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Biomaterial strategies for improved intra-articular drug delivery

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Abstract

Osteoarthritis (OA) is a joint degenerative disease that has become one of the leading causes of disability in the world. It is estimated that OA affects 50 million adults in the U.S.A. Currently, there are no FDA-approved treatments that slow OA progression and its treatment is limited to pain management strategies and life style changes. Despite the discovery of several disease-modifying OA drugs (DMOADs) and promising results in pre-clinical studies, their clinical translation has been significantly limited because of poor intra-articular (IA) bioavailability and challenges in delivering these compounds to tissues of interest within the joint. Here, we review current OA treatments and their effectiveness at reducing joint pain, as well as novel targets for OA treatment and the challenges related to their clinical translation. Moreover, we discuss intra-articular (IA) drug delivery as a promising route of administration, describe its inherent challenges, and review recent advances in biomaterial-based IA drug delivery for OA treatment. Finally, we highlight the potential of tissue targeting in the development of effective IA drug delivery systems.

Keywords

Osteoarthritis; drug delivery; intra-articular; tissue-targeting

INTRODUCTION

Osteoarthritis (OA) is a joint degenerative disease characterized by cartilage loss, which leads to joint pain, swelling and stiffness. OA affected 303 million people in the world in 2017[(1)] and it was estimated that 30.8 million adults in the U.S.A. suffered from OA in 2011[(2)]. OA prevalence in the U.S.A has increased over the last years[(3)] and it is estimated to affect around 50 million people in 2020.[(4)]. In 2008, around 14 million people over 25 years old were affected by knee OA alone and around 50% of those cases required a total knee replacement[(5)]. Annual medical care expenses associated with OA are approximately $185.5

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billion dollars annually in the U.S.A.[6]. In a country with rapidly aging population and high incidence of obesity, the prevalence of OA is expected to increase[7]. A population-based study conducted in Sweden estimated that by 2032, around 30% of adults over 45 are expected to have consulted a physician for OA, and around half of those cases would be related to knee OA[3].

Despite the increasing prevalence of OA, no FDA-approved disease modifying OA drugs (DMOADs) exist[8] and its treatment is limited to pain management strategies and life style changes. Depending on the severity of the disease, OA patients require interventions ranging from weight management, physical therapy[9], dietary supplements[10] and systemic administration of anti-inflammatory and analgesic drugs[11],[12], and in more severe cases, intra-articular (IA) injections of hyaluronic acid (HA) [13] and total joint replacement[5]. However, these treatment strategies present limited long-term benefits and do not prevent or slow OA progression[9],[14],[15].

A variety of promising DMOAD candidates have been investigated[16],[17]. However, achieving appropriate IA bioavailability after systemic administration remains a major challenge [8]. Intra-articular injection offers an attractive route of drug administration for OA treatment[8]. Nevertheless, free drugs injected in the IA space are rapidly cleared, resulting in poor retention and insufficient drug concentrations in the tissues of interest[18]. This challenges evidence the need for biomaterial-based drug delivery vehicles able to improve the drug bioavailability into the relevant tissues[8].

In the following sections, we discuss current understanding of OA pathophysiology as well as the effectiveness of current treatment strategies. Furthermore, a section summarizing novel OA targets and promising DMOAD candidates is presented. We also describe the advantages and unmet challenges of IA drug delivery and present recent advances on IA drug delivery systems.

OA PATHOPHYSIOLOGY

According to its cause, osteoarthritis can be classified in idiopathic and secondary OA. The former has its origin on non-traumatic conditions, where factors such as age and gender have been identified to play a role[19]. It is estimated that by 2030, adults older than 65 years will account for around 50% of the total OA cases in the U.S.A[20]. Additionally, the prevalence of OA in men over 60 years is 10%, whereas it is 13% in women, who additionally experience more severe symptoms[7].

Secondary OA can develop as a result of metabolic disorders, traumatic events or mechanical misalignment[9]. In these cases, the etiology of OA is not fully understood, but it has been recently recognized that it is a multifactorial disease. Joint injury, abnormal joint development, metabolic disorders, obesity, age, biochemical reactions and inflammation have all been reported as possible OA causes[9],[19]. Some research groups have suggested that these factors could elicit changes in joint biology, mechanics and structure leading to impaired joint remodeling and the associated progressive degenerative changes characteristic of OA[21].

OA affects the joint as a whole and induces articular cartilage degeneration, subchondral bone remodeling and osteophyte formation, ligament laxity, weakening of peri-articular muscles and joint swelling[9] (Fig. 1). The exact mechanisms involved in OA progression and the interplay between articular tissues remain under investigation[22]. However, recent research has identified biological mechanisms and measured biomarker levels that have been used to partly recreate OA progression[8].

