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Targeting macrophage polarization as a promising therapeutic strategy for the treatment of osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is a chronic osteoarthropathy characterized by the progressive degeneration of articular cartilage and synovial inflammation. Early OA clinical treatments involve intra-articular injection of glucocorticoids, oral acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), which are used for anti-inflammation and pain relief. However, long-term use of these agents will lead to inevitable side effects, even aggravate cartilage loss. At present, there are no disease-modifying OA drugs (DMOADs) yet approved by regulatory agencies. Polarization regulation of synovial macrophages is a new target for OA treatment. Inhibiting M1 polarization and promoting M2 polarization of synovial macrophages can alleviate synovial inflammation, relieve joint pain and inhibit articular cartilage degradation, which is a promising strategy for OA treatment. In this study, we describe the molecular mechanisms of macrophage polarization and its key role in the development of OA. Subsequently, we summarize the latest progress of strategies for OA treatment through macrophage reprogramming, including small molecule compounds (conventional western medicine and synthetic compounds, monomer compounds of traditional Chinese medicine), biomacromolecules, metal/metal oxides, cells, and cell derivatives, and interprets the molecular mechanisms, hoping to provide some information for DMOADs development.

1. Introduction

Osteoarthritis (OA) is the most common joint disease. As of 2020, more than 500 million people worldwide are affected by OA. The incidence of OA increases with age, and one third of the population over 65 years old suffers from this disease [1]. The typical feature of OA is the progressive degeneration of cartilage, with pain and joint swelling. OA is a complex disease that can be due to a variety of predisposing factors, including aging, obesity, gender, sports injury, and genetic factors, but the pathogenesis is unclear [2–4]. In pathophysiology, increasing evidence suggests that low-grade synovial inflammation (synovitis) is closely associated with radiographic progression and joint pain in OA [5–8] (Fig. 1). According to the Kellgren-Lawrence (KL) classification, 38 % of patients with KL grade 2–3 OA and up to 83 % of patients with KL grade 4 have synovitis of the patella [9]. Therefore, in addition to joint replacement surgery, which is usually the ultimate treatment for patients with advanced or end-stage OA, conservative medical treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are widely used to relieve joint inflammation. However, the above-mentioned treatment methods only relieve pain, and they cannot inhibit further deterioration of joint structure. Such methods are often accompanied by side effects (such as gastric bleeding and increased risk of osteoporosis in female patients), which limit their application [10–13]. Therefore, exploring new treatment strategies for OA is crucial.

The synovium is formed by two layers, the lining layer and the sub-lining layer. The lining layer consists of resident macrophages and fibroblasts, and plays a key role in maintaining the homeostasis of healthy synovial tissue [14]. The sub-lining layer contains interstitial

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macrophages, fibroblasts, adipocytes, circulating monocytes, and blood vessels [15]. Interestingly, the resident macrophages provide an anti-inflammatory barrier around the joint that is disrupted during OA [16]. And non-resident macrophages derived monocytes accumulate and infiltrate in OA joints and drive synovial inflammation [17] (Fig. 2). Synovial infiltrating macrophages may also play an important role in peripheral mechanisms of OA pain sensitization [18,19], which are a potential target for OA therapy. In recent years, an increasing number of studies have focused on the important role of synovial macrophages in joint homeostasis, and confirmed that immunomodulation can prevent articular cartilage degeneration and promote cartilage repair [20].

2. Macrophage polarization

2.1. Typing of synovial macrophages

Traditionally, synovial macrophages can be broadly classified into classically activated M1 macrophages and alternately activated M2 macrophages, which can exert pro-inflammatory and anti-inflammatory/tissue repair functions in response to stimuli from their microenvironment [21]. M1 macrophages have pro-inflammatory functions, and they are responsible for the release of factors critical for joint inflammation. M1 macrophages (CD80 and CD86 as M1 surface markers) are stimulated by interferon-γ (IFN-γ), tumor necrosis factor α (TNFα), lipopolysaccharide (LPS) and other toll-like receptor (TLR) ligands, and produce a large number of pro-inflammatory cytokines and mediators by activating JAK/STAT signaling pathway, NLRP3 signaling and NFκB/MAPK signaling pathway [17,22,23]. By contrast, M2 macrophages (CD206 and CD163 as M2 surface markers) have anti-inflammatory functions, contributing to tissue repair and inflammation resolution, and promoting wound healing. M2 macrophages can be further divided into specific subtypes. M2a, M2b, and M2c can be induced by interleukin 4 (IL-4), IL-10 and IL-13, play an anti-inflammation response and wound-healing role by producing cytokines such as IL-1RA, IL-10, CCL-18, and TGF-b [24–26]. M2 macrophage induction depends on JAK/STAT3, JAK/STAT6, and PI3K/Akt signaling pathway [23] (Fig. 3).

Interestingly, although the M1 and M2 macrophages are polar extremes in vitro, they do not adequately reflect the complex profile of tissue macrophages in vivo. Studies have revealed the heterogeneity of macrophages in OA joints using advanced cell sequencing and analysis technology such as single-cell RNA sequencing (sc-RNA-seq). A study applied flow cytometry, mass cytometry, and sc-RNA-seq to analyze T cells, B cells, monocytes, and fibroblasts from 51 samples of synovial tissue of OA and IA patients. They identified 18 unique cell populations, including 4 different monocyte subpopulations: *IL1B*$^{+}$ pro-inflammatory monocytes (SC-M1), *NUPR1*$^{+}$ monocytes (SC-M2), *C1QA*$^{+}$ monocytes (SC-M3), and IFN-activated *SPP1*$^{+}$ monocytes (SC-M4). They found that SC-M1 highly express genes related to lipopolysaccharide response, and mainly exist in RA samples, and the proportion of SC-M2 cluster in OA patients increases. SC-M1 are similar to TLR-activated IL-1-producing pro-inflammatory monocytes, and SC-M4 express genes induced by type I and type II IFN. However, the transcriptional profiles of SC-M2 and SC-M3 are not consistent with known activation states, which may indicate that these subgroups exist in unique synovial homeostasis environments [27] (Fig. 2). Macrophage heterogeneity emphasizes the limitations of M1/M2 paradigm, and that a more comprehensive evaluation of macrophage phenotype is necessary for precise targeted OA treatment.

2.2. Metabolic reprogramming in macrophage polarization

Recent studies have shown that macrophage polarization is closely related to the cellular metabolic state, and metabolic pathways not only provide energy but also regulate macrophage phenotype and function. M1 macrophages convert arginine to nitric oxide (NO) by inducible NO synthase (iNOS), whereas M2 macrophages metabolize arginine away by arginase 1 (Arg1) to promote tissue repair [28] (Fig. 4).

Parallel to arginine metabolism, the metabolic shift in glycolysis and oxidative phosphorylation (OXPHOS) is another key feature that defines different subtypes of macrophages. M1 macrophages exhibit enhanced glycolytic metabolism characterized by increased expression of glucose transporters and glycolytic enzymes and rapid ATP production, in contrast to the induction of OXPHOS in M2 macrophages, which is slower but produces more ATP [29,30]. The transition from OXPHOS to a highly metabolic active glycolytic state can lead to the accumulation of reactive oxygen species (ROS). Elevated levels of glycolytic metabolism in M1 macrophages also feed the pentose phosphate pathway, which supports inflammatory macrophage responses by inducing ROS and NO production and promoting nucleic acid and protein synthesis. However, this pathway is inhibited by the sedoheptulose kinase CARKL in M2 macrophages [30–32]. ROS are involved in neuropathic pain by activating TRPA1 in nociceptors [33]. High-level ROS causes hyperperoxidation, protein carbonylation and DNA damage, which damage chondrocyte function [34,35]. Moreover, ROS/NO promote the synthesis of inflammatory mediators, inhibit cartilage matrix synthesis by regulating PI3K/Akt and MAPK pathways, and promote cartilage matrix degradation by promoting the expression of matrix metalloproteinases (MMPs), thereby aggravating OA disease progression [36,37].

