

Evolving functional hydrogel strategies for cartilage engineering: from fundamentals to functional regeneration

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Abstract

Articular cartilage injury is a significant concern in osteoarthritis (OA), and while traditional pharmacological treatments and surgical interventions have provided some pain relief and promoted cartilage regeneration to a certain extent, long-term therapeutic outcomes remain suboptimal. The advancement of cartilage tissue engineering has introduced novel perspectives for cartilage regeneration. Hydrogel scaffolds, as crucial components in tissue functionality, have evolved from their initial role of physical coverage or single functionality to current combinations of diverse functionalities. This review thoroughly examines recent applications of functional hydrogels in cartilage regeneration. This article begins by discussing essential background information, including treatment strategies for cartilage defects and the fundamental characteristics of hydrogels. Next, within the framework of cartilage tissue engineering, we analyse five categories of functional hydrogels, emphasizing their distinctive physicochemical properties, drug delivery capabilities, and stimulus-responsive features for cartilage repair. The discussion extends to their mechanisms of action, classification, and limitations. Clinical products related to hydrogels in this field are also summarized. Finally, recommendations are offered to address current challenges and future directions in the development of functional hydrogels for cartilage regeneration.

Keywords: Osteoarthritis; Cartilage tissue engineering; Functional hydrogel; Cartilage regeneration

Highlights

- This study is the first comprehensive review of advanced functional hydrogels used for cartilage repair, covering almost all types of functional hydrogels used in tissue engineering.
- The article provides a detailed review of commercially available hydrogel products for cartilage repair.

Background

Osteoarthritis (OA), which is prevalent in elderly individuals, most commonly affects the hand, hip, and knee joints, with knee OA being particularly common [1]. It causes joint damage and pain, reduces quality of life, and may lead to joint deformities, quadriceps atrophy, and disability from prolonged immobilization [2]. The difficulty in repairing cartilage injuries is multifaceted. The primary reasons for the challenging self-repair ability of articular cartilage include three main factors [3, 4]. First, articular cartilage lacks blood vessels, nerves, and lymphatic tissues and relies primarily on

synovial fluid for nutrient supply. This limited vascularization hinders the efficient exchange of nutrients and substances. Consequently, when cartilage is damaged, an insufficient supply of blood and nutrients impedes the timely initiation of tissue repair mechanisms. Second, mature chondrocytes are highly differentiated and enveloped by an ECM composed of collagen fibres and HA, restricting their mobility. Additionally, there is a limited connection between cartilage and subchondral bone, and the multipotent stem cells residing in the bone cannot easily migrate to the site of cartilage defects. As a result, the damaged area lacks cells and the ECM secreted by these

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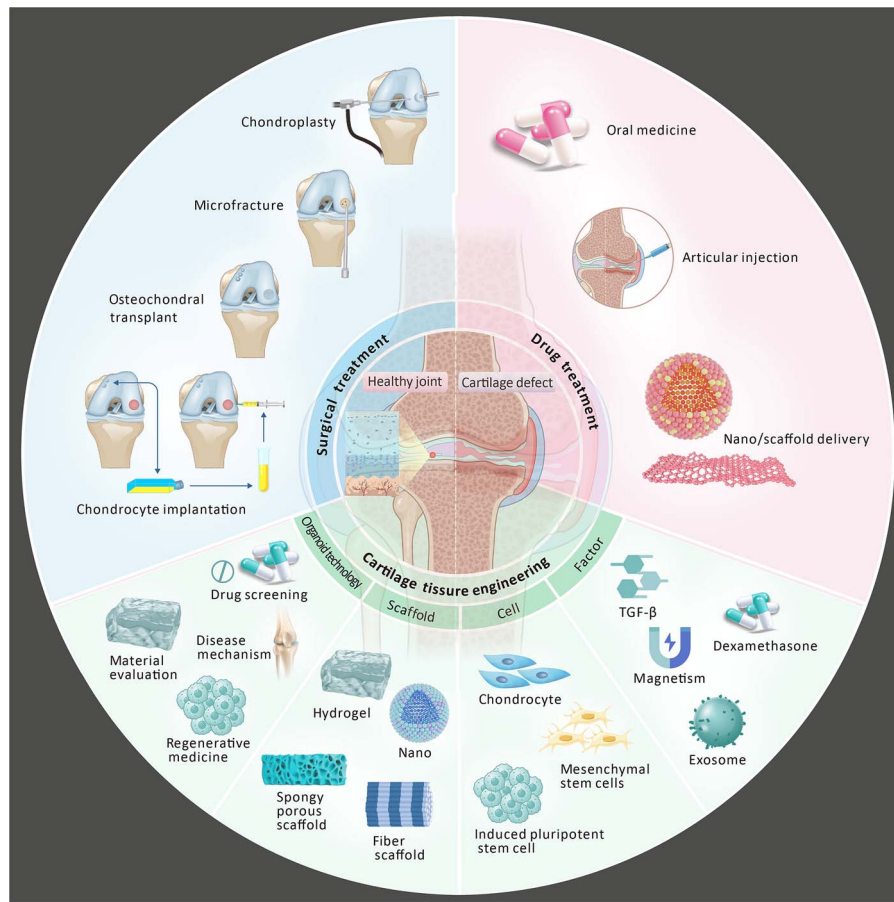


Figure 1. Schematic illustration of therapeutic approaches for cartilage injury, including drug treatment, surgical treatment, and emerging cartilage tissue engineering methods

cells, hindering effective repair. Third, with increasing age, the number of chondrocytes gradually decreases, leading to an overall decline in the capacity for ECM synthesis.

Current clinical approaches to cartilage injury repair include pharmacological treatments (local and systemic medications and intra-articular injections) and surgical interventions. While these methods focus on symptom relief and quality of life improvement, they are noncurative. Pharmacological approaches carry risks such as joint infections from frequent injections [5]. Surgical options, although suitable for young, active patients with severe symptoms or full-thickness injuries, often result in fibrous cartilage regeneration with less-than-ideal long-term outcomes [6].

In recent years, the rapidly advancing field of cartilage tissue engineering has focused on creating a conducive regenerative environment for cartilage repair through the integration of three key elements: seed cells, bioactive factors, and a biological scaffold. Among these components, significant research emphasis has been placed on the development of biological scaffolds [7]. Biological scaffolds employed for cartilage repair should ideally mimic the ECM of cartilage in terms of both material composition and structure. This mimicry facilitates cell distribution, adhesion, proliferation, differentiation, and matrix secretion. Hydrogels composed of natural or synthetic polymers exhibit significant potential in cartilage tissue engineering because of their advantageous biological and biochemical properties, including degradability, microstructure, and cellular interactions for cell adhesion and communication [8, 9]. The functionality of hydrogels has evolved from initially serving as mere physical coverage or offering single

functionalities to the current trend of combining multiple functions, indicating continuous development [10]. However, comprehensive summaries regarding the application of functional hydrogels in cartilage regeneration are lacking.

In this review, we provide a comprehensive overview of the current state of cartilage defect treatments and the application of functional hydrogel scaffolds. We begin by discussing existing treatment strategies for cartilage injuries, including pharmaceutical interventions, surgical approaches, and emerging concepts such as cartilage organoids and tissue engineering. Next, within the framework of cartilage tissue engineering, we examine the fundamental material characteristics, component selection, and structural considerations of hydrogel scaffolds. We then highlight the application of five functional hydrogels in cartilage repair, focusing on their distinctive physicochemical properties, drug delivery capabilities, and stimulus-responsive features. This analysis encompasses their respective repair mechanisms, classification, and limitations. Clinical products related to hydrogels in this domain are then summarized. Finally, we offer a summary and outlook on the future prospects of hydrogel scaffolds (Figure 1).

Review

Current landscape of treatment for articular cartilage defects

Clinical therapy for cartilage defects

Pharmaceutical treatments, such as symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), such as glucosamine and chondroitin, and intra-articular injections, including

corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and mesenchymal stem cells (MSCs), aim primarily to alleviate symptoms of OA [11, 12]. However, these treatments are noncurative and often rely on placebo effects for pain relief [13]. These methods have several limitations, including rapid drug clearance, poor absorption by cartilage, and the need for frequent injections, which increase the risk of joint infections [14]. Surgical options, such as chondroplasty [15], bone marrow stimulation [16], osteochondral repair [17], and cell-based techniques [18], such as autologous chondrocyte implantation (ACI) and matrix-assisted chondrocyte implantation (MACI), provide varying degrees of success. However, these methods face challenges such as suboptimal long-term outcomes, fibrocartilage instead of hyaline cartilage formation, high costs, immune rejection, and complications from donor site trauma. These limitations highlight the urgent need for more durable, restorative treatments. Cartilage tissue engineering offers a promising alternative, aiming to regenerate damaged cartilage by creating more effective, biologically integrated solutions.

Cartilage tissue engineering

Cartilage tissue engineering creates a regenerative environment conducive to cartilage repair by employing three crucial elements: seed cells, stimulating factors, and a biological scaffold.

Seed cells include primary chondrocytes (autologous and allogeneic chondrocytes) and stem cells (including embryonic stem cells [ESCs], induced pluripotent stem cells [iPSCs], and adult stem cells such as MSCs). The utilization of each type of seed cell presents advantages and disadvantages, necessitating the consideration of factors such as secondary trauma, immune rejection, and ethical concerns that require resolution [19]. Recently developed decellularized scaffold methods rely on the recruitment of endogenous cells to the site of cartilage defects, circumventing the issue of seed cell sourcing. This approach offers a novel perspective for *in situ* joint cartilage regeneration [20].

Stimulating factors, in the form of growth factors or biophysical signals, influence cell growth and phenotype. The proliferation of chondrocytes and the differentiation of stem cells into chondrocytes involve several growth factors, including transforming growth factor- β (TGF- β) [21], bone morphogenetic protein (BMP) [22], insulin-like growth factor (IGF) [22], and fibroblast growth factor (FGF) [23]. Biophysical signals are crucial components of the microenvironment for cartilage repair. Proper mechanical signals [24], magnetic signals [25], ultrasound (US) signals [26], electrical signals [27], and other signals can promote the chondrogenic differentiation of stem cells or stimulate the release of loaded drugs or cells from the scaffold.

Tissue-engineered biological scaffolds have the ability to mimic the ECM of chondrocytes in terms of material composition and structure, facilitating cell adhesion and matrix secretion. Both synthetic and natural materials have been employed to produce various biological scaffolds, which can be broadly categorized based on shape as hydrogels, sponge-like porous scaffolds [28], nanofiber materials [29], micro/nanospheres and vesicles [30, 31] and 3D-printed scaffolds [32]. Hydrogels are particularly favoured because of their high water content, porosity, and injectability, allowing for minimally invasive implantation and effective integration with damaged tissue [33].

Although hydrogels have shown potential for cartilage regeneration in animal experiments (such as partial regeneration with only hydrogel groups and better repair with cell-loaded hydrogel groups) [34], their long-term clinical effects still need to be verified. For example, the effect of cartilage regeneration *in vitro* is still unsatisfactory, which may be related to the insufficient mechanical properties of hydrogels or the mismatch between the degradation rate and tissue regeneration [35, 36].

Cartilaginous organoids

Organoid technology is an emerging strategy for cartilage repair. This approach involves culturing isolated and expanded stem cells or autologous digested cartilage cells in a simulated environment mimicking the natural ECM, inducing their self-organization into cartilaginous organoids [37]. Cartilaginous organoids can simulate the structure and function of joints, providing a platform for studying the microenvironment of joints and the development and regeneration of cartilage, as well as screening drugs for intra-articular implantation and evaluating biomaterials [38, 39]. Compared with traditional 2D culture and animal models, cartilaginous organoids are more operationally convenient and conducive to in-depth biological research. They offer the advantage of replacing damaged joint cartilage with tissues cultured *in vitro*, presenting a promising alternative. Yang et al. employed HA and hydroxyapatite to construct a gelatine-based microcryogel [40]. This custom-designed microcryogel demonstrated excellent cell compatibility, inducing both chondrogenic and osteogenic differentiation of MSCs. Additionally, it exhibited the ability to self-assemble into bone-cartilage organoids. Abe et al. successfully created cartilage consisting of chondrocytes and ECM from iPSCs by differentiating them into chondrocytes, which are subsequently transferred into 3D cultures to allow iPSC-derived chondrocytes to produce and accumulate ECM around themselves to form cartilaginous tissue particles [41]. Allogeneic iPSC-derived cartilage organoids survive and integrate and are remodelled into articular cartilage in a primate model of chondral defects in the knee joint.

The construction of cartilage-like organoids is an intricate process, and the scalability and reproducibility of organoids pose challenges, with variations in their production often hindering their clinical translation. This process requires meticulous control over cellular differentiation and structural organization, which can be resource intensive. Additionally, ensuring effective integration with the host tissue upon implantation is problematic, as issues such as inadequate vascularization and potential immune responses persist. By providing a supportive scaffold, hydrogels can improve the biomechanical properties of organoids, enhance nutrient diffusion, and promote vascularization, which are essential for the survival and functionality of organoids postimplantation. This makes hydrogels a valuable adjunct to organoid-based approaches, potentially improving their clinical translation by ensuring better integration with host tissue and facilitating the formation of functional cartilage.

In conclusion, while cartilaginous organoids hold considerable promise for cartilage repair, they face challenges related to production and integration. Owing to their tuneable properties and ability to mimic the mechanical environment of cartilage, hydrogel-based approaches present a complementary

strategy that could enhance the performance and clinical application of cartilage organoids [42].

Basic strategies of applying hydrogels for cartilage repair

Hydrogels, key materials in cartilage tissue engineering, require precise property optimization. They need an optimal pore size/porosity for cell infiltration and tissue formation without compromising structure, synchronized degradation rates with cartilage regeneration, and biocompatible degradation products [43]. Mechanically, they should mimic native cartilage for efficient load transfer and ECM production. Biocompatibility is key for supporting cell adhesion and integration with surrounding tissue to ensure successful cartilage repair [44–46]. For self-formation strategies, chemical cross-linking provides high mechanical strength but may introduce cytotoxicity, whereas physical crosslinking offers better biocompatibility with weaker mechanical properties. Photocrosslinking allows for precise control and *in situ* formation, making it ideal for targeted tissue engineering applications [47]. Partially functionalized hydrogels rely on precise crosslinking techniques, such as photocrosslinking or enzymatic reactions, and are difficult to produce on a large scale [48–50]. In addition, there is batch-to-batch variation in biogenic materials such as decellularized extracellular matrix (ECM), which affects reproducibility [50, 51].

