Chinese Chemical Letters 37 (2026) 111723

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Advances in injectable hydrogel-based intra-articular treatment systems for osteoarthritis therapy

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ARTICLE INFO

Article history:
Received 19 May 2025
Revised 12 August 2025
Accepted 14 August 2025
Available online 14 August 2025

Keywords:
Osteoarthritis
Injectable hydrogel
Intra-articular
Localized therapy
Delivery system

ABSTRACT

Osteoarthritis (OA), as a multifactorial degenerative joint disorder, is pathologically characterized by structural joint destruction and functional impairment, ultimately leading to chronic locomotor dysfunction. Clinically, intra-articular (IA) injection remains the preferred approach for localized OA treatment due to its advantages of high bioavailability, precise dosing, and minimal systemic side effects. However, frequent IA interventions may induce complications such as patient discomfort, pain, or even infection. Hydrogel materials, with their unique hydrophilic network structures and viscoelastic mechanical properties, are regarded as ideal joint cavity supplements and efficient drug carriers, making them a promising platform for localized therapy. This article systematically reviews recent advances in injectable hydrogel-based OA treatments. First, from a materials science perspective, it comprehensively analyzes the classification of injectable hydrogels (natural/synthetic polymers), their crosslinking mechanisms (chemical/physical/ionic), and environmental responsiveness (temperature/pH/ion triggers). Subsequently, it delves into their therapeutic potential in OA management, covering three major applications: controlled release of small-molecule drugs, cell delivery, and gene therapy. Despite the demonstrated prospects of hydrogels in OA therapy, attributed to their mechanical adaptability, biodegradability, and biocompatibility, key scientific challenges persist, particularly in maintaining IA mechanical homeostasis and long-term structural integrity. The review emphasizes that future research should focus on optimizing hydrogel architectures and enhancing delivery system functionalities to achieve sustained therapeutic efficacy in OA.

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1. Introduction

Osteoarthritis (OA) represents the most prevalent form of arthritis and is a degenerative joint disease that progressively affects cartilage, the synovial membrane, bone, and periarticular tissues, leading to chronic disability [1–3]. Commonly impacted areas include the knees, hips, fingers, and lower spine, resulting in chronic pain, inflammation, and stiffness. According to the World Health Organization (WHO), symptomatic OA affects 9.6% of men and 18.0% of women over the age of 60 [4]. A significant portion of OA patients face movement limitations, with 80% experiencing some degree of impairment and 25% being unable to perform major daily activities. Among individuals over the age of 70, 40% suffer from knee OA, which incurs an estimated medical care cost of US $185.5 billion annually for the 27 million diagnosed patients in the United States, averaging to US $6870 per patient [5].

To advance novel treatments for OA, a comprehensive understanding of joint anatomy and OA pathophysiology is essential. Healthy joints are characterized by the presence of two bones enveloped by cartilage, with stabilization provided by the mechanical function of ligaments, muscles, and menisci [6]. The intra-articular (IA) space is enclosed by a synovial membrane capsule, which retains synovial fluid. Articular cartilage, intricately shaped to the

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https://doi.org/10.1016/j.cclet.2025.111723
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bone ends, typically measures 1–5 mm in thickness and is composed of chondrocytes embedded within an extracellular matrix (ECM). This matrix consists of <5% chondrocytes, 60%–85% interstitial fluid, and a solid component made up of approximately 15%–22% type II collagen, 4%–7% proteoglycans, and other protein macromolecules [7,8]. The tensile strength of cartilage is due to the collagen network, while hydrophilic proteoglycans, particularly aggrecan, facilitate water absorption, allowing the cartilage to withstand compression and distribute load.

OA is a multifactorial condition arising from various disorders that lead to the structural or functional breakdown of joints [4]. There is a complex interplay between cartilage and adjacent tissues. In OA, the subchondral trabecular bone undergoes architectural changes, resulting in reduced volume and increased cortical bone density. This is accompanied by an imbalance in the activities of osteoblasts, which synthesize bone, and osteoclasts, which break down bone tissue, leading to bone densification and altered morphology [9–12]. In OA-affected synovial membranes, the presence of immune cells such as T cells, neutrophils, and macrophages leads to an upregulation of cytokines, chemokines (*e.g.*, tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, and IL-15), and inflammatory mediators (*e.g.*, nitric oxide and prostaglandin E), which contribute to cartilage degradation and inflammation [13]. Additionally, the altered lymphatic vessels in OA patients result in inadequate synovial fluid drainage, further exacerbating the inflammatory response.

The management of damaged articular cartilage in the knee poses a significant challenge due to its limited self-repair capacity and complex structure, which lacks neural, lymphatic, and vascular networks, thereby constraining spontaneous repair and necessitating the involvement of reparative stem cells [8]. Unlike bone, which has substantial regenerative potential, cartilage's reparative capacity is constrained by the absence of vascular support.

Oral administration of drugs is a prevalent approach for managing knee OA, with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids commonly utilized. However, these medications are associated with adverse effects such as gastrointestinal reactions, obesity, and osteonecrosis, which limit their clinical use. Due to the significant systemic adverse effects, oral administration has waned in favor among clinicians, patients, and researchers [14]. Despite a focus on systemic treatments, these agents carry a substantial risk of systemic adverse events, as evidenced by cardiovascular and gastrointestinal side effects associated with most NSAIDs and cyclooxygenase-2 (COX-2) inhibitors [15,16]. Furthermore, while prodrug [17] and particulate carrier [18] technologies have attempted to achieve targeted drug delivery *via* systemic circulation, the localized nature of OA renders IA drug injection an exceptionally attractive therapeutic option. This approach enables direct drug delivery to the affected joint, thereby minimizing systemic side effects. Unlike many other pathologies, OA can be treated with both systemic and local IA interventions [8]. Given the typically limited number of joints affected by OA, IA drug administration is a suitable strategy for localized treatment [4]. The local administration of drugs, particularly through direct injection into the affected joint, is a frequently utilized and effective treatment option for OA [8]. Implementing local drug delivery strategies has the potential to significantly improve treatment outcomes for OA, including reducing local joint inflammation and destruction, alleviating pain, and restoring patient mobility and joint function [19]. IA injections allow for the precise delivery of therapeutic doses to the affected tissues in OA and offer an alternative for drugs with limited oral bioavailability [4]. Compared to oral administration, this method avoids systemic exposure and the associated risk of adverse effects [20]. The IA route of drug administration is a promising approach for targeted delivery of therapeutic agents to the affected tissues in arthritis treatment, reducing the adverse effects associated with systemic drug administration [21]. Several studies have demonstrated the cost-effectiveness of IA treatments over conventional therapies [22,23]. Notably, the cost per quality-adjusted life year (QALY) gained with IA hyaluronic acid (HA) injections ranges from US $5785 to US $9039, which is significantly lower than the cost of conventional care (US $10,716) [22].

Current treatment options for OA are primarily limited to symptomatic relief and lack therapies that can effectively stabilize or reverse disease progression. Pharmaceutical interventions are often suboptimal, frequently causing adverse effects and requiring frequent administration, while surgical interventions offer only temporary relief. There is an urgent need for the development of disease-modifying treatments [4]. The development of IA formulations capable of prolonged compound release presents a significant challenge. Strategies such as the use of hydrogels, nanoparticles, or microparticles, and liposomes are being explored to achieve sustained release products. The implementation of such formulations may be advantageous for both newly developed OA drugs and existing treatments, as they can extend the duration of drug release into the joint space, reducing the frequency of required injections. Thus, the exploration of innovative pharmacological agents alongside novel sustained release formulations offers a promising avenue for effective therapeutic interventions for OA [8].