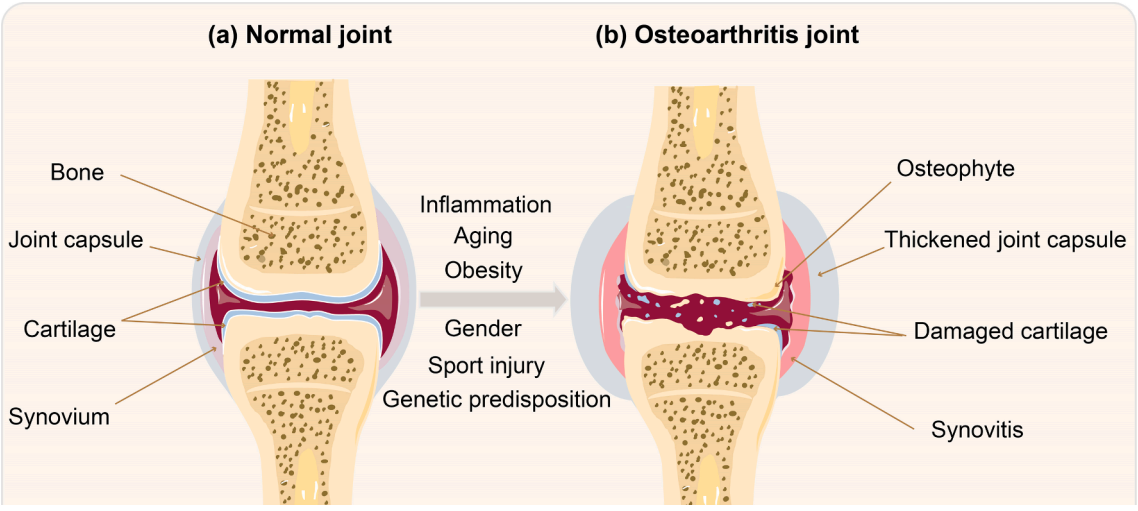


Fig. 1. Pathogenic factors of osteoarthritis and structures of normal (a) and osteoarthritis (b) joint. Age, chronic inflammation, obesity, gender, sport injury, and genetic predisposition are the main risk factors of osteoarthritis. Common features of osteoarthritis include cartilage loss, osteophyte and synovitis.

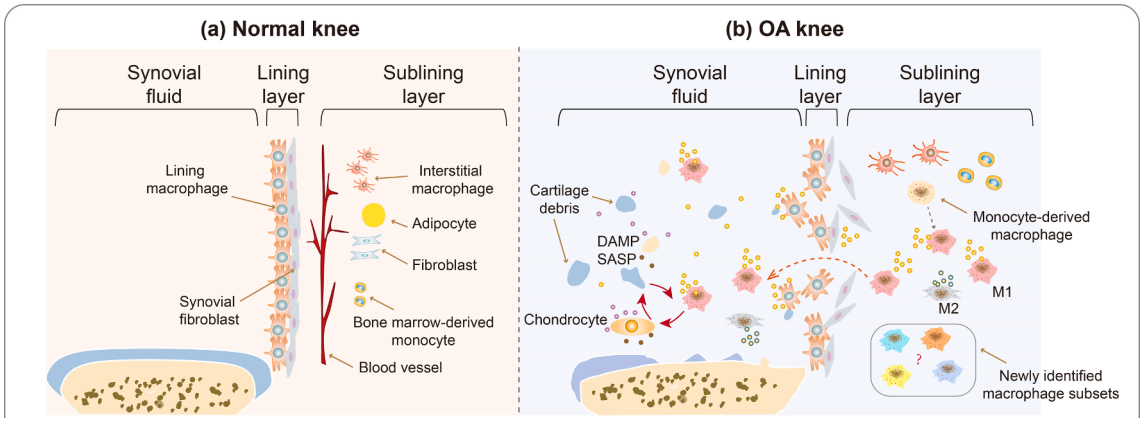


Fig. 2. Pathology and macrophage involvement in OA joint. During OA, lining macrophages are damaged, and bone marrow-derived monocytes enter the synovial fluid and infiltrate into the injured sites. Infiltrated monocyte can further differentiate into M1-like or M2-like macrophages, and intra-articular DAMPs and SASP promoted the generation of more M1 macrophages. M1 macrophages produce pro-inflammatory mediators, causing inflammatory environment and cartilage damage. sc-RNA-seq identified new synovial macrophage subsets, including *IL1B*$^{+}$ pro-inflammatory monocytes (SC-M1), *NUPR1*$^{+}$ monocytes (SC-M2), *C1QA*$^{+}$ monocytes (SC-M3), and IFN-activated *SPP1*$^{+}$ monocytes (SC-M4), but their specific roles require to be further clarified. DAMPs: danger-associated molecular patterns; SASP: senescence-associated secretory phenotype; sc-RNA-seq: Single-cell RNA sequencing.

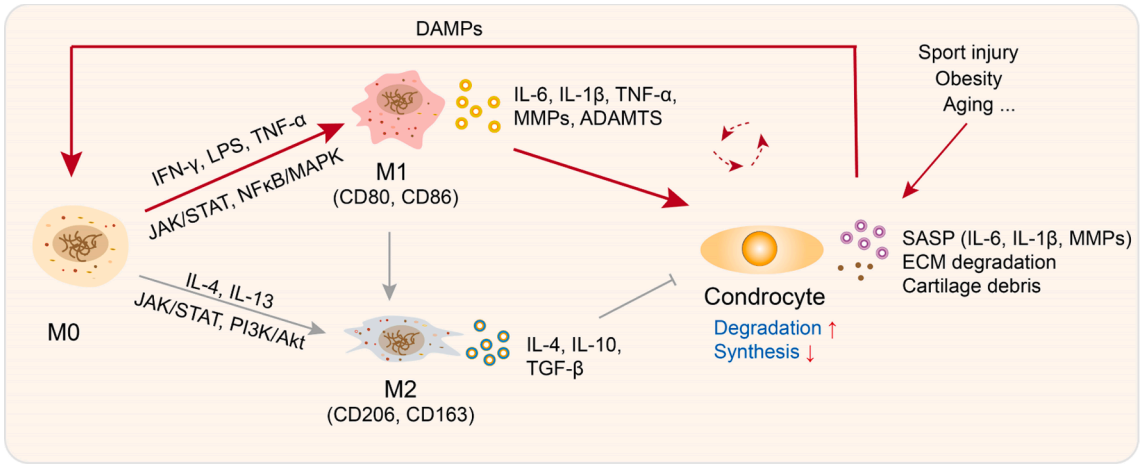


Fig. 3. Crosstalk between macrophages and chondrocytes in OA. The degradation of ECM and cartilage fragments caused by mechanical and non-mechanical factors such as sports injury, obesity and aging act as DAMPs to stimulate the M1 polarization of macrophages. The activated macrophages secrete pro-inflammatory mediators, further promoting the degradation of ECM. Similarly, degraded ECM and cartilage fragments activate macrophages, resulting in a repeating cycle of inflammation and cartilage degradation. ECM: extracellular matrix; DAMPs: danger-associated molecular patterns.

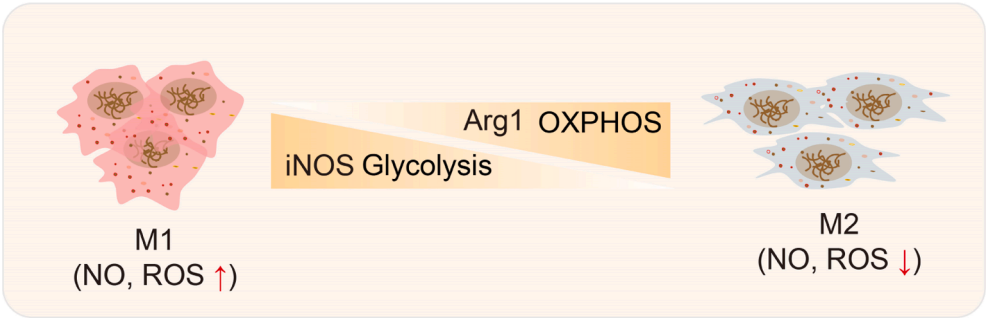


Fig. 4. Metabolic reprogramming of macrophages. The convertion of arginine metabolism pattern and glucose metabolism pattern is one of the characteristics of macrophage polarization. INOS, glycolysis and pentose phosphate pathway in M1 macrophages promote the generation of ROS and NO, resulting in inflammation, which are inhibited in M2 macrophaged by Arg1 and OXPHOS.

Therefore, specifically scavenging the over-expressed ROS in the articular cavity can significantly reduce the local inflammatory and articular cartilage lesion response of OA.