Since the advent of tissue engineering in cartilage repair, scaffold research has expanded significantly, with a focus on composition, structure, function, and preparation methods. This review highlights recent advances in scaffold composition and structure for cartilage repair.

Basic material compositions of hydrogels for cartilage repair

Hydrogels for cartilage tissue engineering can be derived from various sources, including natural and synthetic origins, broadly categorized as polysaccharides, proteins, peptides, synthetic polymers, hybrid polymers, and nucleic acids.

Natural hydrogel materials.

Polysaccharides

Common natural polysaccharides used in cartilage repair include HA, chondroitin sulphate, chitosan, alginate, agarose, carrageenan, and cellulose. HA, a key component of the ECM, inhibits cartilage degradation and the progression of OA [52]. However, HA-based hydrogels have poor adhesion and mechanical properties [7]. While chondroitin sulphate and other polysaccharides can aid in cartilage repair, they also face challenges, such as limited mechanical strength and poor cell adhesion, often requiring combination with other polymers or bioactive molecules for enhanced performance [53–55]. Research on cellulose- and agarose-based hydrogels for cartilage tissue engineering is still limited, with these materials primarily used as injectable forms [56, 57].

Proteins

Proteins such as collagen [9], gelatine [58], fibroin [59–61], silk fibroin [62], and elastin [63] serve as foundational materials for protein-based hydrogels. Like other natural polymers, they exhibit excellent biocompatibility and biodegradability. Importantly, to mitigate the impact of *in vivo* proteases on

scaffolds, the addition of protease inhibitors to the gel is necessary to increase the stability of the scaffold [64].

Peptides

Advances in protein engineering have also spurred the development of various peptide materials. One of the research trends in recent years has been the design of multifunctional peptide-based hydrogels by functionalizing peptide sequences to not only provide structural support for cartilage repair but also facilitate the biological process of cartilage repair [65, 66]. Hydrogel scaffolds based on self-assembling peptides exhibit biomimetic and tuneable mechanical properties resembling those of the natural ECM. Examples include elastin-like polypeptides (ELPs) [67], silk-like polypeptides (SLPs) [68], collagen-like peptides [69], RADARADARADADA (RADA16) [70], and KLDLKLDLKLDL (KLD-12) [71]. These materials have also been employed to address challenges in cartilage repair.

Deoxyribonucleic acid-based hydrogels

Deoxyribonucleic acid (DNA), owing to its advantages, such as biocompatibility, low toxicity, precise molecular recognition, and ease of programmability, has emerged as an excellent molecular candidate. Since 2019, with the development of molecular biology, nanotechnology and 3D printing technology, the application of DNA hydrogels in cartilage repair has further expanded [72, 73]. In several recent studies, Shen et al. and Zhou et al. used DNA-based hydrogels to promote the chondrogenic differentiation of bone marrow stem cells (BMSCs) and enhance cartilage regeneration *in vivo*, indicating that the use of DNA-based hydrogels represents a promising and novel therapeutic strategy for cartilage regeneration [74, 75]. However, challenges such as purifying DNA to prevent the spread of pathogens limit the biomedical applications of DNA-based hydrogels.

Synthetic hydrogel materials. Poly(ethylene glycol) (PEG) [76], poly(vinyl alcohol) (PVA) [77, 78], poly(caprolactone) (PCL) [79, 80] and poly(lactic-co-glycolic acid) (PLGA) [81, 82], a copolymer of PLA and PGA, are used in the fabrication of synthetic polymer-based hydrogels. They offer better control over molecular weight, degradation rate, and industrial-scale production. Additionally, their mechanical properties are generally greater than those of natural polymer hydrogels. However, the common drawbacks of synthetic polymers include biocompatibility issues and slow degradation. Fortunately, these challenges can be addressed by modifying the molecular weight [83], introducing other molecules, or incorporating cell integrin-binding motifs to increase the performance of synthetic polymer hydrogels [8, 84]. Ingavle et al. introduced arginine–glycine–aspartate (RGD) peptides into a PEG network to increase cell adhesion and vitality, resulting in a cartilage repair scaffold with high mechanical strength and excellent cell compatibility. Moreover, combining natural and synthetic polymers can harness the advantages of each, compensating for their respective drawbacks [85]. Annabi et al. introduced elastin into a PCL scaffold, which not only improved the water absorption capacity but also enhanced the adhesion and proliferation of chondrocytes within the joint. These findings demonstrate that PCL/elastin composite scaffolds are more suitable for cartilage tissue engineering [86]. In addition to natural protein polymers, Yang et al. incorporated chitosan into polyethylene glycol hydrogels, improving the mechanical

properties and biocompatibility of the hydrogel. *In vitro* experiments also confirmed that the hydrogel loaded with ADSCs promoted cartilage repair [87].

Hydrogels based on natural polysaccharides such as HA and chitosan are inexpensive, but functional modifications, such as the introduction of bioactive molecules or synthetic materials, may significantly increase the cost [50, 88]. The complex preparation process of composite hydrogels, such as that of the GelMA-ethylene glycol chitosan system, further increases the cost [89, 90]. More specific examples of hydrogel materials are provided in Table 1 [55, 57, 60, 63, 69, 73, 75, 79–82, 90–114].

Basic structure of hydrogels for cartilage repair

The cartilaginous tissue can be divided, from superficial to deep, into articular cartilage, calcified cartilage, and subchondral bone, with the articular cartilage further divided into the superficial zone, transitional zone, and deep zone [115]. To simulate the anatomy of the bone–cartilage unit accurately, scaffold designs have evolved from simple monophasic structures to more complex biphasic, triphasic, and even multiphasic or gradient structures, each offering distinct advantages and limitations in clinical applications.

Monophasic hydrogels. Monophasic scaffolds have uniform material properties, including porosity and modulus, throughout their structure and are still the most widely used scaffolds in cartilage tissue engineering [116–119]. To improve integration with native cartilage, Li et al. fabricated a granular hydrogel from gelatine microspheres and tannic acid, which demonstrated excellent tissue adhesion, reactive oxygen species scavenging, and plasticity. This design resulted in newly formed cartilage that filled defects and integrated well with native cartilage and subchondral bone (Figure 2I) [119]. Monophasic hydrogels are primarily used in the treatment of early-stage cartilage defects because of their ease of fabrication and cost-effectiveness. However, their inability to mimic the complex gradient of bone–cartilage tissue limits their long-term efficacy in treating deeper osteochondral defects. Achieving consistent integration at the bone–cartilage interface and systematic regeneration remains a challenge, leading to potential graft failure in load-bearing regions.

Biphasic hydrogels. Osteoblasts and chondrocytes require distinct environments for development. Biphasic scaffolds, with separate cartilage and bone phases, create environments conducive to the differentiation and proliferation of these cells, promoting the regeneration of both tissues. The upper cartilage phase acts as a temporary ECM, whereas the lower bone phase mimics the structure and biomechanics of natural bone (Figure 2II) [22, 58, 122, 123]. Compared with monophasic scaffolds, biphasic scaffolds offer tailored microenvironments for cartilage and bone regeneration, better mimicking natural tissue structures. However, challenges remain with bonding at the bone–cartilage interface, which can lead to separation and compromised repair effectiveness *in vivo*.

Triphasic and multiphasic hydrogels. Compared with biphasic scaffolds, triphasic hydrogels more accurately mimic the native osteochondral structure by incorporating an intermediate layer that simulates the calcified cartilage zone. This highly mineralized layer facilitates the transition from viscoelastic cartilage to rigid subchondral bone, enhancing mechanical

integration and preventing cartilage ossification, a common limitation in biphasic models [124]. The triphasic scaffold strategy has been incorporated into cartilage tissue engineering [120, 124–126]. Qiao et al. designed a trilayered scaffold (superficial cartilage, deep cartilage, and subchondral bone) that induced MSCs to differentiate toward both chondrogenic and osteogenic lineages. The superficial cartilage layer provided a lubricating and wear-resistant surface for the regenerated cartilage (Figure 2III) [120]. Although triphasic scaffolds have demonstrated superior results in preclinical models, their complex fabrication process and limited mechanical durability under dynamic joint conditions present significant challenges for clinical application. At present, their use remains largely experimental.

Gradient hydrogels. Gradient hydrogels represent the latest evolution in scaffold design, offering continuous transitions in physical and chemical properties instead of discrete layers. This gradient structure mimics the heterogeneous nature of the osteochondral interface, reducing the risk of delamination commonly observed in multiphase scaffolds [127]. Sun et al. simulated a biomimetic structure with gradient anisotropy and signal transduction methods in different layers, demonstrating its ability to induce region-specific chondrogenic differentiation and ECM deposition (Figure 2 IV) [121]. Compared with monophasic, biphasic, and triphasic hydrogels, gradient hydrogels offer superior mechanical integrity, enhanced biological integration, and better load distribution across the bone–cartilage interface [121, 128, 129]. However, technical challenges in terms of fabrication, increased costs, and limited long-term clinical data currently restrict their widespread adoption.

Functional hydrogel strategies for cartilage repair

Functional hydrogels—including those that are adhesive, high strength, and injectable and exhibit functional delivery and intelligent responses—address challenges in cartilage regeneration. Adhesive hydrogels improve integration via stable fixation in irregular defects. High-strength hydrogels mimic native cartilage mechanics for weight-bearing joints. Injectable versions offer minimally invasive, patient-specific solutions with self-healing properties. Hydrogels for functional delivery enable precise bioactive agent release to promote regeneration, although their clinical use is limited by variability and manufacturing issues. Intelligently responsive hydrogels provide spatiotemporal drug control based on stimuli, but further research is needed to determine their scalability, safety, and efficacy. Although hydrogel therapy may reduce the medical burden of multiple operations or long-term drug use in patients, its research, development and production costs (such as aseptic processing and quality control) still need to be optimized [130]. The standardization of production processes and large-scale manufacturing is the key to reducing costs [131, 132].

Collectively, functional hydrogels enhance scaffold integration, mechanical properties, drug delivery, and environmental responsiveness, yet ongoing research is essential to advance their clinical translation.

Functional hydrogels with special physicochemical properties

Biological materials are essential in regenerative medicine, with the design of their physicochemical properties forming

Table 1. Overview of materials commonly used for hydrogels in cartilage tissue engineering

Material	Name	Advantage	Disadvantage	Model	Main outcomes	Ref.
Polysaccharide	Hyaluronic acid	1. Biocompatibility 2. Rapid degradation 3. Most abundant GAG in native cartilage	1. Poor adhesion 2. Weak mechanical properties	Sprague–Dawley (SD) rats OA model	Sulphated HA hydrogels reduced the cartilage abrasion and hypertrophy.	[91]
				Rabbit full-thickness cartilage defect model	Fibrocartilaginous tissue laterally integrated into the articular cartilage.	[92]
				Rabbit full-thickness cylindrical osteochondral defect model	Controlled release ability of growth factors and hyaline cartilage regeneration	[93]
	Chitosan	1. Can be dissolved by lysozyme present in the ECM 2. Antibacterial and haemostatic properties	1. Difficult to dissolve 2. Weak mechanical properties and elasticity 3. Low cell-matrix interaction	Bovine cartilage	Hydrogels could be readily degraded by lysozyme.	[94]
				Fresh bovine stifle joints	Hydrogels had greater adhesion to cartilage and tissue regeneration potential.	[90]
				Rat cartilage defect model	New cartilage tissue was regenerated with multi-interaction hydrogel.	[95]
	Alginate	1. High porosity and biocompatibility 2. Mild gelation conditions	1. Weak cell adhesion and infiltration capacity 2. Lack of degrading enzymes	Rabbit full-thickness articular cartilage defect model	Repair of cartilage defects without access to bone marrow	[60]
	Agarose	1. Thermoreversible gelation 2. Stability	1. Bioinertness 2. Weak mechanical properties	Bovine multipotential mesenchymal stem cells	The ability of MSC to regenerate cartilage was weaker than that of chondrocytes.	[96]
				Bovine chondrocytes and mesenchymal stem cells	Agarose hydrogels inoculated with MSC improved the mechanical properties of functional cartilage.	[97]
				Bovine articular chondrocytes	Agarose hydrogels had the highest sulfated GAG/DNA ratio.	[98]
	Chondroitin sulphate	1. Sulphated GAG	1. High cost 2. Short half-life	Mouse subcutaneous implantation model	Enhanced cell proliferation and increased cartilaginous ECM deposition	[55]
	Cellulose	1. Most abundant organic macromolecule 2. Injectable	1. Difficult to dissolve without cellulase	Mouse subcutaneous implantation model	Stable over the long term with slow degradation	[99]
Proteins	Gellan gum	1. Mild gelation conditions 2. Biocompatibility	1. Weak stability and mechanical properties 2. High gelation temperature	Human MSCs	Greater mechanical properties and antibacterial properties with the addition of lignin	[57]
				Human MSCs	Consistent expression of collagen II and high synthesis of GAGs and proteoglycans	[100]
	Collagen	1. ECM components 2. Biocompatible 3. Biodegradable	1. Rapid degradation 2. Immunogenicity 3. Weak mechanical properties	Nude mice	Collagen hydrogel provided good expansion and mechanical support for neotissue.	[101]
	Gelatine	1. Low immunogenicity 2. Active cellular interaction 3. Gelation under physiological conditions	1. Low thermal stability	Rabbit knee microfracture model	Hydrogels supported cell adhesion, proliferation, recruitment and cartilage differentiation.	[102]
	Fibrin	1. Low cost 2. Injectable	1. Easily degradable	Stromal cells from the infrapatellar fat pad	Hydrogels functionalized with cartilage ECM microparticles generated cartilage tissue.	[103]
	Silk fibroin	1. Structural similarity to cartilage collagen 2. Stable <i>in vivo</i> 3. High mechanical strength	1. Difficult to degrade	Mouse subcutaneous implantation model	Silk GMA hydrogel could be applied when strong mechanical properties are needed.	[104]
	Elastin	1. Elasticity 2. Biocompatibility	1. Cytotoxic crosslinking reagents 2. Lack of control on the gelation	Rabbit full-thickness cartilage defect model	Hydrogel allowed for faster bone regeneration and the recruitment of native chondrocytes.	[63]

(continued)

