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Advanced application of stimuli-responsive drug delivery system for inflammatory arthritis treatment

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ABSTRACT

Inflammatory arthritis is a major cause of disability in the elderly. This condition causes joint pain, loss of function, and deterioration of quality of life, mainly due to osteoarthritis (OA) and rheumatoid arthritis (RA). Currently, available treatment options for inflammatory arthritis include anti-inflammatory medications administered via oral, topical, or intra-articular routes, surgery, and physical rehabilitation. Novel alternative approaches to managing inflammatory arthritis, so far, remain the grand challenge owing to catastrophic financial burden and insignificant therapeutic benefit. In the view of non-targeted systemic cytotoxicity and limited bioavailability of drug therapies, a major concern is to establish stimuli-responsive drug delivery systems using nanomaterials with on-off switching potential for biomedical applications. This review summarizes the advanced applications of triggerable nanomaterials dependent on various internal stimuli (including reduction-oxidation (redox), pH, and enzymes) and external stimuli (including temperature, ultrasound (US), magnetic, photo, voltage, and mechanical friction). The review also explores the progress and challenges with the use of stimuli-responsive nanomaterials to manage inflammatory arthritis based on pathological changes, including cartilage

Abbreviations: AIA, adjuvant-induced arthritis; ACLT, anterior cruciate ligament transection; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AMF, alternating magnetic field; APCs, antigen-presenting cells; BBR, berberine; CAT, catalase; CaP, calcium phosphate; CD44, cluster of differentiation 44; CEL, tripterine; CEL-PRNPs, RGD-modified PLGA enzyme-responsive nanoparticles loaded with tripterine; CIA, collagen-induced arthritis; CTSK, cathepsin K; DCF, diclofenac; Dex/Oxi-α CDNPs, 4-phenylborate-cyclodextrin biomaterial loaded with dexamethasone; DEX-P, dexamethasone sodium phosphate; DMARDs, disease-modifying anti-rheumatic drugs; DMM, destabilization of medial meniscus; ECM, extracellular matrix; ELP, elastin-like peptide; ERK1/2, extracellular signal-regulated kinase 1/2; FLSS, fibroblast synovial cells; fMRI, focusing magnetic resonance imaging; GPX, glutathione peroxidase; GSH, glutathione; HA, hyaluronic acid; HIFU, high intensity focused ultrasound; HM, hollow microsphere; IBU, ibuprofen; IGF-1, insulin-like growth factor-1; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; KAFAK, KAFAKLAARLYRKALARQLGVAA; K/BxN, the T cell receptor transgene KRN and the MHC class II molecule; KGN, kartogenin; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MFGCN, methotrexate-loaded folate-conjugated glycol chitosan nanoparticles; MHC, major histocompatibility complex; MMPs, matrix metalloproteinases; MNPs, multifunctional nanoparticles; MOF, metal-organic framework; MP-HANPs, mineralized nanoparticles; MPEG-PPF, methoxy polyethylene glycol-polypropylene fumarate; MRI, magnetic resonance imaging; MTX, methotrexate; NADPH, nicotinamide adenine dinucleotide phosphate; NFATc1, nuclear factor of activated T cell cytoplasmic 1; NGPEGSS, nanoparticles with degradable disulfide crosslinks; NIR, near-infrared; NO, nitric oxide; NP, nanoparticle; NP-gel, nanoparticle-hydrogel hybrid system; Nrf2, nuclear factor erythroid 2-related factor 2; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; PCA, protocatechuic acid; PDT, photodynamic therapy; PEG-PLGA-Au, polyethylene-glycol polylactic-glycolic acid gold-containing nanoparticles; PEVS, platelet-derived extracellular vesicles; P-HA, polyethylene glycol hyaluronic acid; PLCG1, phospholipase C gamma 1; PLGA, polylactic-glycolic acid; PON1, paraoxonase-1; PTH, parathyroid hormone; PTT, photothermal therapy; Q, a tripeptide sequence QAW; PAMAM, poly (Ninylisobutyramide); PDEPT, pre-enzyme drug therapy; PEOx-PPOy-PEOz, poly (ethylene oxide)-*block*-poly (Oxypropylene)-*block*-poly (ethylene oxide); PICsomes, polyion complex vesicles; PMEOMA, poly [2-(2-methoxyethoxy) ethylmethacrylate]; PNC, bisphosphonate-modified nanocellulose; PNIPAM, poly (*N*-isopropyl acrylamide); POxs, poly (2-oxazoline); PPS, polyphenylene sulfide; RA, rheumatoid arthritis; RANKL, nuclear factor-kappa B ligand; Redox, reduction-oxidation; RFA, radiofrequency thermal ablation; RGD, arginine-glycine-aspartic acid; RMTQ, RGD-MMP-TAT-QAW peptide; ROS, reactive oxygen species; SBC, sodium bicarbonate; SOD, superoxide dismutase; SPION, superparamagnetic iron oxide nanoparticles; T, cell-penetrating peptide; TA, triamcinolone acetonide; TAT, transcription-transactivating; TATQ, TAT-QAW; TG-18, triglycerol monostearate; T cell, thymus cell; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor; TolDex, tolerogenic dendritic cell-derived exosomes; TR1, type 1 regulatory; US, ultrasound; VEGF, vascular endothelial growth factor; β-TCP, β-tricalcium phosphate.

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degeneration, synovitis, and subchondral bone destruction. Exposure to appropriate stimuli induced by such histopathological alterations can trigger the release of therapeutic medications, imperative in the joint-targeted treatment of inflammatory arthritis.

1. Introduction

Inflammatory arthritis is a chronic disease, characterized by pain in the joint, severely restricting the patient's activities of daily living. If not timely treated, related inflammatory arthritis complications can cause serious loss of joint function [1]. Currently, the incidence of arthritis has increasingly shown a younger trend in obese people, athletes, manual workers with joint injuries, and the middle-aged and elderly population [2]. We effortlessly know that inflammatory arthritis is used to illustrate a group of diseases triggered by an overactive immune system, including more than 150 diseases such as rheumatoid arthritis (RA), lupus arthritis, gout, and so on [3]. While osteoarthritis (OA) is generally classified as non-inflammatory arthritis, recent pieces of evidence suggest a more sophisticated inflammatory OA with the release of inflammatory mediators from cartilage, bone, and synovium, which may also present with inflammatory characteristics such as pannus synovitis, although much milder than RA [4]. Furthermore, it's becoming increasingly clear that inflammatory response and cartilage destruction in OA are intertwined and influenced by each other. Therefore, inflammatory arthritis can include not only RA characterized by synovial hyperplasia and progressive joint destruction but also inflammatory OA represented by cartilage loss and progressive joint degeneration [5,6]. Overall, both forms of arthritis are complex processes driven by multiple inflammatory and metabolic factors. For instance, the risk factors for inflammatory OA include aging, obesity, joint trauma, repetitive activity, etc., whereas the risk factors for RA include genetic, immune, and environmental factors, among others [7,8]. In most cases, the two forms of arthritis share corporate disease features, including monocyte infiltration, inflammation, synovial swelling, vascular pimple formation, joint stiffness, and articular cartilage destruction [9]. However, RA is specific to smaller joints, especially hands and wrists, whereas inflammatory OA is specific to both large and small joints, inheriting the characteristics of classic OA. The hip and knee are the two most usual large joints, while metatarsophalangeal and interphalangeal joints of the toe are the most usual small joints [10].

Although treatment options for arthritis are aimed at reducing pain and disease activity and preventing inflammation and destructive processes, this disease remains incurable [11]. Conventionally, anti-arthritis treatment approaches are divided into drug therapy and non-drug therapy. According to the routes of administration, the former encompasses oral administration, injection, local topical use, etc. [12]; while the latter includes physiotherapy, replacement therapy, and surgical therapy [1]. Among them, we have to mention immunotherapy which is burgeoning and has a broad prospect [13]. This approach aims to treat arthritis by suppressing the immune system and driving effective immune tolerance. Usually, it can be combined with nanomaterials to cure arthritis in two ways: 1. Deliver auto-antigen to antigen-presenting cells (APCs) via nanoparticles (NPs) and induct autoimmune tolerance; 2. Using *N*P-based artificial APCs fabricated from peptide-major histocompatibility complex (MHC) molecules to trigger the production and proliferation of antigen-specific type 1 regulatory (TR1)-like thymus (T) cells directly [14]. But for all that, the current research on the dynamic process of immunosuppressive nanomaterials *in vivo* and their interaction with immune cells are not precise and elaborate enough, and the safety still demands to be further tested. When it comes to classical drug therapy, at present, commonly used are non-steroidal anti-inflammatory drugs (NSAIDs) for controlling pain and inflammation, glucocorticoids for blocking long-term joint erosion, traditional disease-modifying anti--rheumatic drugs (DMARDs) for treating diseases, and biological response regulators (biological agents) for selectively restraining specific molecules of the immune system [5]. Their efficacy, however, is unsatisfactory due to inferior water solubility, low cell permeability, adverse pharmacokinetics, and *in vivo* distribution. Moreover, uncontrolled drug release, earlier degradation before reaching target sites, adverse side effects and other defects, and traditional mode of administration remarkably confine the bioavailability of drugs [15]. Although nano-drug delivery systems have been developed, the existing nano-targeted drug delivery systems have drawbacks, including poor flexibility, inferior nanometer characteristics, unsatisfactory cycle time, low targeting efficiency, terrible penetration, uncontrolled drug release, among others. Therefore, a novel drug delivery system is needed urgently to resolve the existing issues [16]. An ideal drug delivery system would be able to cross biological barriers, release, at the appropriate time and site of action, active drugs at the required concentration. In addition, it is more desirable if natural derivatives with exquisite biocompatibility can be utilized for drug delivery at the cellular or molecular level, just like the recent breakthrough in arthritis treatment, so as to ensure the security of drug delivery materials. For example, platelet-derived extracellular vesicles (PEVS) loaded with berberine (BBR) for the treatment of RA [17] and reactive oxygen species (ROS)-responsive tolerogenic dendritic cell-derived exosomes (TolDex) [18].

In this view, stimuli-responsive drug delivery carriers that ensure highly specific and sensitive drug delivery, are emerging. Stimuli-responsive nano-carriers are structured into core (hydrophobic or hydrophilic region) containing therapeutic hydrophobic or hydrophilic drugs and hydrophobic-drugs-loaded shell consisting of amphiphilic stimulus-responsive polymers which are sensitive to miscellaneous endogenous and exogenous stimuli [15]. Stimuli-responsive drug delivery carriers are induced by various internal and external stimuli by an organism via different disintegration mechanisms (including, specific protonation, hydrolytic cleavage, molecular/supramolecular conformation changes, etc.). As such, the drug release is regulated to ensure sufficient amounts in the target lesion [19]. The conveyance can be assembled in different architecture and applied to trigger accurate and timely drug release, ensuring great flexibility of stimuli-responsive material systems. Eventually, this would improve the therapeutic efficacy of arthritis [20].

The key to developing irritant nano-carrier therapy is to have an in-depth understanding of physical and chemical diversities between dysfunctional and normal cells. This allows for the location of a suitable specific release target to unload the drug to counteract abnormal molecular changes in the injury process. There are two major categories of responsive nanomaterials for treating diseases based on the source of responsive stimuli (endogenous stimuli and exogenous stimuli). Endogenous stimuli in organisms are induced by enzymes, ROS, pH, glutathione (GSH), etc., whereas exogenous stimuli are induced by temperature, photo, magnetic field, and ultrasound (US), among others [21]. Of note, various pathological changes, including cartilage degeneration, inflammatory arthritis-related synovitis, and subchondral bone restoration, are predominantly induced by changes in factors (such as abnormal levels of degradative enzymes [22], the disorder of intracellular reduction-oxidation (redox) system [23], and increased acidic environment [24,25]). That is to say, these abnormal changes can act as specific stimuli to drive the release of therapeutic medications, aimed at joint-targeted management of inflammatory arthritis. This review further introduces the application of a stimuli-responsive drug delivery system targeted at the lesion site to manage inflammatory arthritis.