As OA advances, the articular cartilage experiences a continuous degeneration process characterized by partial surface lamina loss, chondrocyte hypertrophy and the appearance of cartilage fibrillations, calcified erosions and lesions[8]. These morphological damages are accompanied by cartilage matrix compositional changes such as proteoglycan depletion and collagen type II cleavage[22]. Furthermore, the activation of the nuclear factor NF-κB in hypertrophic chondrocytes, synovium macrophages and fibroblasts leads to the up-regulation of catabolic proteins including matrix metalloproteinases (MMPs), aggrecanases, cathepsins and A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) [4],[8],[22]. Moreover, the expression of transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) in chondrocytes, promotes blood vessel penetration into the hypertrophic cartilage and calcification[22]. This unbalanced bone remodeling induces subchondral bone sclerosis, cysts and osteophyte formation, which result in severe pain[4],[22]. Furthermore, the synovial membrane is affected by the infiltration of T lymphocytes, neutrophils and macrophages[22], which secrete pro-inflammatory mediators, cytokines and chemokines such as IL-1, IL-6, IL-15, TNF-α, nitric oxide and prostaglandins, which further exacerbate joint inflammation and cartilage degeneration[24]. Additionally, synoviocyte secretion of synovial fluid components is impaired, leading to poor viscous lubrication and shock absorption capacity[8]. In healthy patients, the hyaluronic acid concentration in the synovial fluid ranges from 2.5 to 4 mg/mL and has a molecular weight between 6300 and 7600 kDa; however, as a result of OA progression, its concentration and molecular weight decrease up to 1 – 2 mg/mL and 1600 – 3480 kDa, respectively[25].

Despite advances on elucidating the mechanisms involved in OA progression, there is still much investigation needed to fully comprehend OA pathophysiology. The lack of understanding of the underlying mechanisms of OA onset and development, in addition to difficulties in clinical trial design, as well as the need for more sensitive techniques to better detect changes related to OA progression[26], are all limitations that have hindered the development of appropriate disease-modifying OA drugs (DMOADs)[4],[8],[22].

CURRENT CLINICAL TREATMENTS FOR OSTEOARTHRITIS

Non-pharmacological management

Non-pharmacological approaches constitute the first line of treatment at early stages of OA progression and intend to reduce pain and improve joint functionality. The absence of mechanic loading increases cartilage degeneration[27], whereas excessive mechanic stimuli are also deleterious for joint health[9]. Therefore, physical therapy are key components of non-pharmacological OA treatment. Exercises types recommended for OA patients at this stage include proprioception, stretching and resistance[9]. In the case of overweighed

patients, not only physical therapy is recommended, but an initial 10% weight loss is necessary in order to significantly reduce joint pain[28]. Even though weight loss has been associated with a significant reduction in the risk of developing symptomatic knee OA in female patients with a body mass index (BMI) greater than 25 kg m^{-2}, no effect of weight loss on OA was observed in women with BMI < 25 kg m^{-2} [28]. These results suggest that weight management strategies may only be effective in overweighed populations. However, given the progressive character of this disease, and the inability of many obese patients to maintain a significant weight loss over time[28], patients often require pharmacological treatment.

An alternative to alleviate the pain is the use of dietary supplements, which account for US$25 billion annual sales[10]. Approximately 70% of OA patients take oral supplements for pain management, with glucosamine and chondroitin sulfate being the most consumed compounds, accounting for a third of the oral supplements market value (US$872 million annual sales)[10]. Despite the high sales volume, oral supplements have failed to induce clinically significant improvements in pain management in OA patients. Liu *et al.* in a meta-analysis study reviewed 69 randomized placebo-controlled clinical trials that evaluated the effects of 20 individual oral supplements for the treatment of hand, hip or knee OA. The results demonstrated that no supplements exhibited a clinically important effect on pain or physical function in the long term (>6 months). Between 4 and 6 months, only undenatured type II collagen and green-lipped mussel extract, a supplement rich in anti-inflammatory compounds such as omega-3, eicosapentaenoic acid and docosahexaenoic acid (DHA)][29], showed a significant clinical effect on pain reduction[10]. Even though glucosamine and chondroitin sulfate are the most consumed dietary supplements among the OA population, according to Liu *et al.*, these compounds only statistically improved pain scores at short term (<3 months), but their clinical effect is debatable[10]. Additionally, clinical trials and meta-analysis studies have shown that the use of glucosamine and chondroitin sulfate in combination does not induce a relevant reduction in pain compared to placebo in most OA patients [30]–[32]. Although glucosamine can be detected in the synovial fluid after oral administration[33], insufficient IA concentrations could be related to the poor outcomes seen in clinical trials. In fact, 90% of orally administered glucosamine is absorbed, but its concentration in plasma is significantly reduced due to the first-pass effect, leading to a bioavailability of 26–44%[33]. On the other hand, oral delivery of chondroitin sulfate is challenging due to its high molecular weight (10 – 50 kDa)[33]. Around 90% of orally administered chondroitin sulfate is absorbed as low molecular weight derivatives[34] and exhibits a plasma bioavailability of 5–15%[33]. These challenges in the oral delivery of glucosamine and chondroitin sulfate may explain why these compounds have not induced a clinically relevant reduction of OA symptoms in several clinical trials.