Table 1. Continued

Material	Name	Advantage	Disadvantage	Model	Main outcomes	Ref.
Peptides	Elastin-like polypeptides	1. Nonimmunogenic	1. Depolymerization	Neonatal bovine chondrocytes	ELPs have been shown to promote chondrogenesis.	[105]
	Silk-like polypeptides	2. Adjustable mechanical properties	2. Difficult synthesis	Chondrocytes	Hydrogel presented improved mechanical properties while conserving injectability.	[106]
	Collagen-like peptides	3. Similar to ECM	3. High cost	Human mesenchymal stem cells	Enhanced expression of collagen type II, aggrecan, and ECM.	[69]
	RADA16	4. Mimic the function of proteins		Chondrocytes	Hydrogel supported chondrocyte proliferation and deposition of type II collagen and aggrecan.	[107]
	KLD-12			Bovine bone marrow stromal cells	Encapsulated bovine BMSCs showed cell proliferation and chondrogenesis.	[108]
Synthetic polymers	Poly(ethylene glycol)	1. Easy to prepare and chemically modify	1. Difficult to degrade	Rat cartilage defect model	PLGA/PEG hydrogels significantly promoted new cartilage formation.	[82]
		2. Low cost	2. Biologically inert	Rat cartilage defect model	Hydrogels were cytocompatible and could promote cartilage regeneration.	[109]
	Poly(vinyl alcohol)	1. Chemical resistance	1. Nonbiodegradable	Chondrocytes	The mechanical properties and biomimicry of hydrogels were improved by inorganic material.	[110, 111]
		2. Good water adsorption	2. Biologically inert			
	Polycaprolactone	3. Adjustable mechanical properties				
Hybrid synthetic/natural polymers		1. Adjustable physical properties	1. Poor bioactivity	Rabbit osteochondral defect model	Scaffolds induced articular cartilage formation by accelerating the early subchondral bone regeneration.	[79]
		2. Biocompatibility	2. Difficult to degrade			
	Poly(lactic-co-glycolic acid)	1. Low immunogenicity	1. Acid degradation product	Female nude mouse subcutaneous implantation model	Implants retrieved after 8 weeks revealed enhanced cartilage tissue formation.	[80]
		2. Biodegradable		Rabbit chondrocytes	PLGA hydrogel has potential as an injectable cell delivery carrier for cartilage regeneration.	[81, 82]
		3. Hydrophile				
Hybrid synthetic/natural polymers	HA-PEG	To compensate for the respective shortcomings of natural and synthetic polymers	1. Difficult preparation	Bovine chondrocytes	Incorporating HA into hydrogels increased chondrocyte number and GAG and collagen production.	[112]
	Poly(ethylene glycol)-kartogenin			Rabbit full-thickness cartilage defect model	The regenerated tissues exhibited well-matched histomorphology and biomechanical performance.	[113]
	chitosan (PEG-CHI-KGN)					
Proteo-nucleotide-based polymers	Gelatine/PLGA-PEG-PLGA			Human dental pulp stem cells	The adhesion, viability, and chondrogenic differentiation of human dental pulp stem cells (hDPSCs) were improved by hydrogels.	[114]
	Deoxyribonucleic acid (DNA)	1. Programmable	1. Disease transmission	Mice with osteoarthritis	The hydrogel promoted the mitigation of local inflammation and the rebuilding of articular cartilage.	[73, 75]

DNA deoxyribonucleic acid, ECM extracellular matrix, ELP elastin-like polypeptides, GAG glycosaminoglycan, GMA glycidyl-methacrylate, HA hyaluronic acid, hDPSCs human dental pulp stem cells, KLD-12 KLDLKLKLDL, MSC mesenchymal stem cell, OA osteoarthritis, PEG poly(ethylene glycol), PEG-CHI-KGN poly(ethylene glycol)-kartogenin-chitosan (PEG-CHI-KGN), PLGA poly(lactic-co-glycolic acid), RADA16 RADARADARADARADA, SD Sprague-Dawley

the foundation for further functionalization. The optimization of these properties in hydrogels has become a key focus. Traditional hydrogels have evolved from having a low modulus and poor mechanical performance to having improved mechanical performance and injectable forms. Research on cartilage regeneration now emphasizes the biomimetic

simulation of articular cartilage, considering the layered structure and mechanical properties of bone-cartilage tissues. Hydrogels must also have good adhesiveness to enhance integration with surrounding and newly formed cartilage [4]. The following section highlights the functional physicochemical properties of hydrogels in cartilage

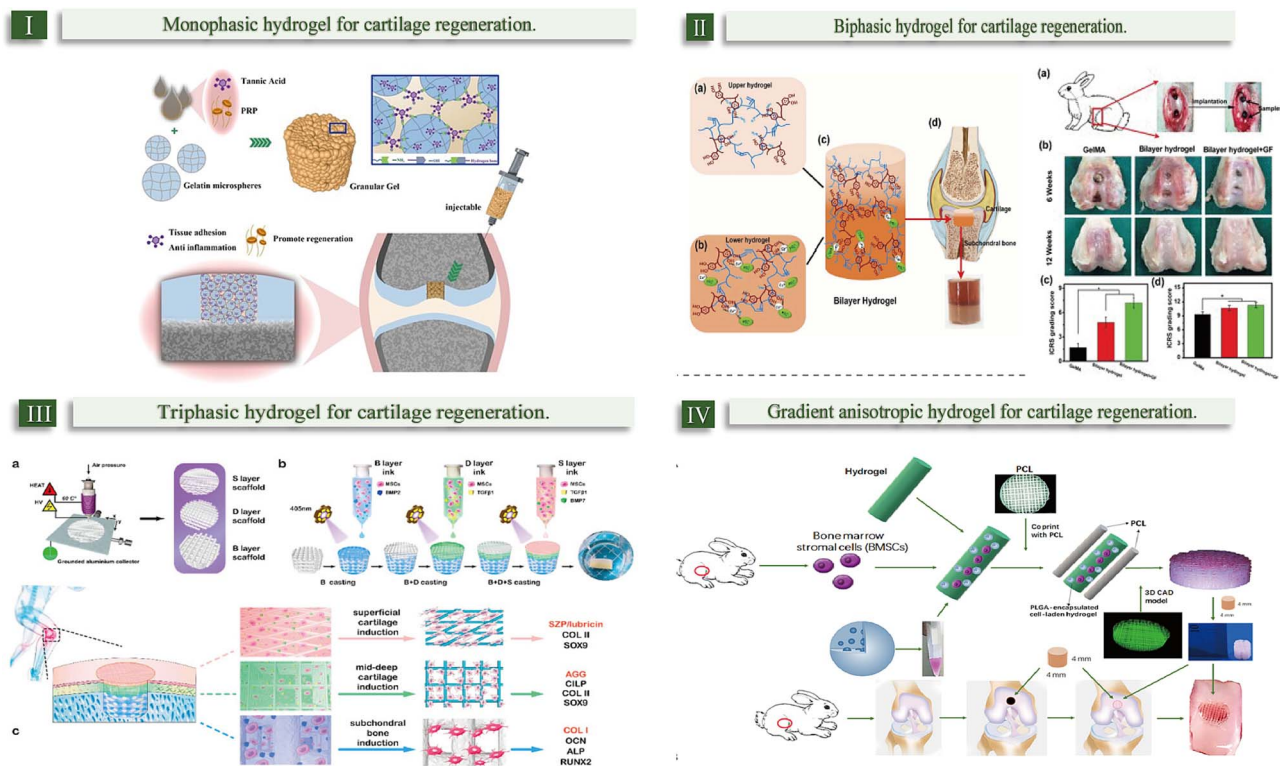


Figure 2. Stratified hydrogels for cartilage regeneration. (I) Gelatine-tannic acid (gel/TA) granular hydrogel carrying PRP for cartilage regeneration. Reproduced with permission [119]. Copyright © Oxford university press 2023. (II) GelMA was mixed with PDA to prepare the upper layer hydrogel, and Ca^{2+} -GelMA was mixed with phosphate ions (PO_4^{3-})-GelMA to mineralize hydroxyapatite *in situ* to prepare the lower hydrogel layer. Gross morphology of samples retrieved from rabbits after 6 and 12 weeks. Reproduced with permission [58]. Copyright © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (III) The preparation process and application of the trilayered fibre-reinforced and growth factor (GF)-loaded hydrogel construct. The trilayered construct facilitated the regeneration of osteochondral tissues with enhanced lubricating properties *in vivo*. Reproduced with permission [120]. Copyright © 2020 Elsevier Ltd all rights reserved. (IV) Schematic illustration of the study design with 3D-bioprinted, dual-factor release and gradient-structured, MSC-laden constructs for articular cartilage regeneration in rabbits. Reproduced with permission [121]. Copyright © 2020 the authors. GelMA gelatine methacryloyl, gel/TA gelatine-tannic acid, GF growth factor, MSC mesenchymal stem cells, PDA polydopamine, PO_4^{3-} phosphate ions

regeneration, including their adhesiveness, strength, and injectability.

Some hydrogels are prone to structural collapse or premature degradation under loading, which leads to a decrease in the reparative effect over time, especially in load-bearing joints [133, 134]. In addition, the repair of large-scale cartilage defects is still technically difficult [133].

Adhesive hydrogels for cartilage regeneration. The stable adhesion of hydrogels to cartilage defects is crucial for effective repair. Well-adhering hydrogels provide a stable microenvironment for cells and growth factors, ensuring effective mechanical load transfer. This stability promotes the integration of newly formed cartilage with surrounding tissue, enhancing overall cartilage regeneration [135–137]. Viscous hydrogels commonly used for cartilage defect repair can be divided into those based on mechanical and physical fixation and chemical connection fixation according to the adhesion mechanism.

Mechanical interlocking physical fixation primarily involves applying a premade gel solution to the cartilage defect site. As certain components of the premade gel penetrate the tissue and gelatinize, a network structure is formed by deep infiltration into the tissue, thus achieving physical fixation at the defect site. This method can be achieved mainly through the grafting of methyl acrylate onto the

material and then photocuring to form a gel [138], gelation through sodium alginate-calcium ion interactions [139], and gelation via the infiltration of fibrin [140]. Many studies have adopted mechanical interlocking physical fixation adhesion methods, such as silk fibroin grafted with methyl acrylate [138], PEG [85], HA [141], sodium alginate [139] and modified fibrin [140], among others. However, current research utilizing mechanical interlocking physical fixation for adhesive hydrogels indicates relatively poor adhesion stability. Moreover, most studies of this kind lack *in vivo* experiments on bone–cartilage repair in animals, raising doubts about the *in vivo* reparative efficacy from a biological effects perspective.

Current approaches for promoting cartilage regeneration using adhesive hydrogels primarily involve chemical fixation. Typically, this is achieved by modifying the material to graft adhesive functional groups, facilitating the adhesion of hydrogels to cartilage. The fixation method based on chemical connection can be broadly categorized into two main types: one involves the formation of amide bonds with carboxyl and amino groups on the cartilage surface, while the other involves the reaction of the catechol functional groups of dopamine with the active hydrogen of amino, thiol, and hydroxyl groups on the cartilage tissue surface [142–144]. Recent studies have grafted dopamine onto chondroitin sulphate or methacrylic acid-modified gelatine, achieving good adhesion and cartilage

regeneration [58, 145]. However, gelation requires stringent conditions, and adhesion and biocompatibility decrease with oxidation. Another prevalent method involves the formation of amide bonds via Schiff base reactions. Zhou et al. used oxidized dextran mixed with methacrylate gelatine to form a gel that adhered firmly to cartilage through Schiff base reactions, promoting regeneration [146]. Despite promising results, the complexity of these methods and moderate long-term adhesion performance remain challenges.

Adhesive hydrogels have demonstrated promising results for addressing small to medium-sized cartilage defects; however, their long-term clinical outcomes remain under scrutiny. These hydrogels facilitate robust adhesion and provide a stable microenvironment conducive to cellular proliferation and attachment. Nevertheless, their efficacy in treating larger and more complex defects has not been fully established. Moreover, addressing the cost-effectiveness and scalability of these hydrogels remains critical for their widespread clinical implementation. Variability in defect size and location can significantly impact the therapeutic efficacy of adhesive hydrogels [147].

High-strength hydrogels for cartilage regeneration. For weight-bearing tissues, such as knee cartilage, hydrogels must possess adequate mechanical strength, toughness, and energy dissipation to be effective. Adhesive hydrogels, however, may not provide the necessary mechanical strength for such demanding applications. High-strength hydrogels enable earlier implantation after cell seeding, reducing the *ex vivo* cultivation time. They can also bear mechanical loads *in vivo* before cells secrete sufficient ECM [148]. On the basis of the composition types contributing to high strength, hydrogels with high strength can currently be classified into several categories: single-network hydrogels, double-network hydrogels, and micro/nanocomposite hydrogels (produced using hydrogel doping, mixed micro/nanospheres, sheets, and crystals), among others.

Single-network hydrogels typically rely on high crosslinking density to maintain certain mechanical properties, such as high-density ionic bonds and chemical bonds. However, the modulus of single-network hydrogels can reach only tens to a few hundred kilopascals [149], whereas the maximum compressive strength of some hydrogels can reach the megapascal range (Figure 3I) [61].

Double-network hydrogels can be classified into double chemically crosslinked hydrogels [152], double physically crosslinked hydrogels [153], and physical-chemical hydrogels [154]. These hydrogels consist of two interpenetrating networks, which are usually synthesized in two steps: the formation of a highly crosslinked, rigid gel and the formation of a loosely crosslinked network. This structure provides high strength and toughness by dissipating energy through sacrificial bonds, which can be covalent or noncovalent. In the current stage of double-network research, the focus is mainly on physicochemical networks, with dual networks combining chemical and ionic networks constituting more than half of the physicochemical network studies [155]. Yang et al. developed a double-network hydrogel by combining acrylamide photocrosslinking with chitosan-sodium citrate, resulting in a modulus of 1.3 MPa and a maximum compressive strength of 40–60 MPa (Figure 3II) [150]. Gong et al. created a dual-network hydrogel through acrylate photocrosslinking while simultaneously incorporating calcium acetate. The inclusion

of calcium ions formed ionic bonds with acrylate, resulting in a hydrogel with a modulus in the megapascal range and a maximum compressive strength of 14 MPa [156].

Micro/nanocomposite hydrogels involve incorporating micro/nanoscale particles, flakes, or crystals (materials with extremely high specific surface areas) into the hydrogel. These materials serve as multifunctional cross-linking sites within the hydrogel network, aiming to increase the modulus and toughness of the material [157]. The focus of research on micro/nanocomposite hydrogels lies primarily in the improvement of incorporated micro/nanoparticles. Jiang et al. achieved enhancements by incorporating oriented graphene oxide nanosheets into a sodium alginate ion network, resulting in a composite hydrogel with a modulus of 198 gigapascals and a tensile strength of 1215 megapascals [158]. Similarly, Kim et al. improved a sodium alginate hydrogel by incorporating parallel and uniformly distributed ultrafine aluminum oxide flakes, resulting in a composite hydrogel with a modulus of 17.9 gigapascals and a tensile strength of 267 megapascals (Figure 3III) [151].

