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Advanced Nanoplatforms for Precise Intervention of Synovial Inflammation in Rheumatoid Arthritis

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Abstract

As a chronic systemic autoimmune disease, Rheumatoid arthritis (RA) is characterized by persistent synovial inflammation, progressive joint destruction, and substantial long-term disability. These arthritic symptoms are mainly driven by fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes (MLS) via secreting pro-inflammatory cytokines, matrix-degrading enzymes, and osteoclast-activating factors. Considerable systemic side effects and drug resistance constrain conventional pharmacotherapies. In recent years, various nanoplatforms have demonstrated significant potential in achieving precise drug delivery and multimodal therapeutic modulation in RA. However, few reviews have centered on MLS and FLS as the framework and elaborated on the corresponding treatment strategies of RA. This review first elucidates the key mechanistic roles of FLS and MLS in RA pathogenesis, then systematically categorizes the design principles of advanced nanoplatforms for targeting or regulating these synovial cell subsets. Moving beyond single-cell or single-pathway intervention, we highlight emerging nanotherapeutic strategies that achieve systems-level modulation of the inflammatory synovial microenvironment. We further discuss the major challenges facing nanoplatform-based precision therapy and propose future directions. Ultimately, this review proposes a logical framework centered on FLS and MLS, and integrates dual-cell regulation, adaptive microenvironment-response, and immune-metabolic reprogramming strategies, which can accelerate the widespread translation of advanced nanoplatforms and provide a systematic roadmap for more effective and precise management of RA.

Keywords: rheumatoid arthritis; synoviocyte; nanoplatform; reactive oxygen species;

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cell polarization

1. Introduction

Rheumatoid arthritis (RA), a chronic systemic autoimmune disease affecting approximately 0.5 - 1% of the global population (over 17 million people), is characterized by persistent synovial inflammation, progressive joint destruction, and substantial long-term disability[1, 2]. While the etiology remains complex and not fully understood[3, 4], current evidence suggests that genetic susceptibility, environmental triggers including smoking and infectious agents, and oxidative stress collectively drive disease onset and progression[5-7]. Uncontrolled RA can lead to progressive joint destruction and deformity. It also involves multiple organ systems, manifesting as extra-articular complications such as vasculitis, pericarditis, and interstitial lung disease[8, 9]. These manifestations substantially impair patients' quality of life and functional capacity[10].

The hallmark pathological features of RA include symmetrical synovial hyperplasia and chronic inflammation[11, 12]. These are driven mainly by resident synovial cells, specifically fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes (MLS). These cells act as key effector cells orchestrating inflammatory amplification, tissue destruction, and disruption of immune homeostasis[13-15]. Conventional therapeutic strategies such as glucocorticoids (GCs), disease-modifying antirheumatic drugs (DMARDs), and biologics can provide clinical symptomatic relief. However, their clinical use is often limited by systemic side effects, off-target toxicity, suboptimal long-term efficacy, and high costs[16, 17]. These limitations underscore the critical need for treatment strategies capable of precisely modulating pathogenic processes within the inflamed synovium[18].

In recent years, various nanoplatforms have shown considerable promise for RA therapy[19-21]. Their unique physicochemical properties, such as nanoscale dimensions, high drug-loading efficiency, and versatile surface chemistry, offer opportunities to circumvent the drawbacks of conventional treatments[22-24]. Moreover, these systems facilitate targeted drug delivery, controlled release kinetics, and responsiveness to

disease-specific microenvironmental cues. This offers new possibilities for overcoming the shortcomings of conventional systemic treatments[25-27]. Given the pivotal roles of synovial cell subsets in RA pathophysiology, this review first elucidates the pathological mechanisms of FLS and MLS, then systematically categorizes advanced nanoplatform strategies for targeting or modulating these cells. We conclude by critically discussing the key challenges and prospective directions for nanoplatform-enabled precision therapy in RA.

2. Pathophysiological Progression and Pathological Mechanisms of RA

RA is a multifactorial and multistage disease driven by aberrant autoimmunity, sustained chronic inflammation, and progressive synovial hyperplasia leading to cartilage and bone destruction[28, 29]. The temporal evolution from health to established disease offers potential intervention windows[30]. The healthy state shows intact joint architecture. When systemic autoimmunity occurs without clinical synovitis, it enters the preclinical RA stage[31]. Further, early RA can present with clinical synovitis onset accompanied by early inflammatory changes[32]. Then, chronic and destructive synovitis with cartilage damage and bone erosion occurs in established RA **(Figure 1)**. Consistent with this pathological progression, recent ultrasound-based studies have demonstrated that both cartilage damage and synovitis in the hand joints of RA patients can be sensitively detected and semiquantitatively graded using standardized scoring systems[33, 34]. In parallel with these pathological changes, the autoimmune response promotes the production of autoantibodies, most notably anticyclic citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF), which serve as critical early biomarkers of RA[35]. Beyond binding to the fragment crystallizable (Fc) portion of IgG, RF may participate in RA-specific immune pathology by recognizing newly identified linear epitopes[36].

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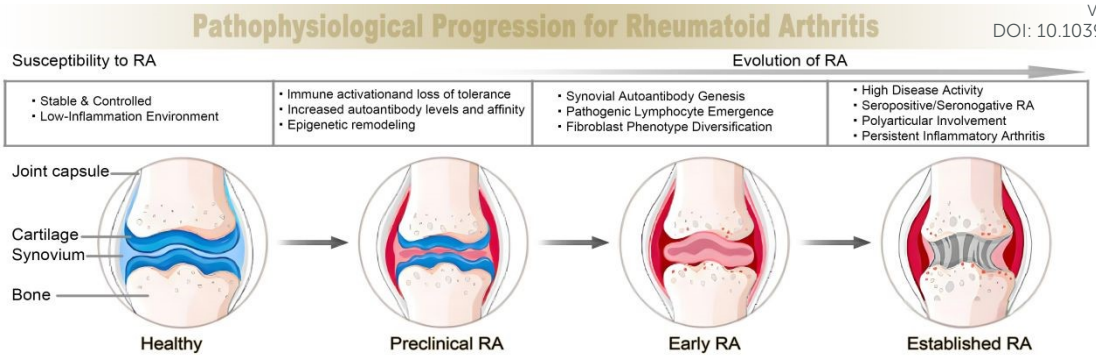

Figure 1. Pathophysiological progression of rheumatoid arthritis.

These autoantibodies and immune complexes deposit in the synovium. There, they activate complement and engage Fc receptors on resident immune cells. This cascade initiates and amplifies synovitis, the hallmark process of RA[37]. Synovitis is the central pathological manifestation of RA. Activated immune cells, including macrophages, neutrophils, and lymphocytes, together with FLS, release large quantities of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β, and interferon-γ (IFN-γ) (**Figure 2**). These mediators form a self-amplifying "cytokine storm" that drives and sustains chronic inflammation[38-40]. Among them, TNF-α plays a pivotal role by activating major signaling pathways, including nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK). This activation promotes the secretion of inflammatory mediators and synovial hyperplasia[41, 42]. Activated FLS acquire tumor-like characteristics, including excessive proliferation, invasiveness, and resistance to apoptosis. They also produce inflammatory mediators, including cytokines such as TNF-α, IL-6, and IL-1β, matrix metalloproteinases (MMPs), and receptor activator of NF-κB ligand (RANKL)[43]. These factors directly promote osteoclast differentiation and cartilage and bone matrix degradation, collectively leading to irreversible joint destruction[44].

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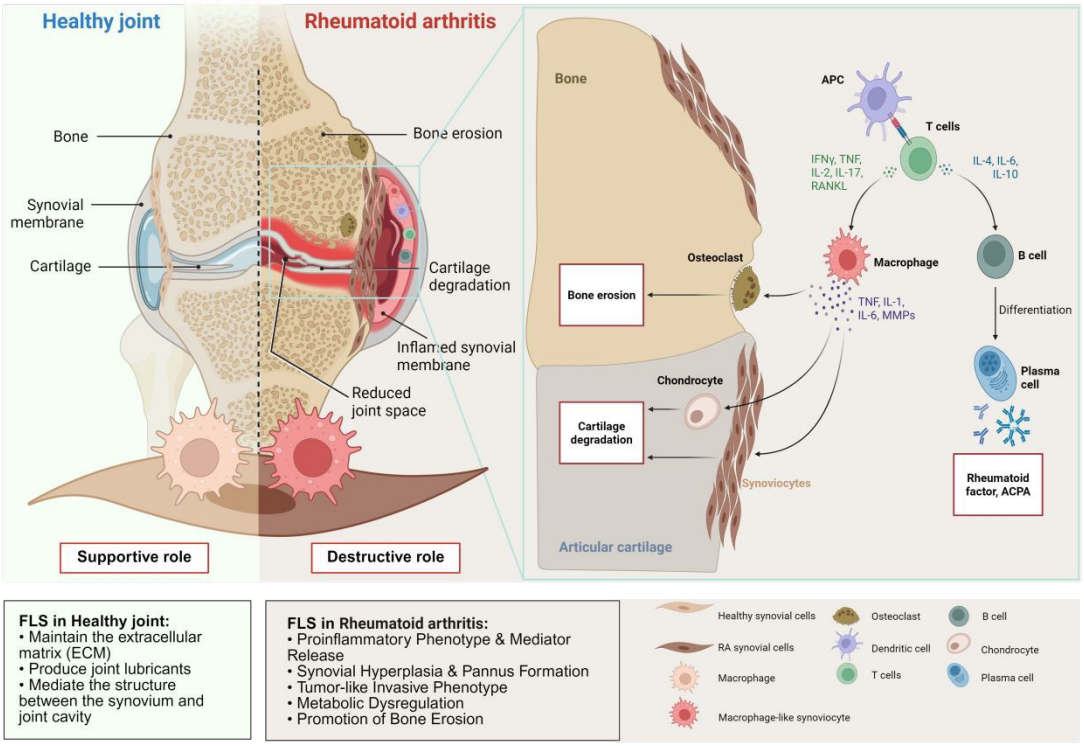

Figure 2. Synovial characteristics and functional alterations in healthy and rheumatoid arthritis joints.