Pharmacological management

Currently there are no approved DMOADs that reduce OA progression, thus treatment is limited to pain management and the regimen depends on the severity of the disease. Commonly used medications include cyclooxygenase inhibitors such as acetaminophen, systemic administration of opioids and non-steroidal anti-inflammatory drugs (NSAIDs). However, their prolonged use is limited due to their secondary effects on the hepatic,

gastrointestinal, renal and cardiac systems, especially in the elderly population that often presents a wide range of comorbidities[8],[9],[35]–[37]. Moreover, recent clinical studies have shown that acetaminophen is inferior to NSAIDs and not-superior than placebo for pain management in moderate and severe OA patients[27]. The use of topical NSAIDs is a safer alternative, but their use has only been shown to be effective during the first two weeks of use[38]. In the case of opioids, increasing awareness regarding their chronic use has limited their administration for long-term pain management. Also, studies have shown that opioids do not improve pain scores in OA patients compared to NSAIDs[39],[40].

In order to minimize adverse side effects associated with systemic administration of therapeutics and to improve drug's bioavailability in the joint space, intra-articular (IA) injections raise an alternative that offers a more localized treatment. IA injection of corticoids has been shown to reduce pain scores and increase joint functionality due to their anti-inflammatory and immunosuppressive effects. Corticoids reduce pain and inflammation by decreasing IL-1 production, prostaglandins, leukotrienes and metalloproteinases[9],[41],[42]. Several corticoids that have been FDA-approved for IA delivery as immediate release formulations include dexamethasone, beta-methasone, methylprednisolone, triamcinolone acetate and triamcinolone hexacetonide[9]. However, their long-term efficacy is questionable primarily due to the short retention time. For example, the IA half-life time of cortisone and dexamethasone solutions are 1.5 h and 3.6 h respectively[43],[44]. In an attempt to improve the IA retention of these molecules, crystalline drug suspensions have been used. However, around 10% of the patients experience crystal-induced "steroid flare", characterized by an acute synovitis[45] which usually resolves within few days after injection [46].

Finally, hyaluronic acid (HA) is the only formulation currently approved for OA treatment as a lubricating agent[8],[35],[36],[47], which intends to restore healthy synovial fluid properties[9]. Although clinical trials, systematic reviews and meta-analyses on the effects of HA injections on joint pain present confounding results, primarily due to a high variability in HA formulations, inappropriate blinding and small sample size, most evidence suggest that visco-supplementation may be a safe alternative to achieve clinically relevant pain reduction[13]. A meta-analysis study that evaluated 19 clinical trial publications, with a total of 4,485 patients revealed that overall, HA injection significantly improved pain scores, but its clinical effect was only 29% of the minimal important difference (MID)[14]. However, some evidence suggest that high molecular weight or cross-liked HA formulations are able to induce a clinically relevant reduction in knee pain[14],[25]. In fact, the use of cross-linked HA formulations led to pain improvements closer to the MID (95%) whereas non-cross-linked formulations had a pain improvement of only 25%. However, if these studies are analyzed according to the clinical experimental design, double-blinded trials present a lower treatment effect (49% of MID) compared to studies with insufficient blinding (129% of MID)[14]. Additionally, the use of HA injections did not have an important clinical effect on the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) function or stiffness indexes[14]. Consistent with other meta-analysis studies, the clinical effect of visco-supplementation using HA is unclear, primarily due to the lack of good quality, appropriately blinded studies[15].

NOVEL TARGETS FOR OA TREATMENT AND DRUG CANDIDATES

Considering that OA affects the joint as a whole, in addition to pain, pathways related to inflammation, cartilage catabolism and subchondral bone remodeling have become targets of interest to develop DMOADs. Regarding inflammation, inhibition of the nuclear factor NF-κB or individual downstream proteins (IL-1β, TNF-α, β-NGF, MMPs) has been investigated[16],[17]. For example, a phase I and II clinical study for a small molecule NF-κB inhibitor, SAR113945, demonstrated drug tolerability but failed to show effectiveness 56 days after intra-articular administration[48]. However, an analysis performed on a sub-population of the patients, who presented knee joint effusion at baseline demonstrated that IA injection of SAR113945 significantly reduced WOMAC scores of pain and physical function compared to placebo control[48].

Compounds that inhibit cartilage catabolic activity have also been evaluated. For example, a phase II clinical trial demonstrated that recombinant human fibroblast growth factor 18 (Sprifermin)-treated patients presented a significant reduction in lateral femorotibial cartilage thickness and volume loss compared to placebo control ($p<0.033$ and $p<0.014$, respectively), when treated with 100 μg of Sprifermin. However, patients in all experimental groups, including placebo, exhibited improved symptoms as determined by the WOMAC index at 12 months, with less improvement for patients receiving 100 μg of Sprifermin compared to placebo ($p<0.013$)[49]. Another promising molecule, kartogenin (KGN), has been shown to promote chondrogenic differentiation and reduction of OA progression in pre-clinical animal models[50]–[52]. In fact, Kang *et al.*, demonstrated that chondrocyte pellets treated with KGN present significantly higher expression of collagen type II and aggrecan compared to non-treated pellets ($p<0.001$)[50]. Finally, DMOADs that affect subchondral bone such as the bone resorption inhibitor salmon calcitonin and the anti-osteoporotic agent strontium ranelate have been suggested to have promising effects on OA progression[8].

