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Review

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Biomimetic-smart materials for osteochondral regeneration and repair

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Abstract

Osteochondral injuries represent prevalent clinical conditions with profound implications for functional impairment and diminished quality of life. Despite the considerable potential of tissue engineering in osteochondral repair, substantial strides in clinical implementation remain elusive. Biomimetic materials, designed to emulate natural cartilage, offer a stabilized structure and microenvironment capable of accommodating the diverse properties inherent in different cartilage regions. Smart materials, endowed with the ability to deliver drugs, metal ions, and growth factors contingent on the disease progression, exert precise control over the microenvironment and cellular epigenetic behaviors. This review scrutinizes the nuanced characteristics of cartilage in both physiological and pathological states. Subsequently, a succinct overview of recent applications of biomaterials with bionic and smart attributes in osteochondral regeneration and repair is provided. Finally, we propose our perspectives on the application of biomimetic-smart materials in osteochondral regeneration and repair, emphasizing their potential clinical translation.

Keywords: Osteochondral defect, tissue engineering, biomimetic-smart materials, regeneration and repair

INTRODUCTION

Articular cartilage, an essential constituent of the human musculoskeletal system, plays an indispensable role in enabling everyday movements and experiences ongoing growth and renewal under normal physiological conditions[1,2]. However, various factors, including metabolic, biochemical, and biomechanical abnormalities, can result in cartilage/osteochondral defects, causing joint pain and swelling, and ultimately progressing to osteoarthritis (OA), a condition that affects over 654 million people globally[3,4]. Despite its specialized nature, cartilage has limited self-regenerative capabilities. Consequently, its regeneration and repair, particularly in cases of osteochondral defects, pose significant challenges in the field of regenerative medicine[5].

Diverse therapeutic approaches, ranging from conservative drug treatment to surgical interventions, are utilized for osteochondral defects. While pharmacological treatments, such as corticosteroids, chondroitin, and hyaluronic acid (HA), may offer short-term symptom relief, they fail to achieve complete cartilage repair due to insufficient long-lasting sustained release[6-8]. The limitations of drug treatments also stem from variable drug bioavailability and exposure time within the joint, both influenced by the lymphatic system's clearance effect, resulting in a low concentration[9]. Surgical regeneration treatments, including autologous chondrocytes and stem cell implantation[10,11], micro-fracture[12], and osteochondral autograft transplantation (OATS)[13,14], represent primary approaches for repairing osteochondral defects. OATS is commonly considered the optimal approach for treating such defects. However, these treatments present drawbacks such as the risk of secondary damage, limited donor availability, post-operative infections, and immune rejection[15,16]. These drawbacks significantly affect the quality of life, necessitating urgent attention and innovative solutions.

In recent years, biomimetic-smart materials, a novel category comprising biomimetic scaffold materials, smart materials, or hybrids of both, have been rapidly developed. Biomimetic materials, functioning as scaffolds, replicate the composition and structure of native tissues, creating a microenvironment similar to that found in the body and satisfying the diverse needs of various cells for tissue regeneration and repair. Smart materials, on the other hand, act as drug delivery systems and are engineered to regulate drug release in response to external (e.g., light, piezoelectric, and magnetic) or internal (e.g., pH and enzyme) stimuli, addressing challenges associated with targeted, sustained release and long-term drug efficacy within the body. These biomaterials find broad applications in wound healing[17], skin regeneration[18,19], cardiovascular repair[20], and bone remodeling[21-23]. Some have already been implemented in clinical settings, demonstrating promising therapeutic effects[24]. However, significant scientific advancements in osteochondral repair using biomimetic-smart materials are yet to be achieved.

Recent endeavors have developed various biomimetic materials featuring distinct structures, such as biphasic, triphasic, or multiphasic gradient scaffolds and those integrating smart drug delivery systems. However, the therapeutic effectiveness in animal cartilage defects remains unsatisfactory[25-27]. The complexities of osteochondral regeneration and repair involve multifaceted physicochemical and biological processes. The inflammatory microenvironment significantly influences changes in the epigenetic behaviors of critical cells, leading to abnormal cell proliferation and differentiation, thereby affecting tissue repair processes[28-30]. Therefore, a potential bottleneck in managing osteochondral repair may still reside in precisely designing material structures and compositions that mimic the natural cartilage microenvironment while also regulating cellular behaviors to stimulate and activate endogenous cartilage regeneration and repair.