2. IA injection treatment for OA

A significant drawback of IA injections is the potential for discomfort, pain, and infection, which advises limiting the frequency of such injections. This limitation presents a challenge in IA drug delivery due to the short residence times of IA-administered drugs, which are rapidly absorbed by the circulation, dictated by joint physiology. The clearance of drugs from synovial fluid (SF) is primarily facilitated by lymphatic drainage, with the molecular size playing a significant role. In patients with OA, the clearance rate of albumin from SF was approximately 0.04 mL/min, resulting in a turnover time of about 1 h [8]. Free drugs are eliminated from joints through lymphatic drainage within a few hours or less [4]. Studies have shown that the residence time of NSAIDs in SF can be as brief as 1–5 h [24]. Given the half-lives of methotrexate (Methotrexate), ibuprofen, and diclofenac, which are 0.59–2.9, 1.9, and 5.2 h respectively [25], the development of sustained-release formulations is essential. These formulations would enable a consistent release of the drug from a depot in the joint space over an extended period, ranging from several weeks to months [8].

Micro- and nanocarrier-mediated drug delivery systems, such as polymeric particles, liposomes, and hydrogels, have been extensively studied for achieving sustained release in IA applications. These systems have the potential to extend drug retention time, decrease drug clearance into the joint cavity, enhance patient compliance, and improve the therapeutic efficacy of pharmaceutical agents. This approach ensures prolonged drug activity at the site of action, reducing the need for frequent injections and minimizing the risk of infection [26]. An alternative to repeated injections for achieving sustained therapeutic drug concentrations is the use of an IA slow-release drug delivery device. Research has shown that coupling the desired drug to liposomes, microparticles, or hydrogels can result in sustained IA drug concentrations [27].

Viscosupplementation (VS) is a recommended intervention for knee OA IA injection treatment [28], as endorsed by the American College of Rheumatology (ACR) [29] and OA Research Society International (OARSI) guidelines [30]. Hydrogels, with their high water content and viscoelastic properties, are considered an ideal supplement for *VS* and are commonly used as a drug delivery vehicle due to their high loading efficiency (Fig. 1). Hydrogels consist of a three-dimensional polymer network that is cross-linked chemi-

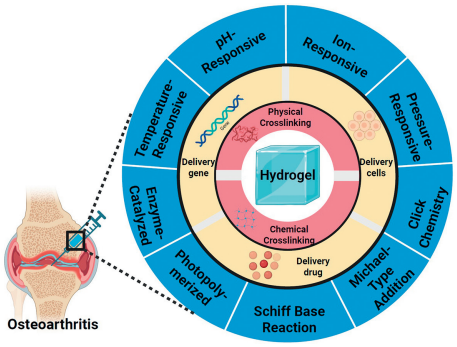


Fig. 1. Schematic of the classification of hydrogels and their application for OA.

cally, physically, or ionically, with water as the primary dispersion medium [31].

3. Types and properties of injectable hydrogels

Hydrogels can be composed of naturally derived materials such as agarose and collagen or synthetic polymers such as poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVA) and can be crosslinked through various means [7]. Their advantages lie in their intricate three-dimensional structures, which can be tailored to exhibit a wide range of physical properties suitable for applications such as medical implants, biosensors, and drug-delivery devices [32,33]. Furthermore, hydrogels can be injected in a minimally invasive manner to fill defects of any size and shape before polymerization [34–36]. After gelation, substances previously dissolved or encapsulated within the hydrogel solvent become localized and can serve as a means of transporting drugs, proteins, or cells in the context of OA treatment strategies (Fig. 2A) [14]. Hydrogels can be classified based on various factors, including their source (natural or synthetic), the type of cross-linking (covalent or physical), the nature of their inner networks (homopolymer, copolymer, interpenetrating, or double networks), and their ultimate fate within the body (degradable or nondegradable) [37–39].

Injectable hydrogels can be classified into distinct categories based on their natural or synthetic origins. The polymeric composition of hydrogels can be further categorized as homopolymeric, copolymeric, or multipolymeric. Additionally, hydrogels are characterized by various cross-linking mechanisms, physical appearances, and network electrical charges. According to the source of materials used (based on the source of materials utilized), polymers constituting hydrogels can be classified into natural (including proteins, polysaccharides, *etc.*), synthetic, and natural-synthetic composite hydrogels [11,40]. These synthetic hydrogels are known for their superior biocompatibility, good biodegradability, and low immunogenicity, properties that are comparable to those of HA-based hydrogels used in the viscosupplementation treatment of OA (Fig. 2B) [41–44].

3.1. Natural hydrogels

Natural hydrogels are derived from biological materials such as collagen, HA, alginate, chitosan (CS), gelatin, dextran, cyclodextrin, and fibrin (refer to Section 1 in Supporting information). These hydrogels are widely recognized for their biocompatibility, porosity, and softness, as well as their ability to facilitate enzymatic degradation, cell adhesion, and migration—properties that collectively contribute to their extensive use in arthritis therapy [45].

For instance, HA, a glycosaminoglycan enzymatically derived from the ECM, exhibits the capacity to promote tissue repair and mitigate inflammatory responses while demonstrating excellent biocompatibility, biodegradability, and superior gel-forming properties. Seo *et al.* developed a click-crosslinkable HA (Cx-HA) depot, which exhibits enhanced hydrogel characteristics and prolonged *in vivo* retention compared to conventional HA depots. methotrexate (Methotrexate)-loaded Cx-HA (MTX-Cx-HA) can be readily formulated into an injectable preparation that rapidly forms a sustained-release depot at the injection site. Upon IA administration, the MTX-Cx-HA reservoir facilitates localized maintenance of therapeutic MTX concentrations, thereby promoting joint repair [46].

CS possesses the ability to reduce and release acetylated CS while serving as an exceptional gel matrix with outstanding biocompatibility, antimicrobial activity, and low immunogenicity [47]. Owing to its biodegradability, favorable biocompatibility, and thermosensitive gelation at physiological temperatures, CS hydrogels are highly effective for the sustained delivery of proteins/peptides, anti-inflammatory agents, and antibiotics, positioning them as a promising tool for articular cartilage repair [48,49]. Pan *et al.* engineered a novel therapeutic platform by integrating black phosphorus nanosheets (BPNs) into a platelet-rich plasma (PRP)-CS thermosensitive hydrogel system. This injectable hydrogel enables precise modulation of BPN degradation product release, providing essential components for bone regeneration. Furthermore, the injectable CS thermosensitive hydrogel not only protects articular cartilage by reducing periarticular tissue friction and enhancing lubrication but also promotes the adhesion and proliferation of mesenchymal stem cells (MSCs) (Fig. 2C) [50].

Alginate, a natural polysaccharide extracted from brown algae, is a biocompatible hydrogel material characterized by low toxicity, cost-effectiveness, excellent gelation capacity, and high bioavailability, making it highly suitable for biomedical applications [51]. Alginate hydrogels are typically formed *via* ionic crosslinking with divalent cations, rendering them ideal injectable scaffolds for cell delivery in tissue regeneration [52]. Díaz-Rodríguez *et al.* demonstrated that alginate-poloxamer hydrogels effectively control the release of indomethacin, which modulates cartilage ECM degradation and stimulates neocollagen synthesis in osteoarthritic chondrocytes [53]. However, the clinical utility of alginate is limited by its poor mechanical stability and progressive degradation [54].

