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REVIEW

Application of Injectable Hydrogels as Delivery Systems in Osteoarthritis and Rheumatoid Arthritis

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Abstract

Osteoarthritis and rheumatoid arthritis, though etiologically distinct, are both inflammatory joint diseases that cause progressive joint injury, chronic pain, and loss of function. Therefore, long-term treatment with a focus on relieving symptoms is needed. At present, the primary treatment for arthritis is drug therapy, both oral and intravenous. Although significant progress has been achieved for these treatment methods in alleviating symptoms, certain prominent drawbacks such as the substantial side effects and limited absorption of medications call for an urgent need for improved drug delivery methods. Injected hydrogels can be used as a delivery system to deliver drugs to the joint cavity in a controlled manner and continuously release them, thereby enhancing drug retention in the joint cavity to improve therapeutic effectiveness, which is attributed to the desirable attributes of the delivery system such as low immunogenicity, good biodegradability and biocompatibility. This review summarizes the types of injectable hydrogels and analyzes their applications as delivery systems in arthritis treatment. We also explored how hydrogels counteract inflammation, bone and cartilage degradation, and oxidative stress, while promoting joint cartilage regeneration in the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). This review also highlights new approaches to developing injectable hydrogels as delivery systems for OA and RA.

Key words: injectable hydrogels; osteoarthritis; rheumatoid arthritis; drug delivery; disease treatment

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Introduction

Osteoarthritis (OA) and rheumatoid arthritis (RA) are the most common chronic joint diseases, which are characterized by synovial inflammation, bone structure changes, joint pain and functional limitations, eventually leading to disability (Bingham et al, 2006; Scherer et al, 2020). These diseases are serious clinical and public health problems, significantly encumbering the patients and the society (Wang et al, 2015). It was estimated that approximately 240 million people worldwide have symptomatic, activity-limited OA, and the global prevalence of RA is approximately 1% (Global Burden of Disease Study 2013 Collaborators, 2015). Both forms of arthritis are pathogenically associated with complex processes driven by multiple inflammatory and metabolic factors. The risk factors for inflammatory

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OA include age and activity (Palazzo et al, 2016), while the risk factors for RA include heredity, immunity and injury (Scott et al, 2010). Characterized by erosion of periarticular bone, synovitis, and osteoporosis, RA is a chronic debilitating and systemic inflammatory disease disproportionately affecting women more than men. Due to its autoimmune nature, RA primarily affects the synovial membranes of joints through inflammation, by generating high levels of pro-inflammatory cytokines, matrix-degrading enzymes, and autoantibodies, all of which contribute to synovial inflammation and joint damage. Eventually, RA might result in permanent impairment and significant joint injury (Guo et al, 2018). The infiltration with inflammatory cells, such as T cells, B cells, and monocytes, is one of the pathogenic factors of RA (Aletaha and Smolen, 2018). Different from the etiologies of RA, the primary causes of OA, a chronic degenerative disease of the joints, encompass aging, trauma, mechanical loading, and obesity (Loeser et al, 2016). It might engender morphological harm and a loss of joint tissue cartilage. The appearance of OA is accompanied by collagen matrix disorganization and collagen fibers breakdown, which results in an increase in water content (Mobasheri and Batt, 2016). Due to the rapid aging of the global population, the prevalence of OA is on the rise. The current treatment for arthritis is merely aimed at reducing pain and disease activity as well as preventing inflammatory and destructive processes, but currently there is still no exact cure for the disease (Bird, 2003). If left untreated, complications related to inflammatory arthritis can lead to severe loss of joint function (Abramoff and Caldera, 2020), which can only be treated with joint replacement (Nissen et al, 2022; Quicke et al, 2022).

At present, the three primary mechanisms in the treatment of OA and RA are: (i) alleviating inflammation and pain; (ii) preserving joint function; and (iii) abrogating further progression of arthritis and joint injury (Arden et al, 2021; Matteson, 2000). The treatment of OA and RA primarily includes drug therapy, non-drug therapy and surgery (Kou et al, 2019). Drugs include but are not limited to non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying osteoarthritis drugs (DMOADs)/disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids (GCs) and biologics (Yi et al, 2022). Other non-drug therapies include naturopathy, thermotherapy, and electromagnetic therapy (Rannou and Poiraudeau, 2010). The therapeutic effects of these treatments, however, are mostly unsatisfactory because medications that can deter joint degradation and functional decline, while being palliative and well-tolerated for most individuals, are scarce (Lee and Weinblatt, 2001). Regarded as the end-stage remedial measure, surgery is applied to remove the diseased synovium to facilitate the rebuilding of joint stability and the restoration of joint function. Due to the complex pathophysiological changes of OA and RA and the harsh local microenvironment, a single-mode treatment is not adequate for repairing the damaged synovial and joint structures and restoring their functions.

Owing to the rapid advancement of tissue engineering and biomaterials technologies, novel therapeutic approaches have been devised for the management of OA and RA (Oliveira et al, 2021). Hydrogel is a highly hydrated polymer material with a three-dimensional (3D) network structure, while possessing a range of desir-

able properties, such as injectability, good biocompatibility and biodegradability, and capacity to adapt to uneven damage (Ding et al, 2023). Injectable hydrogel is a promising therapeutic material, which can be administered via syringe when in a fluid state (Bar et al, 2018; Zeimaran et al, 2021). The injected liquid is then turned into a gel *in situ* to form a tissue-bioengineered scaffold (Mo et al, 2021). Injectable hydrogels can be used as drug carriers directly or to encapsulate smaller drug carriers to deliver drugs or biotherapeutic molecules, in an accurate and controlled manner, to the lesion site to provide safe and effective treatment, and are frequently used in the management of refractory diseases like RA (Oliveira et al, 2021; Wang and Wang, 2021c). Hydrogels can be utilized as delivery systems for cells, medications, or other substances to accomplish long-term controlled release of pharmaceuticals or cell molecules because of their effective encapsulation and stable, controlled release characteristics (Mertz et al, 2019; Wang et al, 2020b).

In this paper, we provide an overview of the different kinds and categories of injectable hydrogels, along with their potential applications as delivery systems in the treatment of OA and RA. This paper also reviews the molecular mechanisms of hydrogels in the treatment of arthritis, in addition to offering methods for arthritis repair. Through this review, we advocate for further research on injectable hydrogel as a delivery strategy for treating arthritis.

OA and RA: Current Treatments and their Limitations

Despite the growing number of clinical treatments available for patients with OA and RA, none of them have demonstrated the potential to reverse disease progression (Zhang et al, 2007). Current treatment strategies for OA and RA are designed to relieve symptoms so as to improve quality of life, rather than being intended to cure the disorders (Bruno et al, 2022). Paracetamol, NSAIDs, opioids, and/or intra-articular corticosteroids are used to treat OA. The drugs used to treat RA include anti-rheumatic drugs, such as low-dose methotrexate, NSAIDs, short-term glucocorticoids (Allen et al, 2018). At present, stem cell therapy and biotherapy also show good therapeutic prospects in RA and OA. The potential of stem cells in the treatment of arthritis has been investigated *in vivo* in a number of directions, with some of the research outputs being successfully incorporated into human clinical trials. However, stem cell therapy's potential in treating arthritic disorders remains to be corroborated due to the small number of patients used in certain studies (Liu et al, 2020; Sarsenova et al, 2021; Wolfe et al, 2006).

Mesenchymal stem cells (MSCs) possess substantial immunomodulatory qualities that make them a potentially attractive alternative therapy approach for RA. Given the complex intricacies in the pathophysiology of the disease, MSCs serve as a potential element in stem cell-based therapy. In experimental animal models, MSCs have been routinely employed to treat inflammatory and immunological illnesses. Nowadays, MSC-based therapy is widely applied in clinical settings to address a variety of diseases (Liu et al, 2020). MSCs can be considered a promising alternative approach with the capacity to provide strong immunomodulatory prop-

erties for RA treatment and can serve as a promising tool in stem cell-based therapy (Liu et al, 2020). According to the National Institutes of Health (NIH), more than 350 clinical studies on MSC-based therapy are currently underway, but only about 10 of them are related to RA treatment. Therefore, more research is required to determine the potential therapeutic use of MSCs in the treatment of RA (Sarsenova et al, 2021). Because of their immunomodulatory qualities and capacity to differentiate into chondrocytes, MSCs are recognized as the most investigated type of cells used in OA therapy (Xiang et al, 2022). They may accelerate the healing of cartilage and eventually lead to the restoration of healthy joints. The optimal source of MSCs and the possible function of exosomes are two of the many unresolved concerns surrounding MSCs, despite their promising potential as a therapeutic alternative. To dispel these uncertainties, more *in vitro* and clinical research is required for validation of their treatment potential (Yu et al, 2022). Thus, the prospective clinical application of MSCs in RA and OA treatment needs to be further investigated.

Biologics are proteins created through biotechnological means, possessing the ability to suppress rheumatic inflammation by regulating the cellular and humoral aspects (Wolfe et al, 2006). Biologics represent a new, breakthrough class of disease-modifying treatment options for RA, contributing to a big share of clinical and radiographic improvements. Standard-dose and high-dose biologics (with/without traditional DMARDs) are associated with an increase in serious infections compared to traditional DMARDs in RA. Thus, this warrants a trade-off of benefits and harms before initiating a biologic therapy (Wolfe et al, 2006).

A study has shown that growth factors play an important role in the treatment of RA, with the axis connecting thrombospondin-1, transforming growth factor beta (TGF-β) and connective tissue growth factor (CTGF) being an emerging therapeutic target for RA (Rico et al, 2010). Biological therapy stands as one of the newest and fastest-growing approaches to treating OA, but the signalling pathways and molecular processes underlying the complexity of OA pathogenesis remain poorly understood, posing a challenge to target OA with therapeutic pharmaceutical interventions (Das et al, 2016).