Our review thoroughly overviews recent advancements in biomimetic and smart materials for osteochondral regeneration and repair. Initially, we delve into the structure and components of osteochondral tissues in both healthy and pathological states, providing a succinct introduction to key pathological processes. Subsequently, we explore the application of biomimetic-smart materials in osteochondral regeneration through the lenses of biomimetic scaffold materials and smart materials. The effects of biomimetic scaffold materials (monophasic, biphasic, triphasic, and gradient scaffold materials) on osteochondral repair have been introduced in detail, analyzing their influence on cell behavior and tissue repair based on the structure and composition. As for smart drug delivery materials, the methods for achieving drug-specific release under temporal and spatial control through various exogenous (light, mechanical force, ultrasound, piezoelectric, and magnetic), endogenous (pH, reactive oxygen species (ROS), and enzymatic), and composite stimuli (endogenous combined with exogenous) have been discussed [Figure 1]. Ultimately, we propose that the development of biomimetic-smart materials should be grounded in activating endogenously regenerative capability and regulating the regenerative microenvironment. This strategic approach seeks to facilitate *in-situ* regeneration, structural remodeling, and functional reconstruction of injured cartilage. Furthermore, we advocate for innovative strategies utilizing the modern advanced technology to analyze and elucidate the dynamic evolution and regulatory network of relevant cell attributes during the multiple dimensions of osteochondral regeneration and repair.

THE PHYSIOLOGICAL AND PATHOLOGICAL FEATURES OF ARTICULAR CARTILAGE

Chronic, low-grade inflammation in articular cartilage defects plays a pivotal role in the progression of osteochondral defects. These defects manifest as discernible alterations in the tissue structure and microenvironment, accompanied by abnormal regulation of immune processes, including cartilage loss[31,32], subchondral bone remodeling[33], and microenvironment deterioration in cartilage[34,35]. An enhanced understanding of physiological and pathophysiological aspects before and after the onset of osteochondral defects, particularly the compensatory repair mechanisms activated during the injury process, holds paramount significance in advancing the development of biomimetic and smart materials for cartilage regeneration and repair. Unlike bone tissue, articular cartilage lacks vascular and nervous supply[36] and is organized into layers: the superficial (resists shear and tensile stress), transitional (initial stress defense), deep (withstands compression), and calcified (promotes structural integration) layers. Subchondral bone, rich in Type I collagen and hydroxyapatite (HYP), supports cartilage, absorbs shock, and facilitates smooth joint movement, maintaining joint integrity[37] [Figure 2].

Subchondral bone remodeling is a vital self-repair process following cartilage damage, involving intricate cellular and molecular interactions such as inflammation, stem cell recruitment, cartilage matrix synthesis, angiogenesis, and bone adaptation [Figure 2B]. Cartilage damage triggers inflammation, attracting immune cells to clear debris and guide repair[38]. Chemokines and growth factors regulate mesenchymal stem cell (MSC) migration and proliferation for repair[39]. Matrix synthesis and angiogenesis support tissue formation, though elevated oxygen levels may disrupt chondrocyte functions[40]. Adjacent bone growth compensates for cartilage loss, while tissue remodeling and maturation occur over time. Factors such as inflammation intensity and microenvironment affect this process, with Wnt signaling playing a key role. Increased Wnt16 protects against tissue damage, while decreased sFRP3 leads to excessive Wnt activation, causing tissue degradation and bone remodeling[41].