Additionally, other classes of natural hydrogels are composed of materials such as collagen, gelatin, dextran, cyclodextrin, and fibrin. Collagen, a critical ECM protein, exhibits osteoinductive properties that render it particularly suitable for cartilage regeneration; however, its inadequate mechanical strength and fracture toughness restrict its broader application [55]. Gelatin, a degradable protein primarily derived from bovine or porcine sources, offers strong adhesiveness, plasticity, and biocompatibility but is hampered by insufficient mechanical properties and pronounced hygroscopicity. Dextran, a linear polysaccharide composed of α-(1→6)-linked D-glucopyranose residues, is a highly versatile biocompatible material [56]. Fibrin, formed *via* the polymerization of fibrinogen into a fibrous scaffold, plays a pivotal role in clot formation upon tissue injury. Both dextran and fibrin have received the Food and Drug Administration (FDA) approval and are extensively employed in biomedical applications, including tissue regeneration and inflammation control [57].

In conclusion, while natural hydrogels serve as ideal platforms for drug/cell delivery and facilitate functional joint recovery, their long-term stability and degradation kinetics may influence therapeutic efficacy. Further standardization of purification protocols and comprehensive toxicity studies are warranted to optimize their clinical performance.

3.2. Synthetic hydrogels

Synthetic hydrogels are fabricated through chemical or physical crosslinking of synthetic polymers, offering distinct advantages

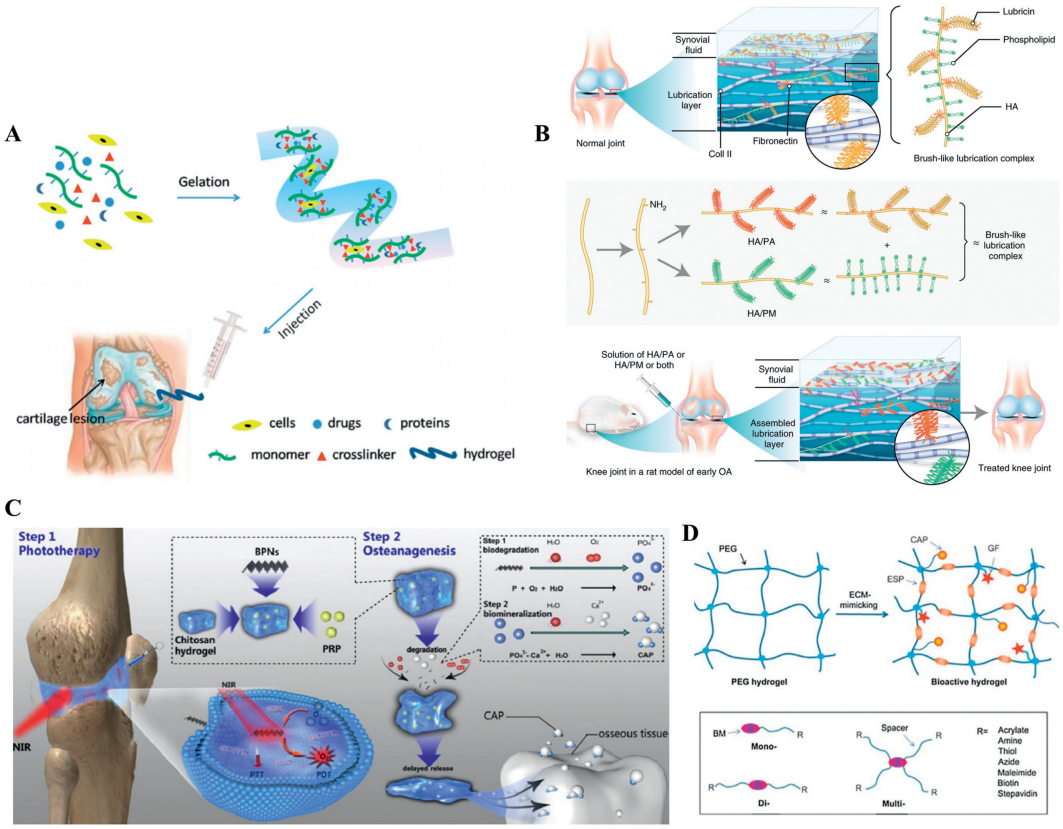


Fig. 2. (A) Schematic representation illustrating the preparation of a hydrogel delivery system to treat knee OA *via* IA injection. Copied with permission [14]. Copyright 2017, Elsevier. (B) Illustration of the overall idea. Copied with permission [43]. Copyright 2021, Springer Nature. (C) Schematic illustration of the PRP-CS thermoresponsive hydrogel combined with BPNs as injectable biomaterial for biotherapy and phototherapy treatment of RA. Copied with permission [51]. Copyright 2020, Elsevier. (D) Bioactive modification of PEG hydrogels. Copied with permission [66]. Copyright 2010, Elsevier.

such as scalable production, highly tunable structures, and precise customization for diverse application requirements [58]. Common synthetic polymers include polyacrylamide (PAM), polyethylene glycol (PEG), poly(ε-caprolactone) (PCL), and poly(2-hydroxyethyl methacrylate) (PHEMA) (refer to Sections 2 and 3 in Supporting information) [59].

Poly(*N*-isopropylacrylamide) (PNIPAm), a well-studied thermosensitive polymer in biomedicine, exhibits a lower critical solution temperature (LCST) near physiological conditions, enabling *in situ* gelation without external stimuli [60]. Below the LCST, PNIPAm forms a homogeneous injectable solution that transitions into a three-dimensional hydrogel upon exposure to body temperature [61,62]. However, its applications are limited by poor biodegradability, weak mechanical strength, low drug-loading capacity, and uncontrolled drug release [63]. To address these limitations, Feng *et al.* developed a semi-interpenetrating polymer network (IPN) hydrogel composed of PNIPAm and polyvinylpyrrolidone (PVP) *via* advanced polymerization. The incorporation of PVP preserved the LCST while significantly improving response kinetics and drug release profiles [64].

PEG, a versatile and biocompatible polymer (Fig. 2D) [65], can be copolymerized with biodegradable polyesters to form thermosensitive hydrogels. By modulating the hydrophilic (PEG) and hydrophobic (*e.g.*, poly(lactic-*co*-glycolic acid) (PLGA)) block ratios and chain lengths, the thermoresponsive properties can be finely tuned. For instance, PLGA-PEG-PLGA triblock copolymers exhibit temperature-dependent sol-gel transitions governed by hydrophilic-hydrophobic interactions, making them suitable for sustained drug delivery [66].

Polyacrylamide hydrogels, composed of highly crosslinked acrylamide networks, demonstrate excellent biocompatibility and hydration capacity [67]. Injectable polyacrylamide hydrogels have been shown to protect cartilage surfaces and promote fibrocartilaginous healing, alleviating OA symptoms [68]. Bliddal *et al.* reported that IA injections of polyacrylamide hydrogels significantly improve clinical outcomes in knee OA by preserving cartilage integrity [69].

Poloxamers, nonionic triblock copolymers of hydrophilic poly(ethylene oxide) (PEO) and hydrophobic poly(propylene oxide) (PPO), are recognized as smart materials due to their thermoresponsive micellization behavior [70]. At critical temperatures and concentrations, these copolymers self-assemble into micelles, enabling their use as drug carriers or anchoring platforms for targeted delivery [71].