3. Macrophages in osteoarthritis

3.1. Cellular crosstalk in OA progression

During OA development, macrophages accumulate in the synovium and joint cavity, and they are activated to M1 phenotype by endogenous damage-associated molecular patterns (DAMPs) such as cartilage debris and aggrecan, or exogenous pathogen-associated molecular patterns (PAMPs). Activated macrophages can induce synovial inflammation by producing cytokines, ROS, NO, MMPs, as well as a disintegrin and metalloprotease with thrombospondin type 1 motifs (ADAMTS). Inflammatory factors and MMPs then shift the balance of synthesis and degradation of extracellular matrix (ECM) maintained by chondrocytes into catabolism by degrading native collagen and aggrecan [38,39]. This metabolic imbalance leads to cartilage damage and osteophyte formation. The disordered joint environment further stimulates activated macrophages to produce inflammatory response [40,41] (Fig. 3). Cartilage degradation are also related to senescence-associated secretory phenotype (SASP). Age is the main pathogenic factor of osteoarthritis. In age-ralated OA joint, the clearance defect of senescent chondrocytes leads to their continuous accumulation, thus maintaining the production of SASP, and promoting chronic low-grade inflammation [42]. Correspondingly, senescent macrophages exhibit reduction of phagocytosis and enhancement of the inflammatory cytokine response [43].

3.2. Macrophage polarization and osteoarthritis

Histological studies have observed an increase in the number of activated macrophages in the synovium of OA. Etarfolatide labeling combined with SPECT-CT imaging detected the accumulation of activated macrophages in 76 % of OA knee joints in vivo, and the number of activated macrophages was significantly correlated with OA knee pain ($R = 0.60$, $P < 0.0001$) and radiographic severity, including joint space narrowing ($R = 0.68$, $P = 0.007$) and osteophytes ($R = 0.66$, $P = 0.001$) [44]. Moreover, the ratio of M1/M2 macrophages was positively correlated with the KL grade of patients with knee OA. The ratio of M1/M2 macrophages in synovial fluid and peripheral blood was significantly higher in patients with knee OA compared with healthy controls [45]. Synovial macrophage M1 and M2 polarization exacerbate and attenuate OA progression, respectively; thus, synovial M1 and M2 macrophages play a key role in OA development [33].

Therefore, macrophage polarization is a potential target for OA therapy. Various approaches have been demonstrated to improve OA symptoms by modulating macrophage polarization. Herein, we summarize the research progress of small molecule drugs (conventional western medicine and synthetic, monomer compounds of traditional Chinese medicine), biomacromolecules, metal/metal oxides, cells, and cell derivatives in the treatment of OA over the past five years.

4. Macrophage-based therapeutic strategies for OA

4.1. Conventional western medicine and synthetic compounds

Chronic pain is associated with OA disease and affects millions of people worldwide. Studies suggests that the synovitis, rather than cartilage and bone defect, is associated with OA pain severity due to absence of afferent nerve innervation in the latter [46–48]. Conventional western medicines, such as glucocorticoids and NSAIDs, have been used for anti-inflammation and pain relief. Studies have shown that some of them can alleviate inflammation by regulating macrophage polarization, thus delaying the progress of osteoarthritis [49]. However, inevitable side effects limit their lone-term use [50,51]. In order to solve various adverse effects caused by oral and multiple injections of drugs, intra-articular drug delivery systems have been developed, which can prolong retention time, increase local bioavailability, and reduce systemic exposure [52].

4.1.1. Triamcinolone

Triamcinolone is a synthetic glucocorticoid that can be used to treat OA and relieve pain. Michiel and colleagues revealed that triamcinolone strongly induces monocyte differentiation into $CD163^+$ and $FR\beta^+$ macrophages in vitro, promoting IL-10 expression and preventing osteophyte formation in a rat OA model [53].

Intra-articular injection of triamcinolone into arthritis patients can eventually lead to drug resistance and serious local and systemic side effects. In this respect, the use of nanomaterials with low toxicity, high cell targeting capacity, and sustained drug release ability to regulate immune response is a valuable strategy. Triamcinolone–gold nanoparticle complex was found to promote the transition of synovial macrophages from M1 to M2 phenotype and the cartilage regeneration in OA [54]. Another study developed a CD90 + mesenchymal stem cell-derived microvesicle (MSC-MV)-coated Poly (lactic-*co*-glycolic acid) (PLGA) nanoparticle encapsulated with triamcinolone acetonide (T-CD90@NP). MSC-MV has been reported to promote repair and regeneration of osteochondral defects and alleviate OA degeneration[55]. It is shown that T-CD90@NP promotes the regeneration and reduced apoptosis of chondrocytes, and enhances M2 polarization of macrophages to regulate inflammation in rat and rabbit OA models [56].

4.1.2. Dexamethasone

As one of the common glucocorticoid family members, dexamethasone (DEX) has historically been applied topically to improve cartilage matrix degeneration and joint inflammation microenvironment [57]. Studies have found that DEX inhibits M1 macrophages while promoting M2 macrophages, and has anti-inflammatory effects on IFNγ + TNFα-stimulated synovial explants [58].

Hydrogel as a drug delivery system has been used to prolong the retention time of drugs in joints and reduce the side effects caused by repeated injections and long-term administration. Zhou et al. constructed injectable self-healing hydrogels through the Schiff base reaction of hydrazide-grafted hyaluronic acid (HA-ADH) and aldehyde-modified dextran (Dex-ALH), and dexamethasone acetate (DA) loaded poly(ethylene glycol)-*b*-polythioketal-*b*-poly(ethylene glycol) (PEG-PTK-PEG) micelles were encapsulated into hydrogels to build a ROS-scavenging and drug-release platform, solving the problem of sustained drug release. Intra-articularly administered multifunctional injectable hydrogels effectively reduce inflammation and significantly alleviates OA symptoms by depleting ROS and inhibiting inflammatory cytokines, as well as downregulating the proportion of pro-inflammatory M1 macrophages in a rat OA model [59].

4.1.3. Celecoxib

Celecoxib (CLX), a selective cyclooxygenase-2 inhibitor belonging to the NSAID class, is used to release long-term osteoarthritis pain [60]. Fang and colleagues loaded DEX (DM) on microspheres composed of sodium alginate and hyaluronic acid, fabricated CLX microcrystals (CM) by ultrasonic method, and finally cross-linked poloxamer 407 (P407) and Gantrez® S97 (GS97) to synthesize GZF gel to encapsulate DM and CM to construct intra-articular injection gel (DM/CM/Gel). The DM/CM/Gel system shows a favorable safety profile in vitro. It can inhibit M1 polarization of macrophages, and downregulate inflammation, chondrocyte erosion, and chondrocyte loss in vivo [61].

4.1.4. Metformin

Metformin is the first-line pharmacologic treatment for type 2 diabetes. In addition to the hypoglycaemic effect, metformin has been proven to have anti-inflammatory, anti-ageing and weight lose effects [62–64]. And studies have reported that metformin can inhibit the progression of OA by targeting AMP-activated protein kinase (AMPK) in chondrocytes [65,66]. Li et al. revealed that metformin decreases apoptosis and catabolism in chondrocytes, inhibits the infiltration and

M1 polarization of synovial macrophages, thus protects against knee OA. In high-fat diet (HFD) OA mice, metformin additionally reduces leptin secretion from adipose tissue to protect OA knee [67].

4.1.5. Kmup-1

KMUP-1 is a chemical synthetic xanthine-based derivative developed by Yeh and his colleagues. Their group has found that KMUP-1 possesses multifunctional properties, including anti-inflammatory, cardioprotective, and neuroprotective roles [68–70]. Based on these findings, they investigated the in vitro anti-inflammatory and in vivo anti-osteoarthritis effects of KMUP-1. In vitro study showed that KMUP-1 downregulates LPS-induced inflammatory cytokines, MMPs and NO in RAW264.7 cells. KMUP-1 plays an anti-inflammatory role by suppressing the activation of MAPK/NFκB signaling pathway, which can be attenuated by SIRT1 inhibitor. In vivo study showed that KMUP-1 reduces mechanical hyperalgesia, inflammation and articular cartilage erosion in OA rats, suggesting that KMUP-1 inhibits articular cartilage degradation by regulating inflammation and is a potential agent for OA treatment [71].

4.1.6. Srt2104

The silent information regulator 2 type 1 (SIRT1) is an antiaging gene, which has been proved to prevent OA development [72]. SRT2104 is a highly selective SIRT1 activator. A recent study showed that both intraperitoneal injection and intra-articular injection of SRT2104 could reduce M1 macrophages and increase M2 macrophages in the synovium of OA mice, and hinder the progression of OA, suggesting that SRT2104 may serve as a new treatment for OA [73].

Information on conventional western medicine and synthetic compounds that regulate macrophage polarization is summarized in Table 1.