2. Histopathological alterations and related cellular and molecular events in multi-sites of the joint during inflammatory arthritis

Inflammatory arthritis is a complex pathophysiological process that occurs in several forms according to the assumed starting point or concentration point of the disease progression. Among them, OA predominantly shows characteristics of a degenerative cartilage lesion, while immune-mediated RA is characterized by preferential synovial hyperplasia in progressive joint destruction [26]. The whole joint comprises two or more bones attached by articular cartilage to reduce friction and is surrounded by fibrous connective and synovial tissues. Recent evidence shows that these diseases contribute to multi-site injury of joint tissues, which progressively causes cartilage degeneration, synovial inflammation, and subchondral osteosclerosis [27]. Therefore, exploring the mechanism underlying pathological alterations in articular compartments associated with the occurrence and progression of OA and RA is imperative (Table 1). There is evidence that articular cartilage degeneration, synovitis and subchondral bone remodeling are caused by abnormal production of degradable enzymes, cellular redox imbalance, and changes in microenvironment pH in injured joints (Fig. 1). These pathological changes provide novel insights into the treatment of inflammatory arthritis.

2.1. Pathological changes of enzymes in multi-sites of the joint during inflammatory arthritis

Inflammatory arthritis induces excessive production of degradative enzymes, which are thought to be partially attributed to the response to downstream pathways triggered by various factors, including ROS production and acid microenvironment [28,29]. Aberrant expression of proteolytic enzymes in the articular compartment degrades the extracellular matrix (ECM) and alters the integrity of cartilage. Two categories of aberrantly produced enzymes in the arthritic joint cavity have been described according to their role in disease progression, including degradative enzymes and activating enzymes [30]. Digestion of ECM components by degradative enzymes causes hyaline cartilage matrix degradation and subsequent loss of joint lubrication and insufficient mechanical transduction while activating enzymes promote proteolysis by augmenting the activity of degradative enzymes in articular cartilage [30].

Matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) are the typical degradative enzymes in inflammatory arthritis. MMP-3 synthesis is significantly increased in synovial tissue at the edge of hyaline cartilage in the pathological joint [31]. There is evidence of the direct association between the increased level of MMP-3 expression and the infiltration of inflammatory cells into the synovium [32]. Similarly, high expression of MMP-1, -2, -9, -13 in serum and synovial fluid of OA patients has been shown to coordinate the degradation of ECM proteins in articular cartilage [5,28]. Moreover, reports indicate that alteration of the expression pattern of serine proteases, cysteine proteases, tissue inhibitor of metalloproteinase-1 and -2 (TIMP-1, 2) [33] in the synovial cavity collectively induces a series of pathological events, including inflammation and hyperplasia of synovium, and the destruction and degeneration of cartilage [34,35].

Table 1
Pathological changes in multi-sites of the joint during inflammatory arthritis.

Stimuli	Articular compartment	Cellular origins	Pathological changes	Refs
MMP-1, -3, −13	Cartilage	Chondrocyte	Degradation of collagen fibers or proteoglycans in articular cartilage or subchondral bone	[28, 146–148]
	Synovium	Fibroblastoid synovial cell		[28,34]
	Subchondral bone	Osteoblast		[149]
MMP-14, −16	Synovium	Fibroblastoid synovial cell, macrophage		[53]
	Subchondral bone	Osteoclast		[150]
MMP-2	Synovium	Fibroblastoid synovial cell		[28]
MMP-9	Synovial cavity	Fibroblastoid synovial cell, macrophage, neutrophil		[151]
	Subchondral bone	Osteoblast, osteoclast		[152]
Cathepsin	Synovium	Fibroblastoid synovial cell, macrophage	Degradation of cartilage ECM, enhance bone resorption and destruction near eroding cartilage	[153,154]
	Subchondral bone	Osteoclast		[155]
TIMP-2	Synovial cavity	Fibroblastoid synovial cell, macrophage, neutrophil	Regulation of the catabolism of ECM	[156]
ADAMTS	Cartilage	Chondrocyte	Degradation of aggrecan in cartilage matrix	[31,148, 157,158]
ROS	Cartilage	Chondrocyte	Induction of protein, DNA and lipid oxidative damage, promotion of chondrocyte senescence and maturation associated with cartilage destruction and inflammation, unbalance of subchondral bone remodeling	[29]
	Synovium	Fibroblastoid synovial cell, macrophage, neutrophil		
	Subchondral bone	Osteoblast, osteoclast		
Lipid peroxidation products	Synovial cavity	Fibroblastoid synovial cell, macrophage, neutrophil	Involvement in cartilage degeneration and synovitis	[159,160]
SOD, CAT, GPX, PON1 and other antioxidant enzymes	Cartilage	Chondrocyte	Imbalance of redox system associated with cartilage destruction and inflammation	[40]
Hydrogen ion	Cartilage	Chondrocyte	Acidification of the ECM	[44–46]
	Synovium	Inflammatory cell, fibroblastoid synovial cell, macrophage, neutrophil		[42]
	Subchondral bone	Osteoblast, osteoclast		[49,91]

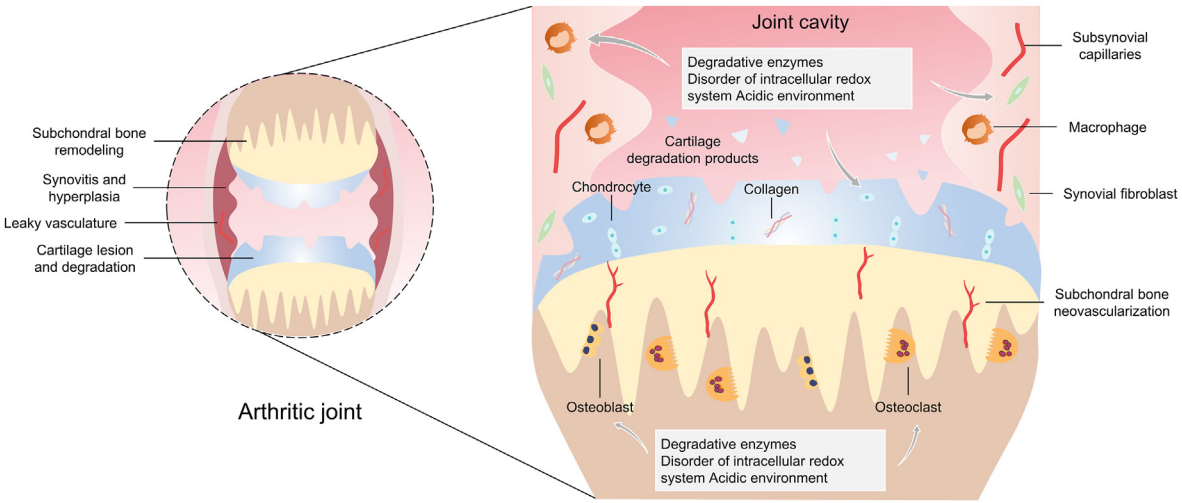

Fig. 1. Histopathological alterations and related cellular and molecular events in multi-sites of the joint during inflammatory arthritis. Pathological changes in arthritic tissue levels: articular cartilage injury, synovial inflammation, and hyperplasia, subchondral bone remodeling; cellular and molecular level: abnormal activity and content of degrading enzymes; imbalance of intracellular redox system; extracellular microenvironment acidification.

Mounting evidence indicates that degradative enzymes in subchondral bone also are abnormally expressed in inflammatory arthritis [32,36]. In OA and RA processes, receptor activator of nuclear factor-kappa B ligand (RANKL) and vascular endothelial growth factor (VEGF) secreted by osteoblasts trigger the chemotaxis and differentiation of osteoclasts by activating the extracellular signal-regulated kinase 1/2 (ERK1/2) mitogen-activated protein kinase (MAPK) signaling pathway [12,37]. Subsequent activation of osteoclasts-secreted MMPs and cathepsin K (CTSK) promote the resorption and destruction of the bone near the eroding cartilage [38]. Meanwhile, abnormal mechanical strain induces the alteration of the metabolism of osteoblasts, upregulating the expression of degradable MMP-3, -9, -13 [27]. Taken together, the abundance and activity of these proteolytic enzymes provide the platform to identify the unique therapeutic targets for inflammatory arthritis treatment. Currently, the abnormality of enzymes in the articular cavity is another promising activation point, in which responsive materials can be disintegrated to promote the pharmaceutical effect of therapeutic drugs for inflammatory arthritis.

2.2. Pathological changes of redox system in multi-sites of the joint during inflammatory arthritis

Disorder of intracellular redox system is ascribed to the destruction of joint homeostasis in arthritis patients [39]. Accumulating evidence indicates that DNA damage in chondrocytes in patients with OA is induced by ROS generation and oxidative stress [29,40]. Additionally, studies have demonstrated a strong positive correlation between ROS and RA severity [41]. Intriguingly, elevated lipid peroxide levels in serum and synovial fluid caused by an imbalance of the antioxidant system accelerate disease progression in OA and RA [39]. Abnormal ROS production, in most cases, is caused by high levels of inflammatory cytokines (including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and reduced levels of antioxidant nuclear factor erythroid 2-related factor 2 (Nrf2) and catalytic enzyme (including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and paraoxonase-1(PON1)) [40]. Elevated oxidative stress weakens the regulation of the GSH antioxidant system, causing a disorder of the intracellular redox system [39]. Abnormal ROS production by chondrocytes is a direct signal intermediary resulting in oxidative damage of proteins, DNA, and lipids, which consequently promotes chondrocyte senescence and apoptosis and promotes matrix degradation by altering the synthesis of collagen and protein [29]. Under inflammatory conditions, excessive ROS production by active organelles (including mitochondria, peroxisome, and endoplasmic reticulum) in neutrophils and macrophages alters the structure and function of intracavity biomolecules. Accordingly, this aggravates synovial inflammation and induces cellular apoptosis in the synovium [42].

Oxidative stress is also a crucial player in subchondral bone deterioration in OA. However, research on redox signaling in subchondral bone remodeling is relatively limited. Recent evidence indicates that RANKL-induced ROS stimulate the phospholipase C gamma 1 (PLCG1) to mediate the activation of nuclear factor of activated thymus cell (T cell) cytoplasmic 1 (NFATc1), promoting osteoclast formation [43]. Meanwhile, ROS-triggered shifts in the phenotypic expression of osteoblasts influence the production of pro-inflammatory mediators. In addition, a high concentration of nitric oxide (NO) causes the redox imbalance which consequently suppresses the maturation and activity of osteoblasts [39]. Considering the close association between imbalanced redox homeostasis caused by abnormal ROS levels and inflammatory arthritis, ROS can be employed to trigger the responsive materials for inflammatory arthritis treatment.

2.3. Pathological changes of pH in multi-sites of the joint during inflammatory arthritis

Aside from cellular phenotypic alteration, inflammatory arthritis also alters the composition and physicochemical properties of ECM, including acidity and alkalinity, permeability, mechanical compliance, and compression resistance. The normal synovial fluid and arthritic synovial fluid are characterized by a pH range of 7.4–7.8 and 6.6–7.2, respectively [42]. Scholars have hypothesized that acidosis characteristic ($pH < 7.35$) is related to the activity of proton transporter and lactate dehydrogenase (LDH) in chondrocytes and high energy and oxygen consumption of infiltrating inflammatory cells. In normal conditions, cells are dependent on H^+ equivalent transporters and sodium-driven H^+ pumps to discharge excess H^+ from intracellular or organelles. Besides, anion exchangers mediate the exchange of Cl^- and HCO_3^-, ensuring synergistic regulation of intracellular pH within the scope of the strict [44–46]. There are also substances in the adjacent microenvironment that buffer the appropriate H^+ concentration excreted by the cells to maintain microenvironmental homeostasis [47]. However, OA and RA conditions effectuate a shift in the metabiotic pattern in synovial inflammatory cells from aerobic to anaerobic processes. This promotes oxygen-independent glycolysis and lactic acid production and lowers the pH in the articular cavity [42]. Furthermore, due to non-vascular characterization, cartilage matrix

hypoxia aggravates the acidosis of the cartilage microenvironment. Moreover, mitochondrial-dependent apoptosis contributes to changes in pH, characterized by mitochondrial alkalization and cytoplasmic acidification [45].