The therapeutic effect and safety of medications are mostly determined by the mode of delivery (Fleischmann et al, 2019). In treating early-stage arthritis, oral and topical/transdermal delivery are the most popular methods. NSAIDs are used as the first-line therapy to treat OA and RA; by taking only a minute quantity of the medication, the active ingredient can reach the target location through the joint's synovial fluid as a result of first-pass effects. NSAIDs may also cause a variety of adverse reactions such as gastrointestinal reactions, which limit their clinical applications (He et al, 2017). Since both OA and RA are local rather than systemic diseases, and the cartilage has no blood vessels, intravenous corticosteroids and biologics can only reach the joint through the circulatory system, causing low drug bioavailability and significant reduction of the drugs' direct actions at the lesion site (Qindeel et al, 2020). There are also risks of digestive tract diseases (such as ulcers and bleeding), as well as liver and kidney damage (Iannitti et al, 2013; Raza et al, 2014). Local or transdermal administration through the use of emulsions or patches can lessen toxicity and irritation, but the skin barrier can block the penetration of

the medicines (Li et al, 2021b). These methods are intended only for patients with mild symptoms and for the relief of symptoms in severely ill patients. If drugs or biologics fail to control the progression of the disease, surgical intervention should be considered, despite the significant trauma and extensive postoperative adhesion, as well as the damage to other normal tissues, caused by this form of treatment (Kadota et al, 2016; Winkler et al, 2013). Intra-articular (IA) injections are an attractive approach to treating arthritis compared to traditional therapies, such as oral, intravenous, and transdermal administration. Intra-articular injection can directly deliver drugs into the joint to treat pain and inflammation, boasting potential advantages over systemic treatment, such as better safety profile higher bioavailability, better control of drug concentration, and reduction of systemic side effects (Song et al, 2022). The costly expenses, the necessity for clinical surgery, and the increased risk of infection are the three major disadvantages of intra-articular injection (Gerwin et al, 2006) (Fig. 1).

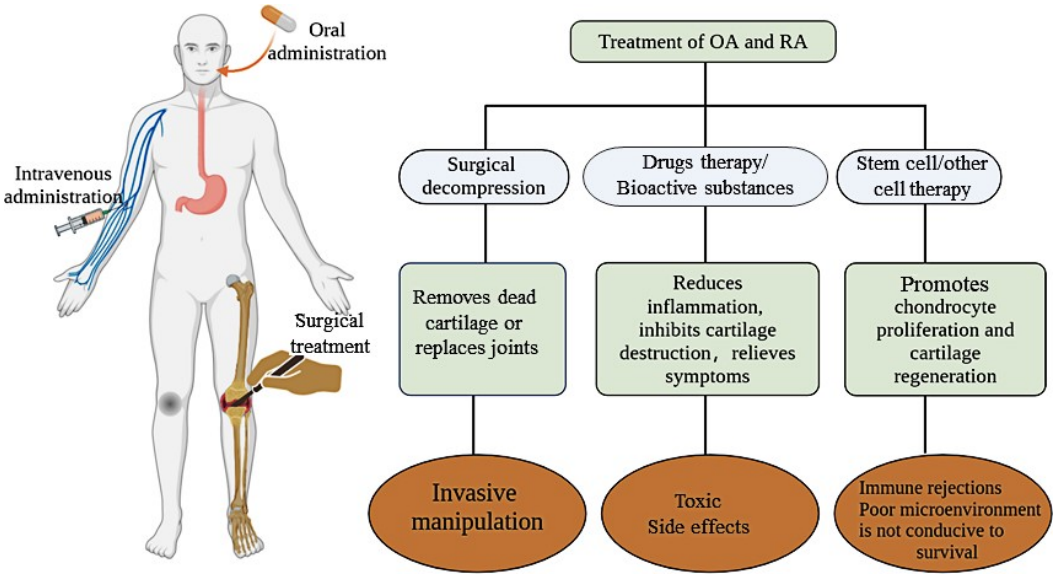

Fig. 1. The roles and constraints of current therapies for rheumatoid arthritis (RA) and osteoarthritis (OA). The image is drawn using the BioRender software (https://app.biorender.com/).

Types of Hydrogels

Hydrogels are water-based, viscous, semi-solid preparations with 3D structures composed of gel matrix and drugs, which can simulate the environment of extracellular matrix (ECM) and support the exchange of nutrients with surrounding tissues, and are commonly employed in tissue engineering, drug delivery, biosensors and other applications (Chen et al, 2023c; Narayanaswamy and Torchilin, 2019). Hydrogels can be formed by physical or chemical crosslinking, and are classified as natural, synthetic, and natural-synthetic composite hydrogels based on the source of materials used (Nguyen and Lee, 2010). The different types of hydrogels are described below.

Natural Hydrogels

Natural hydrogels are made from natural biomaterials, such as collagen, hyaluronic acid (HA), alginate, chitosan, *etc.* (Wang et al, 2018a). Natural hydrogels are known for their biocompatibility, porosity and softness, as well as the ability to induce enzymatic degradation, cell adhesion and migration, all of which drive their broad applications in the treatment of arthritis (Seliktar, 2012; Taghipour et al, 2020).

Hyaluronic Acid

Repetitive units of D-glucuronic acid and n-acetylglucosamine connected by β-1,4 and β-1,3 glycoside linkages are found in anionic non-sulfated linear glycosaminoglycans that are broken down by the ECM enzyme into HA (Xu et al, 2012). The negative charge and hydroxyl group confer hydrophilic properties onto the HA molecules. As the temperature rises, the grafting polymer's hydrophilic and hydrophobic components interact, resulting in increased viscosity and the formation of hydrogels (Chen et al, 2023a). It possesses the ability to mend damaged tissues and lessen the inflammatory response of cells, along with its good biocompatibility, biodegradability and excellent gel formation characteristics (Sepulveda et al, 2023). A previous study has evaluated the *in vivo* properties of HA hydrogel in rabbit OA models, and found that repeated injection of this hydrogel can partially restore OA-induced cartilage defects (Lei et al, 2022). Furthermore, Xu et al (2012) developed a unique repository for click-crosslinked HA (Cx-HA) that can be used to treat RA by means of a click-crosslinked reaction between HA modified with tetraazine and HA modified with trans-cyclooctene (Seo et al, 2019). When the hydrogel is loaded with methotrexate (MTX), an MTX-CX-HA reservoir can be rapidly formed in the joint to maintain therapeutic MTX concentrations at the intraarticular injection site to induce joint repair. In addition, the hydrogel can also prevent the distribution of MTX to surrounding normal tissues and organs, thereby reducing adverse effects on other tissues (Lei et al, 2022).

Chitosan

Chitosan (CS) can reduce and release acetyl chitosan, and it is also an excellent gelling agent with excellent biocompatibility, antibacterial activity and low immune rejection (Cheung et al, 2015). CS degradation products can be metabolized and easily made into hydrogels (Delmar and Bianco-Peled, 2016; Cheah et al, 2019). CS/glycerol phosphate (GP) solution has been reported as a unique drug delivery platform (Supper et al, 2014). In the hydrogels prepared with CS and β-glycerophosphatester (BGP), micro- and nano-scale pores are generated in the gel structure (Cai et al, 2022). Due to its biodegradability, good biocompatibility and temperature sensitivity of hydrogel formation at body temperature, CS hydrogels can be effectively used for the delivery and slow release of proteins/peptides, anti-inflammatory drugs and antibiotics, and are considered potential tools for articular cartilage repair (Ragetly et al, 2010; Shen et al, 2021). Pan et al (2020) found that injectable CS thermosensitive hydrogel could protect articular cartilage by reducing

friction to surrounding tissues and provide good lubrication properties for articular surface, and encourage the growth and adherence of MSCs.

Alginate

As a natural product of brown seaweed, alginate is a biocompatible hydrogel that is of low toxicity, low cost, good gelling ability and high bioavailability, making it is very suitable for biomedical applications (Turnbull et al, 2017). Alginate hydrogel is usually prepared by ion crosslinking through the combination of alginate and divalent cation, and ion-crosslinking injectable alginate gel is an ideal cell delivery scaffold for tissue regeneration (Hernández-González et al, 2020). Alginate hydrogel can be loaded with various substances to improve the internal environment in the contexts of OA and RA (Banihashemian et al, 2024; Chen et al, 2024a). Díaz-Rodríguez and Landin (2015) demonstrated that hydrogel composed of alginate and poloxam could control the release of indomethacin, thereby regulating the degradation of ECM of chondrocytes and promoting the formation of new collagen in OA chondrocytes. In addition, the study has shown that injectable alginate hydrogel can improve joint syndrome of RA (Chen et al, 2023b).

Other Natural Hydrogels

Other classes of natural hydrogels are made of a range of substances, such as collagen, gelatin, dextran, cyclodextrin, and fibrin (Benwood et al, 2021). Collagen is one of the ECM proteins among these naturally occurring polymers. Although their osteoinductiveness is particularly well-suited for cartilage regeneration, their uses are hindered by their weak strength and fracture toughness (Jing et al, 2023). Gelatin is a biodegradable protein that primarily comes from cows or pigs and has strong adhesiveness, plasticity, and biocompatibility. However, their limited mechanical qualities and severe hygroscopicity limit their applicability. Of note, it is a common practice to combine gelatin and collagen with other polymers or to modify them with functional groups to improve their applications (Wang et al, 2019a). Dextran is a d-glucopyranose residue that is linear and has six links. It is an extremely useful and biocompatible chemical (Du et al, 2019). On the other hand, fibrinogen polymerizes to form a fibrillar scaffold, which is the source of fibrin. Fibrinogen and platelets generate fibrin clots when tissue damage occurs. Both dextran and fibrin are widely used in biomedical applications and have been approved by the U.S. Food and Drug Administration (FDA) for functions such as tissue regeneration and control of inflammation (Tanaka et al, 2019).

In general, natural hydrogels are effective scaffolds for OA and RA treatment and functional recovery, and even better scaffolds for drug/cell delivery in OA and RA (Zewail et al, 2021). However, the long-term stability and breakdown of natural hydrogels may restrict their effectiveness in treating OA and RA. The safety and potential dangers of these hydrogels to patients with OA and RA have not been assessed in clinical trials, despite the fact that they have not shown a substantial increase in toxicity in cellular or animal investigations. This suggests the necessity for more standardized purification and toxicity studies before clinical use.