Another class of DMOAD candidates include senolytic agents and autophagy promoters. It has been observed in animal models of post-traumatic OA that senescent cells accumulate in the synovial membrane and the articular cartilage[53]. Also, a reduced expression of autophagy regulators, which participate in protective mechanisms in healthy cartilage, has been observed in pathological human cartilage samples [54]. Therefore, elimination of senescent cells (SnC), as well as re-activation of autophagy pathways have shown promising results at reducing OA progression in pre-clinical animal models. In fact, Jeon *et al.* used a transgenic mice model that allowed for selective elimination of senescent cells to demonstrate that removal of this cell population resulted in reduced cartilage degradation in a post-traumatic model of mice OA[53]. These results were also confirmed using pharmacological elimination of SnC via IA administration of the senolytic molecule UBX0101[53]. Moreover, Xia *et al.* demonstrated that IA delivery of cordycepin induce re-activation of autophagy markers in a mouse model of OA and significantly reduced joint degeneration compared to untreated joints[54].

Although OA pathogenesis does not seem to have an inflammatory origin, some researchers believe that synovial inflammation plays a key role on disease progression and have

suggested the use of anti-rheumatic drugs as possible OA treatments[55],[56]. In fact, anti-rheumatic drugs have shown promising results on *in vitro* models and animal studies, but their efficiency in clinical trials is still questionable[17]. Persson *et al.*, in a systematic review and meta-analysis study, evaluated placebo-controlled clinical trials that investigated the efficacy of FDA-approved anti-rheumatic drugs as possible OA treatments[56]. In the study, small molecule drugs and biologics were investigated, including hydroxychloroquine, methotrexate, anakinra, adalimumab and etanercept. Results demonstrated that although these treatments induce a significant reduction in pain metrics, this effect is not clinically relevant[56].

INTRA-ARTICULAR DRUG DELIVERY STRATEGIES IN OA

Despite the encouraging advances in the discovery of DMOADs, the translation of these drugs into the clinic is limited given the challenging pharmacokinetics of the joints. Free small molecule drugs and even proteins injected in the joint space are rapidly cleared via lymphatic drainage and their retention time does not exceed few hours (Table 1). Also, most of these drugs have poor water solubility and require a delivery system in order to be administered via IA injections[8],[47],[57]. Multiple intra-articular drug delivery vehicles including hydrogels, liposomes, nanoparticles and microparticles have been formulated and will be discussed in the following sections (Fig. 2).

Hydrogels

Various viscosupplementation products, such as lightly cross-linked HA hydrogel formulations (Synvisc-ONE®, EUFLEXXA®, Gel-One® and MonoVisc®)[13], represent an attractive alternative to use as drug delivery vehicles. Several research groups have shown that drug-loaded HA hydrogel formulations can be used to reduce the frequency of IA injections compared to free drug[64],[65]. However, the retention of HA cross-linked formulations is still a concern. Yoshioka *et al.* demonstrated that the commercially available cross-linked HA formulation Gel-One® cannot be detected in the synovial fluid of rabbit knee joints after day 7, only 30% is retained in the synovial membrane at day 7 and 3.3% at day 28[66]. In an attempt to improve hydrogel intra-articular retention, the use of synthetic hydrogels has been explored. For example, poly(caprolactone-co-lactide)-poly(ethylene glycol)-poly(caprolactone-co-lactide) (PCLA-PEG-PCLA) hydrogel, used to deliver celecoxib to horse knees, showed that the drug could be detected at day 28 in the synovial fluid, but more than 90% of it was cleared by day 7[67]. Despite these advances, hydrogels serve as drug depots but are unable to control small molecule drug release rate because their mesh size is usually orders of magnitude larger than the loaded drugs[68],[69].

Liposomes

Liposomes can provide controlled release rates of both lipophilic and water-soluble drugs. Also, compared to crystalline drug suspensions formed by hydrophobic drugs upon IA injection, liposomes are less inflammatory[70]. Studies have shown that liposomes loaded with a model small molecule, such as the contrast agent iohexol, presented an IA half-life time of 134 h whereas the free molecule was not detected after 3 h[71]. However, compared to other drug delivery vehicles like polymeric particles, liposomes have limited long term

stability[72]. Additionally, the elevated oxidative stress seen in OA joints[73] as well as the shear and compressive loads characteristic of the IA space can reduce liposomes stability and induce drug leakage or burst release[68],[72],[74].

Nanoparticles and microparticles

An alternative to overcome the mechanical instability of liposomes is the use of lipid or polymeric nanoparticles. These vehicles have been shown to be susceptible to microvascular and synovial macrophage-mediated drainage and can be retained in the joint space only for few weeks, depending on their size, charge and composition[8],[63],[75],[76]. The use of larger particles that could better avoid lymphatic drainage and cell-mediated particles elimination (Fig. 1) is a potential strategy to achieve IA drug sustained release over longer periods of time. In fact, polycaprolactone (PCL) microparticles with an average size of 16 μm were found to remain in the joint space of rats for up to a month[77]. Janssen *et al.* synthesized celecoxib-loaded polyester amide (PEA) microspheres with a mean particle size of 25 μm and were able to detect around 20% of the injected PEA 12 weeks after IA injection in Lewis rats[78]. Additionally, the company Flexion Therapeutics recently received FDA approval to commercialize ZILRETTA®, an IA formulation of 45 μm triamcinolone acetonide-loaded poly(lactic-co-glycolic) acid PLGA microparticles for pain management in OA patients. The associated clinical trials revealed persistent pain relief until 3 months post-treatment[79],[80]. All together, these studies show the potential of microparticles to provide a sufficient IA retention time able to ensure drug bioactivity during a relevant therapeutic window[8].