Additional polymers, including PVA, synthetic peptides, and DNA, are also employed in hydrogel design [72]. PVA, with its non-antigenicity, mechanical robustness, and ease of modification, is widely used in bone tissue engineering [73]. Synthetic peptides, composed of amino acids, offer exceptional biodegradability, bioactivity, and environmental responsiveness, making them promising for biomedical applications [74]. DNA-based hydrogels, formed *via* rolling circle amplification (RCA), provide stimuli-responsive platforms for biosensing and drug delivery due to their programmable sequences [75].

4. Injectable composite hydrogel treatment system for OA

The mentioned hydrogels display favorable traits such as biodegradability, biocompatibility, and low immunogenicity akin to HA-based hydrogels used in OA viscosupplementation therapy [41–44]. However, unlike HA or HA-hydrogels, they lack inherent therapeutic capabilities beyond acting as lubricants for OA

symptoms. Their advantages stem from intricate three-dimensional structures adaptable to various physical properties for medical implants, biosensors, and drug-delivery devices [32]. Hydrogels can be minimally invasively administered to fill defects before polymerization [34–36], localizing solutes within the solvent upon gelation, making them viable carriers for therapeutic agents like drugs, proteins, and cells in OA treatment strategies.

To prolong hydrogel retention in the knee joint, researchers chemically modify their molecular structures. Hydrogels support diverse drug delivery by forming internal networks during gelation, facilitating targeted drug delivery to joints and agent localization. Recent studies developed localized delivery systems enabling sustained release of drugs, proteins, and cells for knee OA treatment over extended periods [76]. Additionally, hydrogels have been augmented with microspheres and nanospheres of various materials, showing superior localized OA treatment efficacy by circumventing systemic adverse effects [14].

As understanding of OA pathogenesis advances, novel therapeutic agents beyond micromolecules and biomacromolecules are being incorporated into injectable hydrogel systems. For instance, hydrogels can be combined with micromolecular analgesics like bupivacaine, macromolecular active peptides with anti-inflammatory properties, or enzyme inhibitors capable of degrading cartilage-type aggrecan, enhancing knee OA treatment efficacy [77–79]. Encapsulation within hydrogels or hydrogel microspheres protects these agents from tissue factors, prolonging drug activity.

Moreover, hydrogels can serve as carriers for cartilage tissue engineering, facilitating efficient cell delivery for knee OA regeneration. In addition to conventional cell sources such as bone marrow-derived MSCs and chondrocytes, synovial MSCs [80] could be utilized. Novel techniques like microfluidic technology for microsphere preparation may significantly enhance cell encapsulation efficacy and cell viability within microspheres. Microfluidics has enabled the production of photocrosslinkable microspheres containing stem cells (GelMA microspheres), injectable for sustained reparative cell release in bone tissue engineering [81].

4.1. Drug delivery

Intra-articularly injected small molecules are rapidly cleared from the joint space due to lymphatic drainage, with half-lives of methotrexate (Methotrexate), ibuprofen, and diclofenac ranging from 0.59–2.9 h, 1.9 h, to 5.2 h, respectively [25]. Strategies like direct drug modifications (*e.g.*, PEGylation) or synthesis of lipophilic prodrugs can delay systemic drug elimination and increase bioavailability [82]. However, these methods lack sufficient extended activity over weeks or months. Most contemporary active pharmaceutical ingredients (APIs) are small lipophilic molecules, categorized as class 2 drugs with high insolubility in aqueous media and a propensity to form crystal suspensions. Administration of long-acting crystal suspensions risks crystal deposition in the joint, potentially causing crystal synovitis. Hence, lipophilic drugs require suitable formulations. Hydrogels are proposed as viable drug carriers, enabling extended release over prolonged periods [4,83].

A temperature-responsive hydrogel, created using a copolymer of poly(ε-caprolactone-*co*-lactide) and polyethylene glycol (PCLA-PEG-PCLA), remained in a solution state at room temperature but formed an immobile gel at 37 °C. Celecoxib was loaded into the hydrogel by mixing its solvent with the PCLA-PEG-PCLA solvent before gelation. The hydrogel sustained celecoxib release for over 90 days due to gradual polymer hydrolysis, depicted in (Fig. 3A) [84]. This allowed researchers to achieve a therapeutically effective local drug concentration *via* an IA delivery system while maintaining plasma drug concentrations below toxic levels.

Various growth factors, including isoforms of transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), bone morphogenetic protein (BMP), and insulin-like growth factor (IGF) [85,86], have been used to augment chondrogenesis in cartilage. While different growth factors and combinations have distinct effects on MSC proliferation and chondrogenesis [87], the TGF-β superfamily is widely employed to induce robust chondrogenesis in MSCs [88–90]. Even transient presence of the TGF-β superfamily has been noted to reduce hypertrophy [91]. Chung and colleagues demonstrated that MSC-seeded HA hydrogels supplemented with TGF-β (100 ng/mL) significantly enhanced chondrogenesis and matrix production *in vivo* compared to hydrogels without TGF-β. Several research groups have sought to regulate TGF-β release for extended periods, primarily using sequestering peptides like heparin sulfate or TGF-β-loaded particles encapsulated within hydrogels [92–94]. Grafting TGF-β-specific sequestering and protecting peptides onto the HA backbone is a potential approach to prolong release duration and enhance outcomes [94].

4.2. Cell delivery

The initial clinical application of IA cell delivery focused on gene therapy, utilizing genetically modified autologous synovial fibroblasts [95]. This pioneering approach laid the groundwork for subsequent advancements in cell therapy within joint environments. Following this, chondrocytes and various blood cells have also been administered into human joints, expanding the scope of cellular therapies for joint diseases. However, the bulk of research and clinical exploration has centered on MSCs. These cells have garnered significant attention due to their potential to differentiate into various cell types relevant to joint health, their immunomodulatory properties, and their ability to secrete therapeutic factors. This extensive focus on MSCs reflects their promising role in regenerating damaged joint tissues and modulating inflammatory responses, making them a cornerstone of current IA cell therapy research.

Barry and Murphy [96] discussed the potential IA application of MSCs in treating OA, garnering significant interest due to MSCs' anti-inflammatory and immunosuppressive properties that promote tissue regeneration [97–99]. Preclinical studies have yielded promising results in preventing posttraumatic OA, regenerating damaged cartilage, and alleviating pain [100–102]. In equine medicine, IA injection of MSCs from bone marrow or adipose tissue is a common therapeutic approach for OA management, with commercial preparations available for veterinary use. However, its human medicine application is limited, with only a few small-scale clinical case series published. For instance, a study using autologous MSCs in four individuals with knee OA reported inconclusive outcomes [103]. MSCs' immunosuppressive properties suggest successful allografting potential, offering the prospect of universal donor therapy, thereby reducing the cost and complexity associated with developing approved treatments.

Hydrogels are versatile because of their diverse properties, including high water content, biodegradability, porosity, and biocompatibility, making them suitable for widespread use in cell therapy [104,105]. In cartilage tissue engineering, well-designed hydrogel scaffolds can regulate cell proliferation and differentiation. Advanced techniques allow for the fabrication of personalized geometries and compositions of cell-encapsulated hydrogels. Over the past decade, extensive research has focused on various forms of injectable hydrogel systems loaded with cells for cartilage regeneration [7,106]. Cells can be integrated into hydrogels either by seeding into prefabricated porous scaffolds or by encapsulation during the scaffold formation process.