The rheumatoid synovium represents a highly dynamic inflammatory niche composed of resident synovial cells, including primarily FLS and MLS, and infiltrating immune cells, including T cells, B cells, and dendritic cells (DCs)[37]. These cells do not operate in isolation; instead, they communicate through intricate signaling networks that collectively drive chronic inflammation and tissue destruction (**Figure 3**). Immune activation initiated by unidentified antigens leads to $CD4^+$ T cells activation and adaptive immune responses[45]. Activated T cells stimulate MLS and other immune cells to release proinflammatory cytokines, which in turn activate FLS and additional effector populations[46]. This cascade drives synovial inflammation, cartilage degradation, and abnormal bone remodeling[47]. Concurrently, FLS secrete chemokines and cytokines that recruit and activate additional immune cells. These cytokines stimulate FLS through NF-κB signaling pathways, establishing a self-perpetuating inflammatory loop that culminates in irreversible joint damage[13].

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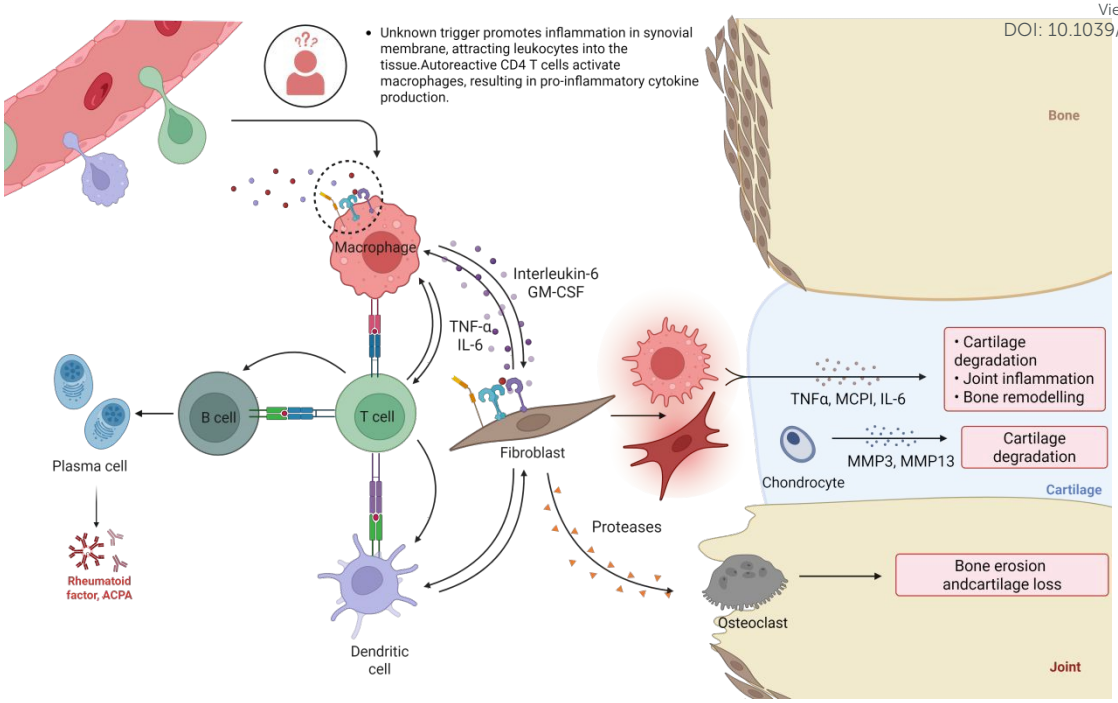

Figure 3. Interaction between synovial cells.

FLS and MLS constitute a central axis driving synovial inflammation and tissue destruction in RA. Proinflammatory cytokines, such as TNF-α and IL-1β, derived from MLS act as potent activators of FLS. These cytokines stimulate FLS through NF-κB signaling pathways. This promotes pathological behaviors, including proliferation, migration, and invasion. They also induce the secretion of additional inflammatory and tissue-degrading mediators such as IL-6 and MMPs. Together, these effects exacerbate synovial inflammation and cartilage/bone erosion[48-50]. Importantly, FLS are not merely passive responders. Instead, they actively secrete chemokines such as C-X-C motif chemokine ligand 1 (CXCL1), C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 8 (CXCL8), and C-X-C motif chemokine ligand 12 (CXCL12), to recruit monocytes into the inflamed joint and promote their polarization toward the proinflammatory M1 phenotype[51]. Additionally, activated FLS produce specific factors that sustain MLS activation. This prevents the resolution of local inflammation [52]. Through shared signaling pathways, including NF-κB and signal transducer and activator of transcription 3 (STAT3), FLS and MLS form a tightly interconnected positive feedback network. This crosstalk underlies the persistence of chronic synovial inflammation. It also promotes pannus formation and drives ongoing destruction of

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cartilage and bone (**Table 1**)[53-55].

Table 1. Core Interactions between FLS and MLS in RA.

Interaction Direction	Key Mediators Mechanisms	Major Pathological Consequences	Ref.
MLS → FLS	Pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) activate FLS.	Promotes FLS proliferation, activation, and enhanced secretion of inflammatory factors and MMPs, leading to increased invasiveness.	44, 49, 56
FLS → MLS	Chemokines (e.g., CCL2, CXCL8, CXCL12) recruitand polarize monocytes/macrophages.	Enhances monocyte infiltration and polarizes MLS toward a proinflammatory M1 phenotype.	57-59
Bidirectional	Shared intracellular signaling pathways (e.g., NF-κB, STAT3, MAPK) drive a pro-inflammatory and tissue-destructive feedback loop.	Sustains chronic inflammation, facilitates pannus formation and maintenance, and exacerbates bone erosion.	49, 54, 60

MLS and T cells play pivotal roles in RA initiation and persistence[61]. Acting as antigen-presenting cells, MLS present self-antigens such as citrullinated proteins *via* major histocompatibility complex class II (MHC class II) molecules to $CD4^+$ T cells, while providing costimulatory signals through CD80/CD86, thereby activating pathogenic T cells[62-64]. MLS also mediates T-cell recruitment through chemokine signaling. For example, MLS secretes C-C motif chemokine ligand 21 (CCL21), which binds to C-C chemokine receptor type 7 (CCR7) on T cells, directing their migration

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into the synovium. Beyond recruitment, CCL21 enhances the proinflammatory phenotype of local MLS, promoting the secretion of IL-6 and IL-23. These cytokines subsequently promote T helper 17 (Th17) cell differentiation and establish a self-amplifying feedback loop that sustains synovial inflammation [65, 66].

3. Advanced Nanoplatforms for the Treatment of RA

Although conventional GCs, small-molecule DMARDs, and biologics have achieved significant symptomatic relief, their clinical application remains limited by low bioavailability, high systemic toxicity, frequent dosing, and elevated costs. These limitations restrict long-term, safe, and precise disease management[67-69]. This underscores the urgent need for novel, highly efficient, and targeted therapeutic strategies. The central pathogenic roles of FLS and MLS, along with the limitations of conventional GCs, DMARDs, and biologics, collectively underscore the pressing need for more precise and effective therapeutic strategies.

3.1 Lipid- and Polymeric-based Nanoplatforms for Drug Release

In recent years, lipid- and polymeric-based drug delivery systems have attracted significant attention for enabling precise cell targeting and stimuli-responsive drug release in RA therapy[70-72]. Various nanocarriers, including liposomes, nanoemulsions, solid lipid nanoparticles, nanomicelles, nanocapsules, and nanogels, offer significant advantages owing to their tunable size, high surface area, and easily functionalizable surface chemistry (**Figure 4**)[73]. These nanoplatforms enable high local accumulation of therapeutic agents at inflamed synovial sites either through passive targeting strategies (e.g., the enhanced permeability and retention effect, EPR) or via active targeting via ligand-receptor recognition[54]. Functionalization with specific ligands further enables selective binding to cell surface markers in diseased tissue, enhancing therapeutic efficacy while minimizing systemic toxicity [74, 75].

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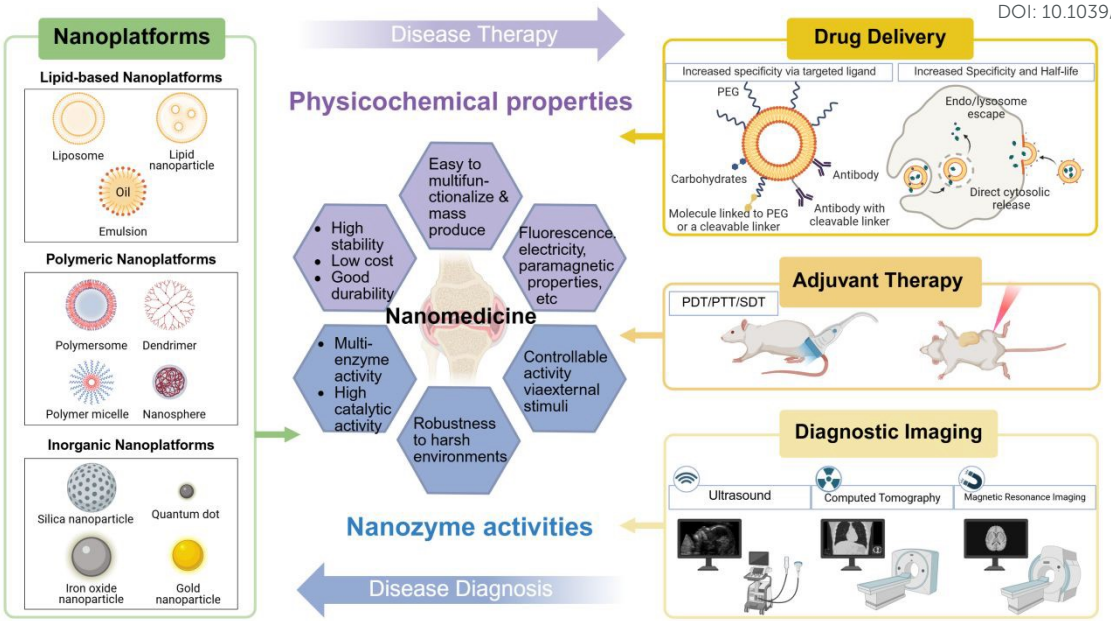

Figure 4. Nanoplatform-based strategies can effectively regulate the immune system and achieve high therapeutic efficacy for RA.

