation-targeting. Due to the high affinity between HA and CD44 receptors, nanoparticles constituted or modified by HA are capable of targeting the cells with highly-expressed CD44 molecules such as activated lymphocytes and macrophages in inflamed sites of RA. Alam et al. prepared a pH-responsive nanoparticle by incorporating mineralized calcium phosphate onto PEGylated HA-based nanoparticles. They showed that the presence of calcium phosphate ensured the controlled release of encapsulated MTX in acidic conditions. The HA segments on the surface of the nanoparticles ensured the targeted delivery in inflammatory lesions, consequently improving arthritis pathology with remarkable safety even at high drug dose. To selectively deliver prednisolone to the inflamed tissues, Gouveia et al. formed HA-conjugated pH-sensitive liposomes and demonstrated that they were more effectively taken up by activated macrophages and fibroblasts. Dextran sulfate (DS) is a specific ligand for scavenger receptor class A, which is overexpressed in the activated macrophages in inflamed joints. Due to its superior biodegradability, biocompatibility and specific targeting, DS has been widely employed in targeted delivery for RA treatment in the past decades. Kim et al. conjugated DS to a hydrophobic block PCL to form an amphiphatic copolymer (DS-b-PCL), which would self-assemble into micelles. Biodistribution studies showed that accumulation of DS-b-PCL micelles in the affected joints of RA was approximately 10 times higher than that in control groups, indicating good active targeting efficiency of DS modification.

3.1.3. Peptide-based targeted delivery
Arginine-glycine-aspartic acid (RGD) and its derivatives have been widely used for enhancing the delivery efficiency of therapeutic agents. They are recognized as a specific ligand for αvβ3 integrin receptors, which is associated with the occurrence of angiogenesis in tumor or inflammation. Nanocarriers coupling with RGD or its derivates displayed the remarkable improvement in therapeutic outcomes. Apart from RGD, other peptides used for targeted delivery in RA previously including vasoactive intestinal peptide (VIP), synovial fibroblast-homing peptide HAP-1, macrophage-targeted peptide tuftsin, also showed favorable efficiency of drug delivery. Taking advantages of the phage display technique, Yang et al. identified a 9-amino acid peptide ligand (ADK) that homed selectively to an inflamed joint. In a subsequent study, they found the ADK-modified liposomes revealed higher affinity to endothelial cells and better in vivo accumulation in the inflamed joints compared to unmodified liposomes. It was also found that IL-27-loaded liposomes coupled with ADK were more effective in suppressing RA symptoms in contrast to free IL-27 or unmodified formulation when intravenously administrated after the disease onset. More recently, Cook et al. described the exploration of a series of cystine-dense peptides (CDPs) which could rapidly accumulate in cartilage of rats after systemic administration. These CDPs are usually existed in the venom of spiders, snakes, and scorpions. One of the CDPs, CDP-11R, exhibited the optimal half-life and accumulation in cartilage. When linked to a steroid payload, a peptide-steroid conjugate was formed, which alleviated joint inflammation and avoided the toxicities occurred in steroid treatment. Unlike the regular targeting mechanism, Katsumata et al. discovered a collagen-binding peptide (CBP) derived from decorin, which could bind to the collagens on the surface of cartilages. The harvested complexes formed by conjugating CBP with TGF-β showed the enhanced drug retention at inflamed tissues and thereby improved inflammatory conditions after systemic injections.

3.1.4. Protein-based targeted delivery
Protein-targeted delivery in the treatment of RA mainly focuses on the utilization of antibodies, which accurately guide therapeutic payloads to cells by specifically binding to the antigens at the surface of cell membranes. For example, the CD134 antibody has been modified on the surface of a liposome formulation to precisely target to activated T cells in RA. To specifically target payloads to the hemoglobin scavenger receptor (CD163) in macrophages, a CD163 antibody was conjugated to GCs to facilitate the interaction between macrophages and drug vehicles. Previous researches found the cell metabolism of affected joints in active RA is dramatically increased thereby have high demand for albumin consumption. A recent research revealed that albumin possessed intrinsic high affinity to secreted protein acidic and rich
in cysteine (SPARC), which was up-regulated in the synovial tissues from RA patients and CIA mice. Therefore, albumin has potential for the targeted delivery in inflammatory diseases.