Synthetic Hydrogels

Synthetic polymers are crosslinked chemically or physically to create synthetic hydrogels. It is feasible to mass-produce synthetic polymers, and their highly modifiable features can be adjusted to any application's requirements (Jung et al, 2022). Examples of certain common synthetic polymers include polyacrylamide (PAM), polyethylene glycol (PEG), poly-ϵ-caprolactone (PCL), and hydroxyethyl methacrylate (PHEMA) (Peng et al, 2023).

Poly (N-isopropylacrylamide)

Poly (N-isopropylacrylamide) (PNIPAm) is a typical temperature-sensitive material and one of the most well-studied thermosensitive polymers for biomedical applications (Karimi et al, 2016). Hydrophilic amide (-$CONH_2$) and hydrophobic isopropyl (-$CH(CH_3)_2$) side chains make up PNIPAm (Kim et al, 2018). In water, the lower critical solution temperature of PNIPAm is nearly body temperature, and under physiological conditions, the polymer solution can gel in place without the need for external stimuli (Okano et al, 1993). PNIPAm is used in many biomedical applications, such as heat-modulated drug delivery systems (Nagase et al, 2019), tissue engineering, and cell culture substrates for regenerative medicine (Akimoto et al, 2018; Ansari et al, 2022). PNIPAm is a homogenous solution at room temperature and can be directly injected into the body, triggering the formation of 3D hydrogel at body temperature (Matanović et al, 2014). However, the application of PNIPAm is limited due to its low biodegradability, poor mechanical strength, relatively low drug loading and uncontrolled release of drug molecules (Alexander et al, 2014). However, the hydrogel's temperature response time can be reduced by adding more polymers to create an interpenetrating polymer network (IPN), thus altering its drug loading and drug release mode (Feng et al, 2018).

Polyethylene Glycol

Polyethylene glycol (PEG) is a multipurpose polymer that is regarded as innocuous (Ibrahim et al, 2022). PEG can be copolymerized with biocompatible polyester to prepare thermosensitive hydrogels. The thermal sensitivity of hydrogels can be improved by adjusting the composition and length of hydrophilic PEG blocks and hydrophobic polyester blocks. PEG, poly lactic-co-glycolic acid (PLGA) and ethyl acetate can be combined to create a BAB triblock copolymer PLGA-PEG-PLGA. Copolymers' temperature sensitivity is regulated by the hydrophilic and hydrophobic groups (PLGA) present in the polymer (Nie et al, 2012). At low temperatures, hydrophilic PLGA and hydrophobic PEG nuclei shells self-assemble into micelles. On the other hand, increasing ambient temperature would lead to dehydration and micelle aggregation of PLGA shells, resulting in scaffolds with varying drug release rates (Aghaie et al, 2019; Peppas et al, 1999; Yu et al, 2009).

Polyacrylamide

Polyacrylamide hydrogels are highly crosslinked 3D acrylamide networks with excellent biocompatibility and water exchangeability (Brahm et al, 2012). Injectable polyacrylamide hydrogels have been shown to protect cartilage surfaces to achieve

high-quality fibrocartilage healing, thereby reducing OA symptoms (Mcclure and Wang, 2017). Bliddal et al (2024) found that intra-articular injection of polyacrylamide hydrogel has a protective effect on cartilage, thus alleviating symptoms of knee OA.

Poloxam

Poloxam is a class of water-soluble non-ionic triblock copolymers formed from hydrophilic polyethylene oxide and hydrophobic polypropylene oxide blocks, which are considered smart polymers (Fu et al, 2015). They have stimulus-sensitive properties and can change their structure depending on pH, temperature, and salt concentration (Aguilar et al, 2007; Kim et al, 2018). Poloxam copolymers are more sensitive to temperature, and in aqueous solutions, these copolymers form micelles with ordered structures at appropriate temperature and concentration (Bodratti and Alexandridis, 2018; Thapa et al, 2020). With the increase of temperature, micelles tend to enhance their structural order, facilitating a transition from sol to gel (Abdeltawab et al, 2021). The hydrogel can act as a drug carrier directly or fix other drug delivery carriers at the injury site for controlled release of loaded drugs (Alexander et al, 2014; Zhou et al, 2020b).

Other Synthetic Hydrogels

Apart from the aforementioned polymers, other synthetically derived polymers, such as poly vinyl alcohol (PVA), peptides and synthetic deoxyribonucleic acid (DNA), can be applied for hydrogel formation (Zhang and Huang, 2021). The FDA has approved PVA, a synthetic hydrophilic polyhydroxyl polymer, as a non-antigenic and biocompatible substance. PVA has been widely used in tissues like bone because of its good mechanical properties and ease of modification (Wang et al, 2019c). Amino acids, which make up peptides, can be linked to form a synthetic polymer appropriate for the creation of medicines and biomaterials. They are promising for use in biological applications due to their exceptional biodegradability, biocompatibility, bioactivity, and responsiveness (Sis and Webber, 2019). Originating as a genetic molecule, synthetic DNA has unique and intriguing properties like sequence-dependent designability, tunable multi-functionality, and accurate base-paring recognition ability. These exceptional qualities provide a superb framework for the development of functional hydrogels. DNA can self-replicate into long strands that are cross-linkable to create rolling circle amplification (RCA) hydrogels. The functional DNA within these hydrogels provides an excellent platform for detecting external inputs (Zhou et al, 2020a).

These synthetic polymers clearly have a wide range of potential applications, including tissue engineering, drug delivery, and the treatment of OA and RA injuries.

Composite Hydrogels

Composite hydrogels combine the mechanical and physical qualities of synthetic hydrogels with the biocompatibility of natural hydrogels. Li et al (2024) combined sodium alginate (SA) and HA to construct a composite hydrogel scaffold,

and combined MSC-derived extracellular vesicles with icariin to create a combination therapy for synergistically promoting the proliferation and migration of MSCs and chondrocytes, inhibiting inflammatory response, stimulating the synthesis of cartilage matrix components, activating cartilage formation in chondrocytes, and inhibiting cartilage degradation, thus promoting the repair of articular cartilage defects. Yang et al (2022) prepared gelatin (Gel)-glucosamine hydrochloride (GH) crosslinked-cyclodextrin metal-organic framework (G-GH/CL-CD-MOF) composite hydrogel. By submerging the CL-CD-MOF in a high-concentration ibuprofen (IBU) solution, CL-CD-MOF@IBU was created. For the purpose of creating a G-GH/CL-CD-MOF@IBU composite hydrogel, which is a long-term sustained drug delivery system, CL-CD-MOF@IBU was evenly distributed in a mixed solution containing Gel and GH. In summary, the G-GH/CL-CD-MOF@IBU composite hydrogel's unique mechanical characteristics, prolonged drug release pattern, and strong biocompatibility indicated that it has a potential role in sustaining long-term nutritional supplementation and inducing anti-inflammatory responses concurrently in OA treatment (Yang et al, 2022).

Furthermore, a composite system incorporating tri-block polyethylene glycol injectable hydrogel (3B-PEG IH) and neural epithelial growth factor-like protein 1 (Nell-1) was successfully developed by Wang et al (2021a), and its therapeutic impact on temporomandibular joint osteoarthritis (TMJOA) has been examined. PolyL-Lactide-co-caprolactone (PLCL)-PEG-PLCL/Nell-1 has the ability to both decrease and increase chondrogenic expression *in vitro*. The primary characteristics of TMJOA rabbits *in vivo* were the breakdown of subchondral bone and the disruption of cartilage structure. On the other hand, PLCL-PEG-PLCL/Nell-1 may be able to halt the breakdown of the subchondral trabecula, repair the surface's proliferative and fibrous layers, and lessen uneven hyperplasia of the fibrocartilage layer. Following an evaluation of the characteristics of various 3B-PEG IH, this study concluded that 20 wt.% PLCL-PEG-PLCL hydrogel is a suitable material. Osteochondral degeneration induced by TMJOA may be reversed by the PLCL-PEG-PLCL/Nell-1 composite, with the Nfatc1-Runx3 signalling pathway playing a mechanistic role. Therefore, this study offers a novel, minimally invasive therapeutic approach for the clinical treatment of TMJOA (Wang et al, 2021a).

Gels created using solid lipid nanoparticles (SLN) loaded with sulfasalazine have shown favourable results in the treatment of RA. Sulfasalazine SLN-based gel showed considerable anti-inflammatory effects and dramatically suppressed the levels of tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6 ($p < 0.0001$). Besides, the sulfasalazine-loaded SLN-based gel also demonstrated sustained drug release for up to 24 hours, a characteristic that makes it appropriate for topical use in the therapy of RA (Mishra et al, 2023). Separately, Rui et al (2023) created silk fibroin hydrogel encapsulated with olfactory ecto-mesenchymal stem cell-derived exosomes (Exos@SFMA), which was photo crosslinked *in situ* to enable a long-lasting therapeutic effect on RA's immunological milieu. The exceptional biocompatibility and flexible mechanical qualities showcased by this *in situ* hydrogel technology make it a suitable tool for preserving tissue surfaces in joints. Crucially, Exos@SFMA prevented the development of germinal centre

(GC) B cells into plasma cells and considerably decreased the response of T follicular helper (Tfh) cells, thereby preventing synovial inflammation and joint degradation. When combined with exosomes, this silk fibroin hydrogel offers a potent therapy option for RA and other autoimmune illnesses (Rui et al, 2023).

Taken together, composite hydrogels boast many advantages, such as biocompatibility, safety, and efficacy, which are crucial attributes in OA and RA treatments.