Intriguingly, different from chondrocytes and synovial inflammatory cells, polarized osteoclasts manifest the most prominent feature, that is, the formation of a plasma membrane complex containing a large number of "nail-like" vacuum proton pumps and acidification of the osteoclast-bone interface microenvironment [48]. Bone degradation is initiated by a sealed actin-rich area, separating the absorbing microenvironment from the general extracellular space. The entry of H^+ generated by carbonic anhydrase II, into the microenvironment is driven by proton pumps present on the folded membrane. Consequently, the pH of the microenvironment shifts to nearly 4.5, and the ultimate assembly of bone mineral components cause subchondral bone destruction [48].

Parathyroid hormone (PTH) and insulin-like growth factor-1 (IGF-1) also accelerate the acid efflux of osteoblasts, exacerbating the acidic state of the microenvironment [49]. Besides the low pH status in the diseased articular cavity, subcellular compartments in dysfunctional cells also are characterized by different acidic microenvironments. The pH range of early and late endosomes, lysosomes, and Golgi apparatus are 5.0–6.5, the pH of 4.5–5.0, and 6.0–6.7, respectively [50]. In summary, both pathologically microenvironmental acidosis and physiologically acidic subcellular compartments can be used to trigger the site-specific release of therapeutic medications, aimed at joint-targeted treatment of inflammatory arthritis.

3. Internal stimuli-responsive nano-drug delivery systems for inflammatory arthritis treatment

Current pharmaceutical therapeutics for arthritis include anti-inflammatory or analgesic medications (administered via oral, topical, or intra-articular routes), surgery, and physical rehabilitation [12]. However, the properties of these existing medications have several drawbacks, mainly related to severely reduced bioavailability and low efficacy of anti-arthritic agents, such as poor water solubility, low cell permeability, unfavorable pharmacokinetics, and random distribution *in vivo* and unregulated drug degradation before reaching the target sites [15]. Researchers have recently focused on small-sized nanomaterials with large specific surface areas and high loading efficiency. Attributing stimuli-responsive and targetable characteristics to nano-carriers along with their biocompatibility could cope with the requirements of improved efficacy and fewer side effects [15]. Considering the irritant factors in dysfunctional tissues, stimuli-responsive drug delivery systems based on nanomaterials release the anti-arthritic agents which hamper the aberrant cellular changes, thereby blocking the development of inflammatory arthritis. Therefore, the advanced use of responsive nanomaterials to manage inflammatory arthritis is reviewed below according to the source of responsive stimuli, including endogenous (enzyme, redox system, pH, etc.) (Fig. 2) (Table 2).

3.1. Enzyme-responsive nano-drug delivery systems for inflammatory arthritis treatment

The enzyme-responsive nano-drug delivery system has two components; (i) a nanomaterial scaffold containing the enzyme-sensitive portion that disintegrates following contact with enzymes; (ii) encapsulated therapeutic agents attached to the carrier by biodegradable (such as ester) bonds or conjugated via electrostatic interaction between the active ingredient and charged carrier or bounded to outer lipid membrane or lipid core [15]. Functional groups sensitive to aberrantly expressed enzymes in injured joints are introduced into nano-carriers. At the same time, therapeutic agents are released via multiple ways of carrier disintegration (including size shrinkage, surface charge switch, surface ligand activation, and chemical bond break) [16]. As such, it is possible to equip the enzyme-responsive nano-drug delivery system with multiple abilities, for instance, improved internal circulation stability, enhanced penetration into deep tissues, and specific site-dependent release. This would increase the bioavailability of drugs and reduce unfavorable side effects *in vivo* [16,51]. Compared to other endogenous stimuli, enzyme-responsive drug delivery materials have more irreplaceable benefits ascribed to excellent biometric ability and efficient catalytic performance. They can also be titrated and released based on to disease activity of the joints, that is, low disease activity will limit unnecessary drug release, prolonging the duration of therapeutic effect on inflammatory arthritis [52]. For instance, in the emerging concept of intra-articular drug repository of triglycerol monostearate (TG-18), hydrogel responsive materials are formally proposed based on enzyme characteristics.

A series of enzymes are expressed at varying degrees in the occurrence and progression of arthritis. Such enzymes include MMPs, ADAMTS, cysteine protease, and hyaluronidase, tuning the enzyme-

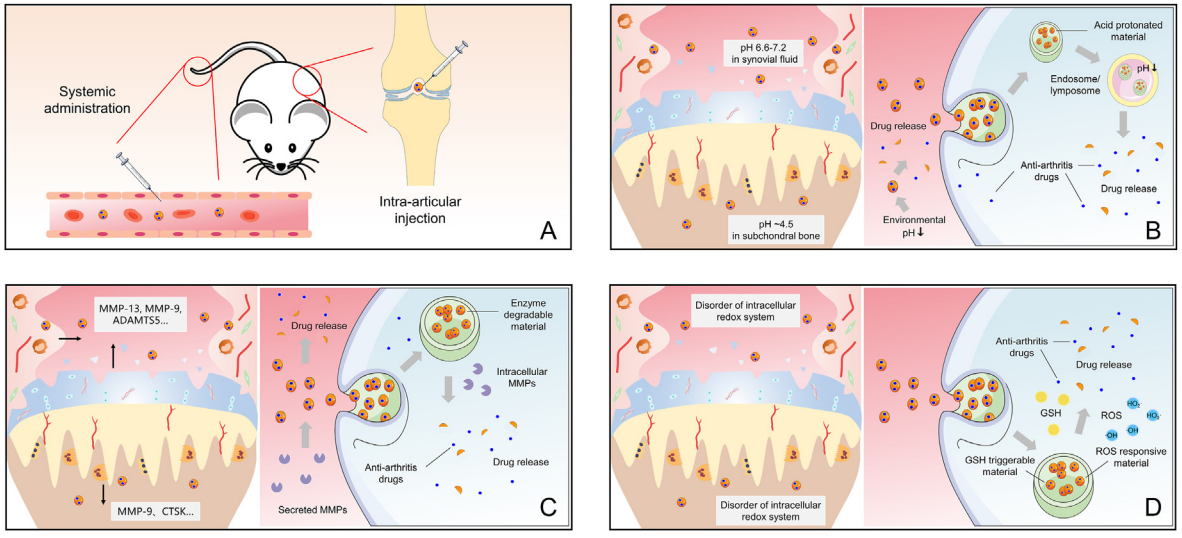

Fig. 2. The principle of endogenous stimuli-responsive materials releasing drugs. (A) Different ways of drug administration: systemic administration or intra-articular injection. (B) Extracellular drug release in acidic synovial fluid or acidic subchondral bone microenvironment from pH-responsive materials; Intracellular drug release in endosomes and lysosomes from pH-responsive materials. (C) Drug release from enzyme-responsive materials induced by extracellular and extracellular aberrant enzyme cleavage. (D) Redox-responsive material drug release, caused by abnormal signals resulting from an imbalance in the intracellular redox system.

Table 2
Multifunctional internal stimuli-responsive nano-drug delivery systems for treatment of inflammatory arthritis.

Internal stimuli	Material	Responsive shell	Bioactive agent	Articular compartments	Target cells	Effects	Models of inflammatory arthritis	Refs
MMP-2, -9	RMTQ	RMT (Cell-penetrating peptide, MMP-2/9 digestive peptide, Q targeting RGD)	Anti-inflammatory peptide (Q)	Synovium	Macrophage	Obviously inhibit TNF-α, IL-6, NO and ROS of inflammatory macrophages	RAW264.7 cells, rat model of AIA	[51]
MMP-2, -3, -9	TA-loaded TG-18 hydrogel	TG-18 hydrogel	TA	Synovium	Macrophage	Reduce TNF-α secretion and increase IL-10 secretion	Primary human synoviocytes and chondrocytes from healthy and RA donors, K/BxN mouse model of IA	[54]
MMPs (mainly MMP-2/9)	BMP-2 nano-capsules (n (BMP-2))	PMPC shells (MPC monomer and MMP cleavable peptide crosslinker)	BMP-2	Subchondral bone	Mesenchymal stem cell	Stimulate the migration of mesenchymal stem cells to initiate bone regeneration and improve the efficiency of bone repair *in vivo*	hUMSC, Sprague Dawley (SD) rats with a tibia fracture	[36]
Redox	KAFAK-loaded NGPEGSS	PEGylated pNIPAM NGPEGSS	KAFAK	Cartilage, Synovium	Chondrocyte, macrophage	Decrease the amount of IL-1β, TNF-α and IL-6	Primary bovine chondrocytes	[63]
	Dex/FA-Oxi-αCD NPs	FA-Oxi-αCD NPs(α-Cyclodextrin (α-CD), folic acid)	Dex	Synovium	Macrophage	Inhibit the expression of iRhom2, TNF-α, and BAFF in the joint	RAW264.7 cells, MH7A cell, CIA mice	[65]
	HM	A shell of PLGA and ethanol and an iron (II) salt ($FeCl_2$), and SBC	Anti-inflammatory drug (DEX-P)	Synovium	Macrophage	Relieve inflammation and reduce cartilage ECM loss	OA mice (intra-articular injection of monosodium iodoacetate through the infrapatellar ligament of the left knee)	[67]
	FOL-MTX&CAT-L	CAT liposomes conjugated with folic acid)	MTX	Synovium	Macrophage	Reduce the levels of serum pro-inflammatory cytokines TNF-α and IL-1β, alleviate the progression of inflammation	RAW264.7 cells, CIA mice	[66]
pH	MOF@HA@PCA	A pH-responsive MOFs system modified by HA	Anti-inflammatory PCA	Cartilage	Chondrocyte	Significantly down-regulate the indicators of iNOS, COX2 and ADAMTSs	Primary chondrocytes, rats underwent anterior cruciate ligament transection (ACLT) on the knee joints	[72]
	PLGA NPs with NH_4HCO_3 containing HA	PLGA NPs with NH_4HCO_3	HA	Cartilage	Chondrocyte	Induce biological changes such as moderation of inflammation, reduction of cytokine-induced enzyme production, anti-oxidant action, effects of cartilage synthesis, and direct analgesia by masking the joint nociceptors	Human chondrocyte cell line C28/I2, C57BL/6Jico mice operated with surgical destabilization of medial meniscus (DMM)	[73]
	MPEG-PPF-IBU polymeric drug conjugates	MPEG-PPF diblock copolymer	IBU	Synovium	Fibroblastoid synovial cell	Significantly reduce the level of prostaglandin E2 and play an anti-inflammatory effect	Rabbit synovial HIG-82 cells	[74]
	MFGCN	FGCN	MTX	Synovium	Macrophage	Lower arthritic signs, improve antioxidant response, and decrease pro-inflammatory cytokines	RAW264.7 cells, AIA rats	[75]
	MP-HANPs loaded with doxorubicin	MP-HANPs, P-HA, 5-cholanic acid, CaP	MTX	Synovium	Macrophage	Lower arthritic signs, improve antioxidant response, and decrease pro-inflammatory cytokines	Macrophages induced by monocyte from murine spleen and bone marrow, CIA mice	[76]
	PNC-β-TCP composite	β-TCP	PNC)	Subchondral bone	Osteoclast, osteoblast	Suppress osteoclast formation and pit formation, enhance osteoblast differentiation	Osteoclasts induced by RAW264.7 cells, human osteoblast-like cells (MG-63), mouse osteoblast-like cells (MC3T3-E1)	[77]