The integration of cells into hydrogels is crucial for the regeneration process, achievable through cell infiltration into the scaffold or the delivery of exogenous cells within the scaffold upon implantation, as noted in reference [107]. MSCs are a promising

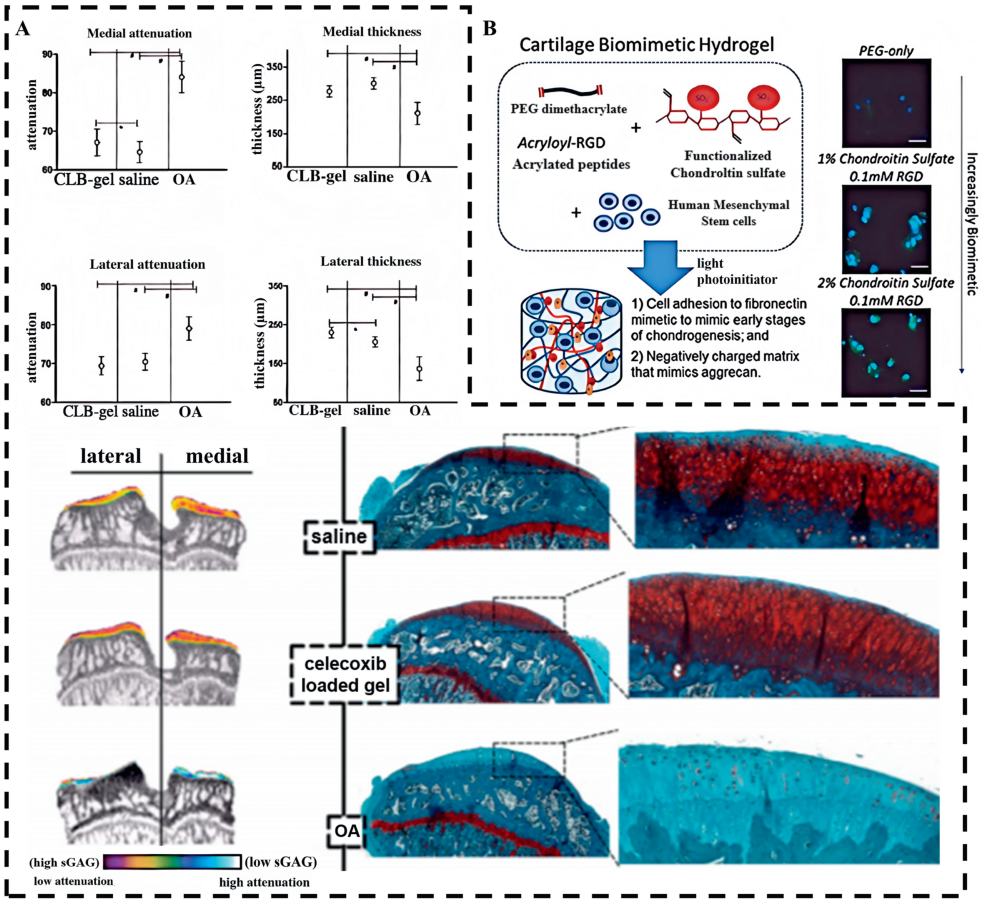


Fig. 3. (A) IA biocompatibility of celecoxib-loaded gel (50 mg/g, 50 mL). Reproduced with permission [84]. Copyright 2014, Elsevier. (B) An example of a cartilage biomimetic hydrogel. The hydrogel is composed of PEG, chondroitin sulfate (ChS), and a cell adhesion peptide, RGD. Copied with permission [110]. Copyright 2017, Wiley Publishing Group.

cell source due to their capacity to differentiate into chondrogenic or osteogenic lineages and target specific layers, more accurately replicating articular cartilage and subchondral bone. Endogenous cell migration into hydrogels can be facilitated by incorporating chemotactic factors that promote cell migration from surrounding bone marrow and synovial tissue. MSCs from marrow and synovium express multiple chemokine receptors, including CXC chemokine receptor 1 (CXCR1), CXCR2, CXCR4, and CCR2, enabling them to home to chemokines [108]. Various chemokines, such as stromal cell-derived factor 1 (SDF-1), IL-8, platelet-derived growth factors (PDGFs), and TGF-β isoforms, have been identified as playing a role in recruiting MSCs [108]. Incorporating SDF-1 into a scaffold has been shown to enhance articular cartilage regeneration following injury, evidenced by increased MSC presence at the injury site [109]. Therefore, developing acellular hydrogel constructs offering chemokine factors to attract endogenous MSCs from adjacent marrow compartments is a viable approach. Additionally, incorporating factors that stimulate cartilage differentiation into hydrogels would promote the formation of articular cartilage tissue by endogenous MSCs (Fig. 3B) [110].

MSCs, along with other promising cell types like induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs), hold potential for future research [111]. ESCs are appealing for their ability to differentiate into all somatic lineages and self-renew indefinitely. Elisseeff *et al.* showed that mesenchymal-like cells from hESCs in RGD-modified PEG hydrogels produced a cartilaginous matrix rich in type II collagen [112]. Later studies indicated that BMP and TGF-β isoforms promote chondrogenesis in hESCs across different cultures [113,114]. However, ESCs face challenges such as selection, purification, culture, and ethical concerns. iPSCs could be an alternative cell source in the future, given their advantages. iPSCs are created by reprogramming somatic cells to achieve pluripotency using methods like retroviral transduction [115]. iPSCs are in early research stages and are not yet widely studied for cartilage regeneration. Major improvements in materials and methods are needed for ESCs and iPSCs to reach the progress made with MSCs in chondrogenesis.

4.2.1. Fully differentiated chondrocyte-encapsulated hydrogels

Autologous chondrocyte implantation (ACI) is effectively used to treat cartilage defects, but fixing grafts in complex-shaped defects through surgery is difficult [116,117]. Injectable scaffolds, like hydrogels, are emerging solutions that support chondrocyte proliferation, maintain cell shape, phenotype, and promote the expression of cartilage-specific proteins [118–120]. Studies, including Jin *et al.* [121], have developed injectable chondroitin sulfate hydrogels that maintain chondrocyte viability and support cartilage matrix development with key components like type II collagen and aggrecan. Similarly, Roberts *et al.* [122] found that hydrogels containing chondrocytes and a specific copolymer promoted the development of a cartilage matrix with aggrecan and collagen types II/VI. However, limitations of chondrocyte-based therapies include the need for tissue harvesting from non-load-bearing areas and long-term culturing, which can cause donor site necrosis and have limited therapeutic effect in the elderly due to reduced chondrocyte bioactivity and proliferation [123,124].