TARGETING FOR IA DRUG DELIVERY

A wide variety of DMOADs are being studied for the treatment of OA and can be classified according to their function as analgesic, anti-inflammatory, cartilage-protective, or bone resorption inhibitors[8]. Depending on their function, these drugs act on specific biologic targets present in different tissues within the joint[47]. Studies have shown that non-tissue specific delivery of these drugs may result in unwanted off-target effects. For example, the use of NSAIDs reduces proteoglycan secretion, thereby increasing cartilage degradation[81]. Other groups have shown that nerve growth factor (NGF) blockade for pain relief induced rapid OA progression and osteonecrosis in a phase III clinical trial[82]. Therefore, drugs that act on inflammatory and pain pathways should primarily target the synovium[47]. Likewise, drugs that induce chondrogenesis should be preferentially delivered to the articular cartilage in order to prevent adverse effects on the surrounding tissues. In fact, IA injection of TGF-β1[83] and the chondrogenic molecule kartogenin[50],[51],[84]–[87], although beneficial for cartilage repair, increase synovium hyperplasia and induce the formation of cartilage-like tissues in ligaments and synovium[84].

Cartilage targeting

Cartilage extracellular matrix, primarily composed of collagen type II and sulfated glycosaminoglycans (GAGs), presents a small pore size (60–200 nm) and high negative charge, which difficult the penetration of molecules into this tissue[88],[89]. Therefore, the size and charge of drug delivery vehicles play an important role on cartilage targeting and

penetration. Drug delivery systems of diverse compositions, ranging from few nanometers up to 100 nm in diameter have been shown to penetrate the articular cartilage matrix[89]–[91]. However, their retention is primarily controlled by their ability to bind to different components of this tissue.

One alternative to achieve cartilage targeting is to use ionic interactions between the negatively charged cartilage matrix and positively charged carriers[88]. For example, Cook Sangar *et al.* recently developed a cysteine-dense peptide (CDP-11R) that due to its high surface positive charge is able to accumulate in mice cartilaginous tissues after IV administration and into human articular cartilage explants *in vitro*[92]. Triamcinolone acetonide conjugated to CDP-11R peptide resulted in a dose-dependent reduction in rat paw inflammation after IV administration in a rat model of RA[92]. Moreover, Geiger *et al.* used a positively charged, cartilage penetrating dendrimer to improve cartilage retention of insulin growth factor 1 (IGF-1), which resulted in significant cartilage protection and reduction of osteophyte formation compared to free IGF-1 in a rat model of OA[93]. Yan *et al.* developed cationic peptidic nanoparticles for IA delivery of NF-κB siRNA able to penetrate into human OA articular cartilage explants and be retained in the chondrocyte lacunae for at least 2 weeks. Additionally, IA delivery of NF-κB siRNA-conjugated cationic nanoparticles resulted in reduction of cartilage lesion length, chondrocyte apoptosis and synovitis in a mouse model of OA[94]. However, it is important to note that passive cartilage targeting based on electrostatic interactions is affected by the state of the disease. In fact, Vedadghavami *et al.* demonstrated that positively charged nano-carriers uptake and retention in articular cartilage explants with lower GAGs content were reduced due to a decrease in the cartilage net negative charge compared to healthy explants[90]. Additionally, Brown *et al.* demonstrated that reduced GAGs content as well as the presence of synovial fluid significantly reduce PLGA NPs retention into articular cartilage explants compared to healthy tissue and saline, respectively[91].

Moreover, targeting cartilage ECM components such as collagen type II and aggrecan has gained attention as a promising strategy to target damaged areas of the articular cartilage (Fig. 3). In fact, monoclonal anti-type II collagen antibodies (MabCII) have been used in multiple drug delivery and diagnostics applications[95]–[97]. For example, Cho *et al.* demonstrated that liposomes functionalized with a collagen type II monoclonal antibody are able to bind cartilage tissue proportionally to the severity of the disease in a mice model of OA after systemic administration[97]. Moreover, Bedingfield *et al.* used MabCII-functionalized polymeric NPs for cartilage-specific MMP13 siRNA delivery. These vehicles significantly reduced MMP13 expression and protected articular cartilage as measured via OARSI scores in a mouse model of OA after IA injection, compared to NPs functionalized with a negative control antibody [98]. Also, single-chain antibody variable fragment (scFv) specific to reactive oxygen species (ROS)-modified collagen II have been reported[95].

More recently, the use of phage display technology has resulted in the discovery of tissue-specific peptides, which compared to larger proteins such as monoclonal antibodies, are easier to manufacture, less immunogenic, smaller in size and more stable[72]. Using this technology, Yanbin *et al.* discovered a cartilage affinity peptide (CAP: DWRVIIPPRPSA) able to specifically bind to rabbit chondrocytes and human chondrocytes isolated from a

patient with OA. Compared to the scrambled peptide, conjugation of the CAP peptide to 50 nm polyethylenimine nanoparticles, a classical and efficient non-viral vector for gene therapy, resulted in particle binding and internalization into chondrocytes *in vitro* and 48 h after IA injection into rabbit knee joints[99]. Later, Cheung *et al.*, discovered two peptide sequences (RLDPTSYLRTFW and HDSQLEALIKFM) via phage display able to preferentially bind aggrecan *in vitro*. However, no scrambled control peptides were used and the ability of these sequences to bind cartilage *in vivo* was not assessed[100]. These aggrecan-binding and CAP peptides have not yet been used by other research groups for intra-articular drug delivery or diagnostics applications.