responsive drug delivery material to mediate the precise drug release in targeted sites [30,35,53]. To synthesize RGD-MMP-TAT-QAW peptide (RMTQ), Li et al. modified the anti-inflammatory tripeptide sequence QAW (Q) using cell-penetrating peptide (T), MMP-2/9 digestive peptide (M), and inflammation-targeting peptide (arginine-glycine-aspartic acid (RGD)) [51]. Compared to Q, the designed RMTQ exhibited stronger cytoplasmic transport capacity and a higher degradation rate of pro-inflammatory factors and showed a better response to MMP-2/9. Additionally, RMTQ successfully reduced paw volume, clinical arthritis index, and serum cytokines in adjuvant-induced arthritis (AIA) mouse models. Mechanically, MMP-2/9 mediated the cleavage of MMP-2/9 sensitive peptides from the inflamed synovium. Notably, the released TAT-QAW (TATQ) demonstrated higher intracellular delivery via transcription-transactivating (TAT) protein [51]. In addition to enzyme-sensitive peptides, small molecules requiring chemical modifications and are suitable for large-scale production also show satisfactory responses to MMPs. For arthritis treatment, Joshi et al. proposed the nanoparticle-hydrogel hybrid system (*NP*-gel) integrated with TG-18, a small hydrophilic and lipophilic molecule, to develop a carrier material responsive to MMP-12 in the inflammatory microenvironment of joints loaded with corticosteroid triamcinolone acetonide (TA) (Fig. 3I) [54]. An innovative complete mix of different biomaterials with TG-18 preserved the structural integrity and function of NP contained in hydrogel and offered engineering flexibility. This system demonstrated an outstanding capacity to regulate drug release kinetics and remote drug release "on-demand". The specific release mechanism was that Zn (II) ion of MMPs interacts with external water molecules and are deprotonated to form Zn (II)-bound hydroxides, functioning as nucleophiles to attack carboxyl esters in TG-18 and consequently cleaves ester bond, decomposes the hydrogel and effectuates TA release. Therapeutically, the TA-loaded TG-18 hydrogel decreased the severity of arthritis in the right hind paw of mice induced by intraperitoneal injection of the T cell receptor transgene KRN and the MHC class II molecule (K/BxN) serum as compared to control-treated with empty hydrogel or TA [54,55].

Current research on nano-drug delivery systems responsive to subchondral enzymes for the treatment of inflammatory arthritis is scanty. However, reports have demonstrated that osteoclasts and osteoblasts in the disordered subchondral bone microenvironment are characterized by patterns of aberrant enzyme expression, such as MMP-2, 9, 13 among others [38]. Qi et al. investigated the systemic administration of enzyme-responsive growth factor delivery systems by developing nano-capsules whose sensitivity to MMPs triggered specific degradation for bone repair [36]. It is possible to apply the same material shell and replace inner medications to restore abnormal remodeling of subchondral bone in arthritis and prevent subchondral bone deterioration. The development of novel responsive carrier platforms to optimize drug delivery performance, for example, enzyme-responsive drug delivery materials based on metal-organic framework (MOF) is on the rise among

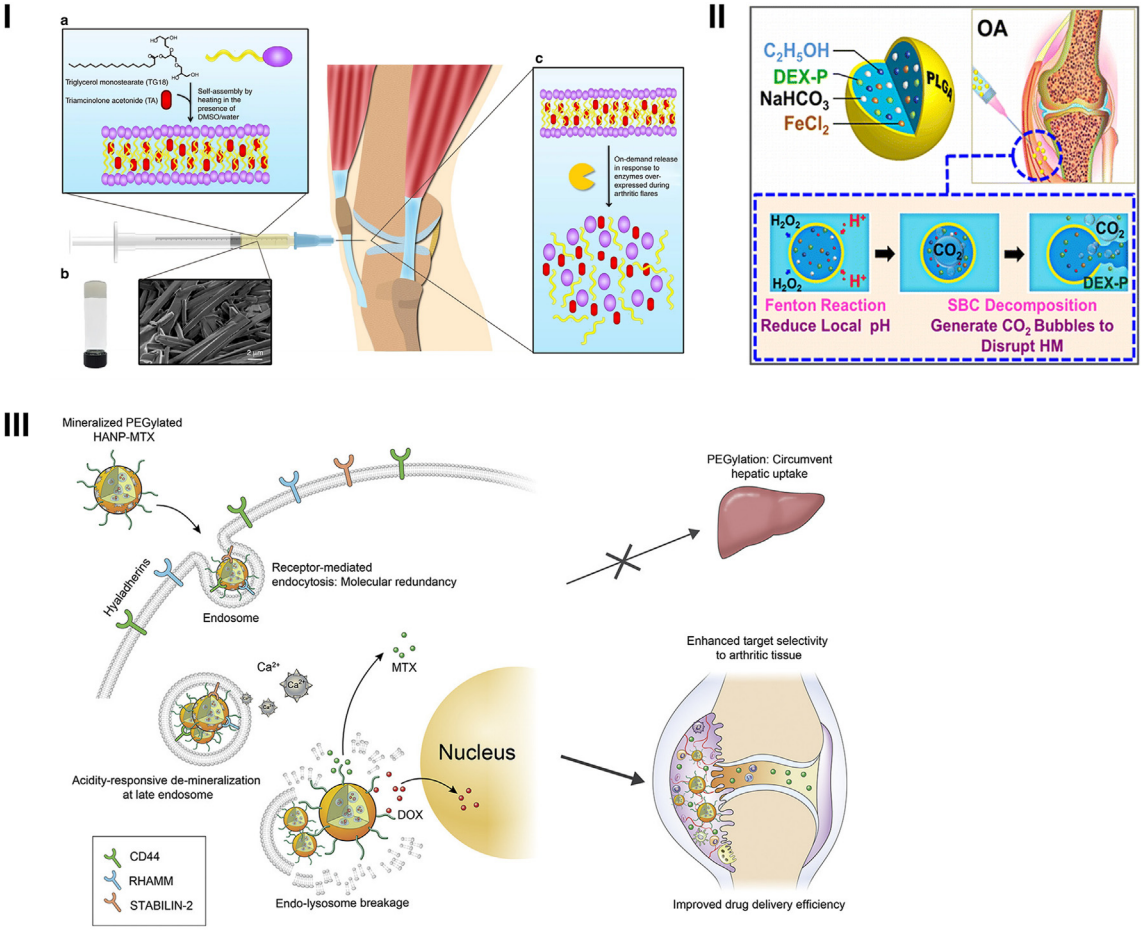

Fig. 3. The composite image shows the structure and the release mechanism of Internal stimuli-responsive materials: (I) The structure of the *NP*-hydrogel hybrid system developed by Josh et al. and the release mechanism of its response to MMP-12 (Reprinted from Ref. [54] with permission from nature publishing group). (II) The structural composition of ROS-responsive HMs designed by Ming-FanChung et al. and drug release mechanism of ROS-responsive joints in OA mice [Reprinted from Ref. [67] with permission from ACS Publications © 2015 American Chemical Society]. (III) (a) The release mechanism of pH-responsive mineral MP-HANPS developed by Alam et al. in response to pH in endosomes (Reprinted from Ref. [76] with permission from ELSEVIER).

researchers [56]. Such materials can be degraded via redox reaction between enzymes and corresponding substances, permitting drug release only at specific sites. However, the MOF carrier-based responsive materials are mainly applied for anti-cancer therapy [56].

Few stimuli-responsive drug delivery platforms with high-efficiency drug delivery performance and good application prospects have been successfully developed using miscellaneous methods. However, the application of these stimuli-responsive drug delivery systems is limited by many restrictions and technical impediments yet to be settled. For enzyme-responsive drug delivery systems, the understanding of quantitative changes in enzyme content at the lesion sites of the joint is poor, though they are elementary in regulating drug release and cell uptake *in vivo* [20]. Only by entirely understanding the mathematical changes of the enzymes in the lesion site can the drug release be extremely restrained and accurately mediated. The current concept of using enzymes to achieve the release of enzyme-responsive drug delivery system *in vitro* has been put forward, also known as pre-enzyme drug therapy (PDEPT) [57]. The therapy begins by injecting patients with a drug-polymer carrier containing an enzyme-sensitive polypeptide substrate that is directed to the disease site. Over time, the precursors accumulate in the target tissue, and only a low concentration of free substances is left in blood circulation, insufficient to react with the enzymes. Another NP containing an effect-type protease is presented solely to activate the precursor stored in the target tissue and mediate local drug release; however, this mechanism does not initiate the drug release in the systemic circulation, thereby minimizing nonspecific toxicity [57].

3.2. Redox-responsive nano-drug delivery systems for inflammatory arthritis treatment

Arthritis occurrence increases the level of ROS both in cells and microenvironment; therefore, a change of redox conditions can stimulate drug release [20]. According to the pathological mechanism, redox-responsive nanomaterials undergo degradation, structural changes, functional regulation, or physical and chemical properties conversion. These events ensure that therapeutic drugs are delivered and released to the lesion site [58]. Compared to other responsive nano-carriers, the redox-responsive material accurately mediates the release of drugs in various cell subcomponents (including cytoplasm, mitochondria, nucleus, etc.) and functions as a therapeutic agent. In particular, the redox-responsive material responds to the stimuli and simultaneously offers effective protection of cells from oxidative stress by eliminating the corresponding oxidative substances [42,59,60]. According to reports, the fracture mechanism of functional groups of redox-responsive materials occurs in two types: amphiphilic transition and bond fracture. For amphiphilic transition, the balanced amphiphilic properties of NPs are destroyed through transitioning from hydrophobic to hydrophilic, causing structural dissociation and subsequent cargo release of polyphenylene sulfide (PPS), hydrophobic monosulfides, monosilane-based or monotellurium polymers, etc. [16]. Bond-breaking is described as the complete fracture of functional bonds in response to redox substances (such as ROS or GSH), which destroy the carrier structure, comprising mainly Boron-containing ester material, Thioketal-containing materials, disulfide bond materials, and diselenide bond materials, etc. [61].

The development of NPs with degradable disulfide crosslinks (NGPEGSS) has enhanced the delivery of the anti-inflammatory peptide KAFAKLAARLYRKALARQLGVAA (KAFAK), to chondrocytes at inflammatory sites. Previous reports revealed a decrease in both the production of cytokine IL-6 in chondrocytes and the inflammatory level in the lesion site, demonstrating its potential as an intraarticular injectable nanocarrier for OA treatment [62,63]. However, there is a concern with the *in vivo* stability regarding the use of disulfide responsive materials because they react with cysteine present in the extracellular lumen, causing an early skin rash [64]. Elsewhere, Ni et al. designed a 4-phenylborate-cyclodextrin biomaterial loaded with dexamethasone (Dex/Oxi-α CDNPs) targeting synovial macrophages to treat RA. Significant accumulation of Dex/Oxi-α CDNPs was reported in inflammatory joints of mice with collagen-induced arthritis (CIA) and reduced joint swelling and cartilage destruction [65]. Despite the successful RA treatment, ROS sensitivity under different conditions is controlled by different ROS types, polymer structure, material form, and exposure time [41], so the biomaterial's sensitivity to ROS warrants further exploration.