Articular cartilage resides within a complex microenvironment, housing diverse cell types, including chondrocytes, synovial cells, MSCs, and immune cells. These cellular constituents communicate through paracrine, autocrine, and endocrine pathways, secreting many metabolic and inflammatory factors that collectively contribute to maintaining articular cartilage homeostasis[42]. Alterations in this communication,

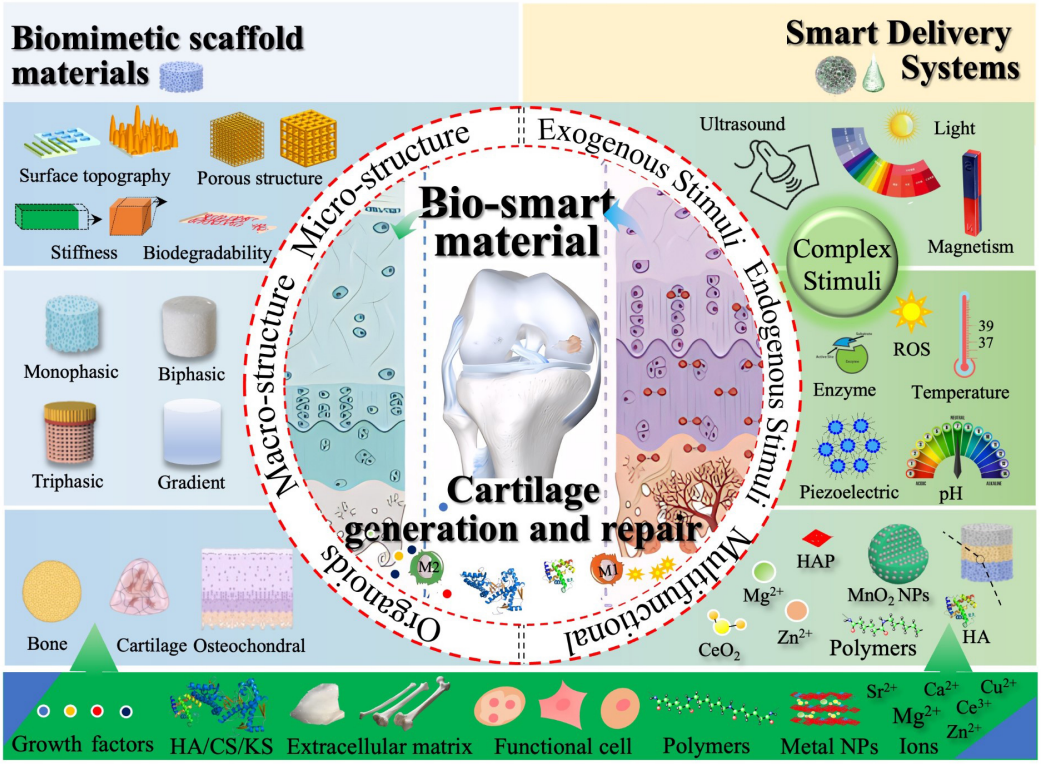

Figure 1. Schematic illustration of biomimetic-smart materials for osteochondral regeneration and repair.

driven by factors such as inflammation, biomechanical injuries, and oxidative stress, impair chondrocyte viability and trigger matrix-degrading enzyme release, leading to cartilage extracellular matrix (ECM) degradation. Such degradation products are released into the synovial fluid as damage-associated molecular patterns (DAMPs) to initiate an inflammatory response of nearby synovial cells such as synovial fibroblasts, macrophages, and mast cells. These cells participate in OA by releasing pro-inflammatory cytokines (e.g., interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α)), growth factors (e.g., transforming growth factor beta (TGF-β)), chemotactic factors, and lipid factors. This cascade further activates matrix metalloproteinases (MMP) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), ultimately leading to local tissue damage and cartilage degradation [Figure 2C][43].

Cartilage degradation is pervasive in cartilage defects, often associated with inflammatory responses that alter the tissue microenvironment. The tissue microenvironment can be reshaped by both intrinsic and extrinsic factors[44,45]. Previous studies have suggested that compensatory repair mechanisms drive macrophages toward M1 polarization during the inflammatory response, secreting inflammatory factors to clear cartilage debris. However, if cartilage damage persists, excessive inflammation can worsen the local tissue environment, causing chondrocyte hypertrophy, matrix degradation, and surface irregularities[35,46-48]. During this period, some macrophages also polarize toward M2 to inhibit cartilage matrix degradation. Nonetheless, a previous study has indicated that activated macrophages produce acidic substances, reducing the pH of the damaged tissue[49]. Various factors contribute to generating an acidic microenvironment in cartilage injuries beyond macrophage activation. Vascular formation, increased oxygen levels, and osteoclast activation also lower pH levels and result in uncontrolled nitric oxide release[49-52]. Additionally, elevated intracellular ROS levels disrupt cartilage homeostasis, causing damage and potentially initiating OA[53,54]. ROS not only induces oxidative damage but also interferes with redox-regulated cell signaling pathways