3.2 Enzyme-Mimetic Multifunctional Nanoplatforms

Beyond targeted drug delivery, certain nanomaterials possess intrinsic enzyme-like activities, mimicking natural enzymes such as superoxide dismutase (SOD), catalase (CAT), and peroxidase (POD)[76-79]. These catalytic activities facilitate the scavenging of reactive oxygen species (ROS), directly alleviating oxidative stress, and indirectly suppressing inflammatory cascades[80, 81]. Such biomimetic nanozymes have shown great promise in regulating inflammation, as recently reviewed by Xue et al[82]. Nanotechnology-enabled combinatorial therapies not only enable the co-delivery of multiple drugs to pathological sites but also integrate emerging therapeutic nanomaterials with innovative treatment modalities[83]. Furthermore, stimuli-responsive nanoplatforms responsive to light, heat, ultrasound, or magnetic fields enable on-demand, synergistic therapy (e.g., photothermal/photodynamic-assisted drug release) and support real-time imaging [84-87]. This facilitates theranostic applications (**Figure 4**), as extensively reviewed in the context of inflammatory arthritis[88]. Such multifunctional nanoplatforms provide simultaneous diagnostic capability, targeted drug delivery, and enhanced therapeutic outcomes. This offers a promising avenue for precision medicine in RA [89, 90].

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4. Synovial Cell–Targeted Nanotherapeutic Strategies

Given the pivotal role of FLS and MLS in RA pathogenesis and the complexity of their crosstalk, developing nanotherapeutic strategies that precisely target and modulate these two cell types has become a major research focus[91]. Such approaches offer multiple hierarchical entry points for highly targeted interventions. Unlike conventional drug delivery systems, smart nanomaterials designed based on pathological cell characteristics can recognize specific membrane receptors, inflammatory signaling pathways, or metabolic features of synovial cells, enabling both targeted delivery and local regulation. For instance, nanocarriers functionalized with hyaluronic acid (HA), folate, anti-CD44 antibodies, or peptide ligands can selectively recognize and accumulate in hyperproliferative FLS[92, 93]. Moreover, stimuli-responsive nanoplatforms can trigger drug release in response to inflammation-associated microenvironmental cues, such as acidic pH, elevated ROS, or enhanced enzymatic activity, achieving precise spatiotemporal drug delivery[94].

4.1 Nanotherapeutic Strategies Targeting MLS

Macrophages serve as central regulators of immune responses, playing a pivotal role in mediating inflammation under various pathological conditions. In healthy joints, a population of resident synovial macrophages maintains tissue homeostasis, forming a physical-like barrier that protects the synovium from exogenous inflammatory infiltration[95]. In RA, this barrier is disrupted, leading to continuous recruitment of circulating monocytes/macrophages to the synovium *via* chemokine signaling, predominantly through the CCL2–CCR2 axis, where they differentiate into proinflammatory M1 macrophages[96]. These inflammatory macrophages exhibit enhanced adhesion and migratory capacities and interact with vascular endothelial cells, further amplifying local inflammation and cellular recruitment[97]. Proinflammatory M1 MLS not only release key cytokines, including TNF-α, IL-1β, IL-6, and MMPs, but also upregulate RANKL and osteoclastogenic signals, promoting osteoclast differentiation and driving progressive subchondral bone erosion and cartilage degradation, ultimately contributing to RA-associated joint destruction[98].

Restoring macrophage homeostasis within the synovium thus represents a promising therapeutic avenue. Key strategies include: (1) inhibiting M0-to-M1 macrophage polarization through apoptosis induction and enhanced antioxidant mechanisms to reduce the proinflammatory cell pool; (2) promoting repolarization of M1 macrophages toward an anti-inflammatory M2 phenotype; and (3) selectively depleting inflammatory macrophages while restoring barrier function. Collectively, these approaches aim to modulate macrophage phenotype, suppress NF-κB signaling and proinflammatory cytokine production, scavenge reactive oxygen and nitrogen species (RONS), and ultimately dampen the proinflammatory cascade while promoting tissue repair and synovial homeostasis (**Figure 5**A).

4.1.1 Passive Accumulation and Active Recognition

Achieving precise modulation of MLS requires efficient accumulation and cellular internalization of therapeutic agents at inflamed sites. Nanomedicines typically integrate passive and active targeting mechanisms to enhance localization within diseased joints. Meanwhile, microenvironment-responsive drug release further refines spatial specificity and minimizes systemic adverse effects. Collectively, these strategies enable a transition from nonspecific inflammatory-site accumulation to selective MLS recognition and controlled intracellular drug delivery.

In RA, persistent inflammation induces abnormal vascular expansion, enlarged endothelial gaps, and extensive infiltration of inflammatory cells within the synovium. These pathological alterations permit colloidal nanoparticles to extravasate from the bloodstream into inflamed joints and undergo local retention mediated by inflammatory cells, a phenomenon often referred to as the inflammation-associated EPR/extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration (ELVIS) effect[99]. Aldayel et al. further demonstrated that nanoparticle size critically influences biodistribution and persistence at chronic inflammatory loci. Smaller nanoparticles (2–10 nm) exhibit enhanced diffusion, whereas larger nanoparticles (100–200 nm) achieve more selective accumulation within inflamed tissues[100]. Thus, passive targeting facilitates local drug enrichment and provides an essential foundation for prolonged synovial retention.

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Active targeting strategies further enhance the specificity of nanomedicines toward MLS by exploiting ligand–receptor interactions and inflammation-associated surface markers differentially expressed on activated macrophages. Representative approaches include folic acid (FA) modification, which enables preferential recognition of M1-polarized macrophages *via* upregulated folate receptors under inflammatory conditions, and TNF-α–specific aptamers that target regions with high local concentrations of proinflammatory cytokines[101]. Ligands for the mannose receptor CD206, although more abundantly expressed on M2 macrophages, also provide efficient endocytic pathways characteristic of the macrophage lineage[102]. Beyond molecular ligands, biomimetic strategies, such as macrophage membrane (MM) coating, confer nanoparticles with self-recognition capability and immune evasion properties. This prolongs circulation and promotes preferential accumulation within the inflamed synovium[103].

4.1.2 Enzyme- and Microenvironment-responsive Drug Release

Enzyme-responsive systems encapsulate therapeutic agents within nanostructures containing enzyme-cleavable substrates or linkers[104, 105]. Exposure to disease-associated enzymes overexpressed or hyperactivated at inflammatory sites induces carrier disassembly or permeability changes, leading to localized drug release [106]. In RA, MMPs and hyaluronidase (HAase) are frequently upregulated and are considered hallmarks of synovial inflammation[107, 108]. Accordingly, an MMP-cleavable peptide–based nanotherapeutic system (2-APB@DGP-MM) was developed by integrating an MMP-sensitive linker into macrophage membrane–coated nanoparticles[109] (Figure 5B). MMP-mediated cleavage acts as a molecular "switch" to trigger drug release within the inflammatory core, with both *in vitro* and *in vivo* experiments demonstrating favorable biocompatibility, improved cellular uptake, and effective reprogramming that shifts macrophages from a proinflammatory M1 phenotype toward an anti-inflammatory M2 state.

The development of smart, stimuli-responsive nanoplatforms has shifted RA treatment paradigms from conventional sustained-release to microenvironment-triggered, on-demand drug delivery. These systems can be broadly categorized into

endogenous stimulus-responsive platforms (e.g., enzyme-, redox-, pH-, hypoxia-responsive systems) and exogenous trigger-responsive platforms (e.g., ultrasound-, light-, or magnetic field-responsive systems)[110]. These nanoplatforms are engineered to sense pathological cues characteristic of inflamed synovium or intracellular compartments of MLS, such as acidic pH, elevated ROS, and aberrant enzymatic activity, thereby enabling spatially and temporally controlled drug release and reducing off-target exposure[111, 112], as summarized in recent reviews focusing on stimuli-responsive and microenvironment-triggered nanomedicine strategies for RA[113, 114]. These features provide a rational basis for designing pH- and ROS-responsive nanoplatforms capable of site-specific or intracellular drug release, with the additional benefit of alleviating oxidative stress[115, 116]. For instance, Hou and colleagues developed a dual pH/ROS-responsive nanoplatform based on CA- and HPAP-modified α-cyclodextrin (CA-HPAP-αCD) for methylprednisolone delivery[117]. Further functionalization with an Arg–Gly–Asp (RGD) peptide enabled targeting of αvβ3/αvβ5 integrins, which are highly expressed on activated macrophages. This system demonstrated efficient cellular uptake, rapid drug release under acidic- and ROS-rich conditions, and significant attenuation of joint destruction *via* NF-κB pathway suppression *in vivo* (Figure 5C).

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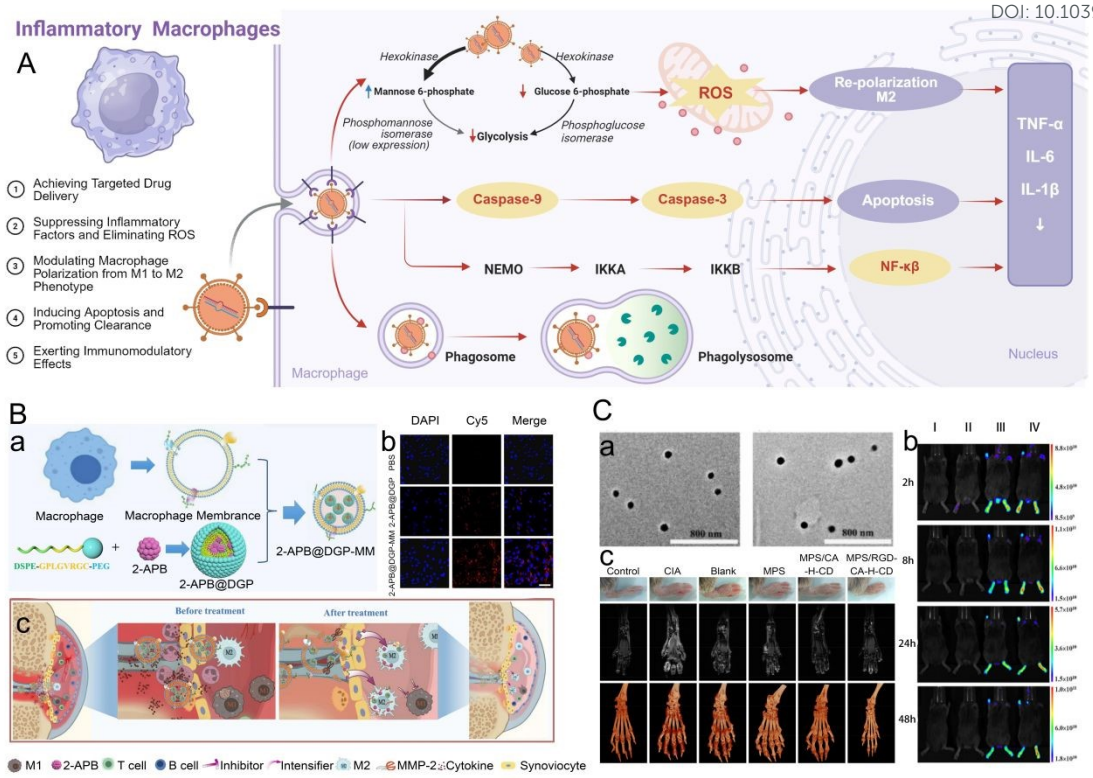