3.1.5. Biomimetic targeted delivery

Biomimetic delivery systems based on cell membrane-camouflaged nanoparticles have gained increasing attention and emerged as a novel strategy to achieve natural targeting to disease sites. A large number of inflammation-related cells would be recruited to inflamed sites by specific chemokines and inflammatory infiltrates in the synovium during the development of RA. A quite high proportion of them are monocytes-derived cells such as macrophages and neutrophils, which adhere to the inflamed endothelium and then extravasate into the affected synovium. Hence, there has been interest in coating nanoparticles with cell membranes to achieve the homing profile of the source cells and the active targeting to arthritic extravasate into the affected synovium. Consequently, there has been in-and neutrophils, which adhere to the inflamed endothelium and then extravasate into the affected synovium. Hence, there has been interest in coating nanoparticles with cell membranes to achieve the homing profile of the source cells and the active targeting to arthritic joints. For example, Li et al. coated PLGA nanoparticles with macrophage membranes by using cytochalasin B to relax the binding between the cytoskeleton and the membrane. Both in vitro and in vivo evaluations showed the improved targeting efficiency in desired sites. After incorporating tacrolimus, the biomimetic nanoparticles significantly suppressed the progression of RA in mice. It was reported that neutrophil would secrete micro-vesicles that are able to bind and neutralize inflammatory cytokines, leading to the protection of the arthritic synovium. Based on this finding, Zhang et al. fabricated a neutrophil membrane-coated nanoparticle to inhibit synovial inflammation in arthritic mice. They showed that these nanoparticles could permeate deep into the cartilage of RA and provide protection for the cartilage against inflammation damage. Ultimately, treatment using these membrane-coated nanoparticles without extra drug loading achieved inflammation resolution and tissues repair.

Inspired by the intrinsic interactions between platelets and inflammatory tissues via P-selectin, a platelet-mimic nanoparticle was constructed for targeted delivery in RA treatment. The platelet-mimic nanoparticles showed the prolonged circulation time in vivo and increased accumulation in inflamed joints. Furthermore, this biomimetic nanoparticle loaded with FK506 significantly improved the joint inflammation in CIA mice. The direct modification of the cell membrane with specific ligands would customize the targeted delivery. However, this approach might disrupt the structure or function of proteins in the cell membrane. Shi et al. used a genetic engineering technique to collect TRAIL-expressing cell membranes from human umbilical vein endothelial cell line (HUVEC). The TRAIL-anchored membranes were fused onto hydroxychloroquine-loaded PLGA nanoparticles to block the inflammatory cytokines and actively deliver therapeutic payloads to RA joints. Upon intravenous injection, the high accumulation and long retention of the biomimetic nanocarriers in inflamed joints were observed, which lead to good therapeutic outcomes.

3.2. Stimulus-responsive delivery systems

The change of physiological parameters is a pivotal indication between normal and arthritis tissues, providing promising targets in designing bio-responsive drug delivery systems. There has been great interest in designing stimuli-responsive drug vehicles, which is able to release drugs in response to the change of specific physiological signals or environmental factors. In the development of active RA, there are massive inflammatory cell infiltration and aggressive proliferation accompanied by the rapid increase of cellular metabolism in the joint tissues, consequently leading to the local acidosis and accumulation of oxidative intermedia. In addition, there are excess MMPs produced by inflammatory cells in the inflamed joints of RA. Various stimuli-responsive nanocarriers were fabricated for achieving the controlled release of drugs in response to the physiological changes in the inflamed joints of RA. We have summarized the details of the inflammatory stimulus used for the development of bio-responsive delivery system in Table 4. This section highlights recent advances in the development of stimulus-responsive drug delivery systems in RA treatments (Table 5).

| Table 4 | Summary of typical inflammatory stimulus in vivo. |
| --- | --- |
| Stimulus | Type | Detail | Ref. |
| pH | — | Acidic pH range: 7.2–5.0 | 107,108 |
| Enzymes | MMP-1 | Produced by chondrocytes, osteoblasts and synovial cells | 109 |
| MMP-3 | Produced by fibroblasts | 110 |
| MMP-9 | Produced by monocytes and macrophages | 110 |
| PLA₂ | Produced by activated monocytes, macrophages and neutrophils | 111 |
| ROS | O₂⁻ | Produced by granulocytes | 112 |
| — | Hydroxyl radical | — |

— Not applicable.