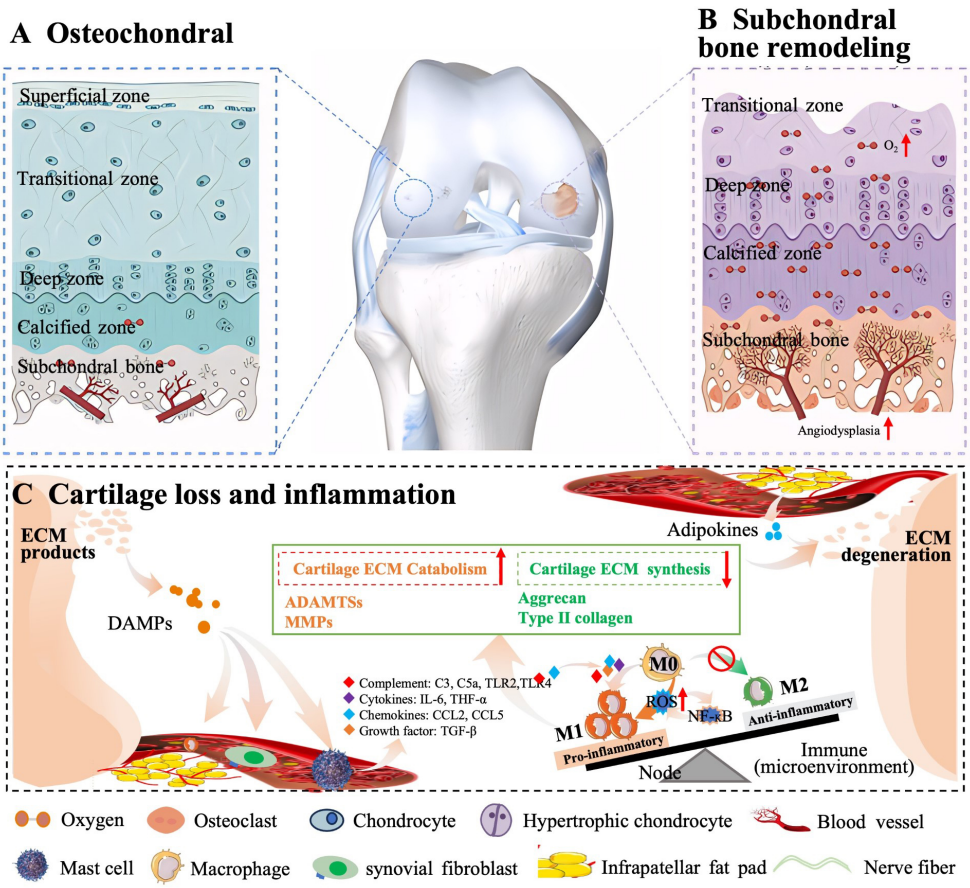

Figure 2. Physiological and pathological characteristics of articular cartilage. (A) Schematic representation of tissue composition along the osteochondral interface[40]. (Open access). (B) Changes of the osteochondral structure in cartilage defects[40]. (Open access). (C) Cartilage loss and inflammatory network during the formation of an osteochondral defect[43]. (Open access).

such as Akt and MAP kinase[55]. This oxidative stress prompts marrow MSCs to differentiate into hypertrophic chondrocytes, affecting cartilage regeneration and repair processes[56,57].

BIOMIMETIC-SMART MATERIALS FOR OSTEOCHONDRAL REPAIR

Given the distinctive structure of bone and cartilage and the post-injury pathological features, great efforts have been made to develop biomimetic-smart materials with diverse structures and functions, including biomimetic scaffold and smart materials. The variations in both the structure and function of these materials lead to differing efficacy and quality in tissue repair. This section will discuss the design considerations of biomimetic and smart materials.