Figure 5. A. Schematic diagram illustrating the mechanism of nanoscale strategies targeting MLS. B. a), c) Preparation of 2-APB@DGP-MM and its mechanisms for inhibiting synovial inflammation in RA. b) Evaluation of Cy5-loaded 2-APB@DGP and 2-APB@DGP-MM uptake in BMDMs (scale bar: 40 μm)[109]. Copyright 2024, Springer Nature. C. a)TEM image of MPS/CA-HPAP-αCD NPs, and MPS/RGD-CA-HPAP-αCD NPs. b) *In vivo* fluorescence images of CIA mice following intravenous injection of free Cy5/MPS or Cy5-labeled NPs. Images were acquired at 2 h, 8 h, 24 h, and 48 h after administration. c) *In vivo* treatment effect of MPS-loaded NPs in CIA Mice[117]. Copyright 2023, Elsevier Ltd.

4.1.3 Reprogramming Macrophage Polarization

Accumulating evidence indicates that MLS are not merely inflammatory effectors but dynamic regulators of synovial immune homeostasis. Accordingly, nanotherapeutic strategies targeting MLS have evolved from simple anti-inflammatory suppression toward system-level modulation of macrophage phenotype, metabolism, and tissue function. Representative designs can be broadly categorized into three interrelated paradigms.

(1) Inhibition of M0-to-M1 macrophage polarization. Sustained activation of M1-polarized macrophages is a key contributor to chronic synovial inflammation and joint destruction in autoimmune arthritis. Consequently, preventing the initiation or amplification of M1 polarization has long been considered a promising therapeutic strategy[118, 119]. For instance, Shen and colleagues developed dextran sulfate–based nanoparticles loaded with garcinol, a P300/CBP-associated factor (PCAF) inhibitor. These nanoparticles selectively targeted M1 macrophages in inflamed joints *via* scavenger receptor–mediated uptake, and their efficacy was validated in a collagen-induced arthritis (CIA) model [120]. Compared with free garcinol, nanoparticle delivery significantly enhanced intra-articular accumulation and therapeutic efficacy, highlighting the potential of nanocarriers to interfere with epigenetic regulators of macrophage polarization (**Figure 6**A). Collectively, such designs illustrate how nanotechnology can convert molecular inhibitors with limited bioavailability into functionally effective modulators of macrophage fate *in vivo*.

(2) Reprogramming M1 macrophages toward M2 phenotype. Beyond suppressing M1 activation, increasing attention has shifted toward active reprogramming of macrophage phenotype, aiming to restore immune balance rather than merely dampen inflammation. Methotrexate (MTX), although a first-line RA therapy, suffers from poor solubility and non-specific distribution, limiting its long-term efficacy. To address this, Sun et al. engineered a multifunctional nanoplatform combining folic acid–mediated macrophage targeting with TNF-α–specific aptamers, thereby achieving dual recognition of inflammatory macrophages and cytokine-rich microenvironments[121]. The incorporation of MnO_2 and polydopamine further enabled ROS scavenging and oxygen generation, collectively promoting M1-to-M2 repolarization and markedly improving therapeutic outcomes in CIA models (Figure 6B). Similarly, Meng and colleagues developed mannose-modified polymeric vesicles for MTX delivery, which exhibited high drug-loading capacity and glutathione-responsive release, preferential macrophage uptake, and efficient induction of an anti-inflammatory M2 phenotype both *in vitro* and *in vivo*[122]. These studies underscore a paradigm shift toward immune-reprogramming nanomedicines that reshape the

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inflammatory microenvironment rather than simply suppress it.

(3) Elimination of inflammatory macrophages and restoration of tissue barrier function. At a more integrated level, advanced nanotherapeutic systems have begun to address the broader pathological ecosystem of RA, including oxidative stress, hypoxia, mitochondrial dysfunction, and impaired tissue repair. Elevated ROS and hypoxic stress promote mitochondrial damage and Ca^{2+} overload, reinforcing M1 polarization and impairing osteoimmune coupling. Han et al. addressed this challenge by constructing a nanozyme-functionalized titanium surface ($MnFe_2O_4$@TiO_2), capable of decomposing H_2O_2 to scavenge ROS and generate oxygen, thereby alleviating mitochondrial stress and reprogramming macrophage metabolism toward oxidative phosphorylation *via* the Ca^{2+}–AMP-activated protein kinase (AMPK)–mammalian target of rapamycin (mTOR) axis [123] (Figure 6C). This strategy not only promoted M2 polarization but also restored osteointegration in RA-associated bone defects. Complementarily, Chang et al. developed a biomimetic macrophage membrane–coated porous carbon nanosphere-based platform for targeted delivery of Iguratimod, integrating ROS scavenging, high drug loading, and pH/NIR-responsive release[124]. This system effectively attenuated synovial inflammation and joint destruction in CIA models, offering a promising route toward sustained synovial homeostasis.

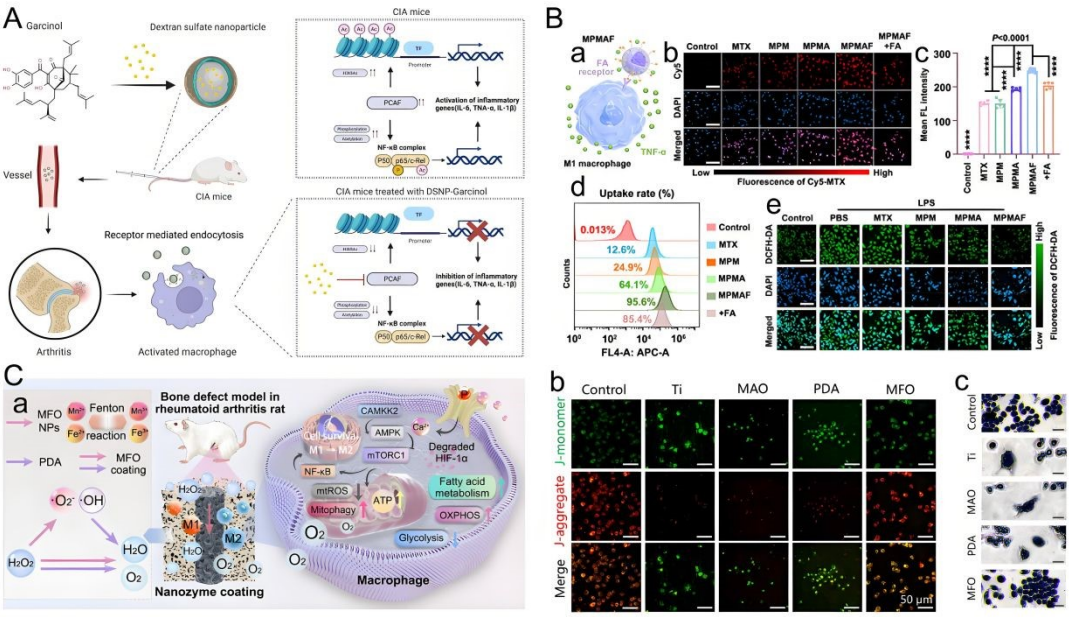

Figure 6. A. Schematic diagram showing the DSNP-mediated enhancement of the anti-inflammatory activity of garcinol in the mouse CIA model[120]. Copyright 2023, Springer Nature. B. a) Schematic illustration of the targeted accumulation mechanism of the dual-targeting MPMAF nanoplatform. b) Specific targeting of confocal images of RAW 264.7 cells for 4 h. c) Quantitative analysis of Cy5 fluorescence intensity within RAW 264.7 cells. d) Flow cytometry detection of Cy5 fluorescence signal in RAW 264.7 cells. e) Confocal microscopy images showing intracellular ROS (green fluorescence) labeled with the DCFH-DA probe in LPS-prestimulated RAW 264.7 cells[121]. Copyright 2025, WILEY-VCH. C. a) A nanozyme-mimicking coating reprograms macrophage metabolism by modulating mitochondrial function via ROS scavenging and O_2 generation. b) Representative images of JC-1 aggregates (red) and monomers (green) showing fluorescence in RAW264.7 on the surfaces of different samples at 24 h of incubation. c) TRAP staining of the cells cultured on the samples[123]. Copyright 2025, American Chemical Society.

Taken together, MLS-targeted nanotherapeutic strategies have progressed from simple drug encapsulation toward precision-engineered systems integrating active targeting, stimuli-responsive release, and immune–metabolic reprogramming. By intervening at multiple regulatory nodes, including cellular phenotype, oxidative stress, metabolic state, and tissue repair, these approaches provide powerful tools for dismantling the inflammatory core of RA and re-establishing synovial immune equilibrium. A systematic overview of representative MLS-targeted nanotherapies is provided in **Table 2**.

Table 2. Rational Design of Nanocarriers for Targeted Delivery to MLS in RA

Strategy Classification	Core Mechanism	Nanocarrier Examples	Function and Efficacy	Ref.
Targeted Drug Delivery	Utilizes active targeting (folate, RGD peptide modification) or pass	Lipo/MTX-HSA PLGA @oil/NPs 2-APB@DGP-	Enhances drug bioavailability at the lesion site, improves anti-inflammatory	109, 125, 126

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	ive targeting (EPR effect)	MM	/immunomodulatory efficacy, and reduces systemic toxicity and related side effects.	
Microenvironment Regulation (Antioxidant Stress)	Leverages the enzyme-mimicking catalytic activity (SOD-, CAT-like) of nanomaterials to specifically scavenge ROS	CeO_2 Nanozymes MnO_2 (H-MnO_2)	Reduces intra-articular ROS levels, inhibits key inflammatory signaling pathways (NF-κB), and alleviates oxidative stress damage and subsequent inflammatory responses.	127, 128
Microenvironment Regulation (Polarization Modulation M1→M2)	Reprograms the metabolism and phenotype of MLS from pro-inflammatory M1 to anti-inflammatory M2	R@HSNs 2-APB@DGP-MM Col/Cs	Downregulates pro-inflammatory factors (IL-1β, TNF-α, IL-6, iNOS) and upregulates anti-inflammatory/repair factors (IL-10, TGF-β, CD206)	109, 129, 130
Intelligent Smart Collaborative Therapy	Constructs "smart" nanoplatforms responsive to endogenous disease signals (pH, ROS, enzymes) or exogenous stimuli	PEG-PBA-TGMS PPT MnO_2-CQ4T-GOx (MCGNM)	Enables precise spatiotemporal control of drug release and achieves synergistic therapeutic outcomes with enhanced efficacy and re	131, 132

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	(light, heat, magnetism) for on-demand drug release, and integrates multiple treatment modalities.	duced toxicity through combined mechanisms (chemotherapy + PTT).