Application of Hydrogels as Delivery Systems in OA and RA

Therapies for OA and RA are available in different forms, namely stem cell therapy, drug therapy, bioactive factor therapy, and exosome therapy (Kou et al, 2019; Rannou and Poiraudeau, 2010; Yi et al, 2022). Injectable hydrogels, which are minimally invasive and capable of *in situ*, are suitable drug delivery carriers for encapsulating different substances, such as cells, drugs, and biomolecules (Li et al, 2021a; Miller et al, 2021) (Fig. 2), which can be released slowly in a controlled manner within the joint cavity, thereby improving drug utilization and efficacy (Table 1).

Stem Cells

Stem cells possess a range of versatile abilities, including self-renewal, differentiation, repairing of damaged tissues, improvement of microenvironment, and regenerative capacity (Zakrzewski et al, 2019). Cell therapy, which involves transplanting live cells into damaged organs or tissues to restore function, could be a viable treatment for OA and RA (Burdick et al, 2016; Lopez-Santalla et al, 2021; Sabi et al, 2022). Currently, pluripotent stem cells (PSCs) and MSCs are commonly used to treat OA and RA by secreting therapeutic regenerative bioactive factors to foster a balanced inflammatory and regenerative microenvironment in the damaged tissues (Collins et al, 2023; Shi et al, 2018). Successfully demonstrated in preclinical models and early-phase clinical trials, intra-articular injection facilitates the migration of MSCs (chemotaxis) to the injured area, reducing pain and eliciting protective effect on cartilage or inducing healing (Mancuso et al, 2019). However, cell transplantation alone cannot achieve the desired effect, mainly because the microenvironment at the lesion site (which is inundated by inflammation and oxidative stress) and the cell flow are not conducive to the long-term residence and survival of stem cells. In addition, the implanted stem cells cannot attach to the damaged joints to form functional networks (Liu et al, 2021). However, integrating the cell delivery system with hydrogel provides a means to stabilize and protect the cells at the injured site, while improving the hydrogel's function and imitating the environment of ECM (Suzuki et al, 2023).

Capitalizing on the unique advantages of hydrogels, researchers created a range of hydrogel scaffolds with stem cell grafts using tissue engineering techniques to improve the treatment and healing of arthritis (Burroughs et al, 2022). Hydrogels paired with stem cell therapy offer three significant advantages for treating and re-

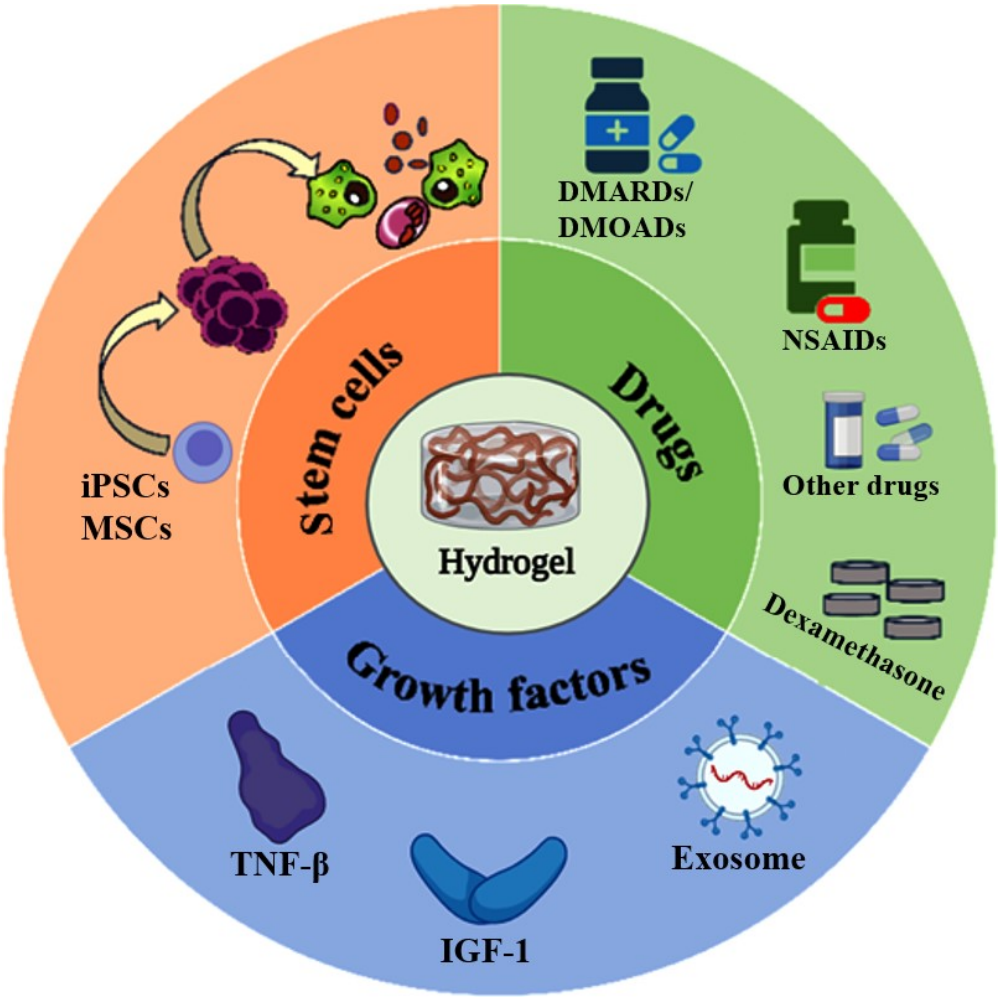

Fig. 2. Hydrogels enriched with stem cells, drugs, and growth factors. The image is drawn using the BioRender software. DMARDs, disease-modifying anti-rheumatic drugs; DMOADs, disease-modifying osteoarthritis drugs; IGF-1, insulin-like growth factor 1; iPSCs, induced pluripotent stem cells; MSCs, mesenchymal stem cells; NSAIDs, non-steroidal anti-inflammatory drugs; TGF-β, transforming growth factor beta.

pairing OA and RA: hydrogel can be employed as a carrier for stem cells and can reduce cell loss to surrounding tissues; offer 3D support for cell proliferation, migration and differentiation; and control the microenvironment of the injured site and preserve the biological function and activity of stem cells (Choi et al, 2010; Park et al, 2015; Tsou et al, 2016). Bone marrow mesenchymal stem cells (BMMSCs) combined with diverse structures prepared from natural or synthetic materials have been extensively studied in the medical field (Liao et al, 2014; Seo et al, 2014). For example, Liu et al (2018) found that PEG-polypeptide triblock copolymer hydrogels enhanced the adhesion and proliferation of BMMSCs *in vitro* and mediated cartilage differentiation of BMMSCs and *in situ* deposition of ECM, resulting in better regeneration of hyaline cartilage and reduced formation of fibrous tissue, thus promoting cartilage repair. These results indicate that these hydrogels have great potential as biomimetic materials in the repair of osteoarthritis. Poly (N-isopropylacrylamide-co-acrylic acid) derivatives covalent bond can hydrolytically

Table 1. Application of hydrogels as delivery systems in OA and RA.

Encapsulated substances	Hydrogel composition	Specific substances	Function	OA/RA	Ref
Stem cells					
	PEG, polypeptide	MSCs	Promote cartilage differentiation of BMMSCs and *in situ* deposition of ECM, and promote cartilage regeneration	OA	(Liu et al, 2018)
	Poly (N-isopropylacrylamide-co-acrylic acid)	MSCs	Promote the proliferation and differentiation of MSCs, induce chondrogenesis and relieve cartilage defects	OA	(Zhang et al, 2020)
	Alginate	MSCs	Enhance MSC proliferation, reduce inflammatory response, and prevent RA progression	RA	(Shi et al, 2023)
	Chitosan, alginate, HA, and ECM	ADSC	Reduce inflammation, protect cartilage, and promote bone mineral density	RA	(Zhu et al, 2023)
Drugs					
	Chitosan and borax and BGP, CS and Pluronic F-127	Dexamethasone	Inhibit inflammation, synovitis, bone destruction and cartilage destruction	OA and RA	(García-Couce et al, 2022b; Wang et al, 2021b)
	HA, CS oligosaccharide	DMARDs	Delay the progression of RA, improve joint function, and limit progressive joint damage	RA	(Bajpayee and Grodzinsky, 2017)
	PCLA-PEG-PCLA, CS	NSAIDs	Significantly reduce inflammation and destruction of cartilage and bone	OA and RA	(Chen et al, 2017; Petit et al, 2014; Qi et al, 2016)
	CS and Pluronic F-127	Etanercept	Inhibit inflammation, prevent cartilage degeneration and synovial inflammation	OA	(García-Couce et al, 2022a)
	Fibroin *in situ* hydrogel	Sesbania, sesbania ex tract	Relieve symptoms of RA	RA	(Pham et al, 2022)

Table 1. Continued.

Encapsulated substances	Hydrogel composition	Specific substances	Function	OA/RA	Ref
Growth factors					
	Gelatin, PEGDA	IGF-1	Promote cartilage formation and differentiation and cartilage ECM deposition, and enhance the regeneration of osteochondral tissue	OA	(Cho et al, 2020)
	HA, calcium alginate	TGF-β3	Improve cartilage microenvironment and regeneration of cartilage defects	OA and RA	(Mierisch et al, 2002)
Exosome	SF-HA, Pluronic F-127, HA	——	Inhibit inflammatory response and promote the proliferation, migration and differentiation of chondrocytes	OA and RA	(Anastasiadou et al, 2018; Rui et al, 2023)

Abbreviations: ADSC, adipose-derived stem cells; BGP, β-glycerophosphatester; BMMSCs, bone marrow mesenchymal stem cells; CS, chitosan; DMARDs, disease-modifying anti-rheumatic drug; ECM, extracellular matrix; HA, hyaluronic acid; IGF-1, insulin-like growth factor 1; MSCs, mesenchymal stem cells; NSAIDs, non-steroidal anti-inflammatory drugs; PCLA, poly (chitosan-g-lactic acid); OA, osteoarthritis; PEG, polyethylene glycol; PEGDA, polyethylene glycol diacrylate; RA, rheumatoid arthritis; SF, silk fibroin; TGF-β3, transforming growth factor-beta 3.

degradable crosslinking agent N, O-dimethyl acrylamide hydroxamide or prepare macroporous hydrogels modified by different surface charges. The implantation of human MSCs-embedded hydrogels into the joints of OA rats has been shown to promote ECM deposition and expression of genes linked to chondrocytes, thereby alleviating cartilage deficiencies and promoting chondrogenesis (Zhang et al, 2020). In addition, alginate gel is an ideal scaffold for MSC delivery in RA. Encapsulating MSCs with injectable alginate gel can improve the viability, retention and proliferation of MSCs *in vivo*, inhibit the maturation of dendritic cells and the secretion of pro-inflammatory cytokines, reduce inflammatory response, and prevent the progression of RA (Shi et al, 2023).