ACI has long served as a treatment option for focal chondral lesions, producing generally favorable clinical outcomes. Nonethe-

less, concerns persist regarding the tendency of chondrocytes to dedifferentiate into a fibroblast-like phenotype, as highlighted in existing literature [125]. To mitigate this issue, third-generation ACI techniques such as matrix-induced ACI (MACI) have been introduced. These advanced methods employ scaffolds that not only prevent chondrocyte dedifferentiation during culture but also enhance the overall efficacy of the treatment. Predominantly, MACI scaffolds are composed of either type I or III collagen, or hyaluronic acid. Recent studies have demonstrated the long-term clinical efficacy of the MACI technique in treating focal chondral lesions of the knee. Nevertheless, the technique is associated with several limitations, including donor-site morbidity, the complexity of the multi-step process involving chondrocyte harvest, expansion, and reimplantation, and diminished regenerative capabilities in patients over 50 years of age. This age-related decline is attributed to reduced cell proliferation and ECM secretion capabilities as the donor ages. Innovations in hydrogel technology aim to preserve the chondrogenic phenotype of chondrocytes. For instance, Buschmann *et al.* [126] investigated a CS-based hydrogel that gels *in situ*. This hydrogel not only adheres to the defect site but also preserves the phenotype and potential of chondrocytes. Similarly, Schneider *et al.* [127] reported that bovine chondrocytes, when encapsulated in a photopolymerizable PEG hydrogel, retained their phenotype and synthesized an array of cartilage-specific ECM proteins, including types II, VI, IX, and XI collagens, aggrecan, and biglycan. Importantly, the synthesis of these proteins increased over time. Additionally, the study found that the behavior of chondrocytes within 3D charged hydrogels, specifically ChS and PEG, varies significantly with dynamic loading. Under unloaded conditions, both cell proliferation and proteoglycan synthesis are markedly reduced, while collagen synthesis remains relatively unaffected. In contrast, when dynamic loading is applied, there is a noticeable increase in both cell proliferation and the synthesis of proteoglycans and collagen. Removing the loading stimulus leads to a rapid decline in these enhanced synthetic activities [126]. These findings underscore the critical role of mechanotransduction and extracellular cues in modulating both cellular behavior and the functional outcomes of hydrogels.

4.2.2. Stem cells encapsulated in hydrogels

Therapies employing mesenchymal “stem” (or stromal) cells (MSCs) cannot be classified uniformly as homogeneous cellular treatments due to their varied nature and outcomes, as noted in recent literature [128]. Most current clinical trials focusing on MSCs are primarily preliminary, low-powered safety studies that often lack a control group. This deficiency significantly impedes the ability of systematic reviewers to draw clinically applicable conclusions regarding the efficacy of IA MSC treatments [129–132]. Despite this limitation, the rising promotion of "stem cell" therapies in orthopedic clinics across the United States has prompted a need for more rigorous scrutiny of these treatments [133]. While a comprehensive review of MSC injections for knee OA will not be provided here, as the topic has already been extensively covered in existing reviews [130–132,134], it is crucial to highlight that certain aspects of this therapeutic approach are often overlooked and warrant further clarification. This discussion aims to address these frequently neglected details, contributing to a more nuanced understanding of the potential and limitations of MSC therapies in orthopedics.

MSCs were first identified in the early 1990s, originally termed as MSCs [135]. Since their discovery, the terminology and definitions surrounding these cells have evolved [136]. In an effort to provide clarity and consistency in the field, the International Society for Cellular Therapy (ISCT) established a widely accepted definition in 2006. This definition rebranded MSCs as mesenchymal stromal cells, while intentionally preserving the “MSC” acronym to reflect a shift in understanding their capabilities without entirely discarding their historical nomenclature [137]. According to the ISCT, the defining characteristics of MSCs include adherence to plastic in standard culture conditions, the expression or absence of specific cell surface markers, and the capacity for trilineage differentiation. This means MSCs are capable of differentiating *in vitro* into osteoblasts, adipocytes, and chondrocytes, highlighting their potential in regenerative therapies [138]. This clarification has been crucial in distinguishing the broader potential of MSCs from the more narrowly defined "stem cell" properties, aiding both academic research and clinical applications.

Despite some exceptions [129,130], the majority of literature reviews remain optimistic about the potential of mesenchymal stromal cells (MSCs) as a treatment for OA and cartilage repair [131,132,134,139,140]. However, significant discrepancies exist between the encouraging results of *in vitro* and preclinical studies and those observed in human clinical trials [141]. Moreover, the heterogeneous nature and generally inadequate quality of the research published to date inhibit the possibility of a quantitative synthesis of the data [132]. Adding to the complexity, randomized controlled trials often focus on improvements within groups or differences between groups, frequently overlooking the importance of reporting or demonstrating within-group improvements [140]. Consequently, the lack of robust clinical evidence suggests that the efficacy claims regarding MSC therapy for knee cartilage pathology may be premature and potentially overstated. Given the variability and inherent incomparability among different MSC treatments, drawing broad efficacy conclusions offers limited practical value. Therefore, akin to biologic therapies, each MSC therapy should be assessed individually, taking into account its specific characteristics and the context in which it is used [142]. This tailored approach acknowledges the complexity of MSC treatments and emphasizes the necessity of rigorous, well-structured clinical trials to substantiate their therapeutic potential.

In the realm of biomedical therapies for cartilage regeneration, combining stem cells with hydrogels is a prevalent strategy. This approach typically employs various types of stem cells, including ESCs, MSCs, iPSCs, and predifferentiated MSCs. ESCs, sourced from early-stage embryos, are known for their unlimited self-renewal capacity and pluripotent differentiation potential [143]. However, the broad pluripotency of ESCs presents challenges in controlling their differentiation pathways. Hwang *et al.* [112] have shown that integrating biomimetic hydrogels with growth factors such as TGF-β1 and bone morphogenetic protein creates an environment conducive to chondrogenesis. Within such hydrogels, ESCs can differentiate into chondrogenic cells and contribute to the production of neocartilage ECM [112]. MSCs, derived from various tissues including bone marrow, adipose tissue, and umbilical cord blood among others, are particularly notable for their ability to respond to local biochemical signals and produce growth factors that facilitate tissue regeneration [144,145]. Their widespread use in biomedical applications is supported by their abundant availability, low immunogenicity, minimal ethical concerns, and low teratoma formation risk [144]. Research has extensively explored the encapsulation of MSCs in chondrogenic 3D injectable hydrogels like agarose and HA to promote chondrogenic differentiation and targeted cartilage reconstruction [107,146–149]. However, it’s important to note that *in vitro* studies have indicated a decline in the proliferation and differentiation potential of MSCs with advancing age and age-related diseases, which may limit their utility in older patients. iPSCs have garnered significant attention due to their ability to mirror the pluripotent characteristics of ESCs, opening multiple pathways for differentiation [150,151]. Xu *et al.* [152] demonstrated that human-derived iPSCs, maintained within a polylactic-based scaffold, could regenerate cartilage in osteochondral defects in rabbits within six weeks, showcasing their regenerative capabilities. Advances in cel-

lular reprogramming techniques have made the integration-free production of iPSCs a safer and more regulatory-compliant option for clinical applications [153]. Additionally, recent findings suggest that predifferentiated MSCs from peripheral blood, obtained with minimal invasiveness, possess chondrogenic differentiation capabilities comparable to traditional MSCs, though further research is needed to assess their suitability for use in injectable scaffolds [154,155]. Despite the promising attributes of ESCs and the synergistic effects observed when combined with biomimetic hydrogels and growth factors, their use is tempered by ethical concerns regarding their embryonic origin [156]. Consequently, there has been a shift towards utilizing adult-derived stem cells, like MSCs, which not only avoid these ethical issues but also show substantial potential as precursors to cartilage in regenerative therapies.