4.2 Nanotherapeutic Strategies Targeting FLS

FLS have a central role in the pathogenesis of RA. Zhang et al. used single-cell and spatial transcriptomics to map synovial cell populations and spatial gene expression. Their analysis revealed that activated FLS constitute a dominant fraction in RA synovium (**Figure 7**A)[133]. Activated FLS exhibit hyperproliferation and excessive secretion of MMPs and other extracellular matrix (ECM)-degrading molecules, leading to cartilage destruction. They also secrete chemokines that recruit macrophages, T cells, and B cells to the joint, amplifying inflammation[134]. Furthermore, dysregulation between anti-apoptotic and pro-apoptotic molecules, such as Bcl-2 upregulation, confers resistance to TRAIL-mediated apoptosis, promoting FLS hyperplasia and persistent synovial expansion[135, 136].

Given their pivotal role in driving synovial proliferation and joint damage, FLS represent a critical therapeutic target. Nanomedicine approaches aimed at FLS focus on inhibiting aberrant proliferation, reducing invasiveness, inducing apoptosis, or reprogramming pro-inflammatory phenotypes, thereby arresting synovial hyperplasia and bone erosion at the source. Optimized nanoparticles can selectively induce RA-FLS apoptosis while simultaneously mitigating structural joint damage (Figure 7B).

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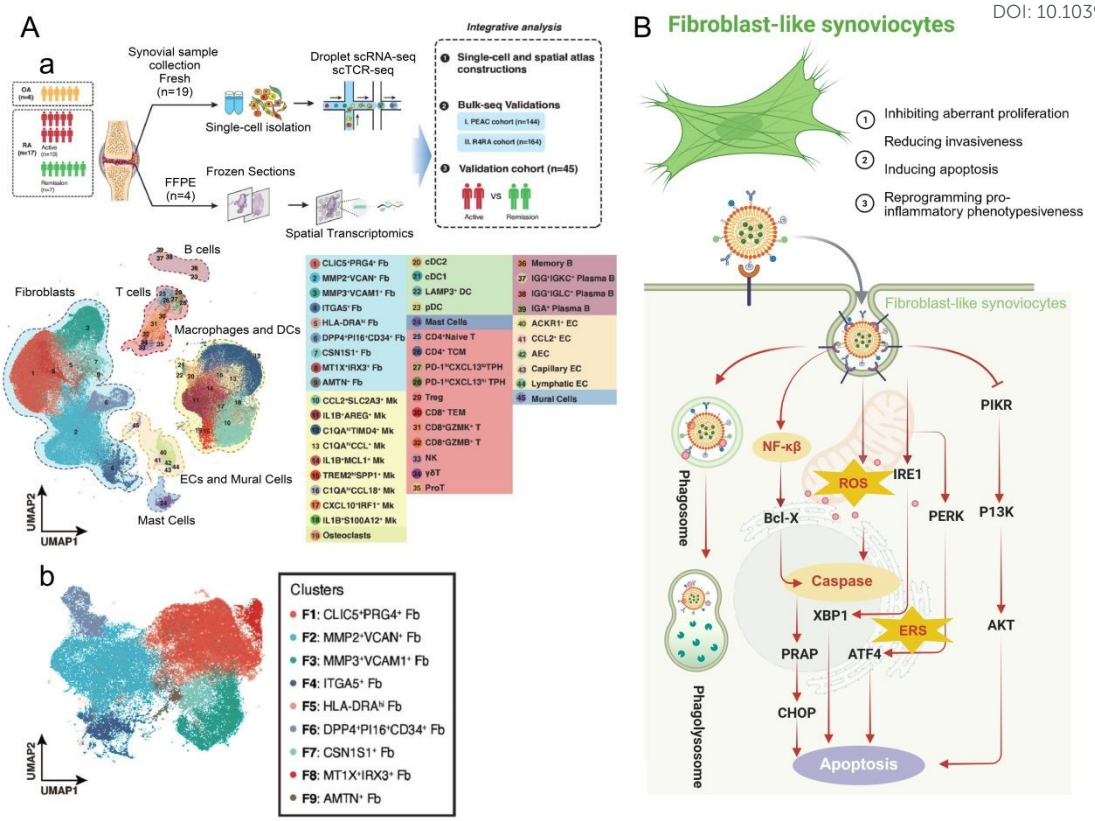

Figure 7. A. a) Single-cell RNA sequencing of synovial tissues from 19 individuals, including patients with osteoarthritis and RA at different disease activities, generated an atlas of 169,797 cells and identified major synovial cell populations, with FLS emerging as a prominent and heterogeneous stromal compartment in the RA synovium. b) Single-cell analysis further delineated multiple functional FLS subsets with distinct proinflammatory, immunoregulatory, and tissue-invasive phenotypes, underscoring FLS as central pathogenic drivers and promising therapeutic targets in RA[133]. Copyright 2025, Elsevier Ltd. B. Schematic illustration of the mechanisms underlying nanoparticle strategies targeting FLS.

4.2.1 Microenvironment- and exogenous stimulus-responsive release.

Functionalization with ligands enables selective FLS recognition and efficient cellular uptake. Common targets include CD44, recognized by hyaluronic acid[137]; integrin alpha-v beta-3 (αvβ3), targeted by arginine-glycine-aspartic acid (RGD) peptides[138, 139]; and homologous FLS membrane coating for self-recognition. RA synovium features acidic pH and elevated MMP levels [140, 141], which can serve as

triggers for on-demand drug release at the inflamed site, enhancing the therapeutic index and minimizing off-target toxicity. In addition to these endogenous cues, exogenous stimuli such as photothermal therapy (PTT) and photodynamic therapy (PDT) can be applied to further amplify local ROS production and induce programmed cell death in RA-associated cells, including FLS and inflammatory macrophages. For example, multifunctional nanoparticles combining PTT and PDT markedly enhance ROS generation and reduce inflammatory cell viability. At the same time, curcumin-mediated PDT (CUR-PDT) triggers ferroptosis in RA-FLS *via* the nuclear factor erythroid 2–related factor 2 (Nrf2)–cystine/glutamate antiporter (xCT)–glutathione peroxidase 4 (GPX4) pathway, suppressing FLS proliferation and invasive behavior [142-144].

4.2.2 Therapeutic Efficacy and Phenotype Reprogramming

Chemotherapeutic or small-molecule-loaded nanoparticles (NPs) can simultaneously trigger apoptosis and suppress pro-inflammatory cytokines. For example, Wen et al. constructed a tetrahedral framework nucleic acid (tFNA) cargo system loaded with nobiletin, which enhanced the flavonoid's bioavailability and promoted apoptosis in pathological synovial fibroblasts **by** inhibiting the phosphatidylinositol 3-kinase (PI3K/Akt) and NF-κB pathway[145]. In another study, Dual-drug nanoparticles loaded hydrogel (DD NP HG) co-delivering phenethylisothiocyanate (PEITC) and MTX generated ROS to induce apoptosis and significantly reduced TNF-α, IL-17A, and IL-6 in CIA models [146] (**Figure 8**A). Similarly, pH-sensitive injectable bismuthene nanosheet/polyethyleneimine (BiNS/PEI) hydrogels loaded with MTX enable combined PDT/PTT to selectively eliminate FLS, inducing apoptosis *via* caspase activation under acidic conditions [147] (Figure 8B). Li et al. developed a concave-cubic rhodium (Rh) nanozyme incorporating the sonosensitizer sparfloxacin (SPX) and loaded with human serum albumin (HSA) (Rh/SPX-HSA), which integrates ultrasound-activated SPX with POD- and CAT-mimicking activities[148]. The system alleviates hypoxia, enhances ROS-mediated SDT efficacy, and induces apoptosis in RA-FLS through synergistic mechanisms (Figure 8C).

RA-FLS rely heavily on glycolysis for energy in hypoxic microenvironments,

limiting the efficacy of glucose oxidase (GOx)-mediated starvation therapy[149]. Geng et al. developed V-HAGC, a CuS-based hollow mesoporous NP system that co-delivers GOx and atovaquone (ATO), *via* a "dual-energy deprivation" strategy[150]. The pH/NIR-triggered release allows GOx-catalyzed glucose consumption and H_2O_2/acidification, enhancing CuS Fenton-like reactions, while CuS-mediated PTT provides synergistic cytotoxicity. This multi-modal design reprograms energy metabolism and exacerbates oxidative stress to efficiently inhibit FLS activity (Figure 8D).