MMPs, matrix metalloproteinase; PLA₂, phospholipase A₂; ROS, reactive oxygen species.
3.2.2. Redox

The excessive accumulation of oxidative intermedia and high oxidative stress would often associate with inflammatory signaling cascades and tissues damage. Due to the higher level of reactive oxygen species (ROS) in inflamed tissues than that in normal tissues, ROS-sensitive groups such as thioether, selenium-containing compounds, thioketal and phenylboronic ester have been considered as potential means to manipulate the release behavior of drugs. Recently, Xu and co-workers established FA-decorated ROS-responsive nanoparticles by incorporating a 4-phenylboronic acid (4-PBA) pinacol ester linker. The nanoparticles showed the ROS-responsive drug release profile and the efficient elimination of H₂O₂ in activated macrophages. After being loaded with Dex, the treatment with ROS-responsive nanoparticles significantly reduced histological damage and alleviate inflammation in CIA mice. Fan et al. formed berberine-loaded micelles by the self-assembly of a selenocystamine-based polymer, which is cleavable by ROS. The ROS-responsive micelles released the encapsulated therapeutic cargo at the inflammatory microenvironment in response to ROS. The treatment of berberine-loaded micelles exhibited 10-fold higher efficacy than that of free berberine. Chen et al. synthesized an FA-modified liposome co-encapsulating MTX and catalase to actively target to arthritic joints. The encapsulated catalase is able to catalyze the production of oxygen in the presence of ROS. They found that the elevated ROS level within cytoplasm would trigger the generation of oxygen, which could destabilize and destroy the liposomes, eventually facilitating MTX release.

3.2.3. Enzyme

Disease-associated enzymes have also served as specific stimulus for designing bio-responsive nanomedicines. The upregulated expression of MMPs within the inflamed joints is a distinguishing feature in RA. Therefore, stimuli-responsive nanocarriers based on the aberrant secretion of MMPs have been extensively explored for the controlled drug delivery in RA. Previously, MMP substrate peptides, which would be recognized and cleaved by MMPs, were frequently incorporated into the drug delivery systems for manipulating drug release or deshielding of PEG shell to improve cellular uptake or tissue penetration. More recently, He et al. reported a facile method to prepare MMPs-responsive nanoparticles by the co-assembling of triglycerol monostearate (TGMS) and DSPE-PEG. The ester bond within TGMS is cleavable by MMPs, ensuring the rapid release of Dex in response to highly-expressed MMPs in inflamed sites. After being

### Table 5 Stimulus-responsive drug delivery systems.

| Stimulus | Responsive unit | Delivery strategy | Drug | Ref. |
|----------|-----------------|-------------------|------|------|
| pH       | Hydrazide bond  | PEG-based micelles| Dexamethasone | 19 |
| Anhydride linkage | mPEG-PPF micelles | Ibuprofen | 113 |
| Acetone-based ketal | AKP-Dex nanoparticles | Dexamethasone | 114 |
| Calcium phosphate | MP-HA nanoparticles | Methotrexate | 94 |
| MMPs     | Triglycerol monostearate | DSPE-PEG/TGMS nanoparticles | Dexamethasone | 115 |
| ROS      | Manganese ferrite and ceria | MFC-MSNs nanoparticles | Methotrexate | 117 |
| O₂       | -Se-Se- | TPP@PMM micelles | Prednisolone | 118 |
| Magnetic | Fe | Fe-EC nanoparticles | Diclofenac sodium | 121 |
|          | Fe | PSS-doped CaCO₃ microcapsules | Prednisolone | 122 |

PPF, polypropylene fumarate; AKP, acetone-based ketal-linked prodrugs; MP, mineralization of PEGylated; TGMS, triglycerol monostearate; MFC-MSNs, manganese ferrite and ceria nanoparticle-anchored mesoporous silica nanoparticles; TPP, two-photon prednisolone; PMM, PMPC (2-methacryloyloxyethyl phosphorylcholine)—PMEMA (2-(methylthio) ethanol methacrylate); VES, vitamin E succinate; Oxi-aCD, oxygen species α-cyclodextrin; EC, ethylcellulose; PSS, poly(sodium 4-styrenesulfonate).
systemically injected to AIA rats, the Dex-loaded MMP-responsive nanoparticles significantly reduced the degree of joint swelling and inhibited the inflammatory level. Other than MMPs, the expression of phospholipase A2 (PLA2) is also closely related to the severity of RA and cancer. PLA2, usually produced by activated macrophages, neutrophils and monocytes in inflammatory regions, is able to catalyze the hydrolysis of phospholipids. It has been utilized as a trigger for lipid-based drug vehicles in the treatment of RA. Recently, Wang et al. fabricated a lipid tube self-assembled by DC8,9PC molecules. After subcutaneous administration to the arthritic rats, the overexpressed PLA2 at the inflamed sites facilitate the drug release from DC8,9PC lipid tubules on-demand, providing a sustained drug supply over a long time.