MSCs are harvested from a diverse array of adult tissues including bone marrow, synovium, adipose tissue, periosteum, umbilical cord, and peripheral blood. Research has demonstrated that chondrogenic differentiation of MSCs can be effectively induced by culturing them within 3D hydrogels that are specifically designed for this purpose, such as agarose, hyaluronan, PEG, and alginate. However, it is important to note that studies have also highlighted a decline in the proliferative and differentiative capacities of MSCs with aging and the presence of age-related diseases, which may constrain their therapeutic potential in older patients [157]. This underscores the urgent need to develop strategies that not only enhance the chondrogenic differentiation of MSCs but also prevent their differentiation into non-desired lineages. Innovations in hydrogel technology could provide potent chondrogenic cues while suppressing undesired differentiation pathways. Simultaneously, ongoing research is exploring novel cell sources such as iPSCs, which are adult cells reprogrammed to an embryonic-like pluripotent state [158]. The utilization of iPSCs is particularly promising for rejuvenating cells from elderly patients, enhancing their regenerative and functional capabilities. For instance, in a study by Xu *et al.* [152], human iPSCs were maintained in their pluripotent state on a poly-lactic acid-based scaffold, effectively promoting the repair of osteochondral defects within six weeks in a rabbit model. The development of integration-free cellular reprogramming techniques has further advanced the generation of iPSCs, making them safer and more compliant with regulatory standards for clinical applications [153]. Although these advancements reduce the risk of aberrant tissue formation, continued research is crucial to fully understand the long-term implications and benefits of using human iPSCs in articular cartilage tissue engineering.

4.3. Hydrogels for gene delivery

The pathogenesis of OA is typically associated with aging, abnormal mechanical stress, cellular metabolism, protease activity, and inflammatory changes [159,160]. Under stimulation by these factors, excessive expression of various matrix-degrading enzymes occurs, leading to progressive degradation of the cartilage ECM [161]. Concurrently, persistent inflammatory and oxidative stress damages chondrocyte mitochondria, resulting in metabolic imbalance and impaired self-regulatory functions, thereby exacerbating cellular damage and accelerating senescence [162]. Articular cartilage is a highly specialized tissue with limited vascular supply, which restricts its intrinsic repair capacity [163,164]. Consequently, maintaining functional resident chondrocytes within cartilage is crucial for joint health. Thus, promising OA therapeutic strategies should fundamentally address chondrocyte matrix degeneration and maintain chondrocyte homeostasis. However, a major challenge persists regarding whether exogenously administered MSCs can achieve long-term survival and functional maintenance post-transplantation, particularly in severely diseased joint environments where unfavorable microconditions or excessive mechanical stress may compromise cell viability. As an emerging approach, gene therapy has made significant advances in recent years. For instance, siRNA and miRNA have been demonstrated to regulate various pathological processes during OA by modulating target gene expression [165,166]. Notably, miRNA-874–3p not only downregulates matrix metalloproteinases to attenuate ECM degradation but also participates in chondrocyte differentiation and growth, making it a promising therapeutic candidate for OA [167,168]. Nevertheless, gene therapy still faces substantial challenges in nucleic acid delivery, particularly concerning sustained release and transfection efficiency.

A promising method for ensuring a stable therapeutic concentration of gene products in affected joints is through local gene transfer. This can be accomplished either by the *ex vivo* modification of cells or by direct IA injection of viral or non-viral vectors [169]. The present study evaluates the efficacy of IA gene therapy, a topic previously reviewed in this journal in 2011, in ongoing phase I clinical trials for patients with rheumatoid arthritis (RA) and OA [170]. Notably, a phase II trial for RA, which employed adeno-associated virus to administer etanercept, experienced a fatality among its participants. Despite this serious incident, the trial was permitted to proceed to completion [171]. Concurrently, phase II trials for OA are employing allogeneic cells engineered to express TGF-β1. These trials are actively being conducted in both Korea and the United States, reflecting the international effort to advance this therapeutic approach [172].

RNA interference (RNAi), mediated by small interfering RNA (siRNA), represents a powerful technique for suppressing gene expression within cells by binding and degrading target mRNA, thereby silencing the gene of interest. While siRNAs can be effectively applied to cells *in vitro* using modified siRNAs that do not require transfection agents, the application of this gene silencing strategy *in vivo* faces significant challenges, including molecular instability and inefficient cellular uptake [172]. The laboratory has recently shown that modifications of the native melittin led to the formulation of a self-assembling, ~55 nm peptide-siRNA nanocomplex that deeply penetrates cartilage to specifically silence nuclear-factor kappa B (NF-κB), a signaling pathway that controls the expression of several matrix-degrading enzymes involved in the remodeling of cartilage matrix [173]. The sustained presence of this nanocomplex in human cartilage explants offers a promising and clinically relevant strategy for addressing the challenges associated with siRNA delivery. Moreover, the versatile formulation of the nanocomplex allows for siRNA multiplexing, enabling the simultaneous targeting of multiple pathways or the incorporation of any unmodified RNA without the need for backbone or end modifications. This flexibility is anticipated to provide significant advantages in cartilage preservation and therapeutic applications. The peptide-siRNA nanocomplex has also demonstrated a favorable safety profile, showing no evidence of innate or adaptive immune responses following multiple intravenous administrations. A simple 10-min mixing protocol allows for the rapid self-assembly of good manufacturing practice (GMP)-compliant siRNA and peptide components, facilitating immediate use without the need for costly processing or purification steps [173]. Additionally, our approach includes chondrocyte-targeted nanoparticles as a promising method for delivering siRNA to cartilage [174]. This technology has been applied to deliver various therapeutic agents, such as TGF-β-activated kinase 1 (TAK1) [175], matrix metalloproteinase 13 (MMP-13), and a disintegrin and metalloproteinase with thrombospondin motif 5 (ADAMTS-5) [176], aiming to prevent cartilage degeneration.

The emerging understanding of the catabolic and anabolic effects of microRNAs (miRNAs) on OA cartilage has ignited interest in their IA administration as a therapeutic strategy. Notably, recent research has explored promising approaches such as conjugating

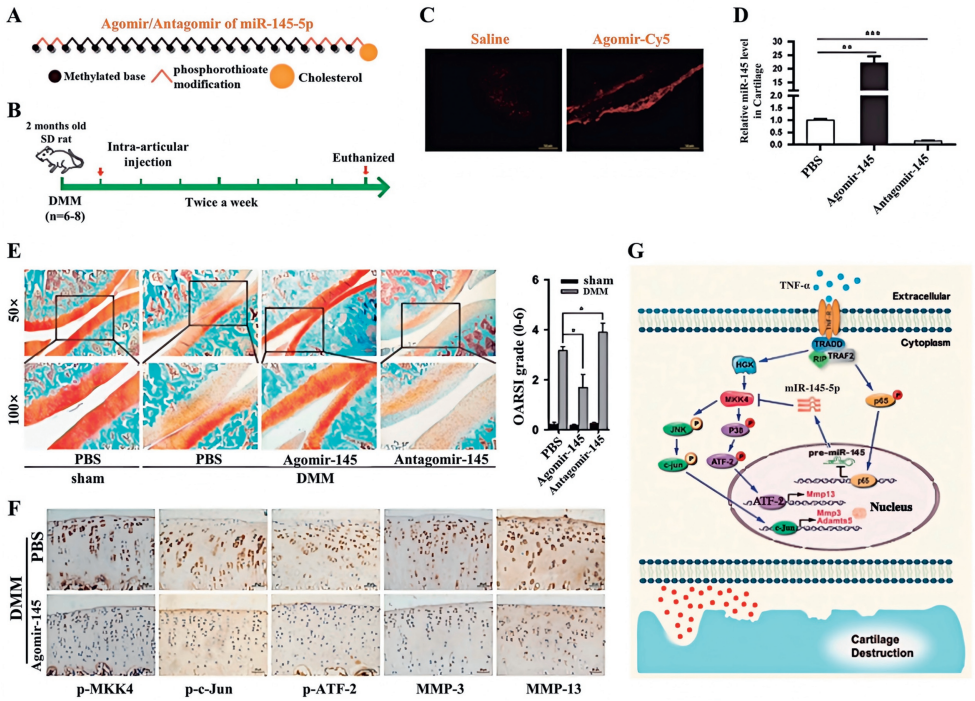


Fig. 4. MiR-145 counteracts cartilage matrix degradation in surgery-induced OA. Copied with permission [180]. Copyright 2017, Springer Nature.