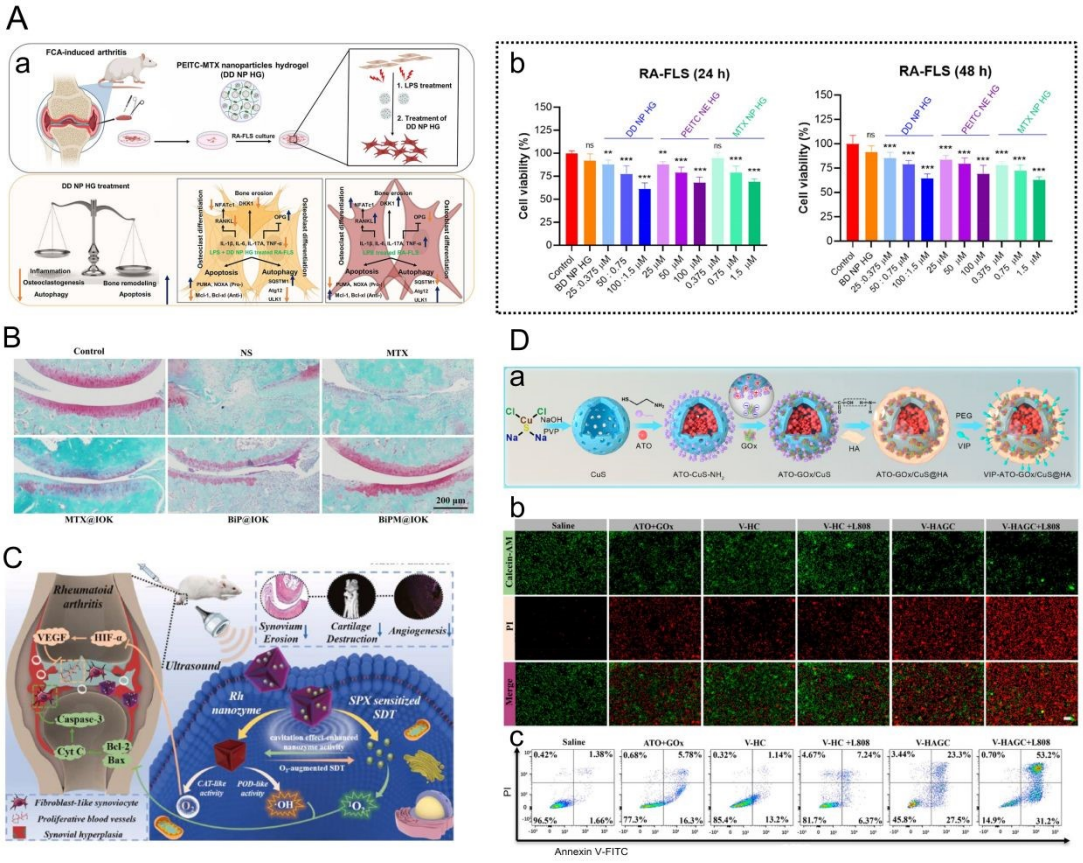

Figure 8. A. a) Dual-drug nanoparticle hydrogel (DD NP HG) induces apoptosis, suppresses proinflammatory cytokines, and modulates gene expression in RA-FLS, highlighting its potential for targeted RA therapy. b) Cell viability (%) of healthy FLS cells at 24 h and 48 h[146]. Copyright 2024, Elsevier Ltd. B. *In vivo* treatment efficacy of BiPM@IOK hydrogel: Safranin O staining of joints after various administrations[147]. Copyright 2024, Springer Nature. C. Schematic depiction of the fabrication of Rh-SPX/HSA and its underlying mechanisms in RA treatment[148]. Copyright 2021, Elsevier Ltd. D. Characterization and therapeutic evaluation of V-HAGC nanoplatforms. a)

Schematic of the synthesis and dual-responsive mechanism. b) Live/dead staining. c) Flow cytometry analysis of FLS cells for 24 h[150]. Copyright 2022, American Chemical Society.

In summary, integrating active targeting with smart, stimulus-responsive strategies enables nanomedicines to achieve precise recognition and delivery to FLS, resulting in superior therapeutic outcomes. These approaches provide a powerful platform to halt RA-associated synovial hyperplasia and joint destruction. In addition, image-guided theranostic nanoplatforms integrating diagnostic imaging (e.g., MRI, fluorescence, photoacoustic imaging) with targeted FLS regulation have emerged as a rapidly developing direction in RA nanomedicine, as comprehensively discussed in recent reviews[151, 152]. **Table 3** summarizes representative nanomedicine strategies targeting FLS over the past few years.

Table 3 Rational Design of Nanocarriers for Targeted Delivery to FLS in RA

Strategy Classification	**Nanocarrier Examples**	**Core Mechanism of Action**	**Primary Functionsand Therapeutic Outcomes**	**Ref.**
Active Targeting	Ligand-modified nanomaterials (HA,FAP, short peptides)	Achieves specific uptake byFLS *via* ligand–receptor recognition.	Enhances cellular internalization of nanoparticles, increases drug accumulation in joints	150, 153, 154
Biomimetic Targeting	FLS membrane or membrane protein-coated biomimetic nanovesicles	Utilizes homologous targeting and mimics FLS homing ability to enhance synovial accumulation and evade immune clearance.	Significantly improves synovial targeting efficiency and effectively alleviates synovitis symptoms.	93
Microenviro	pH-sensitive	Carrier structural c	Enables precise drug	125, 1

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nment-Responsive Therapy • pH-Responsive	liposomal nanoparticles (Lipo/MTX-HSA, siCD86MP, BiMP)	hanges triggered by the acidic (low pH) microenvironment at inflammatory sites, leading to rapid drug release and specific induction of apoptosis in hyperproliferative FLS.	release at lesion sites, increases local drug concentration, enhances anti-inflammatory and anti-proliferative effects, reduces synovial lining thickness, inhibits pannus formation, and alleviates joint inflammation.	155
Microenvironment-Responsive Therapy • ROS-Responsive	ROS-scavenging/ROS-responsive nanocarriers (HC@PTM)	Chemical bond cleavage in the highly ROS synovial environment, resulting in controlled drug release.	Specifically suppresses inflammatory factor expression in FLS (IL-6, TNF-α), reduces oxidative stress, and mitigates inflammation.	156
Theranostics Integration	Gold/Iron/Gold multi-shell nanoparticles	Integrates multiple functions such as MRI, magnetic targeting, and PTT.	Achieves synergistic diagnosis and treatment, enhances therapeutic efficacy *via* photothermal effects, and enables real-time monitoring of disease progression.	157

4.3 Synergistic Targeting of FLS and MLS

In the RA synovium, FLS and MLS engage in tightly coupled positive feedback

loops. Together, they form a pathological cellular unit that sustains chronic inflammation and joint destruction. Aggressive FLS proliferation reinforces persistent M1 polarization of MLS, while pro-inflammatory MLS-derived mediators further enhance the invasive and apoptosis-resistant phenotype of FLS. This reciprocal amplification constitutes a "cellular co-driving axis" underlying RA progression. Accordingly, nanotherapeutic strategies that simultaneously modulate both FLS and MLS, rather than targeting either cell type in isolation, are increasingly recognized as essential for sustained disease control.

Recent advances have witnessed a conceptual shift from simple combinatorial delivery toward intelligently coordinated nanoplatforms that disrupt the FLS–MLS pathological circuit through spatially and temporally orchestrated interventions. Representative strategies can be broadly categorized as follows.

4.3.1 From Functional Addition to True Therapeutic Synergy

Ge et al. developed an implantable pH-sensitive peptide hydrogel that integrates gene silencing (siRNA), chemotherapeutic intervention (MTX), and physical ablation (PTT/PDT) within a single platform[155]. This system simultaneously suppressed key inflammatory regulators (CD86, p65, and p38) in both MLS and FLS. This attenuated NF-κB/MAPK signaling and MMP secretion at the molecular level, while phototherapy selectively eliminated pathogenic FLS. Notably, gene modulation lowered the apoptotic threshold of FLS, rendering them more susceptible to subsequent photothermal/photodynamic treatment. This molecular sensitization–physical eradication paradigm exemplifies a refined form of synergy that transcends simple functional stacking (**Figure 9**A).

4.3.2 From Hostile Microenvironment to Therapeutic Driving Force

Another emerging strategy exploits the hostile inflammatory microenvironment itself, such as elevated ROS and acidic pH, as a therapeutic driving force. Cao et al. engineered a heparin–phenylboronic acid–based lipid platform (Hep-Lips/CLT) that simultaneously targets macrophages and FLS while enabling ROS-responsive drug release[158]. This system promoted macrophage repolarization and induced ferroptosis in

FLS, achieving coordinated immunomodulation and stromal suppression. Moving beyond single-trigger responsiveness, Li et al. designed a ROS/pH dual-responsive, size-shrinkable micellar system that undergoes stepwise activation [159]. ROS-triggered polyethylene glycol (PEG) shedding in the synovial cavity exposes hyaluronic acid ligands, enabling a transition from passive accumulation to CD44-mediated active uptake by M1 macrophages and FLS, followed by intracellular acidic-triggered drug release. By converting RA-specific biochemical cues into hierarchical "switches," this platform concurrently suppresses M1 polarization and FLS invasiveness, effectively targeting both the inflammatory "seed" and the stromal "soil" (Figure 9B).

4.3.3 From Immune Evasion to Active Cell-Mediated Delivery

Biomimetic strategies leverage endogenous cellular components to enhance immune evasion and inflammatory homing. Cai et al. reported a multilayer membrane–camouflaged nanoparticle termed HA-M@P@HF, which is a hyaluronic acid (HA)–modified hybrid membrane (M)–camouflaged poly(lactic-co-glycolic acid) (PLGA) nanoplatform for HF delivery, integrating red blood cell membranes for prolonged circulation, macrophage membranes for inflammatory tropism, and HA for CD44-mediated recognition of both MLS and FLS[160]. This hierarchical disguise enables deep penetration into the synovial niche, analogous to a "Trojan horse" strategy. Moving beyond passive camouflage and dual targeting, emerging biomimetic systems are increasingly engineered to actively modulate the inflammatory microenvironment. Xie et al. developed a macrophage membrane–camouflaged Prussian blue nanoparticles loaded with siRNA targeting TNF-α (MACP siTNF-α nanoparticles) integrating nanozyme-mediated ROS scavenging with gene silencing therapy. Preferential uptake by inflammatory M1 macrophages and glutathione-responsive siRNA release established a redox-responsive therapeutic circuit. Through coordinated TNF-α suppression and oxidative stress modulation, this system attenuated inflammatory activation and supported synovial immune homeostasis[161] (Figure 9C). While membrane camouflaging mainly facilitates immune evasion and inflammatory targeting, employing living immune cells marks a transition toward more active cell-mediated delivery and dynamically responsive therapeutic actions. At a higher level of

biomimicry, Shen et al. employed living macrophages as cellular carriers for the delivery of Fe_3O_4 nanoparticles and sulfasalazine[162]. These engineered cells actively homed into inflamed joints and, upon near-infrared light exposure, released their payload *via* photothermal activation, inducing ferroptosis in pathogenic FLS and infiltrating immune cells. This approach integrates cell-mediated targeting, external stimulus-triggered release, and non-apoptotic cell death into a single therapeutic axis (Figure 9D).