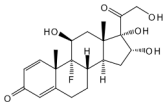
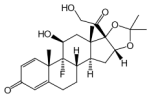
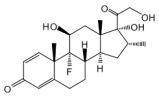
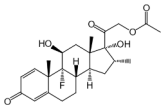
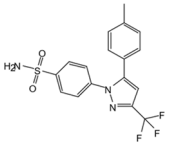
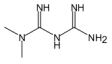
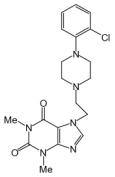
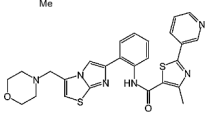
4.2. Monomer compounds of traditional Chinese medicine

In addition to the drug delivery systems, the investigation of traditional Chinese medicine (TCM) monomer compounds with anti-inflammatory and cartilage protective effects is another way to develop DMOADs.

4.2.1. Liquiritin

Liquiritin, is an antioxidant isolated from *Glycyrrhizae uralenis* with neuroprotective, anti-cancer, anti-inflammatory and cartilage protective

Table 1
Summary of information on conventional western medicine and synthetic compounds developed for osteoarthritis treatment.

Small molecules	Chemical formula	Property	Study models	Dosage	Immunoregulatory function	Signaling pathways; Target	Ref.
Triamcinolone		Glucocorticoid	CIA mouse model; J774 cells	2 mg/kg and 5 mg/kg; 500 ng/mL	M1↓ M2↑	Target: glucocorticoid receptor	[54]
Triamcinolone acetonide		Glucocorticoid	ACLT-induced OA rat and rabbit models	20 % (w/w) of the respective solutions during the PLGA core preparation	M1↓ M2↑	IL-10; Target: glucocorticoid receptor	[56]
Dexamethasone		Glucocorticoid	Synovial explants from OA patients; Primary human monocytes	1 μM	M1↓ M2↑	Target: glucocorticoid receptor	[58]
Dexamethasone acetate		Glucocorticoid	MIA-induced OA rat model	12.5 μg in hydrogel	M1↓ M2↑	Target: glucocorticoid receptor	[59]
Celecoxib		A selective cyclooxygenase-2 inhibitor	MIA-induced OA rat model; RAW264.7 cells	5 mg/mL; 25.80 ng/ml	M1↓	Target: COX-2	[60,61]
Metformin		Biguanide; hypoglycemic drug	DMM-induced OA in mice; Mouse bone marrow-derived macrophages (BMDMs); RAW264.7 cells	250 mg/kg/day; 2 mM; 2 mM	M1↓ M2↑	AMPK, mTORC1; Target: P-AMPK	[67]
KMUP-1		A chemical synthetic xanthine-based derivative	MIA-induced OA rat model; RAW264.7 cells	5 mg/kg; 1–10 μM	M1↓	MAPK, NFκB	[71]
SRT2104		A potent SIRT1 activator	DMM-induced OA mouse model	Intraperitoneal injection: 25 mg/kg, 0.2 mL; Intra-articular injection: 17 ng/kg, 10 μL	M1↓ M2↑	Target: SIRT1	[73]

CIA: collagen-induced OA; ACLT: anterior cruciate ligament transection; PLGA: poly(lactic-*co*-glycolic acid); MIA: monoiodoacetic acid; COX-2: cyclooxygenase-2; DMM: destabilization of the medial meniscus; AMPK: AMP-activated protein kinase; mTORC1: mammalian target of rapamycin C1; MAPK: mitogen-activated protein kinase; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; SIRT1: silent information regulator 2 ortholog 1.

activities [74–76]. He et al. developed a composite carrier with dual antioxidant effects based on liquiritin-loaded liposomes and the injectable chondroitin sulfate hydrogel (ChsMA@Lipo). ChsMA@Lipo inhibits macrophage M1 polarization and the inflammasome activation by suppressing the MAPK and NFκB signaling pathways, attenuates IL-1β-induced extracellular matrix (ECM) degradation in chondrocytes, and alleviates the progression of OA, which is a promising treatment for OA [77].

4.2.2. Quercetin

Quercetin, a natural flavonoid, can regulate synovial macrophage polarization to M2 phenotype by activating STAT6/Akt signaling pathway, and inhibit chondrocyte inflammation and apoptosis in vitro. Therefore quercetin provides a pro-chondrogenic environment in vivo and is a potential drug for the treatment of OA [78].

4.2.3. Kinsenoside

Kinsenoside, a major active ingredient isolated from *Anoectochilus roxburghii*, inhibits inflammation signals by targeting IKK phosphorylation [79]. The authors further revealed that kinsenoside reduces the infiltration of M1 macrophages and promotes the infiltration of M2 macrophages in the synovium by inhibiting the NFκB/MAPK signaling pathway, thereby inhibiting subchondral bone destruction and articular cartilage damage in OA [80].

4.2.4. Pseudolaric acid B

Pseudolaric acid B, a diterpene acid isolated from the roots of Pseudolarix kaempferi Gorden (pinaceae), inhibits NFκB signaling by stabilizing PPARγ, thereby reducing macrophage M1 polarization and angiogenesis, and attenuating articular cartilage degeneration during OA and synovitis [81].

4.2.5. Angelicin

Angelicin is a tricyclic aromatic compound isolated from *Angelica Sinensis* with anti-inflammatory, antibacterial, antitumor and antiviral activities. Angelicin can promote the repolarization of M1 to M2 macrophages by activating the p-STAT3/STAT3 signaling pathway, and decelerate the development of post-traumatic osteoarthritis (PTOA), showing an effective therapeutic value [82].

4.2.6. Fargesin

Fargesin, one of the main components of *Magnolia fargesii*, exerts anti-inflammatory effects in THP-1 monocytes by suppressing PKC-dependent AP-1 and NFκB signaling [83]. Lu et al. showed that fargesin can significantly reduce the number of M1 macrophages, increase the number of M2 macrophages in OA mice by inhibiting p38/ERK MAPK and p65/NFκB signaling, alleviate synovitis and thus improve OA [84].

4.2.7. Capsaicin

Capsaicin, the active ingredient in capsicum, activates the Ca^{2+}/CaMKII/Nrf2 signaling pathway through the ion channel TRPV1 and inhibits M1 polarization of macrophages in the synovium, thereby attenuating OA phenotypes including joint swelling, synovitis, cartilage damage, and osteophyte formation [85].

4.2.8. Frugoside

Frugoside, a cardiac glycoside compound isolated and extracted from *Calotropis gigantea*, inhibits macrophage M1 polarization by down-regulating miR-155 levels, thereby reducing synovial inflammation and delaying OA progression in mice [86].

4.2.9. Digoxin

Digoxin, another common cardiac glycoside, can suppresses inflammation and alters lipid metabolism. Thus, digoxin has been studied for the treatment of atherosclerosis, steatohepatitis and autoimmune arthritis [87–89].And Ouyang et al. revealed that digoxin improves steatohepatitis by suppressing PKM2-ROS transactivation [89,90]. Based on the above researches, Lee et al. focused on the role of digoxin in OA. They suggested that digoxin alleviates synovitis by inhibiting the M1 polarization of synovial macrophages in OA. Mechanically, digoxin controls OA inflammatory microenvironment and promotes chondrogenesis by downregulating the M1 macrophage-derived exosomal miR-146b-5p/Usp3&Sox5 axis [91].

4.2.10. Nicotine

Nicotine, an alkaloid, is the main component of *Nitotiana tobacum* and a potent agonist to nicotinic acetylcholine receptors (nAChRs). Teng et al. found that in monosodium iodoacetate (MIA)-induced OA mice, nicotine markedly inhibits mechanical allodynia and cartilage degradation by activating a7-nAChRs. And in LPS treated RAW264.7 cells, nicotine inhibits the expression of MMP-9 by activating PI3K/Akt, and suppresses NFκB activation, both of which depend on α7-nAChRs. Taken together, nicotine can attenuate joint inflammation and pain in experimental OA via α7-nAChRs/ PI3K/Akt/ NFκB, which is a potential agent for OA treatment [92].

Information on monomer compounds of TCM that regulate macrophage polarization is summarized in Table 2.

4.3. Biomacromolecules

Biomacromolecules are natural active ingredients contained in animals, including proteins, polypeptides, nucleic acids, glycans and lipids. Biomacromolecular drugs have strong specificity, high pharmacological activity, and small dosage. They have unique advantages that traditional small molecule drugs do not have in the treatment of various diseases, and have become one of the most promising hot fields for new drug development.

4.3.1. Macromolecular hyaluronic acid

Intra-articular injection of hyaluronic acid (HA) is a broad treatment option to replace the loss of viscoelastic synovial fluid in OA joints. In OA joints, where HA concentrations in synovial fluid are consistently lower than in healthy joints, additional high-molecular HA supplementation can be used to increase viscosity, reduce inflammation, enhance ECM protein synthesis, and maintain cartilage thickness, area, and surface smoothness [93]. Recent studies have found that in an in vitro inflammation model, macromolecular HA can reduce chondrocyte inflammation caused by co-culture of M1 macrophages, reduce its catabolism level, and have a protective effect on chondrocytes [94]. Mechanistic studies have shown that macromolecular HA inhibits IL-1β-induced synovial inflammation and M1 polarization of macrophages through the GRP78-NFκB signaling pathway [95].