Biomimetic scaffold materials

Cartilage, a specialized tissue predominantly constituted by chondrocytes and the cartilaginous ECM, incorporates components such as collagen, cytokines, and glycosaminoglycans [HA, chondroitin sulfate (CS), and keratan sulfate (KS)][58]. These constituents collectively form the tissue in a three-dimensional (3D) construct, thereby establishing an optimal microenvironment for cellular activities. The 3D architecture of cartilage not only imparts mechanical robustness but also fosters an environment conducive to cell signaling and nutrient exchange. This intricate network of chondrocytes is interwoven within the ECM and is pivotal in preserving the structural integrity and functionality of cartilage. In cartilage tissue

engineering, the key lies in constructing biomimetic scaffold materials by optimizing the scaffold composition and structure and mirroring the natural tissue to regulate cell behaviors and facilitate tissue repair.

The ECM serves as the nurturing environment for chondrocytes, providing essential biochemical components and biophysical cues for cell growth and tissue regeneration. It exhibits tissue specificity, with variations in the structure and composition, resulting in distinct characteristics (e.g., stiffness, dynamic force, and surface topology)[59]. These properties collaboratively interact with the cell membrane, initiating intracellular signal cascades and ultimately translating into cellular responses, including cell adhesion, migration, proliferation and differentiation[60,61]. Concurrently, cells can determine their fate by interacting with the surrounding environment, particularly with the ECM. Conversely, cells can influence the scaffold, reshaping its structure during tissue regeneration and repair[62,63].

To strengthen the interactions between ECM and cellular responses, various scaffolds that mimic native cartilage tissues are progressively developed by optimizing the composition, fabrication processes, and micro-to-macro structures, such as monophasic, biphasic, triphasic, and gradient scaffolds[64-68]. Initially, monophasic scaffolds, comprising a single material or phase, were developed for osteochondral repair. However, they failed to replicate the natural environment of native osteochondral tissues and, consequently, proved ineffective in repairing the interface between the cartilage and subchondral bone. The main issue lies in the poor integration of regenerated cartilage with the subchondral bone[69,70]. To tackle this challenge, multiphasic scaffold materials have been designed to mimic the natural osteochondral tissue structure and microenvironment, including biphasic, triphasic, and gradient scaffold materials, which offer suitable physical, chemical, and mechanical properties to regulate the differentiation and proliferation of various cell types (e.g., MSCs, chondrocytes, and osteoblasts).

A biphasic scaffold composed of two or more ingredients, including materials (e.g., ECM and polymer), growth factors (e.g., TGF-β and bone morphogenetic protein-2 (BMP-2)), and cells (e.g., chondrocytes, MSCs, and osteocytes), fabricated through methods such as 3D bioprinting, freeze-drying, and cross-linking, has been developed for osteochondral regeneration and repair. For example, Xu *et al.* utilized 3D printing to fabricate composite biphasic scaffolds consisting of strontium copper tetrasilicate/β-tricalcium phosphate (Wesselsite [$SrCuSi_4O_{10}$] /$Ca_3(PO_4)_2$, WES-TCP) with varying WES content (1%, 2%, and 4% by weight) for treating rabbit osteochondral defects [Figure 3A][71]. The outcomes revealed that 2WES-TCP (WES-TCP with 2 wt% WES) not only exhibited excellent mechanical properties but also enhanced proliferation and differentiation of bone MSCs and chondrocytes. Meantime, WES-TCP scaffolds significantly promote the cartilage and bone regeneration in rabbits compared to pure TCP scaffolds. This improvement may be related to the sustained and controlled release of bioactive ions (Si, Cu, and Sr). Deng *et al.* showed that Si and Sr are essential components to activate the hypoxia-inducible factor (HIF) signal pathway, stimulating chondrocyte maturation, promoting cartilage repair, and protecting chondrocytes from OA by inhibiting the hedgehog pathway[72]. Moreover, Cu ions can also activate the HIF pathway and promote the macrophage transformation into M2 phenotype, which plays an important role in promoting the differentiation of chondrocytes.