Recently, researchers have developed an innovative, hyper-sensitive ROS-responsive drug release model, in which redox reaction generates a gas that destroys the shell and initiates drug release [41,66]. For example, Chung et al. established a super-sensitive ROS-responsive hollow microsphere (HM) carrier comprising ethanol, $FeCl_2$, sodium bicarbonate (SBC), etc. (Fig. 3II) [67]. The redox reaction between ethanol and H_2O_2 created an acidic environment which triggered the SBC to produce CO_2, destroying the material shell to release drugs. Injection of HM carrier loaded with anti-inflammatory drug dexamethasone sodium phosphate (DEX-P) into the joints of mice with OA demonstrated that ROS-responsive HMs group exhibited more efficient local anti-inflammatory activity in OA treatment than free DEX-P injection. These observations provided evidence that the carrier is a promising novel drug delivery system for arthritis [67]. Elsewhere, Chen et al. [1] designed a novel ROS-responsive liposome targeting folate receptors for RA treatment [66]. It utilized oxygen produced by the catalytic reaction between CAT and elevated intracellular H_2O_2 to promote the structural failure of liposomes and methotrexate (MTX) release. Subsequent MTX-mediated inhibition of M1-like macrophage polarization suppressed RA inflammation [66]. Given the redox imbalance in osteoclasts during arthritis, osteoclasts may be a potential target to repair the abnormal bone subchondral bone remodeling in the development of redox-responsive nanomaterials to manage arthritis [59].

However, for redox-responsive drug delivery systems, five issues must be considered. First, the susceptivity of materials relies on the fundamental chemical bonds, and the structure and hydrophilicity of polymers, which necessitates diverse formulations for various diseases. This presents higher requirements for personalized medicine [41]. Secondly, redox reaction materials should be biocompatible without triggering additional inflammatory responses, which may inadvertently act on ROS-sensitive materials [68]. Third, for optimal efficacy, the rate of drug release through solubility changes and bond breakage should be regulated at pathologically compatible rates. Fourth, a comprehensive analysis of the toxicity of redox-responsive nanomaterials *in vivo* is lacking, which is particularly nontrivial for their clinical application [69,70]. Finally, owing to low ROS levels produced by normal cell activity, materials must be designed to have the potential to distinguish between low ROS levels in normal cell activity and pathologically elevated ROS [68]. Taken together, it is undeniable that redox-responsive drug delivery systems are still attractive in pragmatic applications; therefore, the optimization of such materials can be explored from the aspects of materials science, medicine and biology.

3.3. pH-responsive nano-drug delivery systems for inflammatory arthritis treatment

During arthritis, lesions (such as cartilage degradation) give rise to a weakly acidic environment (pH up to 6.0). Such pH change could be designed as a releasing stimulus of responsive nanomaterial drug delivery systems to control drug delivery [71,72]. The pH-responsive delivery system: (i) improves the efficiency of drug delivery; (ii) regulates drug release rate and enhances cell uptake as required; (iii) has high drug load and reduces the number of dosing frequency [52]; (iv) adjusts pH range of response by changing the ratio of copolymers to achieve good stability at physiological sites (pH 7.4); (v) complete partial hydrolysis on-demand in a weak acid environment in affected joint and mediate further hydrolysis; (vi) release drugs at lower pH of intracellular space [20].

Currently, the main response mechanisms of pH-sensitive materials

include acid-sensitive bond breakage and protonation of chemical groups [16]. The former refers to the introduction of acid-sensitive bonds into the polymer structure as connectors between drugs and carriers. As such, the release of drug molecules is achieved by cracking the acid-sensitive bonds in response to pH changes in the adjacent environment or reversing the charge of the polymer (hydrazine, acetate, and imine) to foster drug entry into target cells [52]. The latter receives or donates protons and undergoes pH-dependent structural and hydrophobic changes to achieve drug release on demand. Notably, the representative groups are weakly acidic (carboxylic acids) and weakly basic (amine groups) [16,52]. In addition, the pH-sensitive materials based on the protonation (such as polyline, polyhistidine, poly dimethyl lactamide, and poly (benzyl glutamate)) also could mediate the escape of nano-carriers from endosomes/lysosomes and delivery of drugs into cells [16,20,52]. Owing to the excellent properties of the pH-responsive nanomaterial delivery system, researchers are loading these pH-sensitive materials with anti-inflammatory or other drugs for anti-arthritis treatment. Results show that such systems have good efficacy to suppress inflammation, repair cartilage and subchondral bone, and alleviate pain in arthritis patients.

The pH-responsive nanomaterials for the treatment of arthritis are developed to target three sites, including the cartilage, synovial and subchondral bone according. Feng et al. developed a pH-responsive hyaluronic acid (HA) -modified anti-inflammatory catechuic acid organic skeleton system (MOF@HA@protocatechuic acid (PCA)) [72], which significantly retarded OA progression by blocking the degradation of type II collagen and the production of IL-1β-stimulated inflammatory mediators. It is notable that their system promoted chondrocyte proliferation and accelerated cartilage regeneration *in vivo*. It also exhibited high drug loading (due to dense pore and large pore size), good biocompatibility, and pH responsiveness. The release of PCA was decreased at pH 7.4 but increased following a drop in pH to 5.6. Subsequently, PCA bound to cluster of differentiation 44 (CD44) on chondrocytes through HA in the carrier material [72]. Zerrillo et al. also designed a pH-responsive polylactic-glycolic acid (PLGA) NP targeting chondrocytes for arthritis treatment [73]. The PLGA NPs used HA and NH_4HCO_3 as carriers. In the acidic OA environment, H^+ passed through the shell of PLGA NPs and reacted with NH_4HCO_3, generating NH_4^+, CO_2. and H_2O. These events increased the internal pressure which collapsed the shell and triggered drug release. However, this system demonstrated a prominent deficiency of sudden release and was incapable of the sustainable release of drugs [73].

Synovial inflammation is another hallmark of arthritis [32]. Researchers have developed numerous pH-responsive nanomaterial delivery systems targeting synovium to alleviate the degree of joint inflammation. Seetharaman et al. prepared a polymeric drug conjugate with self-assembling potential to transition into a pH-responsive micelle, mediating the intelligent release of ibuprofen (IBU), a non-steroidal anti-inflammatory drug, through hydrolysis of anhydride bond between drug and polymer in the acidic environment [74]. The pH-responsive methoxy polyethylene glycol-polypropylene fumarate (MPEG-PPF) prodrug micelles loaded with IBU exerted an anti-inflammatory effect via significant inhibition of the increase of prostaglandin E2 level in rabbit synovium-lining fibroblasts cultured *in vitro*. Aggravation of acidic conditions increased the release rate of IBU, which could be regulated by changing the number of cross-linking agents [74]. Kumar et al. also developed pH-responsive MTX-loaded folate-conjugated glycol chitosan nanoparticles (MFGCN) exerting anti-inflammatory effects when loaded MTX to target activated macrophages in inflammatory joints [75]. Moreover, Mahmudul Alam et al. designed mineralized nanoparticles (MP-HANPs), with polyethylene glycol hyaluronic acid (P-HA) as the hydrophilic shell, 5-cholanic acid as hydrophobic core, and calcium phosphate (CaP) as the pH-responsive mineral, which effectively transported MTX into joints to treat inflammatory arthritis (Fig. 3III) [76].

To our knowledge, Nishiguchi et al. have pioneered the development of a pH-responsive PNC-β-TCP composite composed of bisphosphonate-modified nanocellulose (PNC) and β-tricalcium phosphate (β-TCP), responsive to the osteoclast-created acidic microenvironment [77]. To explain the material response, osteoclast-induced low pH triggers the release of nano-fibers containing pharmacologically active bisphosphonates. However, a drop in pH to about 4.5 promoted PNC-β-TCP composite degradation and release of PNC. These events subsequently inhibit the formation of osteoclasts and pits and promote bone regeneration. Similarly, given osteoclast-created acidic microenvironment during arthritis, osteoclasts can be targeted to repair the abnormal remodeling of subchondral bone. This can guide the development of pH-responsive nanomaterials for arthritis treatment. Moreover, the degradation rate of the composite material can be adjusted by the activity of osteoclasts to prevent excessive drug release from affecting bone regeneration [77].

In the application of pH-responsive drug delivery systems to manage arthritis, we must appreciate that the protonation-induced endoplasmic/lysosomal escape causes the leakage of hydrolase into the cytoplasm, leading to autophagy and cell death [19]. Accordingly, further researches on the pH-responsive mechanism of protonation of chemical groups require to be prudent and focused on their security while testing their effectiveness [15,69,70]. The exploitation of pH-responsive materials based on acid-sensitive bond response theory also is restricted by several factors. Considering acid-sensitive hydrazone bond, its limitations lie in the presence of ketone or aldehyde functional groups in therapeutic drugs and the adverse cytotoxicity of cationic polymer residues [50]. Fortunately, so far, physical expansion states dependent on pH have been utilized to develop polycrystalline pH-responsive dynamic hydrogels. The hydrogels can adjust their structure according to the pH value of the environment to mediate drug release and have superb performance in terms of carrier safety [78]. Another factor to be considered in material research is the stability of synthetic drug delivery systems under different storage conditions, which is of great significance in clinical practice [16].

4. External stimuli-responsive nano-drug delivery systems for inflammatory arthritis treatment

Research on endogenous stimuli is elusive and the intrinsic stimuli are relatively complex and uncontrollable [69]. Therefore, more intelligent nanomaterials that respond to exogenous stimuli (such as temperature, photo, magnetic, and US) have been developed to achieve more accurate and on-demand adjustment and remote control of drug delivery and to enrich the function of the drug delivery system [21]. By applying external stimuli to diseased sites or organs, the nanocarrier is triggered to release loaded drugs as it transits the target sites or organs while maintaining structural stability in other non-targeted areas. To minimize potential damage to normal organs and tissues, exogenous stimuli-responsive drug delivery systems allow for more precise control of the location and intensity of particular external stimuli (e.g., magnetic field and laser exposure) than endogenous stimuli [79]. Meanwhile, as a non-invasive, non-contact, high-precision, and controllable drug delivery system, exogenous stimuli-responsive drug delivery systems can arbitrarily add or remove external stimuli according to request, or provide multiple or continuous stimuli (for example, hours or days) for drug delivery and treatment [79]. This strongly demonstrates that the exogenous stimuli-responsive drug delivery system holds great potential in anti-arthritis treatment (Fig. 4) (Table 3).

4.1. Thermo-responsive nano-drug delivery systems for inflammatory arthritis treatment

The working mechanism of thermo-responsive nano-carriers is that the external thermal stimulus (radiofrequency thermal ablation (RFA), microwave hyperthermia, and high intensity focused ultrasound (HIFU)), creates the thermo difference between the lesion site and normal tissue [52]. Simultaneously, a significant change in the physical and chemical properties of thermo-responsive nano-carriers at the target site can release the loaded drugs. In general, to deliver drugs in locally heated

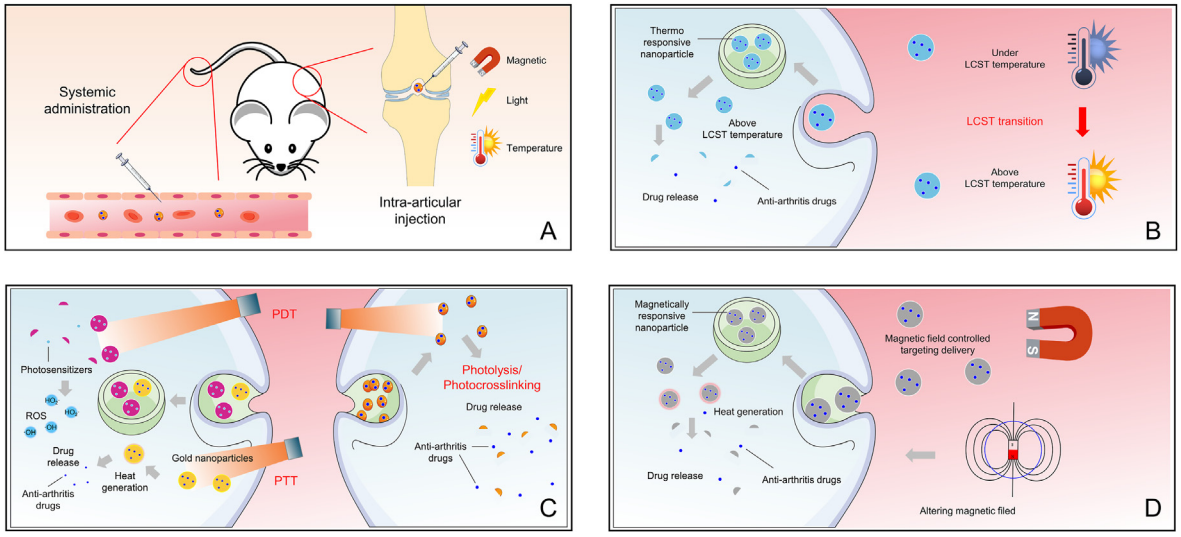

Fig. 4. The principle of exogenous stimuli-responsive materials releasing drugs. (A) Different ways of drug administration under external stimuli: systemic administration or intra-articular injection. (B) Drug release caused by the pyrolysis of thermo-responsive materials induced by external temperature changes. (C) Drug release from photo-responsive materials induced by photo stimulus including photolysis, photocrosslinking, PDT and PTT. (D) Drug release from magnetic-responsive materials induced by magnetic guidance or magnetocaloric effect.