In the current research on high-modulus hydrogels for articular cartilage repair, several challenges exist: (i) The high-modulus hydrogels currently employed for cartilage repair focus primarily on load-bearing replacement rather than tissue regeneration. Strategies relying on cartilage substitutes have numerous drawbacks, such as a lack of integration with surrounding tissues [159], nondegradability hindering regeneration [160], potential wear and tear upon implantation [161], limited lifespan [162], and issues such as infection and immune rejection [162]. (ii) Existing studies often overlook the biodegradability and bioactivity of materials. Prolonged biodegradation time or nondegradation may cause the hydrogel to occupy the defect space and impede cartilage regeneration. (iii) The replacement-oriented approach in current research results in the predominant use of materials such as polyacrylamide and its derivatives or PVA. Natural high-molecular-weight polymers, especially those based on natural materials, are relatively underexplored in hydrogel research.

Because they are designed to endure the mechanical stresses of load-bearing cartilage, high-strength hydrogels are under continuous evaluation concerning their long-term clinical performance. These hydrogels frequently face challenges related to biocompatibility and seamless integration with adjacent tissues. Furthermore, concerns about cost-effectiveness and the scalability of production processes persist, given the often complex manufacturing involved. Patient age and physical activity level may markedly influence clinical success [163].

Injectable hydrogels for cartilage regeneration. Despite the effectiveness of high-strength hydrogels, their minimally invasive application is another critical consideration in cartilage repair. Owing to their unique ability to conform to irregular defect geometries, injectable hydrogels offer a promising solution. They provide a less invasive approach for filling and covering defects while maintaining functionality, which is essential for faster recovery and personalized treatment.

Injectable hydrogels include *in situ*-formed and self-healing hydrogels. Cells or active factors are encapsulated within a polymer-formed network and mixed with the injectable hydrogel, forming a precursor solution injected into the target site. Upon injection into the repair site, gelation occurs through enzymatic, ionic, thermal, or other processes,

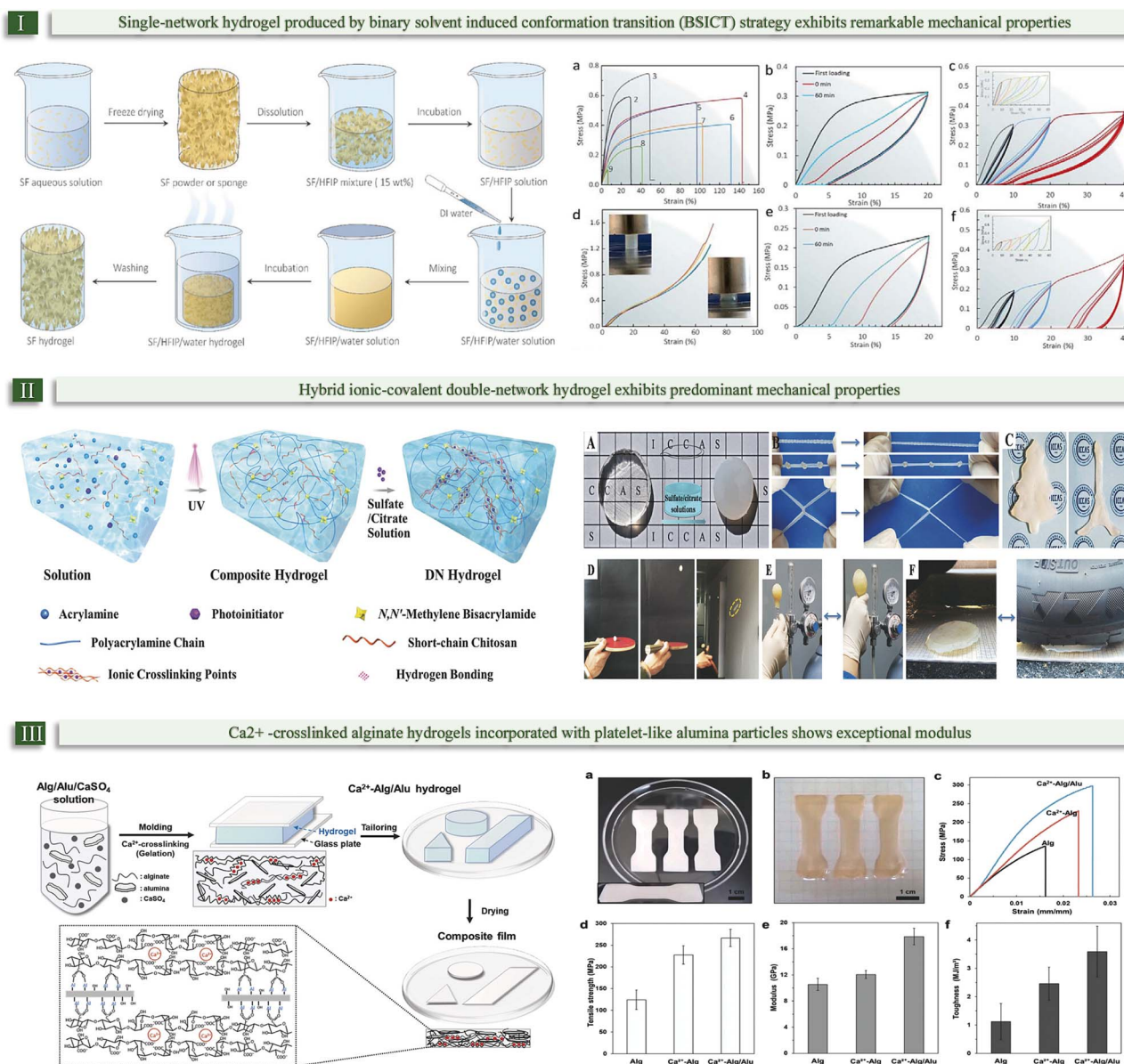


Figure 3. High-strength hydrogels for cartilage regeneration. **(I)** Single-network hydrogels produced via the binary solvent-induced conformation transition (BSICT) strategy exhibit remarkable mechanical properties. The Young's modulus can reach up to 6.5 ± 0.2 MPa. Reproduced with permission [61]. Copyright © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. **(II)** Hybrid ionic-covalent double-network (DN) hydrogels predominantly exhibit strong mechanical properties. Outstanding mechanical performance of double-network (DN) hydrogels under twisted stretching, knotted stretching, and crossover stretching. Reproduced with permission [150]. Copyright © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. **(III)** Schematic illustration showing the preparation process of hydrogel-film casting and the structural model of the composite films. Ca^{2+} -crosslinked alginate/alumina films show exceptional tensile strength (267 MPa), modulus (17.9 GPa), and toughness (3.60 MJ m^{-3}). Reproduced with permission [151]. Copyright © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. BSICT binary solvent-induced conformation transition, DN double network

facilitating *in situ* formation [9]. Self-healing hydrogels exhibit shear-thinning characteristics, forming a soft gel state before injection. During the injection process, the hydrogel is temporarily liquefied by applying shear stress. As the hydrogel is injected into the body and stress is relieved, the mechanical properties of self-healing hydrogels are rapidly restored [164]. In both *in situ* and self-healing hydrogels can be generated through chemical and/or physical crosslinking. On the basis of the mechanism of the sol-gel transition of materials, injectable hydrogels are classified as physical hydrogels and chemical hydrogels. The key distinction lies in the formation of covalent bonds.

Physical crosslinking involves physical gelation achieved through reversible and transient connections. This network is formed through molecular entanglement and secondary forces, including electrostatic or ionic interactions [165], hydrogen bonding [166], hydrophobic interactions [167], metal coordination [168, 169], π - π stacking [170], guest-host interactions [171, 172], and supramolecular chemistry [173]. Physically crosslinked hydrogels are weaker due to noncovalent interactions, making them prone to loosening with changes in temperature, pH, or ion concentration. Consequently, these materials exhibit inferior mechanical properties. Rapid degradation before ECM replacement can

affect chondrocyte adhesion and proliferation, impacting therapeutic outcomes. However, their ease of degradation makes them suitable for drug and biofactor encapsulation for *in vivo* delivery, avoiding the toxic effects of crosslinkers and light radiation.

Chemical crosslinking involves the formation of covalent bonds through various chemical processes. Specific functional groups are introduced into polymers to enable *in situ* gelation within the body without the need for external inducing factors. Common chemical reactions in this context include Michael addition [174], Schiff base formation [175, 176], click chemistry reactions [177], enzyme crosslinking reactions [178], and photopolymerization [175]. Chemically crosslinked hydrogels, which are formed through covalent bonds, have stronger mechanical properties and are not subject to reversible changes. However, their primary drawback is their cytotoxicity.

Self-healing materials are defined as materials that can automatically heal and restore their normal physicochemical properties after being damaged. Traditional hydrogels are prone to damage in load-bearing regions under continuous mechanical forces, leading to a series of issues, such as bacterial infection [179]. In the past, repairing failed hydrogels involved adding adhesives and fillers to the material, releasing healing agents into cracks through microcapsules or vascular networks. However, the therapeutic effect was limited [180]. In the last decade, inspired by the secretion of mussels [181] and the self-healing of the skin [181, 182], self-healing hydrogels have undergone rapid development. The repair mechanism primarily involves the formation of noncovalent interactions (physical crosslinking) and dynamic covalent bonds (chemical crosslinking) between polymers, achieving self-repair through continuous rupture and reconstruction.

In shear-thinning technology, the gelation process of hydrogels subjected to shear stress is faster than that of other types of hydrogels [183], and shear stress does not adversely affect the viability or uniform distribution of cells encapsulated within the hydrogel. Xu et al. demonstrated a self-healing and injectable supramolecular gelatin hydrogel; the prefabricated hydrogel containing encapsulated human bone marrow-derived mesenchymal stem cells (hBMSCs) and chondrogenic agents promoted more sustained release of kartogenin and TGF- β 1, leading to enhanced chondrogenesis of the hBMSCs *in vitro* and *in vivo* (Figure 4a). Ultimately, this self-healing hydrogel not only enhanced the repair of articular cartilage but also enhanced new subchondral bone filling in the entire defect area, illustrating its potential application as an implant for osteochondral regeneration (Figure 4b) [184].

Injectable hydrogels represent a minimally invasive strategy for cartilage repair, with ongoing studies on their long-term clinical effectiveness. While these hydrogels can be modified to accommodate various defect sizes and anatomical locations, their mechanical durability often falls short compared with that of noninjectable options. The economic feasibility and production scalability of injectable hydrogels present additional hurdles, potentially necessitating frequent applications or specialized equipment. Patient comorbidities may further affect treatment outcomes [185].

Delivery of functional hydrogels for cartilage regeneration

In addition to structural support, the delivery of functional cells and bioactive agents, such as growth factors and

anti-inflammatory compounds, can significantly increase the regenerative potential of hydrogels. The delivery of functional hydrogels offers precise control over the release of therapeutic agents, improving the healing process. This strategy is particularly useful in cases requiring specific modulation of biological pathways to promote cartilage regeneration.

The effects of such hydrogels are influenced by age, degree of injury and the joint microenvironment [186, 187]. For example, elderly patients with weak cartilage regeneration may need hydrogels carrying stronger pro-differentiation factors, and the inflammatory microenvironment may accelerate the degradation of hydrogels, necessitating the design of anti-inflammatory functional coatings [188, 189].

Repair mechanism of functional hydrogels. As scientists delve into the pathological mechanisms of OA, various hypotheses have been proposed to explain why cartilage cannot regenerate spontaneously. These hypotheses are mostly related to cell failure and disturbances in the local microenvironment.

With respect to cell failure, current research suggests that the low cellular density in cartilage tissue, coupled with the limited proliferative capacity of mature chondrocytes, is the fundamental obstacle to cartilage regeneration. With ageing, the cell density and proliferative capacity of articular cartilage gradually decline, leading to the apoptosis of chondrocytes. In contrast, stem cells possess high proliferative potential and chondrogenic differentiation capacity. Therefore, cell-based cartilage regeneration strategies involve the enrichment of chondrocytes or stem cells, endogenous cell recruitment, and antiaging interventions, all aimed at increasing the density of chondrocytes [190].

Moreover, the local microenvironment profoundly affects cartilage regeneration. Inflammatory stress and metabolic disturbances disrupt the optimal state of cartilage and the environment conducive for cartilage regeneration. With an increasing understanding of different inflammatory and metabolic pathways, numerous therapeutic targets have emerged. Various drugs, biofactors, genes, and extracellular vesicles are continually being tested to create the optimal microenvironment for cartilage regeneration [190]. Hydrogels, serving as delivery carriers, ensure that the cells and substances encapsulated within them can be targeted and released in a controlled manner at the damaged site.

Classification of functional hydrogels. Hydrogels can be employed for delivering cells or biofactors, including extracellular vesicles and viruses. These factors can be utilized either in combination or separately for therapeutic purposes [191]. On the basis of hypotheses related to cell failure and microenvironmental disruption, treatment strategies targeting cells include direct cell delivery, endogenous cell recruitment factors, antiaging factor delivery, and delivery of factors promoting cartilage regeneration. Treatment strategies addressing the local microenvironment involve the delivery of anti-inflammatory factors and metabolic regulatory factors.