Adipose-derived stem cells (ADSCs) are pluripotent cells obtainable from healthy donors, which play a role in regulating a variety of immune cells (Bhattacharjee et al, 2022; Yuan et al, 2021). ADSCs are commonly used in regenerative medicine and are attractive candidates for RA therapy (Ueyama et al, 2020; Wang et al, 2020d). Under the influence of the microenvironment of the lesion site, the function of ADSCs, which are injected alone, will be lost or even inactivated. Zhu et al (2023) proposed a novel ECM-inspired method that uses peptides (such as dendritic polylysine) or polysaccharides (such as CS, alginate, and HA) to create injectable hydrogel carriers for ADSCs encapsulation. ECM hydrogels loaded with ADSCs have been shown to reverse the dominant macrophage phenotype from M1 to M2 to reduce inflammation, prevent RA fibroblast-like synovial cell migration, protect cartilage and promote bone mineral density.

Drugs

There is currently no known cure for OA or RA, despite the fact that numerous medication candidates have been tested in animal models of the conditions, and current treatments, which are administered through the oral and intravenous routes, mainly function to relieve the main symptoms (Zhang et al, 2016). However, these administration routes generally result in low bioavailability and poor absorption, preventing the drug from accumulating in the joint fluid, and significantly minimizing direct pharmacological effect on the lesion site. It is also worthy to note that most medications have short half-lives and must be taken frequently or in large dosages to reach therapeutic concentrations at the site of damage, which might cause negative side effects (Qindeel et al, 2020). Therefore, this underscores the necessity for effective, targeted, long-term and safe approaches for the sustained release of therapeutic substances to improve recovery from arthritis. The degradability, tunable physical properties and continuous drug delivery characteristics of injectable hydrogels can overcome the shortcomings of these traditional administration routes, and they can be employed as a model of drug transport or as a carrier of particles or carriers that convey drugs (Almawash et al, 2022; Walsh et al, 2022). This makes injectable hydrogels an excellent candidate for developing an intra-articular controlled release platform.

Dexamethasone

Dexamethasone is an important glucocorticoid in the treatment of OA and RA, which can relieve joint symptoms and has a chondroprotective effect (Huebner et al, 2014). Although intra-articular injection can improve bioavailability and reduce off-target effect, there is still a problem with the rapid clearance of therapeutic agents (Zhao et al, 2019). Dexamethasone-loaded hydrogel (DLTH) prepared with CS, borax and BGP, as the carrier, remains in the liquid state at room temperature but becomes gel after being left at 37 °C for 20 minutes (Chen et al, 2012). The injection of the hydrogel into the knee joint of OA rats extended the retention time of dexamethasone in the joint cavity and achieved a high and sustained concentration of the drug at the desired site. Thus, joint bone destruction in mice can be effectively reduced, and the progression of synovitis and OA can be slowed down (Wang et al, 2021b). At the same time, the hydrogel can also limit the spread of dexamethasone into the blood and eliminate the potential side effects of low-frequency treatment (Wu et al, 2017). In addition, in the animal model of collagenic arthritis (CIA) treated with DLTH joint injection treatment, the hydrogel is formed in the joint and attached to the synovial surface, improving local pannus development, synovial hyperplasia and joint degradation, through the extended residence period in the joint and slow discharge of medications. It can also inhibit nuclear factor kappa-B (NF-κB) pathway activity to inhibit inflammatory response (Wang et al, 2020c). In addition, García-Couce et al (2022b) also found that the preparation of temperature-sensitive hydrogel containing dexamethasone by physically mixing CS and Pluronic F-127 can effectively prolong the retention time of dexamethasone in the joint and achieve high and sustained drug concentration at the desired site. Dexamethasone is rarely distributed to surrounding normal tissues and organs, and has the potential to treat damaged articular cartilage locally.

Anti-Rheumatic Drugs

The first-line medications used in the clinical therapy of RA are anti-rheumatic drugs (DMARDs), which can halt the course of RA, improve joint function and limit progressive joint injury (Scott et al, 2010). At present, the most commonly used DMARDs in clinic include methotrexate (MTX) and iguratimod (IGUR) (Mucke, 2012; Tugwell et al, 2000). Traditional oral MTX and IGUR have poor solubility, poor therapeutic effect and reduced bioavailability, as well as major adverse reactions. Therefore, developing innovative medicine delivery systems is crucial for improving their effectiveness. HA hydrogels and chito-oligosaccharide hydrogels have been shown to be loaded with MTX and IGUR, and injectable hydrogels can sustain high medication concentrations for joint repair and have minimal deleterious effects on other tissues (Bajpayee and Grodzinsky, 2017; Lei et al, 2022).

Non-Steroidal Anti-Inflammatory Drugs

NSAIDs represent a class of anti-inflammatory and analgesic drugs widely used in the treatment of RA by interfering with arachidonic acid metabolism. In the treatment of OA and RA, these medications frequently exert a wide range of adverse effects, including renal damage and gastrointestinal problems. Celecoxib

is a type of NSAID and a selective cyclooxygenase-2 (COX-2) inhibitor used to treat rheumatism and other conditions of painful OA (Davies et al, 2000). But conventional oral dosing frequently results in a wide range of negative effects. To avoid adverse reactions, Petit et al (2014) implanted poly (chitosan-g-lactic acid)-polyethylene glycol-poly (chitosan-g-lactic acid) (PCLA-PEG-PCLA) triblock copo lymer hydrogels containing different components of cloccoxib and acetyl into the joints of collagenase-II-induced RA rats. The hydrogels provide a safe drug delivery platform. The continuous and controlled release of cloccoxib within the joint is achieved, thus considerably lowering inflammation and abrogating the deterioration of bone and cartilage loss (Petit et al, 2014). Furthermore, CS can be loaded with diclofenac sodium and ketoprofen to be prepared into injectable hydrogels, which can retain these drugs in the joint cavity after implantation and release them to the lesion site at a slow and steady rate, thus enhancing anti-inflammatory and analgesic effects (Chen et al, 2017; Qi et al, 2016).

Other Drugs

In addition to the drugs commonly used in the clinic, other drugs are also utilized in the treatment of OA and RA. For example, etanercept (ETA) is a TNF inhibitor that has been approved for the treatment of RA and can also be used to relieve knee symptoms associated with OA (Ohtori et al, 2015; Oo and Hunter, 2022). The controlled release of ETA was achieved by injecting ETA-containing CS and Pluronic F-127, an injectable thermosensitive hydrogel with good chondrocyte compatibility prepared by Pluronic F-127 and β-disodium glycerophosphorate into the joint cavity of mice. In *in vivo* studies, the molecules of CS chains in the tangled area face difficulty in migrating to the external hydrogel, and thus, ETA can be retained in the implant site of the joint for a long time, thereby promoting the expression of cartilage matrix compounds, reducing the inflammation generated by chondrocytes, and preventing cartilage degradation and synovial inflammation (García-Couce et al, 2022b). Furthermore, a fibroin *in situ* hydrogel was created by Pham et al (2022) as a drug delivery method for Symbian extract to treat RA. Sesbania extract was found to demonstrate a strong anti-inflammatory impact and can help with ameliorating RA symptoms. The study found that a hydrogel containing sesbania extract can be administered into joints as a liquid preparation, can be rapidly converted into a hydrogel at the lesion site after entering the joint cavity, and can remain at the lesion site for a long time and release the extract continuously to exert anti-inflammatory effect.

Others

In addition to drug and stem cell therapy, bioactive factors, exosomes and non-coding RNAs are employed as treatments for OA and RA.

Growth Factors

Growth factors are effective but sensitive therapeutic compounds that can stimulate the growth of specific tissues. Cartilage is the source of many growth factors and cytokines, such as TGF-β, bone morphogenetic protein (BMP), platelet-

derived growth factor (PDGF) and insulin-like growth factor 1 (IGF-1) (Patil et al, 2011). However, simple growth factor therapy faces several problems such as difficulty in controlling the release kinetics and rapid clearance by the immune system, all of which render the therapy ineffective (Takematsu et al, 2023). Hydrogels are a type of biocompatible biological scaffold that exhibits a strong affinity for glycogen filaments, and can stabilize the growth factor release, control the negative impacts of elevated growth factor concentrations at the injection site, and shield them from enzymatic hydrolysis (Shan and Wu, 2024).

IGF-1 is a biostimulant that promotes chondrogenic differentiation of MSCs by stimulating proliferation, inducing expression of chondrogenic markers, and regulating apoptosis (Aboalola and Han, 2017). Cho et al (2020) implanted an interpenetrating network (IPN) hydrogel (gelatin-SH/PEGDA IPN hydrogel) loaded with IGF-1, ADSC, gelatin and polyethylene glycol diacrylate (PEGDA) into a rabbit knee defect model. Hydrogels containing IGF-1 and ADSCs can effectively maintain the activity of IGF-1 and continuously release bioactive IGF-1 in joints, promoting the chondrogenic differentiation of ADSCs and the deposition of cartilage ECM in osteochondral tissue defects, thus effectively enhancing the regeneration of osteochondral tissue (Cho et al, 2020).