Table 3
Multifunctional external stimuli-responsive nano-drug delivery systems for treatment of inflammatory arthritis.

External stimuli	Material	Responsive shell	Bioactive agent	Articular compartments	Target cells	Effects	Models of inflammatory arthritis	Refs
Temperature	F127/COS/ KGNDCF nanospheres	Nano-spheres based on chitosan oligosaccharide conjugated pluronic F127 grafting carboxyl group	KGN, DCF	Synovium, cartilage	Macrophage, chondrocyte, MSC	Promote chondrogenic differentiation of MSCs, induce cartilage regeneration, and reduce inflammation	U937 macrophage like-cells, primary human chondrocytes, hBMSC, rat models of ACLT and DMM	[86, 87]
	ELP-based fusion proteins	ELPs	IL-1Ra	Cartilage, synovium	Chondrocyte, fibroblast	Inhibit the progression of OA and relieve the pain and swelling of joints	canine models of ACLT-induced OA	[87, 89]
Light	MTX PEG-PLGA-Au	Gold NPs; pegylated-poly (DL-lactic-*co*- 33 glycolic acid) nanospheres	MTX	Synovium	Macrophage	Significantly reduce inflammatory cytokines IL-1β, IL-6 and TNF-α	THP1 differentiated macrophages	[95]
	MNPs	PLGA NPs	MTX	Synovium	Macrophage	Suppress serum levels of pro-inflammatory cytokines and anti-CII IgG, reduce inflammation and pre-vent bone erosion in the joints	FLS, rat model of CIA	[96]

tissue, the load of such materials should remain stable in normal tissues at 37 °C, but sensitive to and responsive to slight temperature changes (such as changing from hydrophilic to hydrophobic) [20]. Temperature-sensitive materials are the key component of thermo-responsive nano-carriers, which mainly include poly (*N*-isopropyl acrylamide) (PNIPAM) [80,81], poly (Ninylisobutyramide) (PAMAM) [82], poly (2-oxazoline) (POxs) [83], poly [2-(2-methoxyethoxy) ethylmethacrylate] [PMEOMA] [84], etc. As far as we know, the affected area of arthritis is characterized by a higher temperature than that of normal tissue even without external thermal stimulus [85]. This observation implies a great potential for the use of thermo-responsive nanomaterials to treat arthritis.

Of note, some thermo-responsive nano-carriers have been triumphantly developed for arthritis management. For instance, to induce cartilage regeneration in OA, Kang et al. prepared a class of thermo-responsive nanospheres (F127/COS/KGNDCF) from poly (ethylene oxide)-*block*-poly (Oxypropylene)-*block*-poly (ethylene oxide) (PEOx-PPOy-PEOz), loaded with diclofenac (DCF) and kartogenin (KGN) (Fig. 5I) [86]. The diameter of the nanospheres ranged from 650 nm at 4 °C to 305 nm at 37 °C, that is to say, the skeleton structure of the nanospheres was loose and the drug was released more promptly at 4 °C. This indicated that local cold treatment could boost the release of drugs from the nanospheres, thus enhancing the therapeutic effect. *In vitro*, the nanospheres were found to effectively inhibit lipopolysaccharide (LPS)-induced inflammation in chondrocytes and U937 macrophage-like cells, and could also reduce synovial inflammation and delay OA progression in rats. Such thermo-responsive nanospheres are unique because they offer dual-functional therapies with anti-inflammatory and cartilaginous protective effects [86]. Moreover, Betre et al. investigated the drug delivery efficiency of a thermo-responsive drug carrier, elastin-like peptide (ELP), in the knee joint of mice [87]. On the view that interleukin-1 receptor antagonist (IL-1Ra) can inhibit OA progression in animal models, relieve pain and swelling of human inflammatory arthritis [88–91], and that ELP has been successfully prepared as a fusion of anti-inflammatory protein drug IL-1Ra [87], they explored the application prospect of ELP in OA. Although numerous researchers have developed plentiful classical thermo-responsive nano-carriers using PNIPAM, their clinical application is extremely restricted due to its

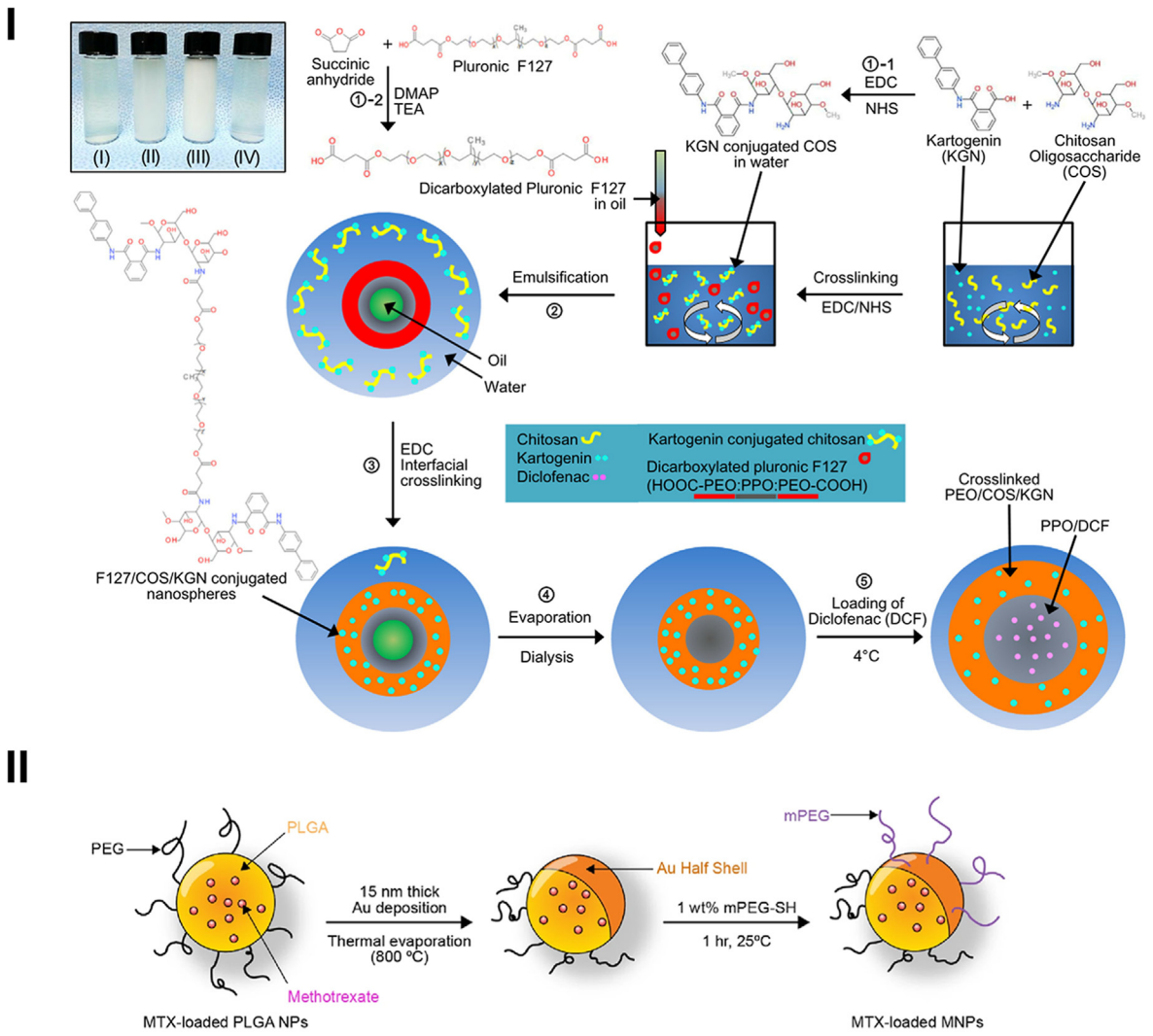

Fig. 5. Representation of the structure and synthetic method of External stimuli-responsive materials: (I) The material structure and synthetic pathway of thermal-responsive F127/COS/KGNDCF nanospheres developed by Kang et al. (Reprinted from Ref. [86] with permission from ELSEVIER). (II) The material structure and synthetic method of MTX loaded MNPs designed by Ha et al. (Reprinted from Ref. [96] with permission from BMC).

non-degradability *in vivo* [92]. In view of this, the development of clinically friendly biodegradable thermo materials such as ELP is a promising future research direction.

4.2. *Photo-responsive nano-drug delivery systems for inflammatory arthritis treatment*

Photo penetrating property is a promising energy source in designing stimuli-responsive biomaterials that can be manipulated by regulating the intensity, frequency, polarization, and photo-direction with high spatial and temporal precision [93]. Therefore, the advantages of the photo-responsive nano-carriers drug delivery system are that its intensity can be accurately adjusted, one can regulate the exposure duration and tissue position (by selecting appropriate beam parameters), and it offers non-invasive photo-regulatory activation [52]. Compared to other stimuli, a photo is a physiologically less harmful option for regulating biomaterials. Generally, the photo-sensitive groups in the structure of photo-responsive nanomaterials are potentially activated by photo-isomerization, photolysis, photo-crosslinking, photo-redox (which can be applied in photodynamic therapy (PDT)), and photothermal trigger (which is associated with photothermal therapy (PTT)) to trigger drug release [94]. Current evidence indicates that several photo-responsive nano-carriers have been exploited, among them, polyion complex vesicles (PICsomes), NPs, polymeric micelle, nanogels, nanorods, nanorattles, etc. The general understanding of photo utilized for photo-activation includes an ultraviolet photo for superficial tissue irradiation and a near-infrared (NIR) photo for deep tissue irradiation [92]. The synovial facet joint is located within the penetration depth of NIR, as such, it is possible to select NIR irradiation for arthritis treatment [95].

To treat RA, Lima et al. developed polyethylene-glycol polylactic-glycolic acid gold-containing nanoparticles (PEG-PLGA-Au) that responded to the NIR photo and used it to load MTX [95]. They demonstrated the anti-inflammatory effect of the nanomaterial on the model of RA, *in vitro,* stimulated and activated by monocytes and macrophages but the material was not validated *in vivo*. Accordingly, Ha et al. successfully developed the multifunctional nanoparticles (MNPs), verified *in vitro* and *in vivo* for RA treatment [96]. They proceeded to investigate the therapeutic effect of MNPs loaded with MTX under NIR irradiation on RA fibroblast synovial cells (FLSS) and CIA mice. Results revealed that MTX-loaded MNPs combined with NIR irradiation exhibited a higher anti-inflammatory effect on synovial cells than chemotherapy alone, and such material was easier to synthesize and less toxic (Fig. 5II) [96]. However, it is worth noting that photo is not entirely safe, for example, Ultraviolet photo may cause damage and carcinogenic effect on cells, whereas NIR radiation may also cause cell thermal damage [94]. Additionally, the biodegradability and safety of some chromophores,

including o-nitrobenzyl and azobenzene-derived compounds are unknown. In this view, the application of photo-responsive drug delivery materials may still be a tough road in clinical practice.