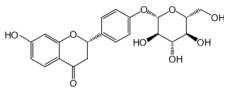
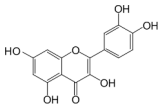
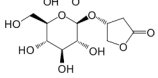
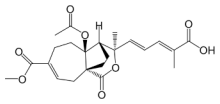
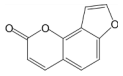
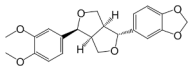
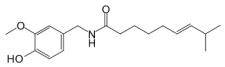
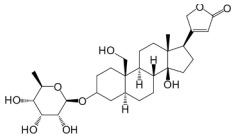
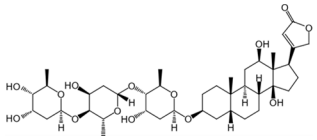
4.3.2. Squid type II collagen

Type II collagen is an indispensable collagen component in articular cartilage and plays a crucial role in the development and maturation of chondrocytes. Therefore, type II collagen or type II collagen-derived composites have attracted more attention and interest in the treatment and research of OA. Squid type II collagen (SCII) has a similar amino acid composition to terrestrial animal type II collagen and is not immunogenic. In addition, studies have shown that SCII can inhibit M1 macrophages by promoting the dephosphorylation of p-STAT1, promote the proportion of M2 macrophages in synovial fluid, and increase the production of pro-chondrogenic cytokines (TGF-β1 and TGF-β3) level, thereby promoting cartilage repair in OA [96,97].

4.3.3. Liraglutide

Liraglutide is a modified human glucagon-like peptide-1 (GLP-1) for the treatment of type II diabetes with anti-inflammatory and anti-catabolic effects. Intra-articular injection of liraglutide reduces pain in a mouse model of OA. In vitro experiments showed that liraglutide shifts the polarized macrophage phenotype from a pro-inflammatory M1

Table 2
Summary of information on monomer compounds of TCM developed for osteoarthritis treatment.

Small molecules	Chemical formula	Property	Study models	Dosage	Immunoregulatory function	Signaling pathways; Target	Ref.
Liquiritin		An antioxidant isolated from *Glycyrrhizae uralenis*	DMM-induced OA rat model	Intra-articular injection at 40 mg/mL as liposomes and 140 mg/mL as ChsMA@Lipo, 50 μL.	M1↓	MAPK, NFκB; Target: MAPK	[75,77]
Quercetin		A natural flavonoid	DMM- and ACLT-induced OA rat model; RAW264.7 cells	Intra-articular injection at 8 μM; 100 μL; 8 μM	M2↑	AMPK/SIRT1, STAT6, Akt	[78]
Kinsenoside		A major active ingredient isolated from *Anoectochilus roxburghii*	ACLT-induced OA mouse model; RAW264.7 cells	Intraperitoneal injection at 2.5, 5 and 10 mg/kg kinsenoside; 6.25–25 μg/mL	M1↓ M2↑	MAPK, NFκB and STAT6; Target: p-IKK	[79,80]
Pseudolaric acid B		A diterpene acid isolated from the roots of *Pseudolarix kaempferi* Gorden (pinaceae)	DMM-induced OA mouse model; RAW264.7 cells	Intra-articular injection at 5 and 10 mg/kg; 0.75 and 1.5 μM	M1↓	PPARγ- NFκB; Target: PPARγ	[81]
Angelicin		A tricyclic aromatic compound isolated from *Angelica Sinensis*	DMM-induced OA mouse model; BMDMs	Intraperitoneal injection at 20 mg/kg; 30 μM	M1↓ M2↑	CD9/gp130/STAT3	[82]
Fargesin		One of the main components of *Magnolia fargesii*	CIOA mouse model; RAW264.7 cells	Intra-articular injection at 5, 10, or 20 mg/kg, 10 μL; 10, 20, and 40 μM	M1↓ M2↑	MAPK, NFκB; Target: PKC	[83,84]
Capsaicin		The active ingredient in capsicum	DMM-induced OA rat model; RAW264.7 cells	Intra-articular injection at 50 μM, 50 μL; 50 μM	M1↓	TRPV1/Ca^{2+}/CaMKII/Nrf2; Target: TRPV1	[85]
Frugoside		A cardiac glycoside compound isolated and extracted from *Calotropis gigantea*	CIOA mouse model; RAW264.7 cells; Primary mouse peritoneal macrophages	Intra-articular injection at 0.2 mg/kg; 25 μM, 50 μM and 100 μM for macrophages	M1↓	miR-155	[86]
Digoxin		A cardiac glycoside	CIOA mouse model; RAW264.7 cells; Human synovial macrophages of OA patients	Intra-articular injection at 0.02 (L) or 0.2(H) mg/kg; 60 μM	M1↓	Target: PKM2	[89–91]
Nicotine		A potent agonist to nAChRs	MIA-induced OA mouse model; RAW264.7 cells	Intraperitoneal injection at 0.5 or 1 mg/kg; 10 μM	M1↓	α7-nAChRs/PI3K/Akt, α7-nAChRs/NFκB; Target: α7-nAChRs	[92]

DMM: destabilization of the medial meniscus; MAPK: mitogen-activated protein kinase; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; ACLT: anterior cruciate ligament transection; AMPK: AMP-activated protein kinase; SIRT1: silent information regulator 2 ortholog 1; STAT: signal transducer and activator of transcription; Akt: protein kinase B; p-IKK: phosphorylated kappa B inhibitor protein kinase; PPARγ: peroxisome proliferator-activated receptor γ; gp130: glycoprotein 130; PKC: protein kinase C; CIOA: collagenase-induced OA; TRPV1: transient receptor potential vanilloid 1; CaMKII: Ca2+/calmodulin dependent protein kinase II; Nrf 2: nuclear factor-erythroid 2-related factor 2; PKM2: M2-type pyruvate kinase; MIA: monoiodoacetic acid; α7-nAChRs: alpha7 nicotinic acetylcholine receptor; PI3K: phosphatidylinositol 3-kinase; BMDMs: bone marrow-derived macrophages.

phenotype to an anti-inflammatory M2 phenotype, and has anti-chondrocyte catabolic activity, thus serving as a candidate for OA treatment [98].

4.3.4. Itch

Ubiquitination is a general protein post-translational modification mediated by ubiquitin E1, E2 and E3 ligases. Ubiquitinated proteins are degraded and thereby lose their biological function. The ubiquitin E3 ligase Itch is a potent negative regulator of inflammation that limits OA progression by inhibiting M1 macrophage polarization [99]. Previous study has reported that Itch can be recruited to A20 by the regulatory molecule TAX1BP1, thus regulating A20-mediated NFκB inactivation and inhibiting inflammation [100]. Therefore, it is speculated that Itch may regulate the polarization of macrophages through the above mechanisms.

4.3.5. Mfg-E8

Milk fat globule-epidermal growth factor (EGF) factor 8 (MFG-E8) has been extensively studied in various organs and diseases as an essential bridging molecule between apoptotic cells and phagocytes.

MFG-E8 can inhibit neuronal inflammation by driving microglial M2 polarization, which may be mediated by modulation of the integrin β3/SOCS3/STAT3 signaling pathway [101]. Loss of MFG-E8 can result in marked progressive articular cartilage damage, synovial hyperplasia, and massive osteophyte formation in OA mice, which can be alleviated by intra-articular injection of recombinant mouse MFG-E8 (rmMFG-E8). Mechanistically, MFG-E8 is inhibited by miR-99b-5p, whose expression is significantly upregulated in OA cartilage, in part by activating NF-κB signaling in chondrocytes, leading to the exacerbation of experimental OA. Whereas rmMFG-E8 can downregulate NFκB signaling, promote macrophage M2 polarization, delay chondrocyte senescence, and thus alleviate OA progression [102].

4.3.6. Alpha-defensin-1

Alpha-defensin-1 is one of the most potent defensins. In vitro experiments showed that it can promote M1 macrophage to M2 macrophage polarization and indirectly protect chondrocytes. In a rat model of OA, α-defensin-1 alleviates the severity of OA, thus can serve as a candidate treatment for OA [103].