Rothenfluh *et al.* reported the ligand WYRGRL, a collagen type II α1-targeting peptide. Functionalization of poly(propylene sulphide nanoparticles and subsequent IA injection in mice knees resulted in a 72-fold increase in cartilage-targeting ability compared to nanoparticles functionalized with the scrambled control[101]. In contrast to other reported peptides, this sequence has been successfully used in pre-clinical models for diagnostics and drug delivery applications[11],[89],[101]–[104]. In fact, the conjugation of this peptide to magnetic resonance imaging (MRI) contrast agents has allowed *in vivo* localization of cartilage hypertrophic changes in a rat model of OA[102]. Other researchers have coupled this ligand to near infra-red probes for *in vivo* imaging and detection of age-related decrease in collagen type II in mice[104]. Furthermore, conjugation of this peptide to dexamethasone has proven to increase its retention into bovine articular cartilage explants and decreased the glycosaminoglycan depletion in an *in vitro* model of OA[11].

Synovial membrane targeting

Although drug delivery into the articular cartilage has been recognized as a key and very challenging aspect in the field, targeted delivery into the synovial membrane has gained interest as well. Originally, synovium targeting emerged as a strategy to minimize the secondary effects of systemic administration of NSAIDs and other anti-inflammatory therapeutics (Fig. 3). Two peptides that bind to inflamed synovial vasculature[105],[106] have been discovered via phage display and have shown promising targeting results after systemic administration in small animal models of rheumatoid arthritis[107],[108]. The first peptide was discovered by screening the ability of peptides administered intravenously (IV) to specifically bind to the vasculature of human synovium grafted into immunodeficient mice[105]. The resulting peptide (CKS: CKSTHDRLC) was later used by Wythe *et al.* to formulate a fusion protein formed by the anti-inflammatory cytokine IL-4 and the synovium-targeting peptide, and demonstrated that this construct elicited a biological response specifically into human synovium grafts implanted into immunodeficient mice compared to the scrambled control[107]. To date, this peptide has not been used in pre-clinical models of OA. Another group reported the discovery of a peptide (ADK: CRNADKFPC) able to bind to inflamed synovial vasculature and showed that IV administration of ADK peptide in a rat model of adjuvant arthritis resulted in reduced inflammation scores, decreased T-cell trafficking and angiogenesis inhibition[106]. Additionally systemic administration of ADK-functionalized liposomes loaded with the immunomodulatory cytokine IL-27 resulted in *in vivo* targeting of arthritic joints and significant reduction in rat paw inflammation compared to non-targeting liposomes or free IL-27 in a rat model of rheumatoid arthritis[108]. Despite

these results, the ADK peptide is also able to bind to inflamed skin[106] and the control scrambled sequence has not been characterized.

A different approach for synovium targeting was proposed by Mi *et al.*, who discovered a peptide (HAP-1: SFHQFARATLAS) that directly binds to synoviocytes[109]. HAP-1-functionalized liposomes loaded with prednisone[110] or an anti-inflammatory NF-κB-blocking peptide[111] showed promising results in terms of liposome localization into the arthritic joints and the reduction of rat paw inflammation after IV injection in a rat model of rheumatoid arthritis. Considering that synovium endothelium is not directly exposed to synovial fluid but synoviocytes are, the most promising strategy to target the synovial lining after IA injection could be HAP-1 peptide.

Multi-target therapy

Current understanding of OA pathology indicates that it is a complex, multi-factorial disease, which suggest that multi-target treatment may be a promising strategy to address the diverse mechanisms involved in OA progression. Although this idea has gained interest in the community, only few studies have explored the concept of multi-target therapy. One of the most investigated approaches is the use of dual-function lubricating drug-loaded nanoparticles[112]. Fan *et al.* developed HA nano-micelles containing the inti-inflammatory molecule, curcumin. These nano-micelles exhibited low friction coefficient and reduced paw inflammation by 30% in a rat model of rheumatoid arthritis[113]. Other researchers have focused on dual drug delivery to achieve multi-target therapies for OA treatment. Kang *et al.* developed chitosan-based thermoresponsive nanoparticles for independent delivery of kartogenin, a potent chondrogenic molecule, and diclofenac for pain and inflammation management[114]. These particles induced chondrogenic differentiation of mesenchymal stem cells *in vitro*, slowed OA progression and reduced the concentration of cyclooxygenase-2 in serum and synovial fluid in a rat model of post-traumatic OA compared to a solution of free drugs. However, the effect of combinatorial treatment compared to mono-therapy was not evaluated[114]. Moreover, Stone *et al.* demonstrated that IA combinatorial gene therapy using viral vectors expressing IL-1 receptor antagonist and lubricin induced the expression of anabolic and cartilage matrix genes, decreased the expression of catabolic and inflammatory mediators and provided significant cartilage protection compared to mono-therapy[115]. Despite the advances in the development of combinatorial therapies, the use of tissue-specific drug delivery vehicles for multi-target treatment of OA is yet to be explored.