4.3. Ultrasound-responsive nano-drug delivery systems for inflammatory arthritis treatment

As a relatively mature and promising medical technology, US has attracted great attention in the field of drug delivery due to its characteristics of effectual energy focus, deep penetration, safety, ease of operation, and cost-effectiveness [97]. Among them, drug delivery based on a US contrast agent (microbubble) is the hottest. Microbubbles are micro-sized (1–10 m) bubbles with gas core structure, which can oscillate under ultrasonic pressure, resulting in volume expansion, contraction, and even rupture, so as to discharge drugs at the desired position [18]. Nevertheless, the excessively limited drug loading space restricts the therapeutic potential of microbubbles [98]. In contrast, nano-size carriers (such as nanobubble [99], nanodroplet [100], liposome [101,102], emulsion [102], and micelle [103]) are more promising in terms of size, drug loading, and *in vivo* permeability. Ultrasonic waves mostly induce the release of drugs through cavitation, mechanical effects (e.g., simple pressure change, acoustic fluid flow), and local thermal effects, which can not only enhance the controllability of drug concentration in the microenvironment but also promote the drug uptake by disturbing the cell membrane [19]. It has been verified in the literature that US alone can intensify the permeability of the cell membrane [104]. Moreover, it can also punch holes in the cell membrane through the shock wave and micro jet generated by inertial cavitation, so as to bypass the degradable endocytosis pathway and realize intra-cytoplasmic administration [105]. TO-PRO-3 (a fluorescent dye) -loaded thermosensitive liposomes and microbubbles releasing drugs by heating with high-intensity focused US verify this concept and the formation of pores in the cell membrane indeed facilitated the uptake of TO-PRO-3 by target cells [106].

Despite the encouraging advantages of US-responsive carriers in drug delivery, we cannot overlook the confines of various carriers in terms of their size, stability, payload capacity and US energy required for activation. For example, US-responsive polymer micelles face considerable challenges in balancing the sensitivity to US response and *in vivo* stability of the carrier [107]. The pivotal influencing cause depends on the degree of cross-linking of the polymer chains of the micelles, both to take into account the ultrasonic response speed and to avoid premature release due to low stability. Perhaps the advancement of polymeric micelles with dynamic cross-linked chemical bonds that swiftly dissociate or open upon exposure to US after reaching the target site can resolve this conflict to the maximum extent. At the same time, factors such as parameters used in ultrasonic irradiation, the concentration and molecular weight of the therapeutic drug loaded into the carrier system will also impact the carrier release efficiency [18]. Pitifully, US has the paramount disadvantage of being strongly attenuated by bone, which may be a major reason for its harsh enhancement in the treatment of arthritis. Although Liao et al. adopted a new route, the use of US-assisted transdermal delivery of DCF sodium gel to joints, which remarkably reduced the level of inflammation in the joints of rats [108]. However, it is still constrained to the application of ultrasonic microbubbles, which is quite distinctive from our ideal realization of controllable drug release of nanomaterials at joints under ultrasonic stimulation. Developed in recent years, the clinical US system in combination with focusing magnetic resonance imaging (fMRI) can provide treatment to the target area in the brain through the complete skull in animal experiments [109], which allows us to expect its application in arthritis treatment. After all, US has gigantic potential in raising the permeability of biological barriers and solving the problem of arduous penetration of dense cartilage matrix [110].

4.4. Magnetic-responsive nano-drug delivery systems for inflammatory arthritis treatment

For the nano platform used in intravenous injection, the vital hindrances are to control the drug transport in the blood flow and the biological distribution of particles [111–113]. Currently, magnetic fields have tremendous feasibility for regulating drug transport in the bloodstream. We can attach therapeutic drugs to biocompatible magnetic NPs. After intravenous injection, a certain magnetic field is applied at a specific target to boost the accumulation of NPs at the target position through magnetic guidance, thereby elevating the delivery efficiency of the drug to a certain extent [20,114]. Undoubtedly, the merits of magnetism are beyond this. It penetrates the body more deeply than light and has few harmful ionization effects, therefore magnetic-responsive materials have been applied in magnetic resonance imaging (MRI), magnetic drug delivery, enzyme quantitative measurement [115], and magnetic hyperthermia therapy [116]. The magnetism of nano-sized magnetic materials refers to a brand-new kind of magnetism called superparamagnetism, which, unlike permanent dipoles, is not affected by magnetic-induced aggregation when injected into the blood and thus flows freely through the micro-vessels [117]. So far, the magnetic NPs include iron oxide (Fe_3O_4, Fe_2O_3), cobalt oxide, nickel oxide NPs, and so on, among which, superparamagnetic iron oxide nanoparticles (SPION) are extensively applied in biological applications [118] due to their upper-level superparamagnetic or ferromagnetic properties, surface volume ratio suitable for efficient functionalization and proven biocompatibility.

According to the distinct mechanisms of magnetic response, the external magnetic field can be divided into two types: one is the constant magnetic field provided by the outside world; the other is the alternating magnetic field (AMF) imposed by the external [19]. Generally, in the process of injecting magnetic response nanocarrier, magnetic guidance is obtained by focusing the external constant magnetic field on the biological target, thereby uplifting the drug accumulation at the lesion. Of course, constant magnetic fields can also play a role in the magnetic-responsive material release. For example, when exposed to the permanent magnetic field, the iron gel composed of superparamagnetic iron oxide NPs and Pluronic-F127 micelles will release along with the iron oxide NPs close to each other and squeeze the micelles [119]. While the AMF is closely related to magnetic hyperthermia therapy due to its property of heating materials, it can also be applied to magnetic-responsive drug delivery. The mechanism of drug release can be attributed to the heat generated by the oscillating or AMF, which causes the change of nanocarrier structure, such as the increase of shell or double-layer pores [120,121], the disintegration of Fe_3O_4 core [122], or the deformation of single crystal nanoshell lattice [123]. Alternatively, the duration of the oscillating or AMF on/off state could modulate the size of the cross-linked PNIPAM hydrogel loaded with Fe_3O_4 NPs, thereby managing the release of the drug [124]. Of course, a high-frequency AMF would activate the magnetocaloric effect of the magnetic NPs, which would release heat and lead to the death of surrounding cells. Despite that, if the thermal dose is properly controlled, the magnetocaloric effect can be used to give promotion to the dissociation of thermo-responsive materials [125]. For example, in the magnetically targeted chemical PTT proposed by Kim et al., they couple MTX-loaded PLGA gold (Au)/iron (Fe)/gold (Au) half-shell NPs with RGD for the treatment of RA [126]. To our regret, the current exploration of magnetic-responsive drug delivery materials is still concentrated in the field of tumors, and its usage in the treatment of arthritis is quite scarce. We hope this review can contribute a lot to the elevation of the application of magnetic-responsive materials for arthritis treatment.

Although exogenous stimuli are more advantageous than endogenous stimuli which are arduous to control, information of the site-specific external stimuli application parameters that affect the delivery depth and focus is scanty [20,52,69]. Any development of exogenous stimuli-responsive materials is futile if the depth and precise location of

the lesion cannot be determined. Moreover, for thermo-responsive nanomaterial drug delivery systems, it remains a challenge to find materials with both upstanding safety and sensitivity to respond to temperature differences at the lesion site [15]. For photo-responsive nanomaterial drug delivery systems, the safety and biodegradability of the typical materials (gold-silver, gold nanorods, azobenzene, and o-nitrobenzyl derivatives) are particularly problematic [19,94]. Besides, ultraviolet light may result in destruction and carcinogenesis to cells, while NIR may cause cell thermal damages [94]. For US-responsive nanomaterial drug delivery systems, how to equilibrize the steadiness and sensitivity of nanocarriers as well as probe their impact on DNA injury [127] remains a headache. For magnetic-responsive nanomaterial drug delivery systems, due to the restriction of the spatial geometry of the magnetic field relative to the target position and the intricacy of the external magnetic field setting [128], magnetic guidance also confronts countless thorny problems. Additionally, for the drug release triggered by the magnetocaloric effect, we are still afraid that the AMF may influence the stability of the chemical bonds within the drug-nanoplatforms and produce uncontrolled local overheating and tissue necrosis. Heretofore, none of the response materials is unassailable. In the view of selecting responsive carrier materials, it is inevitable to comprehensively consider the disease characteristics and indicators, drug composition, physical and chemical properties, administration route, and dosage to pick the most favorable scheme for clinical use (Table 4).

5. Challenges and prospective of stimuli-responsive nano-drug delivery systems for inflammatory arthritis treatment

5.1. Challenges

Stimuli-responsive nanomaterials successfully deliver drugs at proper concentration, correct time, and specific space, which dramatically improves the efficiency of drug delivery and minimizes the adverse effects on normal organs and tissues. It surmounts the shortcomings of premature leakage and sudden release of traditional drug delivery systems and blazes a new and effective trail for arthritis treatment [19,21,38].

Table 4
Features and challenges of internal and external stimuli-responsive nano-drug delivery systems.

Types		Features	Challenges	Refs
Internal stimuli-responsive nano-drug delivery systems	Enzyme-responsive nano-drug delivery systems	1. Excellent and efficient biometric sensitivity 2. Drug release based on disease activity of the joint	1. Quantitative changes of enzyme content in joint lesions 2. Boundary design for normal and abnormal enzyme concentration response 3. Enzyme cleavage sites that respond only to characteristics of typical enzymes	[15,16,20,51,52]
	Redox-responsive nano-drug delivery systems	1. Mediate accurate drug release in various cell subcomponents 2. Eliminate corresponding oxidizing species while responding	1. Different formulations required for various diseases and higher requirements for personalized medicine 2. Respond to inflammatory responses triggered by the material itself 3. Regulated rate of response to ROS stimulation at a pathologically compatible rate 4. Exploration of control of different ROS, polymer structure and exposure time on sensitivity of materials	[42,59,60]
	pH-responsive nano-drug delivery systems	1. Adjust drug release rate as needed 2. Enhance cellular uptake through pH-responsive-mediated charge switching 3. The degradation rate of the intracytoplasmic administered composites could be regulated by the activity of osteoclasts (e.g., pH-responsive PNC-β-TCP composites)	1. Autophagy and death due to leakage of hydrolase into the cytoplasm by proton-induced endosomal/lysosomal escape 2. Adverse cytotoxicity of pH-sensitive hydrazone bonds in the presence of ketone or aldehyde functional groups and cationic polymer residues 3. Stability of synthetic acid-sensitive drug delivery systems under different storage conditions 4. pH-responsive linked esters are influenced by esterases abundant in the systemic circulation	[16,19,20,50,77]
External stimuli-responsive nano-drug delivery systems	Thermo-responsive nano-drug delivery systems	1. Location and intensity of temperature stimulation controlled precisely 2. Stimuli added or removed as needed and multiple or consecutive stimuli provided	1. Safe and sensitive materials to handle slight temperature changes around the physiological temperature of 37 °C required	[15,20,21,52,69,79]
	Photo-responsive nano-drug delivery systems	1. Adjustable exposure time and tissue location, and non-invasive photomodulation activation provided	1. Little information available on site-specific external stimulus application parameters affecting delivery depth and focus 2. Biodegradability and safety of some chromophores (including o-nitrobenzyl and azobenzene-derived compounds) are unclear 3. Ultraviolet light may cause injuries and carcinogenesis to cells, while NIR radiation may also cause thermal damage to cells	[19,52,93,94]
	Ultrasound-responsive nano-drug delivery systems	1. Energy focused, deep penetration, and safe, easy to operate and cost-effective 2. Increase the permeability of certain biological barriers and solve penetration challenges 3. Bypass the degradative endocytic pathway for intracytoplasmic drug delivery	1. Strongly attenuated by bone 2. Difficult to balance the stability and sensitivity of nanocarriers 3. Effects on DNA damage	[18,19,97,105,107,127]
	Magnetic-responsive nano-drug delivery systems	1. Manipulate biological targets to focus on desired areas by magnetic guidance 2. Little physical interaction with the body 3. Penetrate the body deeper than light and have no harmful ionizing effects 4. Used for quantitative enzyme measurements	1. Constraints on the spatial geometry of the magnetic field from the target location 2. External magnetic field setup is complicated 3. AMF may affect the stability of chemical bonds within drug-nanoplatforms 4. Magnetocaloric effect may lead to local uncontrolled overheating	[20,114–116,128]