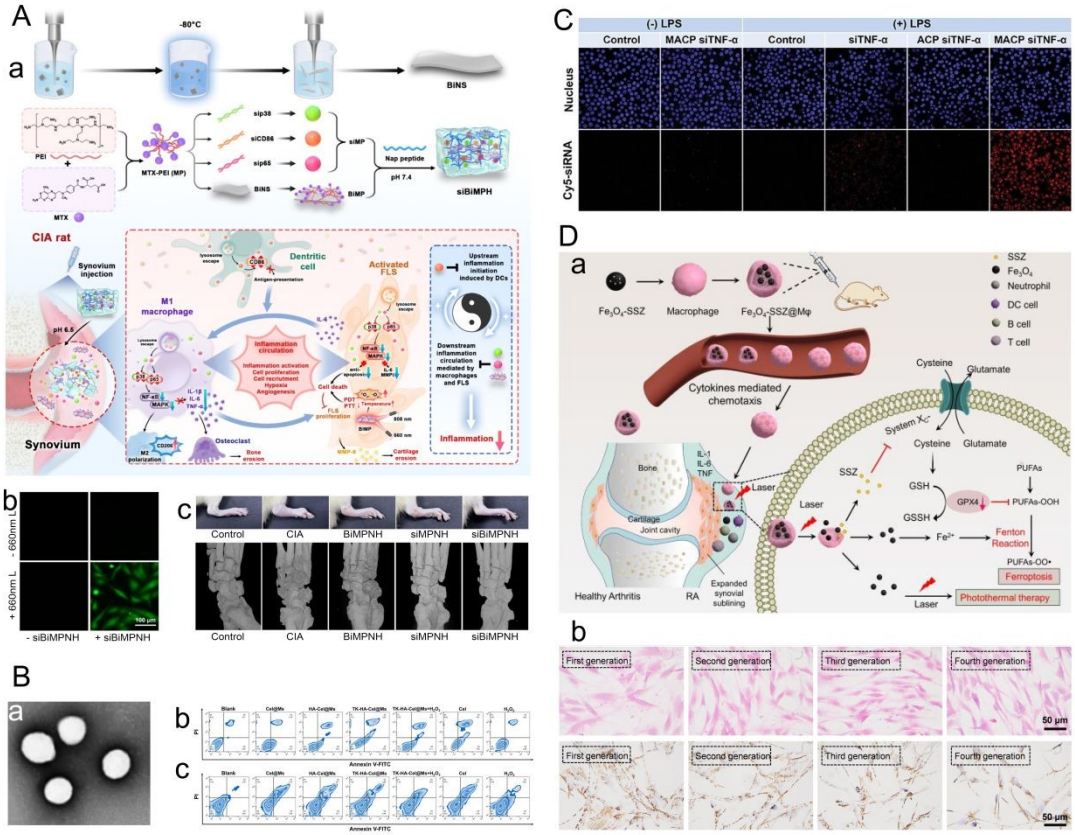

Figure 9. A. Therapeutic strategy and FLS elimination of siBiMPNH. a) Schematic of siBiMPNH preparation and combined RNAi-phototherapy strategy for immune pathway suppression and FLS elimination in RA. b) Intracellular ROS generation and cell viability of MH7A cells. c) Representative images of right hind paws[155].Copyright 2024, Elsevier Ltd. B. a) TEM image of TK-HA-Cel@Ms. b) The apoptosis of RAW264.7 cells. c) The apoptosis of RA-FLSs[159].Copyright 2025, Springer Nature. C. Confocal microscopy images showing cellular uptake in RAW 264.7 cells with or without LPS stimulation[161]. Copyright 2025, Wiley-VCH GmbH. D. Schematic

illustration of Mφ-mediated drug delivery for ferroptosis and PTT of RA. a) Schematic of Fe_3O_4–SSZ@Mφ preparation, inflammatory homing, NIR-triggered drug release, and combined ferroptosis/PTT against hyperproliferative FLSs and infiltrating immune cells. b) Mouse FLS showed spindle-shaped morphology and positive vimentin expression[162]. Copyright 2024, Elsevier Ltd.

4.3.4 From Inflammatory Suppression to Phenotype Rewriting

Beyond functional suppression, several platforms aim to directly reverse pathogenic cell states. Chen et al. developed metformin-derived carbon dots that are internalized by both MLS and FLS, attenuating ROS accumulation and NOD-like receptor family pyrin domain–containing 3 (NLRP3) inflammasome activation while restoring FLS homeostasis *via* IL-6/glycoprotein 130 (gp130) pathway inhibition (**Figure 10**A)[163]. Cao et al. further demonstrated that ROS-responsive heparin–phenylboronic acid liposomes could simultaneously induce macrophage repolarization and ferroptotic elimination of apoptosis-resistant FLS (Figure 10B)[158]. At the metabolic level, Li et al. introduced a photothermal gene delivery system enabling near-infrared (NIR)–triggered heme oxygenase-1 (HO-1) expression, which reprogrammed macrophage and FLS metabolism toward oxidative phosphorylation and suppressed glycolysis-driven inflammation (Figure 10C)[164]. Collectively, these strategies highlight a transition from symptomatic inhibition to active reversal of disease-driving phenotypes[165].

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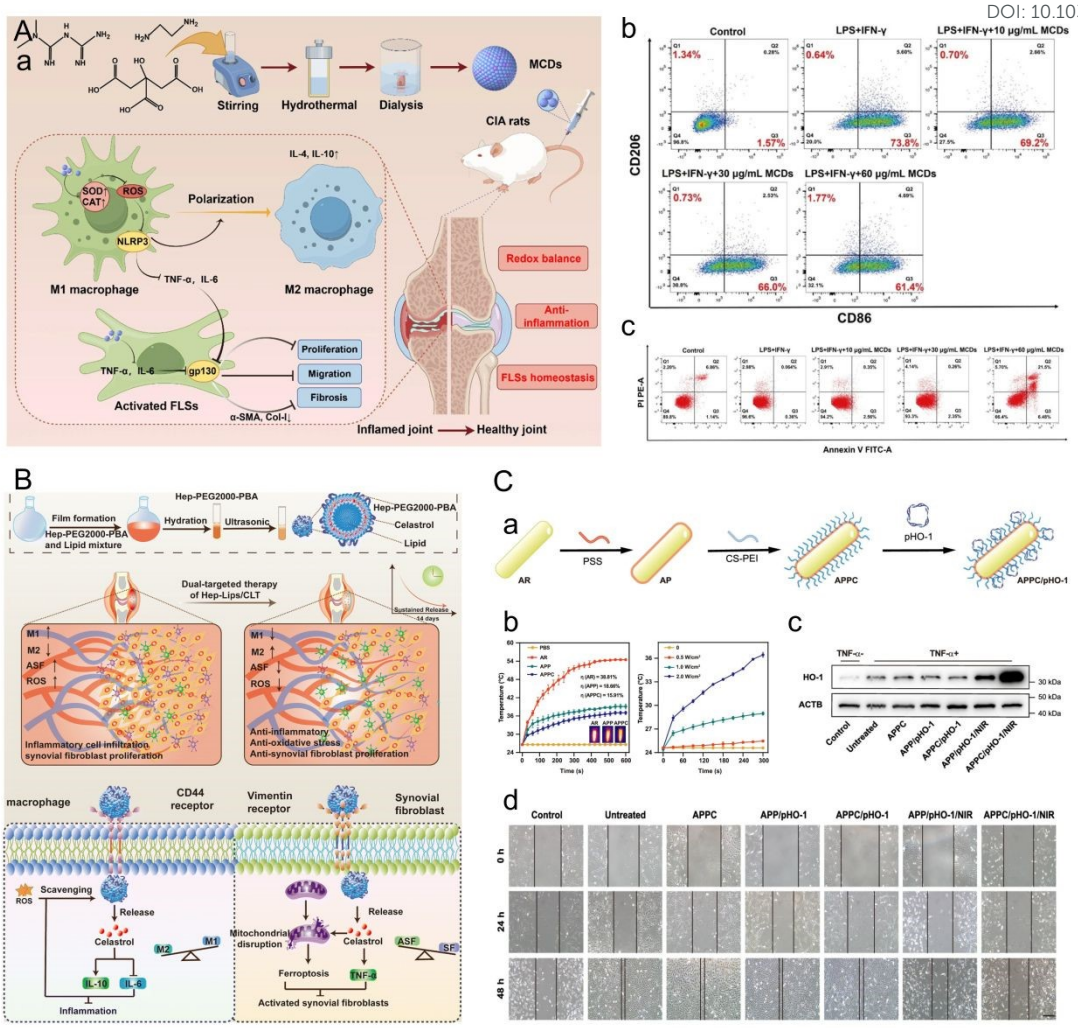

Figure 10. A. Fabrication and immunomodulatory effects of MCDs in RA. a) Schematic of MCDs preparation and therapeutic mechanisms, including ROS scavenging, M1-to-M2 macrophage polarization, and regulation of FLS homeostasis. b) Flow cytometry analysis of M1 ($CD86^+$) and M2 ($CD206^+$) macrophage populations in LPS/IFN-γ–stimulated RAW264.7 cells after different treatments. c) Flow cytometry assay to evaluate the impact of MCDs on inflamed FLSs[163]. Copyright 2025, Springer Nature. B. Schematic illustration of the preparation and therapeutic mechanism of Hep-Lips/CLT[147].Copyright 2024, Springer Nature. C. a) A synthetic route of APPC. b) Temperature profiles of PBS, AR, APP, and APPC under NIR irradiation (2.0 W/cm²) and APPC at different laser intensities (200 μg/mL). c) HO-1 expression in LPS-stimulated RAW264.7 cells following HO-1 transfection, with representative immunoblots from three separate experiments. d) HO-1 overexpression reduces FLS

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migration in a wound healing assay at 0, 24, and 48 h[164]. Copyright 2025, Springer Nature.

In summary, these studies collectively delineate an emerging paradigm for dual-cell–oriented therapy in rheumatoid arthritis, in which FLS and MLS are no longer treated as isolated targets but as an interdependent pathogenic unit. By integrating microenvironment-responsive triggers (pH/ROS/NIR), metabolic reprogramming, gene regulation, photothermal/photodynamic synergism, and biomimetic delivery systems, advanced nanoplatforms enable coordinated intervention at both cellular and microenvironmental levels. Such strategies not only disrupt the reciprocal inflammatory amplification between FLS and MLS, but also promote reconstruction of local immune homeostasis within the synovium. Collectively, these multidimensional, cross-modal nanotherapeutic platforms represent a critical transition from single-pathway suppression toward systems-level modulation of RA pathology, and are increasingly recognized as a central direction for future combinatorial and precision therapies. **Table 4** summarizes representative nanostrategies developed for the synergistic targeting of FLS and MLS in RA.