Hydrogels for functional cell delivery

Cell-laden repair is a traditional tissue engineering strategy that involves the use of biomaterials and external seed cells to repair or replace damaged tissues. Various cell types, including chondrocytes, MSCs, and pluripotent stem cells, have been studied for cartilage repair via this approach. The efficacy of stem cell-loaded hydrogels is influenced by a patient's own

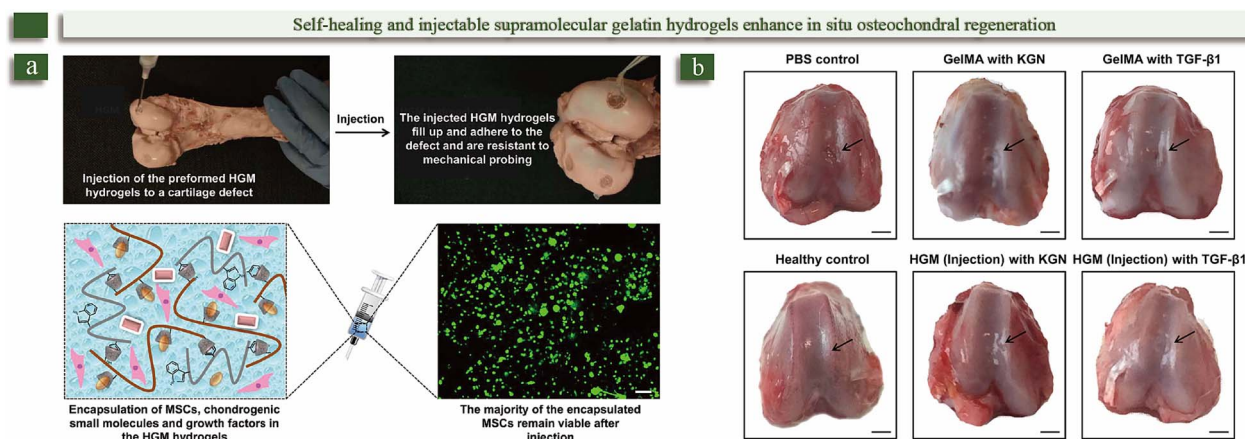


Figure 4. Self-healing hydrogels for osteochondral regeneration. (a) Injection of host-guest macromer (HGM) gelatine supramolecular hydrogels that are encapsulated with MSCs, chondrogenic small molecules and growth factors for cartilage repair. (b) Chondrogenic differentiation of hBMSCs in HGM hydrogels loaded with KGN or TGF- β 1 *in vivo*. Harvested hMSC-laden hydrogel implants after 28 days of subcutaneous implantation in nude mice [184]. Copyright © 2019 Elsevier Ltd. hBMSCs human bone marrow-derived mesenchymal stem cells, HGM host-guest macromer, KGN kartogenin, TGF- β transforming growth factor- β

cellular activity, such as the ability of MSCs to proliferate and differentiate into cartilage, which varies from individual to individual [192, 193]. Endogenous stem cell recruitment strategies such as the use of functionalized hydrogels may reduce the dependence on cells *in vitro*, but the recruitment efficiency still needs to be optimized [194, 195].

Chondrocytes have the ability to diffuse and proliferate within hydrogels while maintaining their cellular morphology and phenotype, accompanied by increased secretion of ECM molecules such as Col II and aggrecan (Agg) [196–198]. Interestingly, cells at the periphery of the gel exhibit more pronounced growth and ECM secretion capabilities than those in the central region, a phenomenon commonly referred to as edge flourishing (EF) [199, 200]. Spatial heterogeneity in cell behaviour (e.g. enhanced ECM secretion at scaffold peripheries) underscores the need for hydrogels with controlled porosity and bioactive gradients to ensure uniform tissue regeneration—a key consideration for scaling up to human-sized defects. Leveraging this phenomenon, Zeng et al. encapsulated chondrocytes within a scaffold composed of gelatine microspheres and alginate hydrogel [201]. Using gelatine as a pore-forming agent, they directed edge chondrocytes into the central region of the hydrogel. At various time points, the expression levels of chondrocyte-specific genes, including Col II, Agg, and cartilage oligomeric matrix protein (COMP), were greater than those in conventional alginate hydrogels. However, owing to the limitations of chondrocytes in treating cartilage defects, recent research on scaffold-loaded cells has focused predominantly on stem cells.

MSCs can differentiate into various cell types and are abundant in diverse sources, including bone marrow, peripheral blood, adipose tissue, synovial tissue, and umbilical cord blood [202]. In the context of *in vitro* experiments focused on articular cartilage repair, much attention has been given to bone marrow-derived MSCs (BM-MSCs), which have been extensively utilized in both large and small animal studies [203, 204]. In addition to BM-MSCs, adipose tissue-derived MSCs (AT-MSCs) have gained prominence in cartilage tissue engineering applications because of their excellent proliferative potential [205, 206]. Compared with BM-MSCs, AT-MSCs can be obtained through less invasive methods such as

liposuction and exhibit behaviour that is unaffected by donor age [202]. However, in both *in vivo* and *in vitro* experiments, the osteogenic and chondrogenic differentiation potential of AT-MSCs is generally considered inferior to that of BM-MSCs [207, 208]. Other sources of MSCs, including human umbilical cord blood-derived MSCs [209] and synovial membrane-derived MSCs [210], have also been demonstrated to be feasible for cartilage repair *in vitro*. Consequently, MSCs are increasingly recognized as the most promising cells in cartilage tissue engineering. Hydrogels serve as a suitable environment for MSCs, preventing undesired tissue differentiation and facilitating the formation of cartilage.

iPSCs are obtained through the reprogramming of somatic cells, maintaining an early differentiation state similar to that of ESCs. They possess the capabilities of self-renewal and pluripotency without ethical or immunological concerns. Numerous studies on iPSCs derived from different cell types have demonstrated that, compared with MSCs, iPSCs exhibit a greater propensity for chondrogenic differentiation and a greater abundance of Col II [211–213]. Notably, chondrocytes derived from iPSCs are prone to dedifferentiation during expansion. To address the need for a substantial quantity of chondrocytes for repairing large defects, it is advisable to expand iPSCs before inducing their differentiation into chondrocytes [214].

Hydrogels for functional endogenous cell recruitment factor delivery

The limitations of cell-laden repair strategies have prompted scientists to shift their focus towards acellular scaffolds. Acellular repair represents an alternative tissue engineering approach based on endogenous cells. This strategy aims to induce the recruitment of native cells in the body through chemotactic factors. Recruited progenitor cells, by modulating the inflammatory environment, facilitate cartilage regeneration either through paracrine signalling, which induces chondrogenesis, or by directly differentiating into chondrocytes. This acellular approach aims to promote cartilage regeneration and achieve tissue repair by harnessing endogenous cellular mechanisms, thus overcoming the drawbacks associated with cell-laden repair strategies [190].

MSCs secrete inductive factors capable of recruiting endogenous stem cells, including chemokines (stromal cell-derived factor [SDF]-1 α [215–217], macrophage inflammatory protein [MIP]-3 α [218], and interleukin [IL]-8 [218]), growth factors (platelet-derived growth factor-BB [219], TGF- β [220], BMP2 [221], and exosomes [222]), and other signalling molecules, such as PRP [93], erythropoietin (EPO) [223], as well as certain nucleic acid small molecules [102]. Ideally, chemoattractants should maintain specific concentrations locally; however, their short half-life and rapid diffusion after injection lead to a quick decrease in concentration. Additionally, studies have shown that while chemotactic factors recruit stem cells, they may also attract inflammatory cells, potentially promoting inflammatory reactions. To address these challenges, it is necessary to embed chemoattractants within scaffolds to evade the surrounding chemical environment and enzymatic degradation. Simultaneously, controlled degradation of the scaffold can be utilized to achieve the gradual release of chemoattractants.

Hydrogels for functional antiaging factor delivery

Cellular senescence is a crucial factor preventing regeneration after cartilage injury and is characterized by permanent cell cycle arrest, apoptotic resistance, and the release of harmful proinflammatory factors into the surrounding environment, collectively known as the senescence-associated secretory phenotype (SASP) [224]. With ageing, senescent cells gradually accumulate in cartilage, leading to reduced cell proliferation and impaired tissue function. Four different strategies can be employed to mitigate the adverse effects of cellular senescence on the body [224–226]. The first strategy involves inducing apoptosis in senescent cells using pro-apoptotic drugs, including single and combination drug therapies. The second strategy is to activate the immune system, including enhancing natural killer (NK) cell activity, to eliminate senescent cells. The third strategy involves interfering with the activity of nuclear factor kappa-B (NF- κ B) or its upstream regulatory factors without harming senescent cells to inhibit the expression of SASP factors such as IL-1, thereby attenuating the inflammatory impact of senescence. Finally, inducing reprogramming allows genetic manipulation of cells to bypass or reverse cellular senescence. The targeting of senescence with senolytics and drug delivery systems is a major research strategy. By loading drugs, such as resveratrol [227] and metformin [228], that target cellular senescence-related genes [229] into hydrogels, researchers aim to delay the progression of cartilage defects. Choi et al. reported that MSCs treated with resveratrol exhibited enhanced cell proliferation and suppressed senescence. They placed a gelatine hydrogel loaded with resveratrol into a rabbit cartilage defect model. Eight weeks postsurgery, compared with the control group, the treatment group presented greater expression of ECM proteins and lower expression of hypertrophic maturation markers (Figure 5I) [227].

Hydrogels for functional osteochondral regeneration factor delivery

Chondrogenesis refers to the process in which MSCs differentiate into chondrocytes, whereas osteochondral regeneration involves the proliferation of cells associated with both osteogenesis and chondrogenesis, promoting the regeneration of bone and cartilage. The bioactive factors that enhance osteochondral regeneration need to stimulate the growth of

both bone and cartilage simultaneously [10]. Research indicates that factors such as TGF- β , BMP, IGF, and kartogenin (KGN) can play a role in osteochondral regeneration by improving the arrangement of chondrocytes and promoting the deposition of proteoglycans. These factors also induce the formation of subchondral bone, contributing to the overall process of bone–cartilage regeneration.

TGF- β Signalling Pathway. TGF- β plays a crucial role in the early development of cartilage and is utilized primarily for inducing mesenchymal stem cell chondrogenic differentiation, promoting cell proliferation, and facilitating ECM formation. When delivered via HA hydrogels, TGF- β 1 enhances cartilage matrix deposition, demonstrating the synergistic role of hydrogels in sustaining bioactive factor functionality [234, 235]. Additionally, TGF- β 3 promotes the synthesis and secretion of sulphated glycosaminoglycans in MSCs [236, 237]. Other studies have suggested that TGF- β , when acting synergistically with certain factors such as ghrelin, can promote MSC chondrogenic differentiation and contribute to articular cartilage regeneration [238].

BMP Signalling Pathway. BMP belongs to the TGF- β superfamily and plays a crucial regulatory role in the process of mesenchymal stem cell chondrogenic differentiation [239]. BMPs are key regulators of MSC differentiation towards chondrocytes and osteoblasts. BMP-2 is known to stimulate the secretion of ECM by MSCs, and its associated hydrogel microspheres have been shown to increase the production of glycosaminoglycans and Col II [240]. Additionally, BMP-7, which is synthesized and secreted by chondrocytes, promotes the synthesis of cartilage matrix while simultaneously reducing the activity of catabolic metabolic cytokines through both the Smad and MAPK pathways [241, 242]. Hydrogels integrating BMP-2 microspheres show enhanced matrix production, underscoring the importance of delivery vehicles in maximizing BMP efficacy [243].

IGF and the ERK1/2-MAPK Pathway. IGF plays a fundamental role in cartilage tissue homeostasis, facilitating proteoglycan secretion and enhancing chondrogenic differentiation alongside TGF- β via the ERK1/2-MAPK signalling pathway [244]. This interaction is critical for maintaining the balance of anabolic and catabolic processes within cartilage tissue. Additionally, in collaboration with the extracellular signal-regulated kinase (ERK)1/2-mitogen-activated protein kinase (MAPK) signalling pathway, IGF-1 and TGF- β 1 can synergistically enhance the chondrogenic differentiation of MSCs [245].

Hydrogels for functional anti-inflammatory factor delivery

In OA, adult articular chondrocytes undergo phenotypic modulation in response to changes in the environment caused by mechanical damage and inflammation. These processes not only stimulate the production of enzymes that degrade the cartilage matrix but also lead to the generation of proinflammatory factors, especially ILs and TNF- α . Additionally, these processes inhibit the expression of genes associated with chondrocyte phenotype differentiation, including collagen type II alpha 1 chain (COL2A1) and cartilage-derived retinoic acid-sensitive protein (CD-RAP). Indeed, the inflammatory processes associated with OA are highly complex and involve the participation of various inflammatory mediators. As our understanding of different inflammatory pathways increases,