For osteochondral tissue, biphasic scaffolds with a gradient structure, facilitating a seamless transition from the cartilage to the subchondral bone, might not sufficiently accommodate the variations in extracellular matrix components, collagen types and orientations, and cytokines. Triphasic and gradient scaffolds, characterized by gradient physical and chemical properties, would be better suited to meet the diverse properties of different regions of cartilage. Cao *et al.* fabricated a novel gradient scaffold of three distinct

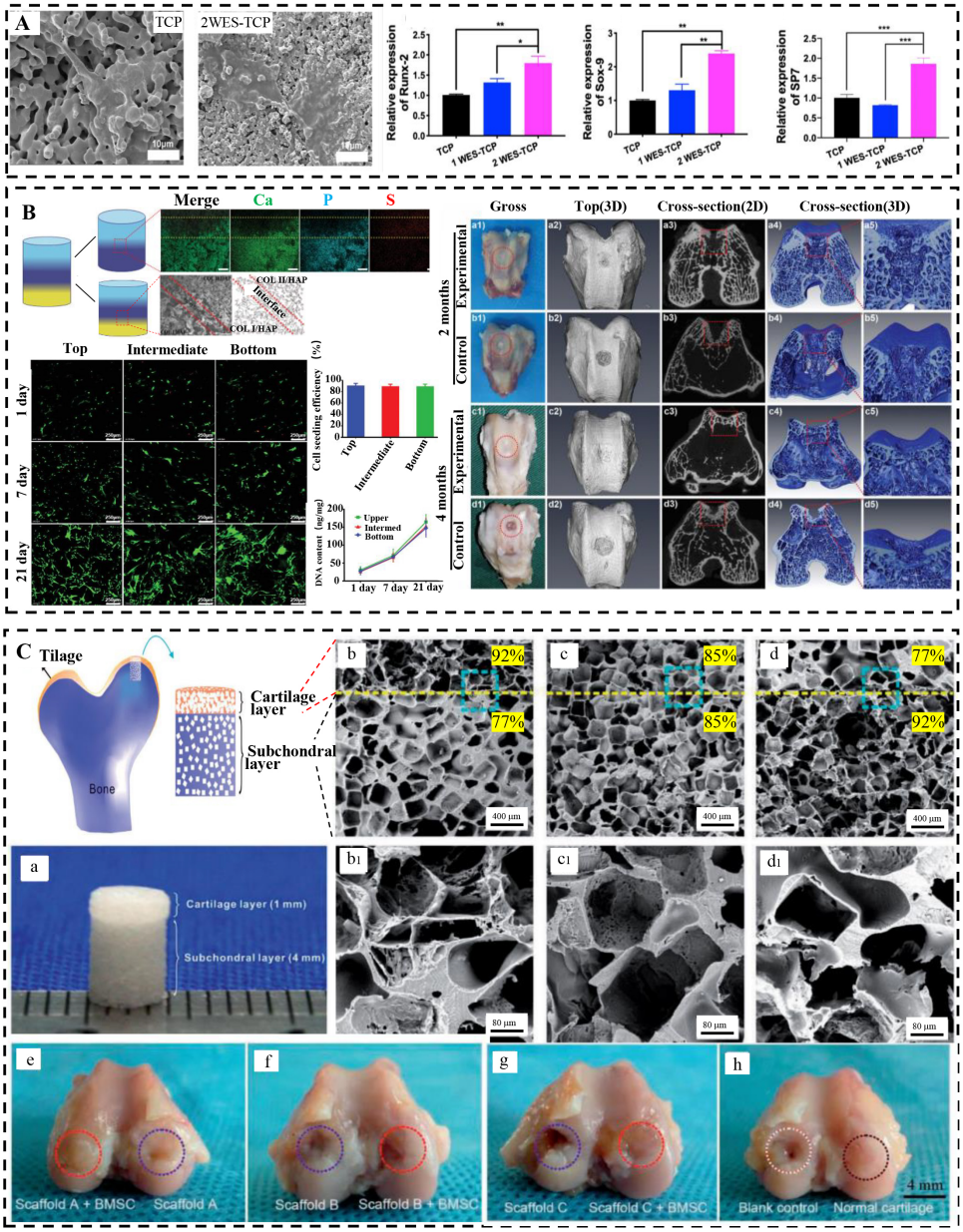

Figure 3. The effects of the physicochemical properties of multiple scaffolds on cell behavior and osteochondral regeneration and repair. (A) TCP/WES-TCP scaffolds enhanced rBMSCs proliferation and differentiation[71] (Open access). (B) The regeneration of cartilage, calcified cartilage, and bone simultaneously using gradient scaffolds. (Reproduced with permission[73].Copyright 2022, *Advanced Healthcare Materials*). (C) Different combinations of void structures showed varying effects on osteochondral repair[82].(Open access).

layers for osteochondral tissue repair [Figure 3B][73]. This multiphasic scaffold comprised three components: Type II atelocollagen and CS formed the interface zone; the intermediate layer was type II atelocollagen with 70% hydroxyapatite (HAP); the bottom layer was type I atelocollagen with 80% HAP. Rabbit bone marrow stem cells (rBMSCs) were seeded onto the three monolayer scaffolds, achieving ≈ 90% cell seeding efficiency on the first day. Continued cultivation for seven and 21 days demonstrated a sustained increase in cell numbers on the scaffolds. The results indicated good cell adhesion, maintenance of cell viability, and proliferative properties of the scaffold materials. Furthermore, *in vivo* animal experiments suggested that the tri-layered scaffold supported simultaneous regeneration of different regions, including cartilage, calcified

cartilage, and bone. Although the gradient scaffold exhibits cartilage and bone repair to some extent, studies on developing gradient scaffolds that imitate osteochondral heterogeneities in structure, biological, and mechanical properties are still limited.