Endowed with improved biocompatibility, HA hydrogel loaded with TGF-β3 (HAT) hydrogel can promote the synthesis of cartilage-specific matrix and collagen, as well as repair defects. HAT can effectively control the release of transforming growth factor-beta 3 (TGF-β3) and induce the differentiation of bone marrow stem cells in microfractures, thus significantly improving the cartilage microenvironment and regeneration of cartilage. In addition, HAT slowly degrades *in vivo* without causing inflammation and toxic reactions (Lee et al, 2024). Furthermore, it has been reported that TGF-β-loaded calcium alginate hydrogel can treat osteocartilage defects in rabbit knees (Mierisch et al, 2002). This suggests that targeted delivery of growth factors using hydrogel scaffolds offers a promising avenue to address the limitations of current OA and RA therapies.

Exosomes

As an important part of extracellular vesicles, exosomes can carry biomolecules such as proteins, lipids and RNA, and play an important regulatory role in the physiological and pathological processes of inflammatory arthritis such as OA and RA. The current research trend concerning the treatment of exosomes is mainly focused on animal experiments (Bei et al, 2021; You et al, 2021). Rui et al (2023) prepared a hydrogel coated with olfactory exosomes derived from external MSCs (Exos@SFMA), which has good mechanical properties and excellent biocompatibility and can protect the surface of joint tissue. The implantation of the hydrogel in the joints of collagen-induced arthritis (CIA) mice can significantly reduce the response of follicular auxiliary cells and further inhibit the differentiation of B cells into plasma cells, effectively alleviating synovial inflammation and joint destruction (Rui et al, 2023). In addition, Sang et al (2022) prepared an injectable hydrogel using *in situ* crosslinking of Pluronic F-127 and HA as a slow-release carrier loaded with chondrocyte-derived exosomes for the treatment of OA. Intra-articular injec-

tion of hydrogel doped with this exosome can maintain therapeutic concentration of primary chondrocyte-derived exosomes in the joint cavity by permanently retaining them in the damaged cartilage site while inducing continuous release of the exosomes. In addition, the hydrogel can inhibit inflammatory response and positively regulate the proliferation, migration and differentiation of chondrocytes, and can significantly prevent cartilage destruction by promoting cartilage matrix formation (Sang et al, 2022).

Non-Coding RNA

Non-coding RNA (ncRNA) includes RNA molecules including microRNA (miRNA), long non-coding RNA (lncRNA), and others that do not encode a protein. miRNAs are small (22 bp or less), non-coding RNA segments that regulate gene expression and are involved in the pathophysiology of numerous disorders. Because lncRNAs are defined as RNA transcripts >200 nucleotides that do not encode protein, their subcellular localization is essential to their activity as they are the functional units themselves (Anastasiadou et al, 2018). A growing body of research indicates that ncRNAs are important for the development and course of RA. Numerous lines of evidence suggest that ncRNA may play a role in the etiology, development, and management of RA, and changes in miRNA expression are linked to pro-inflammatory cytokine release, triggering inflammatory signalling pathways and other mechanisms that sustain a vicious cycle in autoimmunity. As a result, detecting ncRNAs is essential to the diagnosis and treatment process of RA (Anastasiadou et al, 2018). This is because they have the potential to be used as a biomarker for RA screening in high-risk populations, to direct clinical treatment plans through diagnosis, and to develop treatment regimens based on the pattern of expression of a particular ncRNA. Treatments for disorders like diabetes, heart disease, and cancer may be achieved through modifying the expression of ncRNA and its controlled genes. By examining the expression of a particular ncRNA in relation to the activity and advancement of the disease, one may precisely assess the outcome of the treatment in the interim. When it comes to refractory RA, ncRNA also has a significant impact on or control over RA patients' medication sensitivity (Wang et al, 2020a). Certain miRNA analogues or antagonists have been used in the treatment regimens for experimental arthritis models and have shown encouraging therapeutic efficacy because the altered miRNA levels, which are implicated in the disruption of autoimmunity through multiple mechanisms, are common in RA (Evangelatos et al, 2019). A growing body of research revealed that lncRNAs play a role in regulating immune cells and are differentially expressed in a variety of autoimmune disorders, including RA. This suggests that lncRNAs play a crucial role in the development of RA (Hur et al, 2019).

Joint replacement surgery is a treatment option for OA. However, achieving complete repair or regeneration of damaged articular cartilage is a challenging endeavor. Exosomal miR-26a-5p are substantially expressed in OA and have important effects on prostaglandin-endoperoxide synthase-2 and synovial fibroblast damage prevention (Toh et al, 2017). It has been established that mesenchymal stem cells (MSCs) can be used as targets for the treatment of OA and exosomes de-

rived from MSCs display chondroprotective effects. In the rats model study, intra-articular injection of miR-9-5p carried by bone marrow-derived MSCs (BM-MSCs) exosomes resulted in an alleviation of inflammation, this was indicated by down-regulation of inflammatory markers, reduced oxidative stress damage, and lowered matrix metallopeptidase 13 (MMP-13), osteocalcin (OCN), Cartilage Oligomeric Matrix Protein (COMP) and alkaline phosphatase (AKP) levels. These data imply that BM-MSC-derived exosomal miR-9-5p has anti-inflammatory and chondroprotective effects on OA. In the study, the upregulation of exosomal miR-9-5p, which targets the syndecan-1 gene, augmented inflammation and OA damage. Exosome-like vesicles from OA patient chondrocytes have been demonstrated to trigger inflammation and upregulate macrophage production of mature IL-1β via the miR-449a-5p/ATG4B/autophagy pathway, exacerbating synovitis and accelerating the progression of OA. Chondrocytic exosomal miR-8485 promotes the Wnt/β-catenin pathway, which promotes chondrogenic differentiation of bone marrow mesenchymal stem cells (BMSCs), providing creative ideas for cartilage restoration (Jin et al, 2020).

In summary, the drug-encapsulated injectable hydrogel is a drug delivery method that allows controlled release of cells, medications, and biomolecules at the injured site, and has broad application prospects in the treatment of OA and RA.

Therapeutic Mechanism of Injectable Hydrogels for OA and RA

Injectable hydrogels are mainly used to counteract inflammation, osteochondral destruction and oxidative stress, as well as promote articular cartilage regeneration (Table 2).

Through *in vitro* experiments, it has been established that hydrogels can cause macrophages to polarize toward the M2-type phenotype. This, in turn, influences the behavior of cells involved in repairs, such as fibroblasts, epithelial cells, and endothelial cells, through paracrine secretion, which can lead to the promotion of cell migration and the formation of endothelial cell tubes (Zhou et al, 2022). Hydrogels based on synthetic cartilage that have a lubricating effect serve as a potential substitute for damaged cartilage in current treatment modalities including autograft transplantation and focused resurfacing. Moreover, hydrogel systems have been used to combat high levels of reactive oxygen species (ROS) and inflammatory conditions that are acidic (Zhou et al, 2022).

Advanced hydrogels can be tuned to possess mechanical properties akin to healthy cartilage, effectively distributing the load and reducing stress on surrounding tissues. Hydrogels act as carriers for potent anti-inflammatory and chondroprotective drugs, delivering them directly to the affected area while minimizing systemic side effects. As a tissue-engineered scaffold material, hydrogels could replicate the lubricating properties of natural cartilage, or serve as a drug carrier in the process of combating local inflammation. In addition, hydrogels can function as cytoskeletons, promoting the proliferation of stem cells and the regeneration of cartilage. By promoting endogenous cell recruitment and chondrocyte differentiation,

Table 2. Therapeutic mechanisms of injectable hydrogels in OA and RA.

Therapeutic mechanisms	Hydrogel composition	Specific performance	OA or RA	Ref
Counteracting inflammation and inhibiting bone and cartilage destruction				
	HA-PBA-PVA	Clear ROS, reduce inflammation, relieve joint swelling, and reduce joint cartilage wear	OA and RA	(Davidovich et al, 2014; Lei et al, 2024)
	F127-HA-PGA	Inhibit the progression of inflammation, reduce the pain of RA, and delay the destruction of cartilage	RA	(Chen et al, 2020)
	Hydroxypropyl methylcellulose phthalate	Inhibit inflammation and prevent cartilage damage	RA	(Agostini et al, 2021)
	PLGA-PEG-PLGA	Inhibit inflammation, protect cartilage, and relieve OA symptoms	OA	(Yi et al, 2023; Yuan et al, 2019)
Antioxidant	MA, xanthan gum	Clear ROS, alleviate oxidative stress, reduce cartilage matrix degradation, and promote cartilage regeneration	OA/RA	(Chen et al, 2024b)
	PEG	Reduce oxidative stress and improve the anabolic activity of chondrocytes	OA	(Farnsworth et al, 2012)
	NO Clearance and Sequential Drug Release Gel (M-NO Hydrogel)	Reduce oxidative stress and inhibit inflammation	RA	(Kim et al, 2021)
Promoting cartilage regeneration	PEG, oxymethacrylate alginate	Promote ECM differentiation, maintain cartilage integrity, and promote cartilage tissue regeneration	OA and RA	(Lee et al, 2020)
	HA, CS hydrogels and alginate	Promote the proliferation of stem cells and cartilage regeneration *in situ*	OA/RA	(Feng et al, 2016; Hasani-Sadrabadi et al, 2020)
	Heparin and hyaluronic acid	Promote the expression of nerve growth factor, and thus promote the production of cartilage matrix protein and cell proliferation	OA and RA	(Levinson et al, 2019)

Abbreviations: CS, chitosan; ECM, extracellular matrix; F127, Pluronic F-127; HA, hyaluronic acid; MA, methacrylic; OA, osteoarthritis; PBA, phenylboronic acid; PEG, polyethylene glycol; PGA, poly (γ-glutamic acid); PVA, polyvinyl alcohol; RA, rheumatoid arthritis; ROS, reactive oxygen species; PLGA, poly (lactic-co-glycolic acid).

or by implanting multiple cells (such as chondrocytes and stem cells), hydrogels are able to promote tissue regeneration in the complex environment of OA (Jiang et al, 2024).