miRNAs with lipid nanoparticles to facilitate active transport across adipocyte membranes, and employing liposomes as delivery vehicles. Liposomes, which are spherical vesicles comprised of phospholipid bilayers, have been highlighted as effective carriers for controlled drug delivery [177]. Rajagopal *et al.* [178] demonstrated that AmC pegylated with Tocofersolan (AmCTOC) liposomes exhibited significantly superior 3D transfection efficiency compared to other reagents. This was validated through successful knockdown of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in HEK cells and expression of green fluorescent protein (GFP) mRNA in human bone marrow-derived MSCs, confirming its robust 3D transfection capability. These natural, biodegradable, and non-toxic lipid structures are uniquely capable of encapsulating both hydrophilic and hydrophobic drugs, making them well-suited for the targeted and localized delivery of therapeutic agents [179]. This versatility allows for the precise delivery of miRNAs to cartilage tissues, potentially enhancing their therapeutic impacts on OA. However, despite their advantages, conventional liposome formulations face challenges such as rapid clearance from the bloodstream, which can significantly limit their therapeutic efficacy and duration of action [180]. To overcome this limitation, ongoing research is focusing on modifying liposome formulations to enhance their stability and residence time within the joint, thereby maximizing their potential as carriers for miRNA-based therapies.

Exosomes, the extracellular vesicles secreted by cells, play pivotal roles in intercellular communication, protein transport, and miRNA delivery. Their natural ability to evade the immune system and directly fuse with the plasma membranes of target cells makes them exceptionally promising candidates for drug delivery systems. This capability is especially advantageous because it allows exosomes to deliver therapeutic molecules directly into the cytoplasm of target cells, effectively bypassing the endosomal pathway that often degrades or traps such therapeutic agents. Despite the advantages of natural exosomes, there is ongoing research into the development of synthetic carriers for miRNAs, aimed at optimizing the delivery mechanisms for therapeutic purposes. Recent studies have pointed towards lentivirus-mediated IA injections as a particularly effective method for delivering miRNAs into the synovial cavity (Fig. 4) [180]. Peng *et al.* [181] investigated synovial tissue samples from RA patients and employed two experimental models, collagen-induced arthritis (CIA) and collagen antibody-induced arthritis (CAIA) in mice. Using lentiviral (LV)-mediated precursor miR-140 transduction, they induced overexpression of miR-140–3p and miR-140–5p in synovial fibroblasts (SFs) and synovial tissues. Results demonstrated significantly reduced expression of both miR-140–3p and miR-140–5p in SFs and synovial tissues from RA patients and both murine arthritis models. The study confirmed that IA delivery of miR-140–3p and miR-140–5p targeting SFs ameliorates autoimmune arthritis. In contrast, Wang *et al.* [182] reported that IA injection of LV3-miR-483–5p to overexpress miR-483–5p markedly exacerbated the severity of experimental OA. To counteract this effect, they synthesized antago-miR-483–5p to silence endogenous miR-483–5p Their findings revealed that miR-483–5p directly targets cartilage matrix proteins matrilin 3 (MATN3) and tissue inhibitor of metalloproteinases 2 (TIMP2), thereby stimulating chondrocyte hypertrophy, ECM degradation, and cartilage angiogenesis. This mechanism initiates and accelerates OA progression. This method leverages the natural ability of lentiviruses to integrate into the host cell genome, thus offering a potentially more stable and prolonged expression of therapeutic miRNAs compared to non-viral delivery systems. However, while promising, the use of lentivirus-mediated delivery raises concerns regarding safety, such as the risk of insertional mutagenesis and immune reactions. Therefore, further research is essential to refine these delivery systems to ensure they are not only effective but also safe for clinical use. The goal is to develop a miRNA delivery system that achieves an optimal balance between efficacy and safety, leveraging the unique properties of exosomes or synthetic carriers to provide targeted, efficient, and secure therapeutic options.

5. Conclusions and future perspectives

The exploration of alternative strategies for OA treatment is critical due to the limitations of current therapies. This includes

investigating the heterogeneity of MSCs, identifying more reliable cartilage formation markers, and engaging in novel material research [54]. Given the rapid degradation of IA injected molecules and the associated injection risks, developing sustained-release formulations is essential [8]. Injectable hydrogels, especially nanocomposites that mimic the ECM, are promising due to their enhanced mechanical properties and potential for delivering growth factors and drugs. However, overcoming their mechanical weaknesses remains a challenge, necessitating further research into hydrogel interactions with micro- and nano-fillers to enhance the properties of injectable hybrid hydrogels.

Injectable scaffolds, while promising for articular cartilage regeneration, face limitations in fully restoring the cartilage. These scaffolds must not only seamlessly fill defects but also integrate with healthy tissue while maintaining mechanical integrity during gradual degradation and ECM replacement. The integration of MSCs into these scaffolds could facilitate tissue generation as the scaffold degrades, but further investigation into stem cell signaling and mechanisms is crucial for optimizing scaffold performance. Advances in understanding cartilage development and regeneration through fundamental biological research will significantly improve future scaffold designs.

The translatability of these systems at the design stage is crucial. Evaluating biocompatibility, ease of administration, scalability of production, and cost is necessary for successful implementation. Integrating next-generation cartilage tissue engineering with noninvasive or minimally invasive diagnostics could allow for real-time disease assessment and for personalized therapy. Biodegradable cartilage biomimetic hydrogels represent a promising *in vivo* cell delivery and tissue engineering approach, offering advantages over traditional techniques such as injectability and mechanical support. Although preclinical animal models have shown promising results, further studies are required to confirm their clinical efficacy in humans [110].

IA injection of therapeutic agents remains a promising method for localized treatment of joint diseases. The accuracy of these injections can be improved with imaging guidance. Despite their benefits, the rapid clearance of soluble agents from joints presents a significant challenge. The popularity of this method has increased with the use of corticosteroids and hyaluronate for treating OA. There is growing interest in directly injecting recombinant proteins, blood products, cells, and gene therapy vectors into joints, which may offer safety, cost-effectiveness, and efficacy advantages over systemic delivery methods. To mitigate the need for frequent reinjections, there is a crucial need for improved drug formulations that extend the effectiveness of these therapies [183].

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.

CRediT authorship contribution statement

Kai Zhou: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xinlong He:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yue Liu:** Supervision, Formal analysis. **Zhongwu Bei:** Supervision, Methodology. **Kun Shi:** Formal analysis, Conceptualization. **Danrong Hu:** Visualization, Investigation. **Yilin Wang:** Software, Investigation. **Mei Gao:** Software, Investigation. **Bingyang Chu:** Formal analysis, Conceptualization. **Qian Yang:** Supervision, Resources. **Chengli Yang:** Supervision, Methodology. **Zhiyong Qian:** Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Acknowledgments

The authors would like to thank the following funding sources: the National Natural Science Foundation of China (Nos. U21A20417, 82002304, 82402823), the Noncommunicable Chronic Diseases-National Science and Technology Major Project (No. 2024ZD0522800 to P. Tian, No. 2024ZD0522803 to Z. Qian), 1·3·5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (No. ZYGD24003), Sichuan Provincial Health Research Projects (No. 2025-111) and Chengdu Technology Fund Project (No. 2022-YF05-01460-SN).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.111723.

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