CONCLUSIONS AND FUTURE PERSPECTIVES

Current OA treatment strategies do not address the underlying joint degenerative processes and are ineffective at managing long-term pain. The lack of approved DMOADs has not only resulted in poor quality of life for OA patients, but has also made this disease a major cause of disability worldwide. Significant advances on elucidating OA etiology have moved the field forward in terms of developing promising DMOADs. However, much research is still needed in this regard. In addition to developing better DMOADs, there is an unmet need to design appropriate IA drug delivery vehicles that are able to increase drugs' IA retention

time and directly release these molecules into the tissues of interest. Different biomaterials have been proposed in order to overcome the limitations related to IA drug administration including hydrogels, nanoparticles, liposomes and microparticles. To date, there is only one FDA-approved drug formulation that utilizes a biomaterial-based drug delivery system for IA injection in OA patients, which consist of triamcinolone acetonide-loaded PLGA microparticles[80]. Although microparticles generally present longer IA retention compared to other biomaterial-based formulations, extensive research on the use of different drug delivery vehicles, especially at a clinical level is still needed. Additionally, considering the complex nature of the disease, multi-target treatment strategies could represent a promising alternative to address the diverse underlying joint degenerative processes occurring in OA. In this regard, not only the development of appropriate IA drug delivery vehicles is imperative, but also the use of tissue-targeting strategies is essential. Future research on combinatorial drug delivery systems for the administration of therapeutic molecules with different IA tissue targets is still needed and could significantly contribute to the development of effective strategies for OA treatment.

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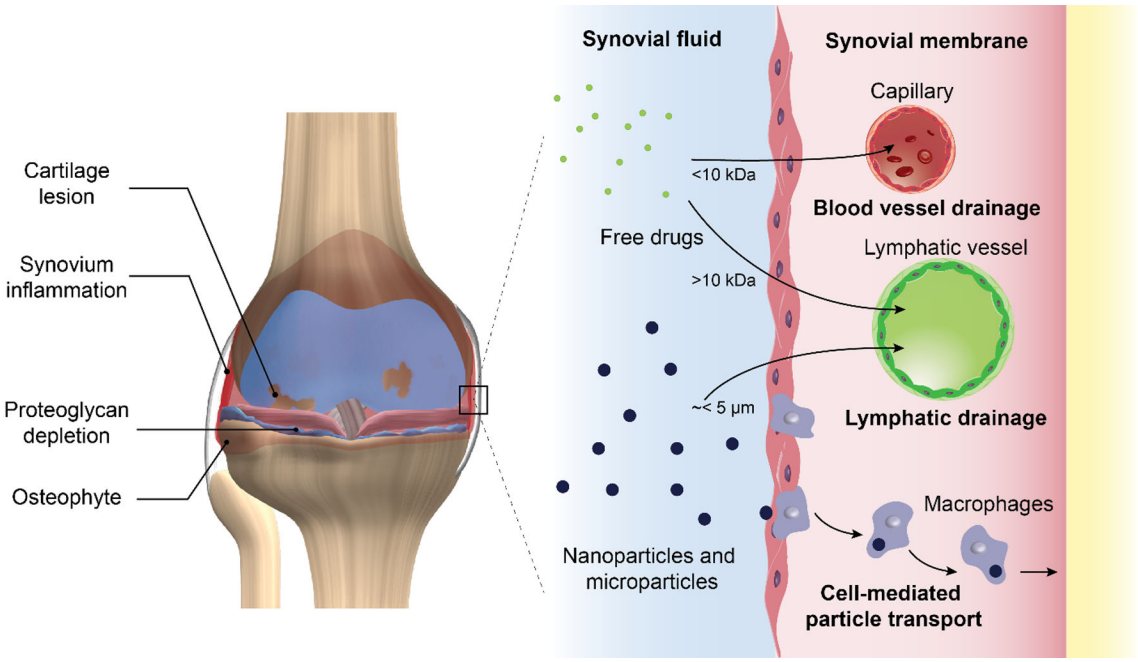

FIGURE 1.

Schematic representation of an osteoarthritic knee presenting signs of cartilage degradation, bone remodeling and synovial membrane inflammation. Clearance mechanisms for free drugs and particulate drug delivery systems after IA injection. Molecules smaller than 10 kDa are eliminated from the joint space via blood vessels whereas larger molecules and particles in the nano-scale and up to few micros are eliminated via lymphatic drainage[8]. Synovial macrophages also play an important role at eliminating particulate drug delivery systems via phagocytosis [23].