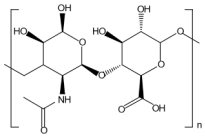
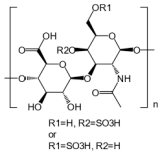
4.3.7. Chondroitin sulfate

Chondroitin sulfate is a sulfated glycosaminoglycan commonly found in connective tissue and cartilage with many beneficial properties, such as anti-inflammatory activity, antioxidant activity, and maintenance of the chondrogenic phenotype [104–106]. As mentioned above in this review, the composite carrier with dual antioxidant effects based on liquiritin-loaded liposomes and the injectable chondroitin sulfate hydrogel (ChsMA@Lipo) inhibits macrophage M1 polarization and the inflammasome activation, attenuates IL-1β-induced extracellular matrix (ECM) degradation in chondrocytes, and alleviates the progression of OA, which is a promising treatment for OA [77].

4.3.8. Il-4

IL-4, a type 2 inflammatory cytokine, is an inducer of macrophage M2 polarization and is well-known for its role in promoting tissue healing. Stimulation of macrophages, osteoclasts, and synovial explants

Table 3
Summary of information on biomacromolecules developed for osteoarthritis treatment.

Biomacromolecules	Chemical property	Property	Study models	Dosage	Immunoregulatory function	Signaling pathways; Target	Ref.
Macromolecular Hyaluronic acid	 M_W 1000–2000 kDa	The viscoelastic component of synovial fluid	Primary synovial cells from OA patients; THP-1 cells	1 mg/mL	M1↓ M2↑	GRP78/NFκB	[93–95]
Squid type II collagen	~110 kDa	Has a similar amino acid composition to terrestrial animal type II collagen	ACLT- and DMM-induced OA rat model; RAW264.7 cells	Intra-articular injection at 3 mg/mL and 10 mg/mL, 100 μL; Cells seeded on SCII-coated plates (3 mg/mL)	M1↓ M2↑	STAT1, STAT6	[96,97]
Liraglutide	$C_{172}H_{265}N_{43}O_{51}$ M. Wt: 3751.25	A modified human glucagon-like peptide-1	MIA-induced OA mouse model; RAW264.7 cells	Intra-articular injection at 20 g; 50 nM	M1↓ M2↑	Target:GLP-1R	[98]
Itch	~40 kDa	Ubiquitin E3 ligase	MLI- or DMM-induced OA in Itch$^{-/-}$ mice; Itch$^{-/-}$ BMDMs		M1↓	Speculated target: the ubiquitin-editing enzyme A20	[99,100]
rmMFG-E8	~45 kDa	A secreted glycoprotein	DMM-induced OA mouse model; BMDMs; RAW264.7 cells	Intra-articular injection at 50 μg/kg; 500 ng/mL	M1↓ M2↑	NFκB; Speculated target: integrin β3	[101,102]
α-Defensin 1	3.4 kDa (30 amino acids)	A multifunctional low molecular weight molecule released from apoptotic neutrophils	MLI-induced OA rat model; THP-1 cells	Intra-articular injection at 10 ng/mL, 250 μL; 10 ng/mL	M1↓ M2↑		[103]
Chondroitin sulfate	 R1=H, R2=SO3H or R1=SO3H, R2=H	An important component of cartilage with inflammatory activity, antioxidant activity, the regulation of enzyme activity, and maintenance of the chondro- genic phenotype.	DMM-induced OA rat model	Intra-articular injection at 100 mg/mL as ChsMA microgel and 140 mg/mL as ChsMA@Lipo, 50 μL	M1↓	MAPK, NFκB	[77,106]
IL-4	13.7 kDa	A type 2 inflammatory cytokine	Human synovial tissue explants; human macrophages from peripheral blood monocytes; BMDMs	10 ng/mL	M2↑	STAT6; Target: IL-4R	[107]

ACLT: anterior cruciate ligament transection; MIA: monoiodoacetic acid; MLI: meniscus ligamentous injury; DMM: destabilization of the medial meniscus; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; STAT: signal transducer and activator of transcription; GRP78: 78-k_D glucose-regulated protein; MAPK: mitogen-activated protein kinase; BMDMs: bone marrow-derived macrophages; GLP-1R: glucagon-like peptide-1 receptor.

with IL-4 in vitro suggests that IL-4 can modulate the immune microenvironment, induce polarization of joint-resident macrophages toward the M2 phenotype, effectively clear pro-inflammatory debris, and maintain steady-state activity levels of osteoclasts in subchondral bone. Thus IL-4 could be a candidate pathway for OA treatment [107].

In recent years, biomacromolecule drugs have gradually emerged, including vaccines, blood component products, cell therapy preparations, gene therapy preparations and recombinant therapeutic proteins, which have been used for the treatment of tumors, autoimmune diseases and metabolic diseases. However, the complex structure of biological macromolecules, the difficulty in development, the difficulty in permeating through biological membranes, and the high clinical cost limit its clinical application.

Information on biomacromolecules that regulate macrophage polarization is summarized in Table 3.

4.4. Metal and metal oxides

Metal/metal oxides have unique physical properties. They can simulate the activity of antioxidant enzymes and catalyze the degradation of superoxide anions and hydrogen peroxide. And metal/metal oxide nanoparticles (NPs) are widely used in drug delivery due to their good stability and cell uptake efficiency.

4.4.1. Magnesium ions

Magnesium ions (Mg^{2+}) can support MSC chondrogenesis and regulate macrophage polarization [108–110]. JDBM is a biodegradable Mg-Nd-Zn-Zr alloy with excellent biocompatibility, strength and ductility. Zhao et al. fabricated JDBM scaffolds coated with polydopamine, which can promote chondrogenesis and effectively attenuate local inflammatory responses by transforming synovial macrophages from the M1 to M2 subtype, representing a promising material for OA treatment [111].

4.4.2. Manganese dioxide

Manganese dioxide (MnO_2) NPs can decompose H_2O_2 and release oxygen, which are used to scavenge ROS in the damaged microenvironment. Zhang et al. fabricated a camouflaged *meta*-Defensome, composed of a SAR targeting ligand, a mitochondrial targeting ligand, an OA synovium targeting (macrophage membrane coated PLGA nanoparticles (MMP) to target M1 macrophages), a mitochondrial iNOS (mtNOS) inhibitor, and MnO_2 NPs. The *meta*-Defensome was demonstrated to transform M1 synovial macrophages into the M2 phenotype by scavenging mtROS and inhibiting mtNOS, thereby effectively suppressing synovial inflammation and progression of early OA. Thus, mitochondrial metabolism reprogramming can serve as a novel and practical approach to repolarize M1 synovial macrophages. The camouflaged *meta*-Defensomes are a promising therapeutic agent for impeding OA progression [112].

4.4.3. Nanozymes

Hypoxia and high ROS levels are the characteristic pathological changes of osteoarthritis, which increase hypoxia-inducible factor-1α (HIF-1α) level, induce the conversion of M1 macrophages, suppress the production of extracellular matrix (ECM), and promote bone resorption. Prussian blue nanozymes have multi-enzymatic-like catalytic activities, which can effectively scavenge ROS and ameliorate the immune microenvironment, but their non-degradability hinders the further clinical translation [113]. Xiong et al. constructed a Hollow manganese Prussian blue nanozymes (HMPBzymes) with good pH-responsive biodegradation, biocompatibility, and multi-enzymatic activities. HMPBzymes suppress HIF-1α expression, decrease ROS level, modulate the conversion of M1 macrophages to M2 macrophages, and alleviate the degeneration of cartilage in OA rat models [114].

Although metal/metal oxides exhibit excellent physical and biological properties, the accumulation of metal/metal oxide NPs and their degradation release metal ions in vivo may lead to potential toxicity, so their long-term safety needs to be further monitored.

Information on metal and metal oxides that regulate macrophage polarization is summarized in Table 4.

4.5. Cells

In recent years, cell therapy has emerged as a promising therapeutic approach with the potential to treat and even cure various diseases. Cell therapy offers unique clinical and therapeutic advantages over traditional small molecules and increasingly biologics. In particular, living cells can simultaneously and dynamically perform complex biological functions that cannot be achieved by conventional drugs [115].

4.5.1. Stem cells

Taking mesenchymal stem cells (MSCs) as an example, MSCs are a class of cells with self-renewal and directed differentiation potential that can differentiate into multiple cell types, such as osteoblasts, adipocytes, and chondrocytes. Currently, MSCs have been widely used in cell-based therapy for clinical, preclinical and tissue engineering applications due to their immunomodulatory and regenerative properties [116]. Bone marrow, human umbilical cord, and adipose tissue-derived MSCs have emerged as a promising therapeutic strategy for the treatment of knee OA [117–119]. In addition to the ability of cartilage differentiation, MSCs have immunomodulatory properties by secreting anti-inflammatory factors, which can modulate macrophage polarization by inducing a transition from M1 to M2 phenotype, thereby attenuating cartilage damage and promoting tissue repair [120–122].