Counteracting Inflammation and Suppressing Bone and Cartilage Destruction

Inflammatory response is a pathological process that occurs after infection or injury (Davidovich et al, 2014; Yeung et al, 2018). A growing line of evidence has shown that inflammation is a key factor in RA and OA processes (Zhang et al, 2023; Testa et al, 2021; Xu et al, 2020). In RA and OA, the inflammatory response is a multifaceted process that is regulated by a variety of cell types and inflammatory agents. In the course of RA and OA, activated inflammatory cells are distributed in the inflamed synovium and lead to inflammatory responses by secreting pro-inflammatory factors. Pro-inflammatory factors such as TNF-α, IL-1, IL-6 and IL-17 induce excessive production of osteoclast differentiation factor (receptor activator of nuclear factor κB ligand (RANKL)) on synovium fibroblasts or osteoblast membranes, thereby promoting osteoclast differentiation, leading to cartilage and bone tissue erosion, and ultimately joint destruction (Alivernini et al, 2020; Pratt et al, 2021; Smolen and Steiner, 2003; Yasuda et al, 1998).

In order to inhibit abnormal inflammation and repair damaged cartilage, a series of injectable hydrogels were developed and tested as treatment candidates for RA and OA (Wu et al, 2024). For example, polyvinyl alcohol (oHA-PBA-PVA gel) hydrogel of hyaluronate-3-aminophenylborate-hydroxyl is considered a promising cartilage replacement material due to its tissue-like viscoelasticity, excellent biocompatibility, biodegradability and high hydrophilicity (Karimzadeh et al, 2022). When injected into the joint cavity, this hydrogel can act as a joint lubricant to reduce friction, and can also clear ROS, reduce inflammation, relieve joint swelling, and diminish joint cartilage wear (Lei et al, 2024). In addition, hydrogels are also used for the controlled release of stem cells, drugs, growth factors, *etc.*, to improve the local microenvironment of RA and OA lesions. Chen et al (2020) constructed F127-HA-PGA-loaded infliximab hydrogel for RA treatment. Injection of the hydrogel into the joint of a rabbit model of RA can significantly inhibit the expression of TNF-α in cartilage and synovial fluid, thereby preventing widespread inflammation, relieving the pain of RA, and delaying cartilage destruction (Chen et al, 2020). Another study on RA found that an injectable thermosensitive hydrogel (MTX-PEC) based on a polyelectrolyte complex (PEC) of hydroxypropyl methylcellulose phthalate could prolong the retention time and drug release of MTX in the joint and maintain a higher drug concentration, thus significantly inhibiting inflammatory response and preventing cartilage damage (Agostini et al, 2021).

Poly (D, L-lactide-co-glycolide)-poly (ethyleneglycol)-poly (D, L-lactide-co-glycolide) (PLGA-PEG-PLGA) possesses good plasticity and biocompatibility, and the ability to encapsulate drugs and cells; therefore, it can be designed as a reservoir to control the release of therapeutic compounds. At the same time, it can solve the systemic side effects caused by oral drugs and extend the bioavailability of drugs injected directly into the joint (Yu et al, 2010). IL-36 receptor antagonist (IL-36Ra)

can effectively control the inflammatory response, thereby protecting cartilage and slowing the development of OA (Yuan et al, 2019). Yi et al (2023) constructed a PLGA-PEG-PLGA hydrogel loaded with IL-36Ra for the treatment of OA. The injectable hydrogel loaded with IL-36Ra was injected into the knee joint cavity of OA mice, and the hydrogel acted as a drug repository to slowly release IL-36Ra and maintain local drug concentration to effectively control inflammation. It can also be injected to the lesion site in the form of lubricant to maintain the surface integrity of articular cartilage, reduce the degradation of cartilage matrix and promote cartilage formation, thus effectively delaying the progression of degenerative OA changes (Yi et al, 2023). In addition, flurbiprofen-loaded PLGA-PEG-PLGA hydrogel can continuously release drugs in the joint cavity of the rat model of knee OA induced by collagenase II, with the purpose of inhibiting OA inflammation by reducing the levels of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α (Li et al, 2020).

In summary, complex hydrogels feature a number of desirable attributes, such as anti-inflammatory properties, and abilities to deter osteochondral destruction, improve the surrounding microenvironment, and accelerate the therapy progress of OA and RA.

Counteracting Oxidative Stress

Oxidative stress is a critical factor in the pathological process of OA and RA, hindering the influence of growth factors on chondrocytes, especially the integration of chondrocytes with ECM, and ultimately leading to apoptosis of chondrocytes (Altay et al, 2015; Olofsson et al, 2003). Excessive ROS plays an important role in intracellular signalling that leads to exacerbated inflammation in joints and chondrocyte death, all of which precipitating the occurrence of joint injury (Bordy et al, 2018; Mateen et al, 2016). It has been reported that hydrogel scaffolds can satisfactorily clear the ROS (Cheng et al, 2017).

Xanthan gum (XG), derived from natural polysaccharides, has excellent antioxidant and anti-inflammatory properties and can protect cartilage from oxidative stress-induced damage (Shao et al, 2013). By using XG modified with methacrylic acid (MA) groups, Chen et al (2024b) developed an XG hydrogel (XGMA) with excellent biocompatibility and biodegradable properties, good ROS scavenging ability and inhibitory effects on oxidative stress, which collectively contributed to reduced degradation of cartilage matrix and improved cartilage regeneration. In addition, Farnsworth et al (2012) developed PEG injectable hydrogel, which can reduce oxidative stress and increase the anabolic activity of chondrocytes after implantation in joint cavities. Injectable hydrogels have also been found to possess anti-oxidative stress properties. Kim et al (2021) designed an injectable nitric oxide (NO) gel (M-NO hydrogel) capable of clearance and sequential drug release for treating RA. The injection of the hydrogel into the joint cavity led to controlled release of the drug, effectively alleviating symptoms in CIA mouse models, enhancing their motor activity, and improving NO and pro-inflammatory cytokine levels (Kim et al, 2021). Therefore, the newly discovered antioxidant properties embodied by the injectable hydrogel offers an innovative treatment concept for OA and

RA. However, developing bioactive stents with excellent antioxidant capacity and excellent biocompatibility for OA and RA treatment remains challenging.

Promoting Joint Cartilage Regeneration

Cartilage destruction is caused by the matrix metalloproteinases generated by synovial fibroblasts, chondrocytes and synovial macrophages, as well as disintegrating proteins and metalloproteinases with platelet pontin motifs (Araki et al, 2016). The existing treatments for cartilage repair are relatively scarce, and conventional drug therapy are unable to achieve reparation of damaged cartilage. The diverse properties of injectable hydrogels may enable cartilage repair, which is an effective therapeutic strategy. With the ability to differentiate and produce anti-inflammatory mediators, growth factors, immunomodulatory substances and anti-catabolic substances, MSCs can promote the regeneration of articular cartilage following their intra-articular injection (Amer et al, 2017). Polyethylene glycol acrylate (PEG) and oxymethacrylate alginate (OMA) hydrogels (PEG/OMA hydrogels) can precisely regulate MSCs and provide favourable ecological niche for MSCs in damaged joints, thus improving their survival. In light of this, a large number of ECM elements are produced to maintain the integrity of cartilage and promote the regeneration of articular cartilage tissue (Lee et al, 2020). In addition, HA hydrogels, CS hydrogels and alginate together provide a gentle environment to preserve the encapsulated MSCs, and concomitantly, by boosting the cell proliferation, *in situ* cartilage regeneration can be hastened (Feng et al, 2016; Hasani-Sadrabadi et al, 2020). In addition, several bioactive factors, such as TGF-β1, have been reported to induce, promote and sustain bone morphogenesis as well as cartilage differentiation and regeneration. The regulated distribution of heparin in the creation of cartilage is achieved by its ability to bind to various growth factors. The hydrogel formed by the covalorization of heparin and HA can support TGF-β1, maintain its biological activity and realize the sustained release of TGF-β1 in joints after injection. This promotes the expression of nerve growth factor in chondrocytes, thus promoting the generation of cartilage matrix protein and cell proliferation (Levinson et al, 2019) (Fig. 3).

Advantages of Injectable Hydrogel in the Treatment of OA and RA

Injection of hydrogels for OA and RA treatment can help improve patient adherence to treatment and thus treatment outcomes. Using injectable hydrogels, drugs can be precisely and specifically delivered to the desired site, thereby enhancing the drug's bioavailability, concentration at the lesion site, and duration of effect. In addition, injectable hydrogels can also prevent the drugs from entering the bloodstream, thereby shielding the liver and kidneys from harm brought on by the toxic metabolites of medicines, improving the therapeutic effect and ensuring better biosafety *in vivo* (Li et al, 2014; Thakur et al, 2018). Due to the softness and elasticity of the hydrogel, the hydrogel reaction mixture was administered into the synovial joint and solidified into an elastic pad structure. This structure, which re-