3.2.4. Others
Apart from abovementioned biological environment-responsive drug delivery systems, external stimulus such as temperature, sonication and magnetic field have been utilized as exogenous triggers to regulate drug release and in vivo performance. Among them, temperature is one of the widely explored stimulus in RA treatment. For example, Costa Lima et al. integrated MTX and gold nanoparticles into PLGA nanospheres through emulsion—diffusion evaporation technique. Upon near-infrared irradiation, the heat generated by gold nanoparticles accelerated the release of MTX at inflammation region, improving the therapeutic effect. In addition to the temperature rise-caused drug release based on light irradiation, some researchers also take advantages of thermo-responsive polymers to control the behavior of drug delivery. Jung et al. developed a temperature-responsive nanocarrier with a temperature-sensitive amphiphilic polyelectrolyte and positively charged etanercept. At the physiological temperature (37.5 °C), which was higher than the clouding temperature of the polyelectrolyte, the long-term stability of etanercept was improved, which was beneficial for the in vivo application of the nanocarrier. As the temperature in normal tissues and inflamed sites in vivo is very close, this formulation is only suitable for local administration such as intra-articular injection. The magnetism is originally employed in magnetic resonance imaging (MRI) for in vivo imaging and diagnosis. Recently, magnetic nanocarriers have been frequently used for manipulating the drug release and in vivo distribution in cancer treatments. While in the treatment of RA, only several in vitro explorations using magnetic field controlling drug release have been reported. Thus, how to regulate the drug behaviors in vivo in response to magnetic field remains to be further confirmed. Ultrasound is a clinically common technique for disease diagnosis and treatment. Recently, ultrasound is also emerging as an external trigger in the development of stimulus-responsive nanocarriers. Zhu et al. prepared ultrasound-responsive nanocarriers, termed as “nanobombs” consisted of a perfluorocarbon (PFP) core surrounded by the shell of an FA-modified PEG-phospholipid. Under the 1 MHz ultrasound stimulation, the explosion of “nanobombs” promoted the targeted drug release from the inner core. The ultrasound-triggered drug release significantly reduced the synovial inflammation and cartilage damages in a CIA rat model. Compared to the internal stimulus-based strategies, the external stimulus-based approach is more convenient to precisely control the drug behaviors by adjusting the parameters of the external stimulus. To achieve desirable drug delivery efficiency using external stimulus-based delivery systems, the researchers should make sure that the stable drug loading before applying external stimulation to the inflamed sites and adequate drug release in response to the external stimulus.

4. Newly emerged promising therapeutic approaches
Efficient RA remission still remains to be a challenge. Exploiting new therapeutic regimens for effective RA treatment is in great demand. As more and more aspects of RA pathogenesis have been discovered, a variety of potential targets or therapeutic insights have emerged increasingly (Fig. 3). Alternative anti-inflammatory approaches which can overcome the multiple physiological barriers in inflammatory disorders are highly desirable. In the following section, most recent advances in the newly emerged therapeutic strategies in RA therapy would be summarized and illustrated.