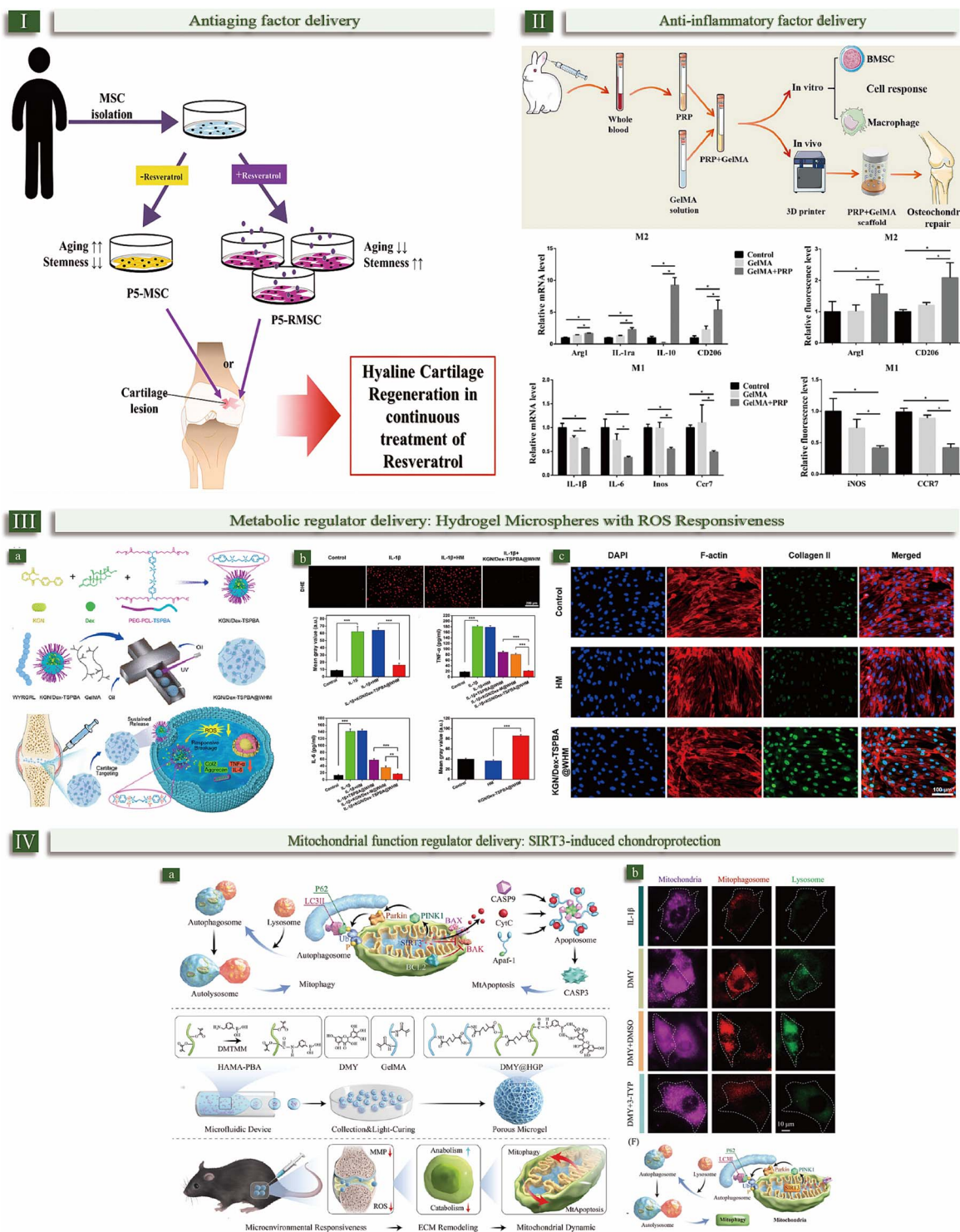


Figure 5. Delivery of functional hydrogels for cartilage regeneration. **(I)** Sustained treatment of MSCs with resveratrol (RSV) from P0 to P5 increased stemness and inhibited senescence. With increased stemness, passage-5 RSV-treated MSCs (P5-RMSCs) presented improved hyaline cartilage regeneration potential. Reproduced with permission [227]. Copyright © 2018, the author(s). **(II)** The combination of the PRP-GelMA scaffold, BMSCs, and macrophages (M1, M2a-c) ensured long-term effects on cartilage and subchondral bone regeneration. PRP reduced M1 polarization and promoted M2 polarization. Reproduced with permission [231]. Copyright © 2021 acta Materialia Inc. published by Elsevier Ltd **(III)** a. ROS-responsive nanoparticles reacted with OA-induced intracellular ROS, resulting in the depolymerization of the nanoparticles, which could eliminate excess ROS and reduce inflammation. b. ROS-responsive nanoparticles resulted in a significant decrease in the ROS level. c. Immunofluorescence staining revealed that the expression of collagen II was significantly increased in the ROS-responsive nanoparticle group. Reproduced with permission [232]. Copyright © 2022 American Chemical Society. **(IV)** a. Retuning the balance between mitochondrial apoptosis/mitophagy via SIRT3-enriched and microenvironment-modulated hydrogel microspheres to prevent OA. b. Mitophagy/lysosome/mitochondria tri-staining assays revealed that suppressing SIRT3 not only decreased the formation of autophagosomes in mitochondria (mitophagosomes) but also impeded the fusion of autophagosomes with lysosomes, leading to autophagic flux failure in mitochondria. Reproduced with permission [233]. Copyright © 2023 Wiley-VCH GmbH. *BMSCs* bone marrow stem cells, *OA* osteoarthritis, *PRP-GelMA* platelet-rich plasma-gelatin methacryloyl, *P5-RMSC* passage-5 RSV-treated MSCs, *ROS* reactive oxygen species, *RSV* resveratrol, *SIRT3* sirtuin 3

more therapeutic targets, including recently discovered neurotrophins and alarmins, continue to emerge [246]. Currently, scientists often intervene in the inflammatory environment by loading hydrogels with drugs [190], genes [247] and stem cell-derived exosomes [248].

Recently, some studies have suggested that an imbalance in M1/M2-polarized macrophages is associated with adverse outcomes in OA [249, 250]. M1 macrophages secrete inflammatory factors, promoting inflammation progression, whereas M2 macrophages release anti-inflammatory factors to facilitate tissue repair. An imbalance between the two may lead to chronic inflammation and ultimately result in tissue fibrosis [251, 252]. Therefore, promoting the transition of M1 macrophages to M2 macrophages has been proposed to improve the immune environment and facilitate cartilage regeneration. Many studies have utilized biological scaffolds, including hydrogels, to modulate macrophage-induced inflammation [231, 253, 254]. Jiang et al. developed a platelet-rich plasma-gelatin methacryloyl (PRP-GelMA) hydrogel and placed it in a rabbit cartilage defect model. At different time points, they reported an increase in M2 macrophage infiltration and a decrease in M1 macrophage infiltration. This M2 polarization was achieved through immune modulation, promoting cartilage repair (Figure 5 II) [231].

Hydrogels for functional metabolic regulator delivery

The articular cartilage resides in a microenvironment characterized by low oxygen and nutrient levels. Upon cartilage damage, the glycolytic pathway is upregulated in chondrocytes, leading to lactate accumulation and acidification of the local microenvironment. Concurrently, the overactivation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase within cells triggers excessive generation of reactive oxygen species (ROS), resulting in mitochondrial dysfunction and ultimately causing oxidative stress-induced cellular apoptosis [255–257]. Hence, strategies such as antioxidant therapy, mitochondrial function modulation, and enzyme regulation have emerged as therapeutic approaches for cartilage repair.

Antioxidant Therapy. ROS constitute one of the byproducts of metabolic disorders, inhibiting the synthesis of glycosaminoglycans and Col II fibres within cartilage while upregulating the expression of Col I, matrix metalloproteinases (MMPs), and proinflammatory cytokines [256]. To counteract the effects of ROS, Xu et al. integrated cartilage-targeting peptides and ROS-responsive nanoparticles into a hydrogel matrix, creating ROS-responsive cartilage-targeting hydrogel microspheres [232]. The ROS-responsive nanoparticles reacted with intracellular ROS, leading to nanoparticle disintegration. This not only eliminated excess ROS and alleviated inflammation but also promoted the *in situ* release of dexamethasone and KGN, resulting in effective cartilage repair (Figure 5 III). Additionally, antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione family proteins, as well as nonenzymatic antioxidant molecules such as vitamin E and curcumin, have been demonstrated to mitigate the impact of ROS on chondrocytes [190, 258].

Mitochondrial function regulation. In animal cells, NADPH and adenosine triphosphate (ATP) are predominantly generated through the functional mitochondrial tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). The maintenance of mitochondrial homeostasis is sustained by

three fundamental biological processes, namely, mitochondrial dynamics, mitophagy, and mitochondrial biogenesis, which are crucial for preserving mitochondrial stability [259]. Bringing mitochondria closer to these biological processes has the potential to restore the viability of chondrocytes. Building upon this concept, Xia et al. treated chondrocytes with the sirtuin 3 (SIRT3) activator dihydromyricetin and the SIRT3 inhibitor 3-(1H-1,2,3-triazol-4-yl) pyridine (3-TYP) separately. They discovered that SIRT3 exerts chondroprotective effects through the inhibition of mitochondrial apoptosis and the activation of mitochondrial autophagy. Subsequently, they injected hydrogel microspheres loaded with dihydromyricetin into an animal model of cartilage wear, further confirming that restoring the balance between endogenous mitochondrial apoptosis and autophagy promoted the recovery of motor function (Figure 5 IV) [233].

Enzyme function regulation. The transition between OXPHOS and glycolysis is regulated primarily by AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR) pathway. Under stress conditions, chondrocytes tend to shift from OXPHOS to glycolysis. Glucokinase, phosphofructokinase-1 (PFK1), and pyruvate kinase control the rate of glycolysis by mediating irreversible reactions. Targeting these switches in glycolysis can effectively regulate the metabolic activity of chondrocytes [190, 256]. Icaritin enhances the expression of glucose transporter 1 (GLUT1). Injecting icaritin-loaded hydrogels into the joint cavity promotes anaerobic glycolysis, thereby increasing chondrocyte viability [259, 260]. Conversely, knocking down the pyruvate kinase gene inhibits the expression of glucose transporter 1, leading to chondrocyte apoptosis [261].

Drawback of functional hydrogels. Functional hydrogels are engineered to dispense targeted bioactive agents, such as growth factors and anti-inflammatory substances, to promote cartilage regeneration. By modulating specific biological pathways, these hydrogels hold significant potential in enhancing therapeutic outcomes. However, their clinical translation is still under evaluation, with challenges such as patient-specific variations, including differences in local microenvironments and immune responses, affecting their efficacy. Furthermore, considerations of cost-effectiveness and production scalability remain important, as the precise control of release kinetics and the need for advanced manufacturing processes add complexity to their widespread application [262].

From the perspective of the cell-encapsulating hydrogels, chondrocytes need to be initially cultured from healthy non-weight-bearing regions, leading to a low cell yield and potential secondary harm to patients during the two-stage cultivation process. In elderly individuals, the therapeutic efficacy of autologous chondrocytes is compromised due to the low proliferative capacity of primary chondrocytes derived from elderly patients. Although stem cells have abundant sources and robust proliferative capabilities, precautions must be taken to prevent their terminal differentiation into hypertrophic cells [263]. Additionally, the repaired cartilage tissue exhibits issues such as endochondral ossification and vascular formation, resulting in the formation of fibrous cartilage with inferior mechanical properties and healing capabilities compared with transparent cartilage [202]. The problem of teratoma formation from iPSCs cannot be overlooked. To prevent the formation of teratomas after implantation, undifferentiated pluripotent cells should be removed from the

treatment site after iPSCs have differentiated into cartilage [197, 214].

In the context of the delivery of biological factors, research on factors other than HGF, IGF, and FGF-1 and FGF-2 within the FGF family is relatively scarce. This could be attributed to the diverse range of target cells for biological factors, making the strategy prone to unpredictable side effects.

Functional, intelligently responsive hydrogels for cartilage regeneration

Owing to the targeted delivery capabilities of functional hydrogels, functional, intelligently responsive hydrogels represent a further advancement in the field. These hydrogels, which respond to endogenous or exogenous stimuli such as changes in pH or temperature, enable spatiotemporal control of drug release, providing the flexibility to tailor the therapeutic response to the evolving needs of the defect site. This strategy is ideal for complex, dynamic clinical scenarios where precise control over the regenerative process is needed. Although injectable hydrogels are suitable for minimally invasive treatment, their rheological properties need to be precisely regulated to adapt to different defect morphologies [264, 265]. In addition, some hydrogels need to be used intraoperatively in combination with cells or growth factors, increasing the complexity of the operation [195, 266].

Repair mechanism of functional stimulus-responsive hydrogels. Various pathological changes, including cartilage degeneration, are primarily induced by abnormal levels of degrading enzymes, disruptions in intracellular redox reactions, and an increase in environmental acidity. Similarly, these abnormal changes can serve as specific stimuli to guide the release of therapeutic drugs and growth factors in a particular space. The release profile can be adjusted according to the needs of the target tissue, preventing inappropriate release rates from causing side effects. Stimulus-responsive hydrogels can alter their physical or chemical properties when exposed to these stimuli, promoting the release of loaded biofactors through processes such as expansion, contraction, or degradation. In the absence of stimuli, the hydrogel can protect encapsulated drugs from degradation and prevent off-target release of biological factors, minimizing harm to nontargeted tissues [267, 268].

Classification of functional stimulus-responsive hydrogels. On the basis of the source of stimuli, hydrogel materials for cartilage repair can be broadly categorized into two classes: endogenous stimulus-responsive materials and exogenous stimulus-responsive materials. Endogenous stimuli within an organism include enzymes, ROS, pH, etc., whereas exogenous stimuli are induced by external factors such as temperature, light, US, magnetic fields, and electricity.

Enzyme-responsive hydrogel scaffolds

Enzymes that are overexpressed in damaged cartilage tissue can serve as stimuli for growth factor delivery, with MMPs being the most utilized enzymes. MMPs can cleave specific amino acid sequences of certain proteins in the ECM. To create enzyme-responsive hydrogels for growth factor delivery, peptides with MMP cleavage sites are incorporated into the hydrogel matrix. Alternatively, growth factors can be connected to hydrogel matrices through enzymatically cleavable peptides, forming enzyme-responsive hydrogels for biofactor

delivery [69]. Moreover, compared with hydrogels degraded by a single type of enzyme, hydrogels susceptible to two or even multiple enzymes appear to have advantages (Figure 6I) [269].

Inflammation-responsive hydrogel scaffolds

As mentioned earlier, the inflammatory microenvironment is characterized by elevated levels of various proinflammatory factors, increased ROS levels, and decreased pH due to lactate accumulation, which collectively inhibit the repair of cartilage tissue. To modulate the inflammatory response, inflammation-responsive drug delivery systems can trigger the degradation and release of drugs in the inflammatory environment, with pH and ROS often utilized as triggering factors in the inflammatory environment [232, 272, 275].

In environments such as those associated with inflammation and infection, the pH curve within tissues differs from that within normal tissues. pH-responsive hydrogels are often employed in pathological tissues to respond to these variations in pH [276]. In the process of hydrogel fabrication, a reversible gel-sol transition occurs on the basis of the acidic or alkaline nature of the solution. A stable gel structure can form within a specific pH range during this gelation process. Strehin et al. developed a chondroitin sulphate-polyethylene glycol (CS-PEG) adhesive hydrogel. They controlled the stiffness, swelling properties, and gel dynamics of the hydrogel by altering the initial pH of the precursor solution (Figure 6II) [272]. In the process of hydrogel dissolution, achieving pH sensitivity involves the formation of pH-sensitive linkages between loaded drug molecules and the hydrogel, such as pH-sensitive hydrazone linkages. Alternatively, polymers containing acidic groups or basic moieties can be employed to construct pH-sensitive hydrogels [10]. Furthermore, ROS-responsive nanoparticles possess significant advantages in terms of ROS responsiveness and ROS consumption, making them widely used for controlled drug release. ROS-responsive nanoparticles are often loaded into hydrogels, increasing the structural stability of the nanoparticles. This integration with hydrogels can further improve the sustained release of nanoparticles, achieving prolonged therapeutic effects [232, 275].