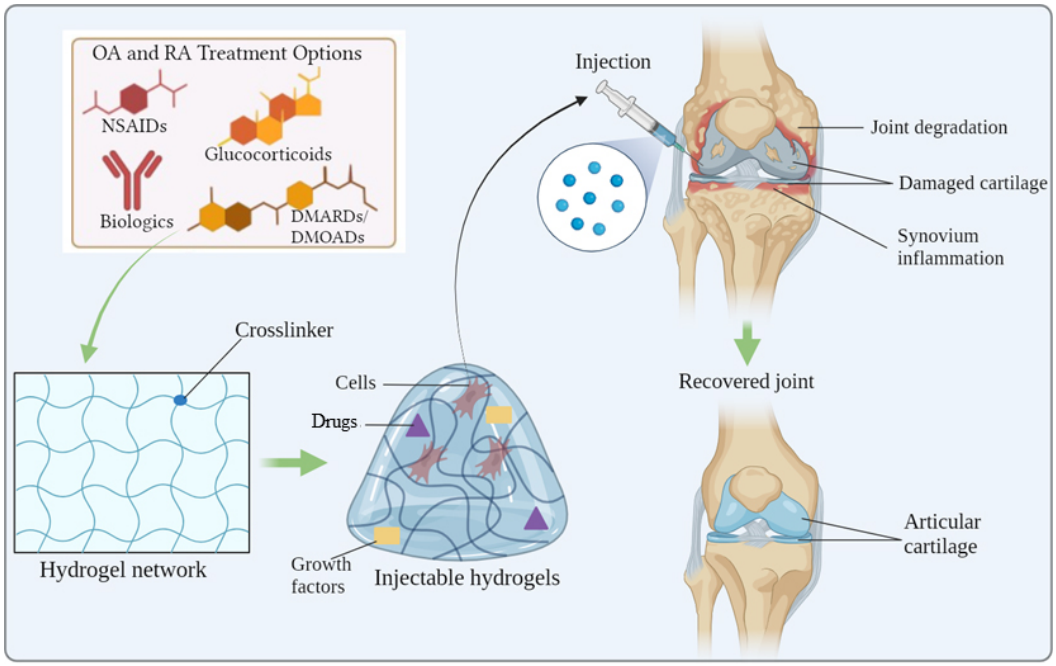

Fig. 3. Schematic diagram of the preparation of a hydrogel-based delivery system, which is administered through intra-articular injection, for the treatment of OA and RA. The image is drawn using the BioRender software. DMARDs, disease-modifying anti-rheumatic drugs; DMOADs, disease-modifying osteoarthritis drugs; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; OA, osteoarthritis.

sembles a cushion, is able to absorb mechanical stress and possesses strong elastic resilience to bounce back from elastic deformation and mechanical strain to its original form (Wang et al, 2018b, 2019b). Injectable hydrogel resistance can be used as a jelly-like lubricant to provide mechanical support for joints and joint surfaces, and reduce friction and degradation between joint linings, as well as between joint surfaces, thus protecting joints in a comprehensive manner (Dehghan-Baniani et al, 2020; Wu et al, 2023). The accessibility of nutrients, oxygen and other water-soluble substances can regulate the biocompatibility of hydrogels, which is conducive to facilitating the growth, repair, and regeneration of injured tissues and scavenging free radicals (Reis et al, 2009; Wei et al, 2021; Xu et al, 2008). By virtue of their excellent biodegradability, when the drugs in the hydrogels have depleted, the properly crosslinked hydrogels would degrade into intermediates that are either less hazardous or nontoxic to the body tissues, which are then eliminated from the body.

Discussion and Summary

The pathological complexity and poor local microenvironment of joint diseases such as RA and OA are the prominent weak points that pose obstacles for improvements. Despite the availability of a variety of therapeutic approaches to control these diseases, satisfactory therapeutic effects on RA and OA cannot be achieved with single therapeutic approach and the application of the rather inefficient, traditional drug delivery methods. Hydrogel is a unique kind of hydrophilic polymer,

featuring a special 3D crosslinked network with good biodegradability, biocompatibility and mechanically tunable features, that permit material exchange. In recent years, there has been a lot of interest in the creation of injectable hydrogels to efficiently repair and replace damaged bone tissue. In addition to the advantages of traditional hydrogels, injectable hydrogel is also equipped with flow characteristics and injectable properties. Before being injected with a syringe, injectable hydrogels are flowable. Once injected, the liquid gels are placed to form a tissue-bioengineered scaffold. In addition, they can be injected into irregularly shaped lesions as low-density water reservoirs containing the necessary components for repairing and enhancing bone tissue. Therefore, injectable hydrogels can be used as excellent delivery carriers of drugs for the treatment of diseases. Numerous studies have shown the significant efficacy of hydrogels encapsulating a combination of cells, drugs, and active factors in animal models of OA and RA. Hydrogels promote joint repair of OA and RA by suppressing inflammation, inhibiting bone and cartilage destruction, hampering oxidative stress, and promoting joint cartilage regeneration (Fig. 4). Despite the significant progress attained in the research on injectable hydrogels for OA and RA, certain shortcomings of injectable hydrogels should be highlighted. First, the majority of hydrogels is devoid of the ability to induce self-healing and may cause mechanical injury during insertion or joint movement. Second, translating the application of injectable hydrogels from preclinical models to clinical settings presents challenges. Most current studies have been conducted on preclinical rodent models of OA and RA, but very few clinical trials have successfully validated the therapeutic effects of injectable hydrogels on OA and RA patients. In future studies, primate models need to be used for preclinical research. If the results turn out to be satisfactory, clinical trials involving human subjects can be considered. Finally, further research is needed to determine the exact mechanisms underlying the therapeutic effect of hydrogel and its time window. Besides, future research should also be directed at improving injection conditions at the injury site and harmonizing the hydrogel's characteristics with the implant location. Therefore, the clinical application of injectable hydrogels loaded with cells, drugs, and active factors in the treatments of OA and RA is not going to be possible any time soon until successful testing on animals in real-world situations has been performed.

Conclusion

In this paper, we present a review on the development of composite hydrogels designed for the treatment of RA and OA. These hydrogels invoke a noticeable effect by injecting various medicinal medications into the joint. Based on the distinctive properties of each type of hydrogel, we propose the following study directions: (1) The combination of drug-loaded nanoparticles with hydrogels has demonstrated promising therapeutic outcomes in the management of RA and OA; therefore, this type of hydrogel should be the focal point in future research endeavours. (2) Directly synthesizing hydrogels using medications and polymer materials is another promising approach to treating RA and OA. By loading therapeutic agents into hy-

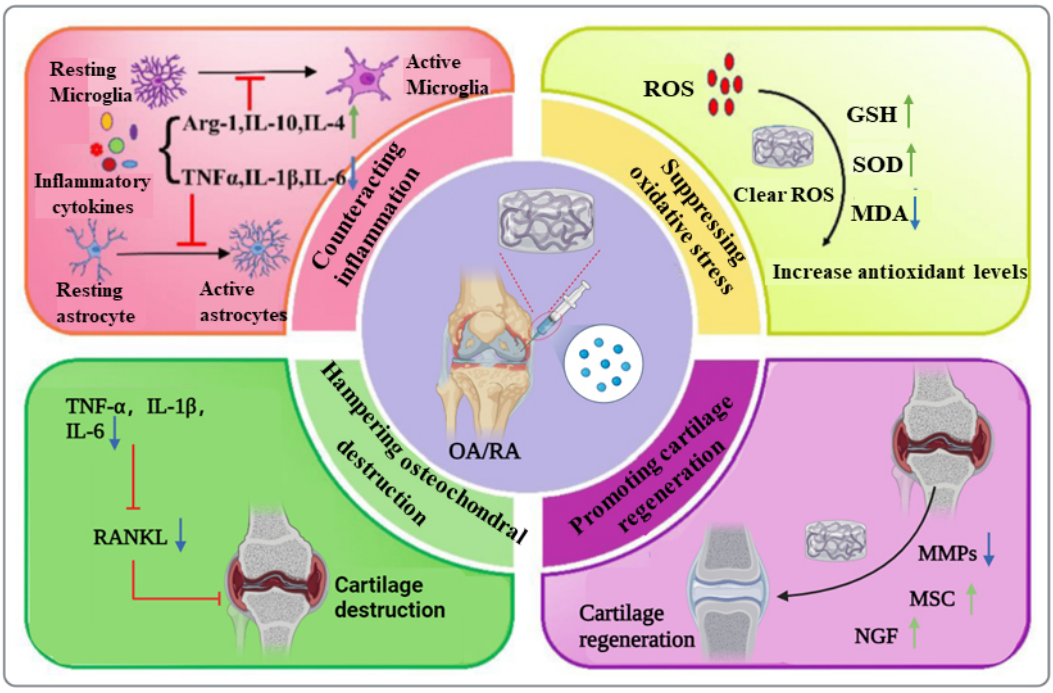

Fig. 4. Mechanisms of action of injectable hydrogels in the treatment of OA and RA. The image is drawn using the BioRender software. Arg-1, arginase-1; GSH, glutathione; IL-10, interleukin-10; IL-4, interleukin-4; IL-1β, interleukin-1β; IL-6, interleukin-6; MMPs, matrix metalloproteinases; MSC, mesenchymal stem cell; MDA, malondialdehyde; SOD, superoxide dismutase; NGF, nerve growth factor; ROS, reactive oxygen species; RANKL, receptor activator of nuclear factor κB ligand; TNF-α, tumour necrosis factor-alpha.

drogels, which then target the lesion site after implantation, these hydrogels serve as carriers for medications or cells, reducing inflammation and protecting cartilage. In addition, hydrogels can be used to treat RA and OA by means of alternative processes, including the removal of excess NO from the joints and the implantation and stimulation of MSCs. The use of hydrogels in the treatment of RA and OA is reviewed in this article, and these hydrogels appear to embody huge potential in this respect. However, the current research on hydrogels is still limited. Improving the overall characteristics of hydrogels through the fusion of several materials is an urgent topic that requires exploration. To speed up experimentation and simulate the fusion of various materials, artificial intelligence-powered approaches can be applied to unravel composite hydrogel materials with improved versatile qualities. Furthermore, the majority of hydrogels used to treat RA and OA can only deliver one kind of medication, possibly constrained by the hydrogel's inherent characteristics and leading to a less-than-satisfactory therapeutic impact as compared to when many medications are applied together. To achieve a greater therapeutic impact, future research should concentrate on exploring synergistic treatment, in which therapeutic agents are co-delivered by hydrogels and other methods.

Key Points

- Osteoarthritis and rheumatoid arthritis are inflammatory joint conditions with different etiologies.
- Injectable hydrogels are a delivery system that delivers drugs to joint cavities in a controlled manner for continuous release.
- Hydrogels can be used as delivery systems for cells, drugs, or other substances to achieve long-term controlled release of drugs or cell molecules.
- Injectable hydrogels can be used as excellent delivery carriers for the treatment of OA and RA.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

RZ, HYL and HLS are major contributors towards the review. HLS conceived and designed the review; RZ and HYL drafted the manuscript. RZ, HYL and YCH made substantial contributions to the acquisition and interpretation of data. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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