Table 4 Representative nanostrategies developed for the synergistic targeting of FLS and MLS in RA.

Strategy Core	**Nanocarrier / System**	**Mechanism of Action**	**Primary Function/ Outcome**	**Ref.**
Synergistic Regulation & Microenvironment Remodeling (Anti-inflammation + Anti-proliferation)	HA-M@P@HF NPs (HA-modified hybrid membrane-camouflaged PLGA nanoparticles)	Induces M1→M2 macrophage polarization; scavenges ROS; inhibits FLS proliferation and pro-inflammatory factor	Synergistically alleviates synovitis and mitigates joint destruction.	160

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		release.		
Co-delivery & Combination Therapy	MTX/PEITC co-loaded nanoparticles (DD NPHG)	Inhibits inflammatory signaling (TNF-α, IL-6, IL-17) and induces apoptosis in FLS; concurrently modulates MLS function.	Achieves combined anti-inflammatory and anti-invasive effects, improving the synovial microenvironment.	166
Signaling Pathway Intervention & Apoptosis Induction	Ultra-small Au nanoclusters; BSA-MTX-CyI nanoplatform	Regulates macrophage M1→M2 polarization; activates ROS-mediated apoptotic pathways in FLS.	Synergistically suppresses synovial inflammation and tissue destruction.	167, 168
Local Delivery & Immunomodulation	Hyaluronic acid-based soluble microneedle nanoplatform	Simultaneously targets FLS and MLS to inhibit the expression of pro-inflammatory factors.	Reprograms the synovial immune microenvironment for highly efficient localized treatment.	169

5. Conclusions and Perspectives

This review underscores that effective nanotherapeutic intervention in rheumatoid arthritis is not merely about enhancing targeting efficiency but instead requires an integrated, design-aware framework that reconciles cellular plasticity, functional duality, spatiotemporal dynamics, and translational feasibility. The overlapping phenotypes of FLS and MLS, their context-dependent roles in inflammation and repair,

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and the distinct temporal requirements of cytotoxic versus immunomodulatory interventions collectively impose stringent constraints on nanoplatform design. Moreover, concerns regarding long-term biosafety, stimulus controllability, and manufacturing scalability further necessitate a shift from proof-of-concept complexity toward clinically grounded simplicity. These considerations collectively redefine the key design principles for next-generation RA nanotherapies and set the stage for future research directions.

FLS and MLS constitute the core cellular drivers of RA pathogenesis, making them prime targets for next-generation nanotherapeutics. Future research is expected to shift from "passive drug delivery" toward active modulation of disease progression, and from "single-target" strategies to multidimensional, synergistic, and personalized interventions, achieving higher targeting precision, intelligent responsiveness, and multifunctional synergy.

5.1 Technical Progress

5.1.1 Precision Targeting and Subpopulation Profiling

Single-cell multi-omics studies have revealed profound heterogeneity within RA synovial cells. THY1 (CD90)–positive, HLA class II DR alpha chain–high (HLA-DRA^high) fibroblasts are primary sources of IL-6, whereas pro-inflammatory monocytes dominate IL-1βproduction, both contributing critically to the RA inflammatory network[170]. Subpopulation analysis further distinguishes fibroblast activation protein alpha–positive (FAPα$^+$), THY1$^+$ immuno-effector fibroblasts, which drive inflammation, from FAPα$^+$ THY1$^-$ destructive fibroblasts mediating bone and cartilage erosion[171]. Synovial lining and sublining fibroblasts also differ in molecular signatures (PDPN, PRG4, THY1, FAP, CD34, CD90) and functional properties[172]. Future nanotherapeutic design should integrate single-cell transcriptomic, proteomic, and epigenomic data, combined with synovial microenvironment cues and cell-surface markers, to achieve subpopulation-specific, high-selectivity drug delivery.

5.1.2 Smart Stimuli-Responsive Nanoplatforms

From a technical perspective, RA synovial microenvironments are characterized by low pH, elevated ROS, overexpressed enzymes MMPs, and hypoxia. Endogenously

responsive nanocarriers that sense these pathological cues can trigger precise, on-demand drug release, maximizing local efficacy while minimizing systemic exposure[173-175]. Beyond single-modality interventions, multifunctional platforms capable of co-delivering small molecules, nucleic acids (siRNA/miRNA), and immunomodulators allow synergistic modulation of inflammation, FLS apoptosis, immune remodeling, and tissue protection, overcoming limitations of mono-therapies in targeting, timing, and dosage[176, 177].

5.1.3 Immunomodulation and Tolerance Induction

At the level of functional integration, nanotechnology offers strategies to restore immune homeostasis, including nanovaccines that deliver autoantigens with immunoregulatory cues and targeted induction of tolerogenic dendritic cells (tolDCs), thereby balancing the Th1/Th2 and Th17/Treg axes[178, 179]. These approaches aim to correct RA autoimmunity at its root, inducing antigen-specific regulatory T cells or tolerance-promoting microenvironments, potentially achieving long-term remission or a functional cure [180].

5.1.4 Technology-Driven Personalized Therapy

Advances in single-cell and spatial multi-omics, together with artificial intelligence/machine learning, enable high-resolution, multidimensional mapping of RA synovial tissue [181-183]. This approach can resolve cellular hierarchies, spatial microenvironments, and intercellular networks, guide molecular signature-based patient stratification, and inform personalized nanotherapeutic design. Importantly, this paradigm has gained clinical relevance in biopsy-driven precision studies. The PEAC study first demonstrated that synovial molecular signatures are associated with csDMARD responsiveness and radiographic progression in early RA[184]. More recently, the STRAP trial extended transcriptomic stratification to biologic therapies, showing that baseline synovial RNA sequencing, combined with machine learning, can predict differential responses to agents such as etanercept, tocilizumab, and rituximab, with independent cohort validation [185]. However, translating such precision frameworks into nanotherapeutic development remains largely preclinical. In the long term, integration of multi-omics analytics with rational nanomaterial engineering may facilitate

biomarker-guided therapeutic optimization and adaptive treatment strategies, ultimately contributing to more individualized and clinically implementable RA management.

5.2 Key Barriers in Clinical Translation

Despite these technical advances, several challenges impede clinical translation of RA nanotherapies:

5.2.1 Biosafety and long-term biological consequences

Biosafety remains a critical bottleneck. Certain inorganic nanomaterials (e.g., layered double hydroxides, metal-based nanoparticles) exhibit limited biodegradability and may persist in joints, potentially triggering immune reactions, foreign-body responses, chronic inflammation, or fibrosis[173, 186-188]. Material composition, physicochemical properties, administration routes, and dosing regimens profoundly influence systemic toxicity and local tissue responses[189, 190]. Comprehensive evaluation of *in vivo* metabolism, long-term retention, and immunological safety is essential for clinical translation.

5.2.2 Limitations of Stimulus-Responsive Systems

Stimulus-responsive systems offer attractive on-demand release capabilities but face substantial practical limitations[112]. Precise control over physicochemical responsiveness remains challenging. Responses to pH, temperature, or redox conditions can be unstable, while exogenous stimuli introduce further constraints. Ultraviolet irradiation poses risks of DNA damage and carcinogenesis, near-infrared exposure may cause thermal injury[191], and ultrasound signals are strongly attenuated by bone, limiting efficacy within joint cavities. Variability in stimulation parameters such as intensity, duration, and penetration depth further compromises delivery accuracy and reproducibility[192-194]. Stimulus-trigger mechanisms must be better aligned with the pathological features of the RA microenvironment. Equally important are improvements in controllability, safety, and material simplicity.

5.2.3 Translational bottlenecks from bench to bedside

To date, most stimulus-responsive nanoplatforms remain confined to preclinical

animal models. Pronounced physiological and pathological differences between animal models and human RA introduce significant uncertainty in predicting clinical efficacy[195]. Furthermore, many studies lack comprehensive toxicological profiling and long-term biodistribution analyses. Equally important, the structural and functional complexity of many nanoplatforms presents formidable challenges for scalable manufacturing, quality control, and regulatory approval[196]. Multifunctional platforms often involve elaborate fabrication, hindering large-scale production and batch-to-batch consistency [197]. In this regard, nanoplatforms with simpler architectures, controllable synthesis, and intrinsic biodegradability may hold greater promise for clinical translation[198].

5.2.4 Tension between personalization and scalability

RA is highly heterogeneous, leading to variable therapeutic responses. Personalized nanotherapeutic strategies guided by synovial molecular profiling potentially informed by single-cell sequencing represent an important future direction [133, 199]. However, such precision approaches often require patient-specific target selection, adaptive dosing strategies, or customized formulation designs, which increase production complexity and cost. The need for multiple tailored formulations challenges standardized manufacturing workflows, regulatory evaluation, and batch-to-batch reproducibility. Therefore, balancing individualization with manufacturability represents a central challenge in advancing nanomedicine for RA.

Together, these barriers make one thing clear: RA nanotherapy must move from targeting-centric design to a framework that embeds biosafety, controllability, scalability, and heterogeneity from the start.

5.3 Future Directions and Roadmap

To overcome the aforementioned translational barriers, next-generation RA nanotherapeutics are moving toward precision, smart, and multidimensional nanoplatforms. Such nanoplatforms should be capable of: (i) selective targeting of pathogenic FLS and MLS subpopulations; (ii) environment-responsive, spatiotemporally controlled drug release; (iii) synergistic integration of anti-

inflammatory, apoptotic, and immunomodulatory cues; and (iv) patient-specific personalization guided by advanced multi-omics analytics. These strategies collectively promise to redefine RA treatment paradigms, shifting from symptom suppression toward coordinated reprogramming of the FLS–MLS pathological unit, and thereby achieving active disease reprogramming and immune homeostasis restoration.

Author contributions

W.L. and M.H. participated in conceptualization, investigation, data curation, visualization, and writing – original draft; Q.C., Y.T., and Y.G. contributed to data curation and software; H.Z., Z.Y., and R.D.R. critically revised the manuscript. Y. T. and L.M. contributed to supervision, project administration, funding acquisition, and writing – review & editing. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability Statement

No new data were generated or analysed in this study. Data sharing does not apply to this article.