Thermoresponsive hydrogel scaffolds

Temperature-sensitive hydrogels form a gel structure at a specific temperature and can be categorized as positive and negative temperature-sensitive systems. Temperature-sensitive hydrogels have an upper critical solution temperature (UCST), and the precursor solution gels upon cooling below the UCST. In contrast, negative temperature-sensitive hydrogels have a low critical solution temperature (LCST), and the precursor solution gels upon heating above the LCST [273]. Thermoresponsive hydrogels with phase transition temperatures close to physiological temperatures are the most commonly used injectable gels in the biomedical field. The temperature change generated by simple injection can induce a phase transition, resulting in *in situ* gelation to encapsulate drugs and therapeutic agents. Within tissues, these hydrogels can respond to subtle temperature changes, ensuring the timely and controlled release of drugs (Figure 6III) [273, 278, 279]. Thermosensitive hydrogels commonly utilize hydrophilic polyethylene glycol (PEG) as a base [76]. In particular, thermosensitive hydrogels composed of well-known poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO),

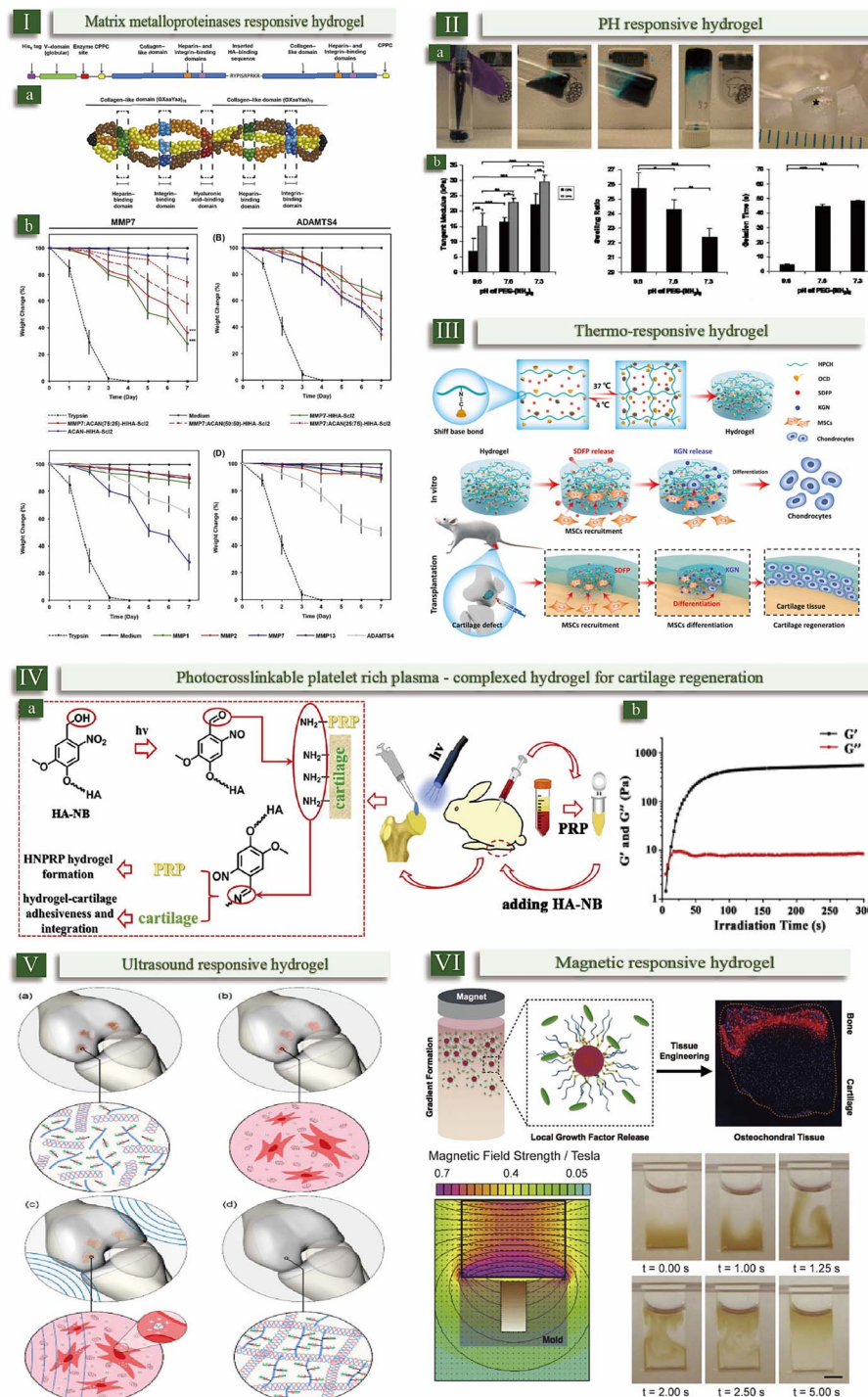


Figure 6. Functional, intelligently responsive hydrogels for cartilage regeneration. **(I)** a. Schematic diagrams of the peptide-functionalized streptococcal collagen-like 2 (ScI2) protein and hydrogel. The 2-arm acrylate-functionalized MMP7 and aggrecanases specifically cleave aggrecan (ACAN) degradable peptides were conjugated to the ScI2 protein via thiol-acrylate reactions to generate hydrogels. b. Degradation profile of acellular ScI2 hydrogels. Reproduced with permission [269]. Copyright © 2016 the authors. Published by Elsevier Ltd. **(II)** a. A CS-PEG tissue adhesive that forms a 3D hydrogel network. The gel also reacts with tissue, serving as an adhesive between the hydrogel and cartilage defect. b. Effects of solution pH on the mechanical, swelling and gelation properties of hydrogels [272]. Copyright © 2010 the authors. Published by Elsevier Ltd. **(III)** Schematic diagram of the thermosensitive hydroxypropyl chitin hydrogel applied to fill irregular cartilage defects. The gel is liquid at low temperatures but quickly becomes a gel under human physiological conditions. Reproduced with permission [273]. Copyright © 2022 Elsevier Ltd. **(IV)** a. Photoinduced imine crosslinking (PIC) hydrogel glue system. The hydrogel glue could conveniently form *in situ*, achieve the controlled release of growth factors, and improve cartilage adhesion. b. Storage modulus (G') and loss modulus (G'') of the HNPRP hydrogel. Reproduced with permission [93]. Copyright © 2017 acta Materialia Inc. **(V)** Ultrasound stimulation of piezoelectric nanocomposite hydrogels boosts chondrogenic differentiation *in vitro*. Reproduced with permission [26]. Copyright © American Chemical Society 2024. **(VI)** An external magnetic field is used to field-align glycosylated SPIONs in an hMSC-laden agarose hydrogel, which is thermally gelled and efficiently sequesters and releases growth factors. Applying a magnetic field from above resulted in a rapid redistribution of the two layers to generate a smooth nanoparticle gradient (<5 s). Reproduced with permission [274]. Copyright © 2020 by the author. ACAN aggrecanases specifically cleave aggrecan, CS-PEG chondroitin sulphate polyethylene glycol, hMSC human mesenchymal stem cell, MMP7 matrix metalloproteinase 7, PIC photoinduced imine crosslinking, ScI2 streptococcal collagen-like 2

Pluronic) triblock copolymers have been extensively studied [280, 281].

Photoresponsive hydrogel scaffolds

Photostimulation is an easily controllable exogenous stimulus that can be manipulated by regulating parameters such as intensity, frequency, polarization, and direction, providing high spatial and temporal precision [268]. One way to influence the swelling and shrinkage of hydrogels is to use photosensitive or photodegradable units in the hydrogel network, such as azobenzene, spiropyran, or *o*-nitrobenzyl (*o*-NB) ether groups. Under light exposure, photosensitive units can undergo cleavage, isomerization, or dimerization, which results in hydrogel degradation, swelling, contraction, and chemical modifications. Photoresponsive hydrogels undergo volume changes upon light irradiation such that they can swell or shrink due to water absorption or release and thus can release drugs in a controlled manner (Figure 6IV) [283].

Ultrasound-responsive hydrogel scaffolds

In recent years, US has garnered increasing attention because of its safety, strong tissue penetration capabilities, and cost-effectiveness [26, 267, 284–286]. Wu et al. constructed a novel ROS-responsive *in situ* nanocomposite hydrogel through enzymatic reactions involving fibrinogen and thrombin (Figure 6V) [26]. An ROS-responsive thioketal (TK)-based liposome was synthesized on the basis of this foundation. This liposome was designed to encapsulate the chondrogenesis-inducing factor KGN, the enzyme thrombin, and the US-sensitive agent protoporphyrin IX (PPIX). Under US stimulation, the TK-based liposome was destroyed, followed by *in situ* gelation of fibrinogen and thrombin. Moreover, the sustained release of KGN was realized by regulating the US conditions and effectively improved cartilage regeneration in a rat articular cartilage defect model. While US-responsive carriers have certain advantages in drug delivery, there is a need to balance the energy required for the carrier response and the stability of the carrier. It is essential to avoid excessive energy requirements that may adversely affect the carrier itself. In the treatment of bone cartilage defects, the major drawback of US lies in its significant attenuation when it passes through bone. However, it still holds tremendous potential in addressing the challenge of penetrating dense cartilage matrix [268].

Magnetic field-responsive hydrogel scaffolds

Magnetic components, such as iron oxide-based (Fe₃O₄) magnetic nanoparticles (MNPs) and cobalt ferrite nanoparticles, can be integrated into the polymer matrix to prepare hydrogels that can respond to a magnetic field [147]. Typically, drugs are loaded onto MNPs. After the injection of these nanodrugs, a constant magnetic field is applied externally to the target tissue, inducing the accumulation of the therapeutic agents in the diseased tissue [268]. Once MNPs bind with cells, they can induce both chondrogenic and osteogenic differentiation (Figure 6VI) [25, 274]. Additionally, the application of an external electromagnetic field can enhance the chondrogenic and osteogenic differentiation of MSCs [283, 284]. Unfortunately, current research on magnetic field-responsive drug carrier materials is predominantly concentrated in the field of oncology, with limited applications in the treatment of arthritis and cartilage defects.

Electroresponsive hydrogel scaffolds

Electroresponsive hydrogels are usually made of polymers with ionizable groups such as polyelectrolytes. Under an electrical field, polyelectrolyte-based hydrogels deshell and release drugs. Upon the release of the electric field, these hydrogels absorb aqueous solutions and swell; thus, they stop releasing drugs. The release rate and the amount of drug released can be controlled by applying an electrical field for a certain amount of time and at a certain intensity [283]. The intensity, direction, and duration of the electrical stimulus, the composition of the polymer, the solution pH, and the ionic strength all affect the electrosensitive behaviour of the hydrogel [147, 285].

Drawback of stimulus-responsive functional hydrogels.

Stimulus-responsive functional hydrogels have characteristics that can be used to modulate the release of bioactive agents in response to discrete stimuli such as changes in pH, temperature, or enzymatic activity. Although their long-term clinical application is currently being investigated, these hydrogels offer precise drug delivery modulation. Nevertheless, patient-specific issues such as microenvironmental and immune response differences can influence their effectiveness. The challenges of economic viability and production scalability remain significant, demanding precise engineering and potentially intricate manufacturing processes [147].

In the context of endogenous stimuli, inflammation often leads to increased expression of MMPs, alterations in pH, and disruption of the intracellular redox system. Consequently, in the context of systemic inflammation, the development of an inflammation-responsive drug delivery system for cartilage tissue may face challenges in ensuring the accurate release of therapeutic agents at target sites. This can result in misplacement or off-target damage, leading to unpredictable side effects. Furthermore, exogenous stimuli can be artificially controlled, but the efficacy of hydrogel-based drug delivery systems that respond to endogenous stimuli is prone to variations among individual physiological states. For hydrogels that rely on exogenous stimuli, the safe dosage of factors such as electric fields and light is difficult to estimate, which poses a risk of adverse effects on living organisms. For example, ultraviolet radiation can induce cell damage and carcinogenic effects, whereas infrared radiation may cause cellular thermal injury [286].

Comparative analysis of functional hydrogel strategies

When selecting the optimal hydrogel strategy for cartilage repair, it is essential to consider the specific clinical context, including the type and severity of the cartilage defect, as well as patient factors such as age and activity level, alongside the desired therapeutic outcomes. Adhesive hydrogels are especially effective for small to medium-sized defects, where strong adhesion to cartilage surfaces is critical. These hydrogels enhance stability and integration into surrounding tissues, offering a conducive microenvironment for cell adhesion and proliferation [287–290]. However, their utility is generally restricted to surface defects and might not be suitable for treating deeper lesions.

High-strength hydrogels are suited for larger, load-bearing defects, especially in weight-bearing joints. These hydrogels provide substantial mechanical support, allowing them to withstand mechanical stresses and ensuring the long-term stability necessary for cartilage regeneration [291–294].

Nevertheless, they may pose biocompatibility challenges compared with natural hydrogels and necessitate careful engineering to balance their mechanical properties with biodegradability.

Injectable hydrogels provide a minimally invasive application route, thereby reducing surgical trauma and expediting recovery. As they are tailorable to atypically shaped defects and able to deliver uniform coverage, these hydrogels are versatile and can be applied to defects of various sizes and in various locations [262, 295, 296]. Compared with noninjectable variants, they might exhibit reduced mechanical strength and need sophisticated release systems for the continuous delivery of bioactive factors.

The delivery of functional hydrogels facilitates the release of specific bioactive agents, including growth factors and anti-inflammatory compounds, to promote cartilage regeneration. By precisely addressing specific biological pathways, their targeted delivery improves therapeutic outcomes, making them valuable for both small and large defects [297]. They demand meticulous control over release kinetics to prevent incorrect dosing of bioactive agents, which can also affect biocompatibility if not well integrated with the hydrogel matrix.

Intelligently responsive functional hydrogels are capable of reacting to specific stimuli, such as changes in pH, temperature, or enzymatic activity, allowing them to control the release of bioactive agents precisely. This capability enhances drug delivery precision and efficacy, minimizes side effects, and improves therapeutic success, making them exceptionally suitable for complex clinical scenarios requiring targeted delivery [298, 299]. The complexity of their design and fabrication, however, may increase the costs and complexity of their clinical application.

By evaluating these strategies within specific clinical contexts, clinicians and researchers can make evidence-based decisions on selecting the most suitable hydrogel strategy for cartilage repair, thereby enhancing treatment outcomes and minimizing potential complications.

Main commercial products of functional hydrogels

Many injectable hydrogel products approved by the FDA and/or European Medicines Agency (EMA) show promise for use in articular cartilage regenerative medicine but require further optimization to improve clinical efficacy and usability [300, 301]. Some hydrogels have entered clinical trials (such as GelMA-based hydrogels or injectable adhesive hydrogels) [34, 302], but long-term follow-up data are limited, and more studies are needed to verify their safety and durability [8, 303].

VitroGel® (TheWell bioscience Inc.)

VitroGel®, a ready-to-use, pH-neutral, transparent, and breathable hydrogel, supports 3D and 2D patient-derived organ growth. It mimics natural collagen, promoting *in vitro* osteoblast differentiation and *in vivo* osteoclast activity, with broad applications in tissue engineering and regenerative medicine [304]. Studies have shown that VitroGel® hydrogels have the potential to mimic the ECM of cartilage [305]. VitroGel® also provides binding sites for cell adhesion through functionalization with the RGD motif, which promotes cell attachment and facilitates cell-matrix interactions by enhancing cellular functions such as cell proliferation, migration, and differentiation [306].