Other stem cell types, such as human dental pulp stem cells (hDPSCs) and amniotic fluid stem cells (AFSCs) have also been shown to have immunomodulatory functions and are used in OA treatment [123,124].

4.5.2. Macrophages

In addition to stem cells, macrophages can be directly injected into the joint site to play an immunomodulatory role and promote tissue repair. Bone marrow mononuclear cells (BMNCs) are a rich source of macrophage progenitors, the number of M2 macrophages and the concentration of IL-10 in the synovium are increased after injection of autologous BMNCs in equine OA joints. Histologically, BMNC- treated joints are comparable to healthy joints. Autologous BMNCs are readily available and may benefit thousands of patients [125].

In addition, Ma and colleagues developed artificial M2 macrophages composed of macrophage membrane as “shell” and inflammatory response nanogel as “yolk”, in which the nanogel was prepared by the physical interaction of gelatin and chondroitin sulfate through ionic and hydrogen bonds. Artificial M2 macrophages can reside in inflamed areas for a long time, down-regulate inflammation, and are continuously released to repair cartilage when there is low inflammatory activity, providing new ideas for OA treatment [126].

Information on cells that regulate macrophage polarization is summarized in Table 5.

4.6. Cell derivatives

Although many cell therapy-based clinical trials have demonstrated promising results, there are some drawbacks such as technical limitations of in vitro expansion, low in vivo survival and potential immune rejection [127–129].

4.6.1. Extracellular vesicles

In fact, numerous studies have shown that the therapeutic potential of MSCs and macrophages is mainly attributed to their paracrine factors, especially small extracellular vesicles (EVs) [130–132]. MSCs-derived EVs (MSC-EVs) have similar biological functions to MSCs, such as promoting cartilage regeneration, suppressing inflammatory responses, and modulating the immune system, and are potential alternative therapies

Table 4
Summary of information on metal and metal oxides developed for osteoarthritis treatment.

Metal/metal oxides	Property	Study models	Dosage	Immunoregulatory function	Signaling pathways; Target	Ref.
Magnesium ions	Function in the form of Mg-Nd-Zn-Zr alloy scaffold	RAW264.7 cells	JDBM extracts (10 mM Mg)	M1↓ M2↑	NFκB; Target: TRPM7	[110,111]
Manganese dioxide	ROS scavenger; Function in combination with a SAR targeting ligand, a mitochondrial targeting ligand, an OA synovium targeting, and a mitochondrial iNOS inhibitor	CIOA mouse model; RAW264.7 cells	Intravenous injection at 1 mg/mL *meta*-Defensomes, 100 μL; 1 mg/mL *meta*-Defensomes	M1↓ M2↑	Mitochondrial metabolic reprogramming; Target: ROS	[112]
Nanozymes	A Hollow manganese Prussian blue nanozymes	MIA-induced OA rat model; BMDMs	Intra-articular injection at 80 μg/mL; 80 μg/mL	M1↓ M2↑	Scavenger active oxygens; Target: ROS	[114]

CIOA: collagenase-induced OA; MIA: monoiodoacetic acid; BMDMs: bone marrow-derived macrophages; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; iNOS: inducible nitric oxide synthase; ROS: reactive oxygen species; TRPM7: transient receptor potential cation channel member 7. JDBM: porous Mg-Nd-Zn-Zr alloy.

Table 5
Summary of information on cell therapies developed for osteoarthritis treatment.

Cells	Study models	Dosage/cells	Immunoregulatory function	Ref.
AMSCs	CIOA mouse model	Intra-articular injection with 20,000 cells in 6 μL mouse serum	M1↓	[120]
BMSCs	Mouse BMDMs	Co-culture with BMDMs	M1↓ M2↑	[121]
hUCMSCs	ACLT-induced OA rat model	Intra-articular injection with 200 μL hUCMSCs (5×10^5),	M1↓ M2↑	[122]
hDPSCs	Cut of the medial parenchyma of the ACL and the meniscus ligament-induced OA rabbit model; Human osteoarthritic macrophage	Intra-articular injection at 2×10^5/knee joint and 1×10^6/knee joint, 250 μL; Co-culture with 2×10^6 osteoarthritic macrophages	M1↓ M2↑	[123]
AFSCs	MIA-induced OA rat model	Intra-articular injection at 5×10^5/knee joint, 50 μL	M1↓ M2↑	[124]
BMNCs	0.5 ng LPS in 2 mL PBS-induced synovitis horse model	Intra-articular injection at 20×10^6 cells mixed with LPS	M2↑	[125]
Artificial M2 macrophages	Papain solution-induced OA mouse model; RAW264.7 cells	Injection with 20 μL AM2M (14.62 mg/kg); AM2M containing 0.6 mg/mL ChS@GC	M2↑	[126]

AMSCs: adipose-derived mesenchymal stem cells; BMSCs: bone marrow mesenchymal stem cells; hUCMSCs: Human umbilical cord mesenchymal stem cells; hDPSCs: human dental pulp stem cells; AFSCs: amniotic fluid stem cells; BMNCs: bone marrow mononuclear cells; AM2M: artificial M2 macrophages; BMDMs: bone marrow-derived macrophages; CIOA: collagenase-induced OA; BMDMs: bone marrow-derived macrophages; ACLT: anterior cruciate ligament transection; MIA: monoiodoacetic acid.

for the treatment of OA [133–135].

Zhang and colleagues demonstrated that EVs derived from bone marrow MSCs (BMSC-EVs) can alleviate cartilage damage, reduce osteophyte formation, and alleviate arthritis by inhibiting M1 macrophage production and promoting M2 macrophage production [136].

Intra-articular injection of human umbilical cord mesenchymal stem cell EVs (hUCMSC-EVs) in OA knees can significantly reduce the proportion of M1 macrophages, increase the proportion of M2 macrophages, and alleviate cartilage damage. Mechanistically, EVs upregulate many proteins related to cartilage repair, which are mainly involved in immune regulation [122,137]. A recent study showed that hUCMSC-EVs inhibit the secretion of pro-inflammatory factors and the degradation of cartilage ECM by lowering the m6A level of NLRP3 mRNA with miR-1208 targeting and combining with METTL3, thereby alleviating OA progression in mice[138].

Adipose-derived mesenchymal stem cells EVs (AMSC-EVs) can prevent cartilage degeneration, inhibit the infiltration of M1 macrophages into the synovium, and significantly slow OA disease progression [139]. Mechanistic studies showed that MSC-EVs highly express a variety of miRNAs, which contribute to chondroprotection and M1 to M2 macrophage polarization [137,140,141].

4.6.2. Platelet-rich plasma

Many studies have reported positive effects of platelet-rich plasma (PRP) administration in patients with knee OA [142–144]. PRP contains high concentrations of growth factors and inflammatory factors that stimulate soft tissue healing and promote bone or cartilage regeneration, and direct injection of PRP can modulate the inflammatory environment of joints [145–147]. One of the molecular mechanisms by which PRP exerts this modulation is to prevent the activation of NFκB target genes [148]. At the cellular level, addition of PRP supernatant to the culture medium of monocyte-derived macrophages and M1 polarized macrophages significantly inhibits M1 macrophage polarization and promotes M2 macrophage polarization, further validating the immunomodulatory effect of PRP [149].

4.6.3. Cell-free fat extract

On the other hand, given the abundant cell populations, excellent paracrine function, and immunomodulatory properties exhibited by secreted factors and EVs in adipose tissue, Zhang and colleagues developed a novel cell-free fat extract (CEFFE) [150]. They mechanistically isolated protein extracts containing a large number of growth factors and inflammatory factors from adipose tissue, and confirmed that CEFFE has anti-inflammatory, anti-apoptotic, anti-oxidative, and pro-cell proliferation properties. A recent study showed that CEFFE can inhibit macrophage M1 polarization, reduce ROS production, and promote cartilage regeneration, thereby inhibiting OA progression [151]. As a new stem cell derivative with no cells, no side effects, unlimited materials and multiple physiological functions, CEFFE will be a promising alternative therapy for OA. The development time of CEFFE is still short, so key issues such as its preparation process and standards, immunogenicity, and largescale clinical application remain to be resolved.

Information on cell derivatives that regulate macrophage

polarization is summarized in Table 6.