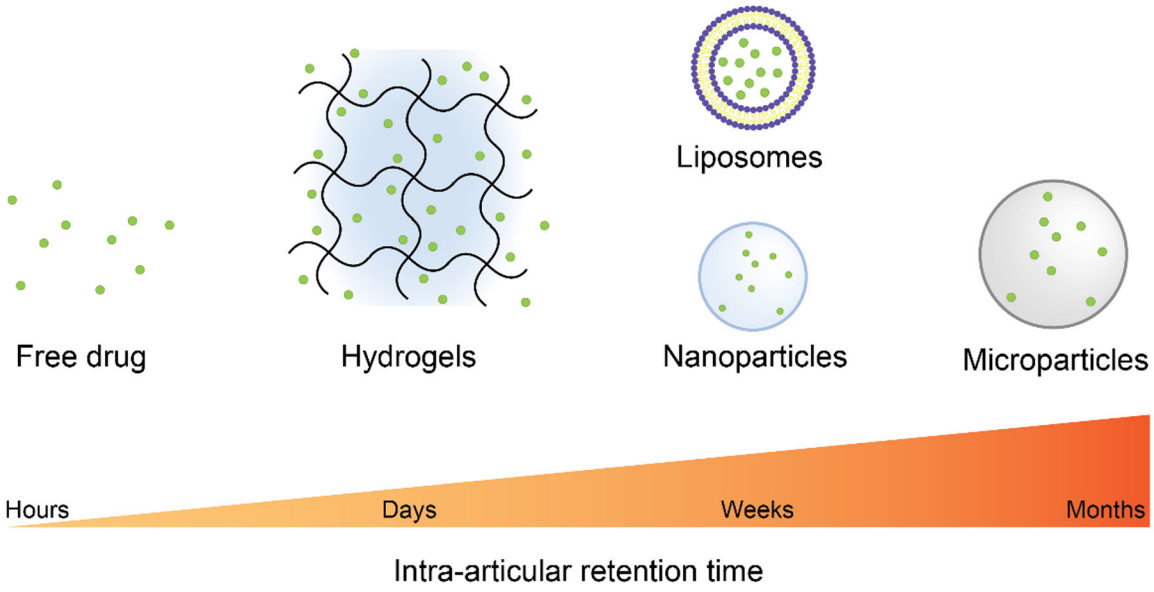

FIGURE 2.

Drug delivery systems typically used for IA drug administration and their IA retention time. Free small molecule and macromolecule drugs are cleared from the joint space in few hours. The use of drug delivery vehicles increases drug IA retention time, typically in a size-dependent manner. Nano-scale vehicles such as nanoparticles and liposomes are generally retained up to a couple of weeks, whereas microparticles can be retained in the joint space up to a month. Hydrogels do not usually control the release rate of loaded drug molecules, thus present an IA retention time in the order of days.

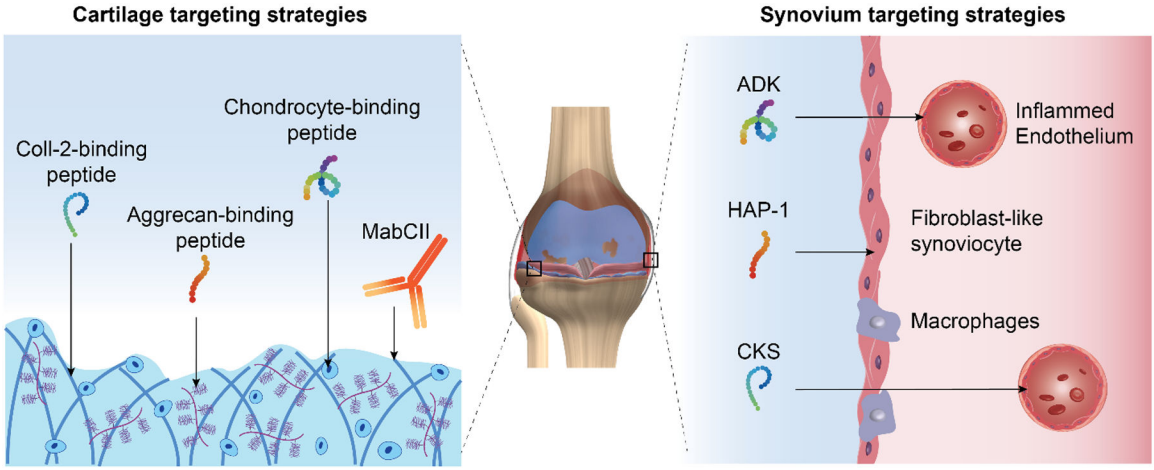

FIGURE 3.

Active IA tissue targeting strategies. Targeting peptides binding articular chondrocytes[99] or cartilage ECM components, including collagen type II (Coll-2) [101] and aggrecan[100], have been reported. Anti-Coll-2 monoclonal antibodies (MabCII) have also been used for articular cartilage targeting[95]–[97]. Synovial membrane targeting can be achieved by the use of inflamed synovial endothelium-binding peptides (CKS: CKSTHDRLC[105], ADK: CRNADKFPC[106]) or peptides targeting fibroblast-like synoviocytes (HAP-1: SFHQFARATLAS)[109].

Table 1.

Half-life of different molecules after intra-articular injection

Molecule	Half-life (h)	Molecular Weight (Da)
Paracetamol[58]	1.10	151
Ibuprofen[59]	2.20	206
Naproxen[60]	1.60	230
Ketoprofen[60]	1.90	254
Diclofenac[58]	5.20	296
Cortisone[44]	1.46	360
Dexamethasone[43]	3.60	392
Methotrexate[61]	2.90	454
Hyaluronic acid[18]	13.20	6,000
IL-1Ra[62]	23.04	65,400
Bovine serum albumin[63]	15.12	66,000