However, in the application of stimuli-responsive nanomaterials to deliver anti-arthritis drugs, other than exploring the drug release at the target site, it is also imperative to account for the impact of disease-specific anatomical and physiological barriers (including high-density non-vascular cartilage ECM, etc.) on the bioavailability of nano-carriers in the target joints [15,38]. Efforts are warranted to explore the specific process of intravenously injected nano-carriers to the injured joints, and the impacts of carrier type, size, shape, and surface modification on drug delivery. The dosage, physicochemical properties, and administration frequency of different arthritis drugs vary tremendously [20,38,129]. As such, the stimuli-responsive drug delivery carriers should be discreetly selected based on the stability, release curve, and drug release kinetics of the loaded drugs. Up to now, the main nano-carriers used for related therapy are liposomes, polymer particles, chitosan NPs, dendrimers, and solid lipid NPs [129]. Liposomes are lipid vesicles that self-assemble and block lipid bilayer, and they can encapsulate both hydrophilic and hydrophobic drugs. Liposomes can be targeted as they respond to stimuli via surface modification of the lipid shell. However, the poor sustained release ability and storage stability of liposomes require creative modification to correct these defects if it is to be utilized for joint drug delivery. Polymer particles made from PLGA and poly (L-lactic acid) are characterized by high loading capacity and prolonged drug release properties and have the potential for use in specific drug release via surface modification. However, a limited number of end groups of these polymer particles available for surface modification hinders their widespread application in arthritis drug delivery [129]. Therefore, the advancement of superior carrier materials with safety and versatility is a key to promoting the growth of stimuli-responsive drug delivery systems. In terms of security and biocompatibility, the latest emergence of updated natural nano delivery platforms composed of natural derivatives (PEVS [17], Ros-responsive TolDex [130,131]) may supply us with feasible ideas. Given that the toxicity of carrier materials has always been a crucial issue affecting their clinical transformation, we may not be constrained to nano-tissue engineering when designing carriers. Natural cell-derived components such as exosomes often have the edge in surmounting nano-toxicity and have more potential to turn into green stimulus-responsive drug delivery carriers.

In addition, stimuli-responsive vectors also face enormous challenges in moving from laboratory to clinical success. First, at present, our cognition of NPs *in vivo* behavior is based on the data of animal models [132], but the curative effect of animal models for species is dependent on physiological parameters and pathologic differentiation between experimental animals and humans, which, therefore, will significantly disturb the accuracy of the predicted therapeutic effects in clinical trials. Second, most of the nanosystems lack a comprehensive assessment of their systemic toxicity as well as the local toxicity in normal tissues. Certain NPs can interact closely with the immune system and may trigger allergies or hypersensitive reactions. Some NPs may alter cell morphology and cytoskeleton, resulting in interruption of intracellular signal pathways and adverse biological interactions. Some NPs may also trigger the overproduction of ROS in the body [13,112]. All of these illustrate the prominence of a comprehensive apprehension of the interactions between the delivery system and the relevant biological components in the systemic environment at diverse time points after drug administration before the triumphant clinical application of carrier materials. Third, in general, the more detailed and remarkable carriers often involve multi-steps or complex synthesis technology, which renders the mass-scale production of vectors tougher. Conversely, the simpler and easier the system is, the greater the opportunity to enter the clinic. ThermoDox [133], a thermo-sensitive liposome already in the clinical stage, is a good example. Although there are advances in mass production technologies (e.g., Microfluidics [134], Non-wetting formwork technology [135] and Coaxial turbulent jet mixer [136]), further breakthroughs are still demanded to speed up the clinical transformation of stimulus-responsive drug delivery materials. Fourth, criteria for toxicity assessment of nanomaterials as delivery systems are lacking, which makes the evaluation indicators for each team in the stage of developing new nanomaterials often varying. For example, not all experiments have appraised the poisonousness of empty carriers [137]. Such flaws may not be discovered until further preclinical experiments, which is undoubtedly not conducive to speeding the enhancement of safe and effective nanomaterials for clinical use. In the course of facilitating the clinical application of stimuli-responsive vectors, perhaps close communication and synergism with personnel working in the field of particle toxicology, optimization of clinical trials, regulatory procedures for materials based on therapeutic requirements as well as market demands, and a reasonable balance of benefit-risk ratios can help.

5.2. *Prospective of nano-drug delivery systems for inflammatory arthritis therapy*

To disentangle the existing hindrances and expedite the clinical transformation of targeted drug delivery of stimuli-responsive drugs to arthritic joints, we not only demand to deepen our understanding of arthritis at the molecular level to further develop molecular pharmacology, but also aggrandize the progression of novel materials to find more target-specific and biocompatible drug carriers, thus achieving a better delivery effect. We can consider it in terms of multiple responsiveness and multiple targets.

There are a series of changes in pH, ROS, and MMPs in normal tissues or subcellular organelles [5,42]. Therefore, relying on a single stimulus mode fails to complete the precise release of drugs in lesions with complex microenvironments with multiple signals, which increases the incidence of “false positive” and injured non-target sites [138]. Interestingly, through rational design, by integrating manifold stimulus-sensitive groups on one carrier, multi-stimuli/multi-functional responsive nanocarriers were invented, fulfilling the superiorities of diverse systems synergistically in a single system, magnifying carrier performance, and achieving precise concentration of “real-time” response and self-controlled drug release at specific sites. Just as, pH and US responsive materials can be used not only for drug release but also to enhance cellular uptake; both magnetic and US responsive materials have a certain temperature-enhancing effect, while magnetic-responsive materials also have unique magnetic guiding properties. It is the unique or shared advantages of each responsive system that endow materials with multiple responsiveness abilities a breakthrough in optimizing carrier performance. By giving materials multi-response capabilities, we can increase the drug release rate, improve the sensitivity of response conditions, control the differential release of drugs, build a multi-stage reaction system for drug delivery, and realize the integration of diagnosis and treatment. An inordinately appealing and universally studied integration of diagnosis and treatment refers to the combination of imaging and therapy through multiple responsiveness, which can not only enable us to control the transmission of drugs but also detect the differences in the lesion, so as to have the opportunity to adjust the dose and type of administration and mightily ameliorate the treatment effect. In the recent past, a new type of MMP-13/pH-responsive ferritin nanocages with cartilage targeting potential for OA treatment has been developed by incorporating the idea of double stimuli. By imbuing these nanocages with MMP-13 enzyme and pH responsiveness, this material can intelligently “turn on” for fluorescence imaging and achieve the release of anti-inflammatory drugs in response to overexpression of MMP-13 and pH in the OA joint cavity [71]. In addition, the MNPs with photothermal control of MTX release fabricated for targeting RA fibroblast-like synovial cells [96] and MTX loaded polyglycolic acid gold NPs manageably triggered by photothermal reaction [95] also demonstrate the competency of multi-responsive systems in alleviating inflammatory activity and augmenting the therapeutic effect of arthritis. Most strikingly, the multi-level response-ability engendered by multi responsiveness of carriers can engender different degrees of alterations in carriers through two or more orthogonal stimuli, so as to allow the distinctive controlled release of goods [139]. After all, combined drug therapy can acquire more

desirable consequences for the most part.

Not only the particularity of drug release should be taken into consideration in the invention of novel materials, but also the accuracy of their targeting. Cogitating the intricacy of physiological variables of blood flow, disease state, and tissue structure [140,143], two or more targeted designs in advance can notably enhance the targeting capability of materials. Deng et al. developed RGD-modified PLGA enzyme-responsive nanoparticles loaded with tripterine (CEL-PRNPs) [141], targeting subchondral osteoclasts and synovial macrophages in RA joints through the interaction of RGD-α with β-3 integrin. Subsequently, the materials induced the apoptosis of the cells by releasing tripterine (CEL) in response to local MMP-9. CEL-PRNPs efficiently were found to decrease the number of bone-resorbing osteoclasts and pro-inflammatory macrophages in rat models of adjuvant arthritis. At the same time, inflammation of rats with advanced arthritis was alleviated and treatment with CEL-PRNPs repaired bone erosion. Elsewhere, Kang et al. exploited a thermo-responsive nanosphere with dual targeting and dual drug loading [86]. The system was supported by thermo-responsive triblock copolymers PEOx-PPOy-PEOz having a core loaded with DCF and an outer layer covalent cross-linked with nucleoprotein. The anti-inflammatory and chondroprotective effects of this drug delivery system are successfully demonstrated in chondrocytes and U937 macrophage-like cells induced by LPS both *in vitro* and in OA rat models. The competence of multiple targets combined with multiple drug releases can comprehensively treat arthritis from multitudinous levels of cartilage, synovium and subchondral bone, which can exceedingly upgrade the treatment effect. At the same time, the balance of the large-scale system is compelled to be dealt with. Generally, the balanced surface modification density is the decisive element to attain the fantastic targeting ability [129,142,143]. Moreover, despite the ginormous benefits and potential of the aforementioned systems, they tend to be overly complex, and many remain just proof-of-concept. To validate the feasibility of these strategies, more verifications of the modulation of responses to each stimulus *in vitro* and *in vivo* are required, and only then can vastly advance in the research of novel materials be actualized. Notwithstanding, it is also inevitable that the above-mentioned research on more advanced and superior multi-responsive carriers is still concentrated in the field of tumor research, and the development of dual/multi-response drug delivery platforms for the treatment of arthritis is still in its infancy. Yet, since tumors and inflammation share several pathological features, they still have momentous significance for the advancement of drug carriers for arthritis treatment.

6. Conclusions

Mounting evidence indicates that various pathological changes, including cartilage hyperplasia, synovitis, and subchondral bone remodeling in inflammatory arthritis, are caused by exposure to stimuli (such as degradative enzymes, a disorder of intracellular redox system, an acidic environment) [1,6,9]. Stimuli-responsive drug delivery system characterized by high drug delivery efficiency and strong drug release control offer upstanding application prospects in the therapeutic strategy for multiple diseases. Such systems are worthy of exploring to enhance their application in clinical practice [144]. Exposure to appropriate stimuli elicited by histopathological alterations could trigger the release of therapeutic medications for the joint-targeted treatment of inflammatory arthritis. There is evidence that stimuli-responsive drug delivery systems targeting these lesion sites (articular cartilage, subchondral bone, and synovium) are applied to manage inflammatory arthritis.

Herein, restrictions and prospective advances of various stimuli-responsive drug delivery carriers are reviewed. Currently, although stimuli-responsive drug delivery carriers have shown prominent efficacy in cancer treatment [8,145], studies on the use of such carriers in anti-arthritis treatment are excessively scarce. Whilst cancer and arthritis share certain semblable mechanisms in disease development, including severe cell proliferation, angiogenesis, and the involvement of immune cells and cytokines [5], stimuli-responsive carriers also hold superb promise in the development of materials for arthritis treatment. Therefore, this review will enrich our understanding of the status quo and bottleneck of the application of stimuli-responsive drug delivery systems for arthritis management. There are still plentiful limitations in the adhibition of stimuli-responsive drug delivery carriers to treat arthritis. However, with the unremitting amelioration of intelligent nanometric carrier technology and drug release mechanism, stimuli-responsive drug delivery systems will triumphantly move from the laboratory to the clinical application.

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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