However, VitroGel® faces clinical challenges, including the need to optimize biocompatibility and mechanical properties for cartilage repair and reduce high costs to better meet clinical demands.

EUFLEXXA® (Ferring Pharmaceuticals Inc.)

EUFLEXXA® is an injectable HA solution for relieving knee pain in OA patients. It replenishes knee HA, improving lubrication and shock absorption. Production in a controlled environment with a precise process results in a purified, hydrogel-like HA fluid. It is recommended for patients with inadequate relief from basic pain medications or conventional therapies [307]. Altman et al. proved that knee OA pain was significantly relieved after 26 weeks of EUFLEXXA® treatment [308]. Webner et al. also concluded that EUFLEXXA® is no less effective than other commonly used HA products [309].

EUFLEXXA® also has limitations. Its treatment requires three weekly injections, inconveniencing patients with repeated medical visits. Common side effects include local pain and swelling, and less frequent systemic include headaches; rare but severe allergic reactions may also occur. Therapeutically, while some patients experience months of pain relief, many experience short-lived effects, potentially requiring repeated injections and incurring greater costs. Additionally, individual factors such as age and disease severity impact therapeutic efficacy, and patients with joint infections, deformities, or HA allergies cannot use HA, restricting its use [310]. When considering it as a treatment, these drawbacks must be weighed against the benefits.

Osteogenic protein-1 (OP-1®)

OP-1® initiates numerous processes at the cellular level, acting on MSCs, osteoblasts, and osteoclasts to stimulate bone growth [311]. As a hydrogel injection material, collagen, carboxymethylcellulose, and recombinant OP-1 can be used in spinal injections for the treatment of posterolateral lumbar fusion [300]. Catros et al. suggested a trend in favour of safe local delivery of OP-1 in higher concentrations of PEG hydrogels to induce faster bone maturation [312]. However, OP-1® has notable drawbacks. Its production is complex and costly, leading to a high price that limits its application in budget-constrained medical settings. *In vivo*, its stability demands further research, as it may degrade or inactivate after injection, affecting its long-term efficacy. Additionally, sufficient evidence of long-term safety and effects on adjacent tissues is lacking, necessitating more comprehensive studies for reliable clinical use [313, 314].

Hyalograft® (Anika therapeutics, Inc.)

Hyalograft® represents a minimally invasive tissue engineering method that involves implanting expanded autologous chondrocytes cultivated on a 3D scaffold composed of HA. This approach is valuable for the treatment of acute cartilage lesions [315, 316]. Hyaloglide® [317] is a transparent, highly viscous barrier gel used to prevent or reduce adhesions after various surgical procedures. However, the cultivation of autologous chondrocytes is time-consuming and usually takes weeks to months. This lengthens the treatment process and increases the risk of complications such as infection during the waiting period [318]. Additionally, the long-term stability of the implanted components is uncertain. Chondrocytes or

scaffolds may degrade over time, potentially requiring further treatment.

Gel-one® hyaluronate (Zimmer Biomet)

Gel-One® is an injectable hyaluronate gel approved for the treatment of OA of the knee [319]. Ishikawa et al. showed that Gel-200 is expected to be a single-injection hyaluronan product with fewer safety concerns for the treatment of knee OA pain [320]. However, Gel-One® hyaluronate has received increased attention as a single-use viscosity supplement because of its greater cost-effectiveness and greater patient convenience [321]. In addition, single-use viscosity supplements reduce the risk of knee injection-related problems such as injection pain, patient discomfort, injection-related inflammation and erythema.

Although it is claimed to have better cost-effectiveness, the overall cost for patients may still be relatively high considering multiple factors, such as potential follow-up treatments and insurance coverage limitations. Some patients might struggle to afford it over the long term. While it aims to reduce injection-related problems, a small percentage of patients may still experience adverse reactions such as severe local swelling or persistent pain after injection, which could impact their quality of life during the recovery period.

FDA-approved functional hydrogel products show promise for cartilage repair but face clinical challenges. Future research should optimize their formulation to improve their mechanical properties, degradation rates, and tissue integration, potentially by incorporating bioactive molecules or growth factors to ensure long-term stability and functionality.

Prospects

This paper provides an overview of articular cartilage injury treatments and emerging cartilaginous organoid and tissue engineering technologies, summarizing progress, applicability, and limitations. As tissue engineering has advanced, hydrogel scaffolds have evolved into more functional, intelligent cartilage repair options, driving the development of commercial cartilage repair products.

Hydrogels are popular scaffolds in tissue engineering, and various characteristics need to be considered in their design, including pore size, degradation time and products, biocompatibility, and mechanical properties. The choice of materials for hydrogels largely determines their physicochemical properties. Natural polymers offer good biocompatibility but weaker mechanical properties, whereas synthetic polymers provide superior mechanical performance but may have biocompatibility issues. Given the compositional, structural, and functional complexity of articular cartilage and osteochondral units, hierarchical hydrogels are better suited for the simultaneous reconstruction of damaged cartilage and osteochondral tissue. Currently, many hydrogels struggle to match the mechanical properties of articular cartilage, making them unable to withstand the mechanical loads borne by weight-bearing cartilage. This can lead to fracture and disintegration of the scaffold. Therefore, future directions involve the development of more resilient hydrogels capable of withstanding long-term compressive and shear forces before cartilage repair. This can be achieved by hybridizing natural and synthetic polymers or incorporating bioactive glasses and inorganic biomaterials, such as hydroxyapatite, to mineralize the hydrogel and increase its compressive modulus [322].

Owing to the unique articular cartilage environment, hydrogel scaffolds must have functional physical and chemical properties to create a suitable regenerative microenvironment. Hydrogels combining viscosity and high strength can enhance implant integration with surrounding tissues, ensure proper scaffold-defect edge alignment, and provide stable biological fixation and mechanical conduction [10]. For irregular defects, self-healing hydrogels can better cover the defect, allowing customization based on individual patients. However, most experimental studies are currently limited to small animal models, with few clinical studies and a lack of research on the mechanisms of scaffold repair for regenerating bone–cartilage defects. Future experiments need to further develop biological functional assessment systems for scaffolds to qualitatively and quantitatively understand their ability to induce bone and cartilage formation.

Tissue engineering involves incorporating exogenous or endogenous cells into biomimetic scaffolds, such as hydrogels. These scaffolds simulate the microenvironment for cell growth and facilitate cell–matrix and cell–cell interactions. Bioactive factors act as mediators for cell migration and adhesion to the scaffold, regulating inherent repair capabilities to promote tissue regeneration at the site of damage [198]. In the context of hypotheses related to cellular dysfunction and local microenvironmental disturbances, various cells, bioactive factors, and combinations of both have been incorporated into hydrogels. This approach aims to correct local inflammatory stress and metabolic disorders. The efficacy and *in vivo* behaviour of hydrogels are based on data from animal models. However, differences in the microenvironment between animals and humans can interfere with the accuracy of predicting therapeutic outcomes in clinical experiments. Furthermore, scaffold degradation also determines the release pattern of loaded substances. In the future, hydrogels with adjustable degradation rates could be designed. This could be achieved by modifying the physical properties of the scaffold (molecular weight, porosity, etc.), introducing hydrolysable functional groups through chemical hydrolysis, or incorporating enzymatically degradable properties to achieve controlled scaffold degradation. Additionally, structural scaffold alterations could be explored to enable spatially targeted release of bioactive factors [217].

Functional stimulus-responsive hydrogels achieve spatiotemporal control and targeted drug release under exogenous or endogenous stimuli. Both endogenous and exogenous stimuli have advantages and disadvantages. Endogenous stimuli are susceptible to the complex *in vivo* microenvironment, leading to misplacement of release or off-target damage. Exogenous stimuli such as UV light or electric fields can potentially harm organisms. Therefore, in the future, it is crucial to accurately determine the optimal dosage of external stimuli and develop safer stimulating factors. Issues related to immune responses, metabolic pathways, biological distribution, and appropriate rates of biodegradation need to be addressed in future research [10].

While hydrogel-based strategies for cartilage repair hold substantial promise, issues regarding their long-term clinical efficacy, as well as potential limitations such as cost-effectiveness and patient variability, warrant further exploration. Future research should focus on optimizing hydrogel formulations to improve mechanical integrity, biodegradation profiles, and native tissue integration. The incorporation of bioactive elements such as chondrogenic molecules or growth factors is essential for long-term stability

and functionality. Overcoming economic and scalability challenges is also crucial for wider clinical adoption of hydrogel-based therapies. Despite numerous challenges, the role of functional hydrogels in cartilage tissue engineering is significant. With further research into cellular mechanisms, molecular mechanisms, and microenvironments, functional hydrogels are expected to gradually address these issues in tissue engineering, alleviating the burden of joint diseases on individuals and society.

Conclusions

We highlight key advancements and challenges in hydrogel-based cartilage repair, emphasizing their evolution from structural supports to bioactive platforms. Hybrid hydrogels combining the biocompatibility of natural polymers with the mechanical strength of synthetic materials, augmented by mineralization, address the hierarchical complexity and mechanical demands of cartilage. Innovations such as self-healing and viscoelastic hydrogels have improved defect integration, yet the physiological load resistance and spatiotemporal control of bioactive release remain critical limitations. Future directions prioritize 4D smart hydrogels with stimulus-responsive degradation (e.g. enzymatic or phototriggered) and spatially patterned molecular delivery systems. Translational success hinges on resolving scaffold–host interactions through advanced biocompatibility assessments and metabolic integration studies. Future efforts should prioritize clinical translation through standardized preclinical models that mimic human joint biomechanics; cost-effective manufacturing for scalable hydrogel production; and long-term safety studies to address immune responses and degradation kinetics.

Abbreviation List

ACI, Autologous chondrocyte implantation; ACAN, Aggrecanases specifically cleave aggrecan; Agg, Aggrecan; AMPK, AMP-activated protein kinase; AT-MSCs, Adipose tissue-derived MSCs; ATP, Adenosine triphosphate; BM-MSCs, Bone marrow-derived MSCs; BMP, Bone morphogenetic protein; BMSCs, Bone marrow stem cells; BSICT, Binary solvent-induced conformation transition; CCS, Corticosteroids; CD44, Cluster of differentiation-44; CD-RAP, Cartilage-derived retinoic acid-sensitive protein; Col I, Type I collagen; Col II, Type II collagen; COL2A1, Collagen type II alpha 1 chain; COMP, Cartilage oligomeric matrix protein; CS-PEG, Chondroitin sulphate-polyethylene glycol; DN, Double network; DNA, Deoxyribonucleic acid; ECM, Extracellular matrix; EF, Edge flourish; ELPs, Elastin-like polypeptides; EMA, European Medicines Agency; EPO, Erythropoietin; ERK, Extracellular signal-regulated kinase; ESCs, Embryonic stem cells; FDA, Food and Drug Administration

FGF, Fibroblast growth factor; GAG, Glycosaminoglycan; GelMA, Gelatine methacryloyl; Gel/TA, Gelatine-tannic acid; GLUT1, Glucose transporter 1; GMA, Glycidyl-methacrylate; HA, Hyaluronic acid; HA-NB, Nitrobenzyl alcohol-modified hyaluronic acid; hBMSC, Human bone marrow-derived mesenchymal stem cells; hDPSCs, Human dental pulp stem cells; HGM, Host–guest macromer; hMSC, Human mesenchymal stem cells; IGF, Insulin-like growth factor; IL, Interleukin; iPSCs, Induced pluripotent stem cells; KGN, Kartogenin; LCST, Low critical solution temperature; MACI,

Matrix-assisted chondrocyte implantation; MAPK, Mitogen-activated protein kinase; MIP, Macrophage inflammatory protein; MMPs, Matrix metalloproteinases; MMP7, Matrix metalloproteinase 7; MNPs, Magnetic nanoparticles; MSCs, Mesenchymal stem cells; mTOR, Mammalian target of rapamycin; M1, Macrophage 1; NADPH, Nicotinamide adenine dinucleotide phosphate; NB, Nitrobenzyl alcohol; NF- κ B, Nuclear factor kappa-B; NHS, N-hydroxysuccinimide; NK, Natural killer; OA, Osteoarthritis; OAT, Osteochondral autograft transplantation; OCA, Osteochondral allograft; ODex, Oxidized dextran; o-NB, o-Nitrobenzyl; OXPHOS, Oxidative phosphorylation; PCL, Poly(vinyl alcohol); PDA, Polydopamine; PEG, Poly(ethylene glycol); PEO-PPO-PEO, Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide); PFK1, Phosphofructokinase-1; PIC, Photoinduced imine crosslinking; PLGA, Poly lactic-co-glycolic acid; PO_4^{3-} , Phosphate ions; PPIX, Protoporphyrin IX; PRP, Platelet-rich plasma; PRP-GelMA, Platelet-rich plasma-gelatin methacryloyl; PVA, Poly(vinyl alcohol); P5-RMSC, Passage-5 RSV-treated MSCs; RGD, Arginine-glycine-aspartate; ROS, Reactive oxygen species; RSV, Resveratrol; SASP, Senescence-associated secretory phenotype; SD, Sprague–Dawley; SDF, Stromal cell-derived factor; SIRT3, Sirtuin 3; SLPs, Silk-like polypeptides; SYSADOAs, Symptomatic slow-acting drugs for osteoarthritis; TCA, Tricarboxylic acid; TGF- β , Transforming growth factor- β ; TK, Thioketal; 3-TYP, 3-(1H-1,2,3-triazol-4-yl) pyridine; UCST, Upper critical solution temperature; US, Ultrasound; UV, Ultraviolet; VEGF, Vascular endothelial growth factor

Author contributions

Aikang Li (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal]), Jingtiao Huang (Methodology [equal], Resources [equal], Software [equal], Validation [equal], Visualization [equal]), Jiaqing Chen (Data curation [equal], Formal analysis [equal], Investigation [equal]), Liangbin Wu (Formal analysis [equal]), Hui Zeng (Funding acquisition [equal], Project administration [equal]), Zhenhan Deng (Conceptualization [equal], Formal analysis [equal], Project administration [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—review & editing [equal]), Peng Liu (Funding acquisition [equal], Writing—review & editing [equal]), Jianjing Lin (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Software [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—original draft [equal]). All authors read and approved the final manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Data availability

The data and materials used in this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as potential competing interests.

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