4.1. Induction of specific immune tolerance
As an autoimmune disease, the development of RA is mainly driven by the undue activation of immune systems. Massive autoreactive T cells and B cells produce autoantibodies and attack own tissues, eventually resulting in inflammation networks and tissue damages. In view of the overactivated immune response in the RA pathogenesis, inducing specific immune tolerance can reprogram autoreactive cells, resulting in long-term immune homeostasis. Tengvall et al. demonstrated the successful induction of specific immune tolerance via lentiviral-mediated gene therapy in a CIA model. They showed that only 5% of the mice suffered arthritis onset after the treatment and the percentage of Treg increased at day 3 in the CII-tolerized mice. Adoptively transferring of B cells or T cells from tolerized mice to naïve mice mediated a certain degree of tolerance, demonstrating the sustainable tolerance to CIA was induced during the course of arthritis. In RA patients, citrullinated protein is a major target of disease-specific autoantibodies and often regarded as a specific biomarker for RA diagnose. Gertel et al. constructed a multi-epitope citrullinated peptide constituted by citrullinated filaggrin, fibrinogen, vimentin, and collagen type II. Arthritic rats treated with the multi-epitope peptides via subcutaneous injection displayed a reduced disease severity. Further investigation indicated this treatment resulted in the increased Treg cell subset and decreased Th17 cells, ultimately leading to the amelioration of RA symptoms. In order to generate the expansion of RA-specific Treg cells to combat this autoimmune diseases, Clemente-Casares et al. fabricated a nanoparticle coated with RA-relevant peptides bound to major histocompatibility complex class II molecules. The systemic injection of the nanoparticles produced the expansion of antigen-specific Treg cell subset in CIA mice models, finally resulting in the remission of established arthritis. The occurrence of nonspecific immunosuppression in conventional anti-inflammatory treatments is often associated with the high risk of infections. Therefore, the induction of specific immune tolerance to modulate the aberrant immune responses in RA would be a feasible strategy. Specifically, the efficacy of this therapeutic
approach is definitively dependent on the discovery of the auto-
antigens that dominantly generate the autoimmune response. As the leading self-antigens in RA have not been completely identified, the therapeutic options might merely remain on fundamental research for the moment.

4.2. Pro-resolving therapy

Chronic inflammation is commonly characterized by a pro-
inflammatory phase and subsequent resolution phase. In the resolution phase, endogenous pro-resolving mediators would engage in inflammation recession and tissue repair. As a result, the persistence of chronic inflammation might be not just due to the excessive proinflammatory mediators but also due to the absence of resolution process. Therefore, the exploitation of pro-resolving mediators for the treatment of RA could promote the cessation of inflammation and homeostasis of the immune response, providing a safe and effective solution to correct inflammatory arthritis. It was reported that neutrophil-derived extracellular vesicles are enriched with pro-resolving mediators. In an experimental inflammatory arthritis, the extracellular vesicles were able to accumulate in inflamed cartilage and protect it from damage. An important mediator of resolution is the glucocorticoid-regulated protein AnxA1, which can modulate neutrophil trafficking and macrophage repolarization. Nanoparticles encapsulating AnxA1-derived peptides substantially achieved the inflammation resolution and showed the protective effect in various inflammatory models. The inflammation resolution-mediated therapy would activate patient’s own protective and reparative processes, leading to favorable anti-inflammatory efficacy and the lower burden of adverse effects. The further exploration and clinical trials by mimicking endogenous resolution mediators are ongoing currently.

4.3. Targeting inflammatory metabolism in RA

One of the fundamental characteristics of RA is the increased metabolic demand of inflammatory resident cells. After undergoing metabolic reprogramming, the cell phenotype would change from a resting state to a highly active subset, further leading to the exacerbation of inflammatory conditions. Therefore, the regulation of the metabolic pathways involved in inflammation developments offers a promising avenue for RA treatment. Mammalian target of rapamycin (mTOR) is a key player in the metabolism of T cells during RA process. The activation of mTOR signaling is often associated with the differentiation of T cells towards to autoreactive phenotypes. In a CIA model of RA, metformin...
treatments restored the immune balance and alleviated arthritis by inhibiting transducer and activator of transcription 3 (STAT3) and mTOR activity\(^\text{155}\). Inflammatory resident cells with elevated metabolism would upregulate the level of aerobic glycolysis. 2-deoxy-D-glucose, a glycolysis inhibitor, could block the aerobic glycolysis by interacting with glucose transporter type 1 (GLUT1), resulting in the normalization of activated inflammatory cells and the mitigation of arthritis\(^\text{155}\). Targeting metabolism in inflamed sites could selectively alter the abnormal function and phenotype of inflammatory cells and have few impacts on other cells with the normal metabolic level\(^\text{155}\). Thus, this approach affords attractive therapeutic insights by regulating inappropriately activated cells in inflamed sites, leading to the cell-specific blockade. When combined with targeted delivery systems, this therapeutic strategy would potentially bring in new hope for RA therapy.