5. Conclusions

Osteoarthritis is a highly prevalent human degenerative joint disorder. At present, there are no approved disease-modifying drug available, which brings a heavy burden to the global health system. Efforts for developing DMOADs have been made. Macrophage polarization is involved in joint pain and OA development, which is the key for OA treatment. In the future, it will be an effective strategy to develop treatment measures for OA through modulating macrophage repolarization (M1-M2).

Small molecule compounds, biomacromolecules, metal/metal oxides, cells, and cell derivatives are the most widely studied macrophage-based therapeutic strategies. (1) Clinical OA drugs, such as glucocorticoids and NSAIDs are not effective in preventing disease progression and are often accompanied by side effects. Traditional Chinese medicines and their monomers, such as Kinsenoside, may bring new hope for the development of DMOADs. In view of the fact that most of the above natural compounds are still in the preclinical research stage, it will take years of development before they can be used in patients with OA; (2) Biomacromolecules have strong specificity and high pharmacological activity, and have broad prospects for drug development. Most biological macromolecules have complex structures and are not easy to penetrate biological membranes, which makes their development difficult and clinically expensive, further limiting their widespread use; (3) Metal/metal oxides as scavengers of ROS are commonly loaded into scaffolds or nanomaterials to play an anti-inflammatory role. The toxicity caused by the accumulation of material degradation products and metal ions in vivo needs to be considered; (4) Stem cell therapy has been a hotspot in disease treatment research in recent years. MSCs have the characteristics of self-renewal, multi-directional differentiation and immune regulation. They can be expanded and cultured in vitro and then transplanted into the injury site for directional differentiation, regulate inflammation at the injury site, and promote tissue regeneration, showing great advantages in bone and cartilage regeneration. Encouragingly, MSCs for osteoarthritis are currently in clinical trials; (5) Stem cell derivatives contain a variety of growth factors and inflammatory factors. They are the main components of stem cells to play a therapeutic role, and they do not require in vitro expansion and have low immunogenicity. However, the high cost, potential risks, lack of standardization in preparations of cells and their derivatives need to be further improved before clinical applications.

6. Perspectives

6.1. Drug delivery systems

All the above treatment schemes face problems such as short drug residence time, poor cartilage permeability, and unstable local drug concentration. Drug sustained-release carrier is a powerful tool to solve the above problems. Microparticles, nanoparticles, liposomes, and hydrogels can improve drug permeability, prolong bioavailability, and greatly improve drug efficacy. Drug delivery systems may be the development direction of intra-articular drug injection.

6.2. Macrophage-targeting therapy

In addition to improving the drug retention rate in the joint cavity, macrophage-targeting therapy is another research emphasis to improve the efficacy.

ligand-decorated NPs were developed to target synovial macrophages. The ligands recognize and bind the typical pattern recognition receptors (PRRs) distributed on the surface of the macrophages. For example, Zhou et al. developed anti-CD16/32 antibody, S-methylisothiourea hemisulfate salt (SMT) and catalase (CAT) modified ZIF-8 NPs, and Zhang et al. developed SAR targeting ligand, SMT and MnO_2 decorated polymeric nanoparticles to target M1 macrophages and regulate intracellular NO and ROS, both of which can successfully attenuate osteoarthritis [112,152].

M1 macrophages in the OA synovium secretes various inflammatory factors and MMPs that can accelerate the degradation of ECM, thereby promoting the apoptosis of chondrocyte [8,153]. These apoptotic chondrocyte debris will be engulfed and cleared by synovial macrophages via efferocytosis [16,154]. Besides, cell efferocytosis has been proven to promote macrophage proliferation and polarization to M2 phenotype [155]. Thus, mimicking cell apoptosis to induce cell efferocytosis is another macrophage-targeting therapy. Kraynak and colleagues synthesized phosphatidylserine-supplemented cell membrane-coated nanoparticles (PS-MNPs) to emulate key characteristics of the apoptotic cell surface. These PS-MNPs reduce inflammatory cytokine expression to promote an anti-inflammatory phenotypic shift in macrophages, without the use of small molecule inhibitors or other drugs [156]. Yang et al. developed metalorganic framework nanoparticles loaded with apoptotic chondrocyte membrane as “eat me” signals and quercetin as immunomodulator to treat osteoarthritis [157]. In addition to apoptotic chondrocyte membrane, membrane of MSCs or extracellular vesicles also can be used to target macrophages.

Macrophage membrane can target and reside in the inflamed area for a long time, which has been use for targeted treatment of osteoarthritis [112,126]. Artificial M2 macrophages with macrophage membrane as “shell” and inflammation-responsive nanogel as “yolk” can reside in the inflammatory area to modulate inflammation and repair cartilage, providing new ideas for OA treatment.

6.3. Direction of clinical treatment of osteoarthritis

Early OA clinical treatments involve intra-articular injection of glucocorticoids, oral acetaminophen and NSAIDs, which will lead to inevitable side effects. At present, there is an immense clinical need for novel

Table 6
Summary of information on cell derivatives developed for osteoarthritis treatment.

Cell derivatives	Source	Study models	Dosage	Immunoregulatory function	Ref.
Exosomes	BMSCs	Modified Hulth technique-induced OA rat model; RAW264.7 cells	Intra-articular injection at 10^{10} particles/mL, 10 μL; 1 μg/mL	M1↓ M2↑	[136]
EVs	hUCMSCs	DMM-induced OA mouse model; THP-1 cells	Intra-articular injection at 10^{11} particles/mL; /	M1↓ M2↑	[138]
Small EVs	AMSCs	MIA-induced OA rat model	Intra-articular injection at 1 × 108 particles, 30 μL per joint	M1↓ M2↑	[139]
PRP	Blood	Monocytes isolated from human peripheral blood	10 % LP-PRP in the culture medium	M1↓ M2↑	[148,149]
CEFFE	Fat tissue	MIA-induced OA rat model; RAW264.7 cells	Intra-articular injection at 0.0357 mg, 0.075 mg, 0.15 mg, 60 μL per joint; 100 μg/mL, 250 μg/mL, and 500 μg/mL	M1↓ M2↑	[151]

EVs: Extracellular vesicles; BMSCs: bone marrow mesenchymal stem cells; hUCMSCs: Human umbilical cord mesenchymal stem cells; AMSCs: adipose-derived mesenchymal stem cells; PRP: platelet rich plasma; CEFFE: cell-free fat extract; DMM: destabilization of the medial meniscus; MIA: monoiodoacetic acid.

DMOADs or regenerative therapies. At present, the OA treatment strategies under development include cartilage-targeting DMOADs, such as sprifermin, bone-targeting DMOADs, such as MIV-711, and inflammation- and pain-based DMOADs, such as XT-150. However, only a very few drugs have resulted in amelioration of joint structure and function and no pharmacological treatment has yet been able to halt or reverse OA progression in the long term [158]. The polarization regulation of synovial macrophages is a new target for OA treatment. Screening and identification of drugs that regulate macrophage polarization is expected to achieve a breakthrough in DMOADs.

For the middle stage of osteoarthritis, oral or intra-articular injection drugs have little effect. Articular cartilage defects caused by sports, aging, trauma, inflammation, etc. bring about disability and worldwide socioeconomic loss. However, due to its avascular and nearly acellular characteristic, cartilage tissue regeneration ability is limited to some extent. MSCs are considered to be a promising therapeutic strategy due to their immunomodulatory properties and multidirectional differentiation potential, including osteoblasts, chondrocytes and adipocytes. Clinical trials have verified the safety and effectiveness of MSCs in the treatment of osteonecrosis, osteoarthritis, spinal cord injury, ischemic stroke, type 2 diabetes, cirrhosis and other diseases. Stem cell therapy may be the future clinical development direction.

In the late stage of OA, extensive cartilage is destroyed, and the joint space is narrowed, so the joint structure needs to be supported by the surgical grafts. At present, the clinical treatment strategies for cartilage injury mainly include autogenous or artificial cartilage transplantation and artificial joint replacement. Artificial joint replacement is the passive choice at the end of severe cartilage injury. This strategy is not only unable to achieve “knee preservation treatment”, but also has a variety of postoperative complications such as joint pain and osteoporosis. Tissue engineering strategies based on smart scaffolds such as decellularized extracellular matrix (dECM) and stem cells maybe help to realize cartilage regeneration. Articular cartilage defect is usually accompanied by subchondral bone degeneration, which is an important and intractable clinical problem. Studies have proved that osteochondral regeneration in vivo can be achieved by integrating different scaffold materials or different modifications to construct an osteochondral integrated scaffold. Thus, the fabrication of biphasic cartilage-bone integrated scaffolds is an attractive strategy for osteochondral repair.

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Data availability

No data was used for the research described in the article.

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.

Data availability

No data was used for the research described in the article.

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