4.4. Others

In recent years, a variety of new attempts has emerged for the management of RA. For instance, the phototherapy including photothermal therapy (PTT) and photodynamic therapy (PDT), which is commonly applied in tumor therapy, has been investigated for RA treatment currently. Inspired by the fact that Cu-based nanoparticles can induce PTT and PDT at the same time, Lu et al.\(^\text{156}\) fabricated Cu\(_{7.2}\)S\(_{4}\) nanoparticles for the phototherapy of RA. The treatment of Cu\(_{7.2}\)S\(_{4}\) nanoparticle under the NIR irradiation inhibited the inflammatory level and improved the bone mineral density of arthritic rats. However, some evidences indicated that phototherapy might also generate inflammatory response and tissue damages\(^\text{157}\), which could exacerbate the RA condition. As a result, the detailed studies on the underlying impact of phototherapy in the treatment of RA are needed.

Nitric oxide (NO) is a bioactive gas molecule secreted by immune cells and monocyte-derived cells. Yeo et al.\(^\text{158}\) suggested the overproduced NO would be highly correlated with the pathogenesis of RA. They developed a NO-responsive nanogel by introducing a NO-cleavable group, which acts as an endogenous NO-scavenger to eliminate the NO in local inflamed sites. The intra-articular injection of the nanogel successfully suppressed the onset of RA. However, other studies reported a conflicting result. The nanoparticles was found to be capable of inducing endogenous NO production\(^\text{159}\). The elevated NO inhibited the activity of inflammatory signaling pathway and reduced the levels of inflammatory cytokines. The contradictory results might be due to the different judgement on NO concentrations in RA. Practically, it is still not clear how the level of NO affects the evolution of RA.

Recent studies suggested that cell-free DNA (cfDNA), originated from the degradation of DNA, played a critical role in RA development\(^\text{160}\). Elevated cfDNA level was observed in the serum and synovial fluids of RA patients and also involved in eliciting immunity response and inflammatory reaction. In order to scavenge the cfDNA in arthritic rats, Wu et al.\(^\text{161}\) developed cationic nanoparticles composed of PLGA and poly(2-(diethylamino)ethyl methacrylate) (PDMA) with a high DNA-binding affinity. The intravenous administration of the cationic nanoparticles mitigated the joint swelling and cartilage damage of RA. Despite the successful anti-rheumatic effects of these newly appeared approaches, their safety issues and dose effects are still needed to be further validated.

5. Perspectives

There has been great interest in the development of effective nanocarriers for RA therapy in the past years. The therapeutic outcomes and in vivo safety of a variety of nanocarriers have been validated. Despite of the great progresses, which have been achieved for these developed therapeutic strategies, there are still challenges remained. It is broadly accepted that these developed strategies are incapable of providing the “full recovery”. In view of the percentages of patients showing low responsiveness to current therapies, the high incidence of adverse effects and the insufficient public awareness of the disease as well as a low rate of remission, RA creates a huge social and economic burden worldwide, making the development of effective and safe therapeutic approaches in great demand. Some rheumatologists believe that reversal of disease progression might become possible by taking advantages of preventative therapies. In other words, interfering the RA development in the pre-arthritic process before the disease has manifested clinically would probably prevent the deterioration of RA and achieve total remission.

Although established animal models mimicking RA are helpful, they do not always accurately replicate the human disease phenotype. The pathogenetic of RA in patients is much more complicated than that of animal models. Therefore, the success achieved in animal model sometimes might be impracticable in RA patients. On the other hand, despite the functions and constitution of nanocarriers are becoming more and more diversified, they are actually far away from clinical applications due to the complicated synthesis, poor biocompatibility, unpredictable in vivo behaviors and difficulty in scale-up production.

The original aspiration of pharmaceutical researchers is pushing the finding of drug formulations from bench to besides. Moving forward, further efforts are still in need to advance the development of potential drug delivery systems in clinical trials and marketing in the field of RA therapy. We expect the rapid progresses for the treatment of RA or other autoimmune diseases are in near future.

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Author contributions

Qin Wang wrote the manuscript. Xianyan Qin drew the tables and figures. Jiyu Fang polished the language. Xun Sun supervised the work. The final version of the manuscript has been approved by all authors.

Conflicts of interest

All authors declare no competing interests.

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