More recently, studies have shown that successful tissue repair and regeneration strategies should focus on leveraging the finer microscopic features of scaffolds to regulate cell behaviors and construct an environment conducive to promoting regeneration. The features include morphology (e.g., pore size, porosity, and shape)[74,75], material stiffness/modulus[76,77], and bioactive ions (e.g., strontium or copper)[78-81]. For instance, Pan *et al.* created poly(lactide-co-glycolide) bilayered scaffolds with varied or the same porosity and evaluated their efficacy for osteochondral defect repair in rabbits. After 12 weeks, the group with 92% porosity in the cartilage layer and 77% porosity in the bone layer yielded the best repair [Figure 3C][82]. The high porosity and large pore size of the scaffold could potentially be advantageous for vascular infiltration, nutrient diffusion, and cell migration[83]. Notably, the modulus of the scaffold also influences the effectiveness of tissue repair and regeneration by altering cell adhesion, migration, proliferation and differentiation. Melica *et al.* used collagen I-coated hydrogels with varying stiffness to influence cell mechanics. The result showed that renal progenitor cells on low-stiffness substrates (0.2-2 kPa) formed clusters with cord-like structures, while on higher-stiffness substrates (4-50 kPa), they grew individually with sheet-like membrane protrusions resembling lamellipodia[84]. The influence of the material modulus on cell behaviors may be related to the integrin expression level[85]. Murphy *et al.* found that stem cells tend to express a high level of SRY-Box transcription factor 9 (SOX 9) and a low level of runt-related transcription factor 2 (RUNX2) when the matrix material has low stiffness, promoting a higher likelihood of differentiation into cartilage. Conversely, as the material stiffness increases, stem cells express more RUNX2 but less SOX9, leading to a propensity for osteogenic differentiation[86].

In addition to material stiffness, recent studies have also emphasized the modification of biomaterials to impart excellent biological properties to promote osteochondral regeneration and repair[87,88]. For example, Malinauskas *et al.* utilized electrospinning to fabricate double-layered poly(ε-caprolactone) (PCL) scaffolds, enhanced hydrophilicity through ozone treatment, and successfully loaded transforming growth factor-β3 (TGF-β3), forming a functional scaffold network. After seeding rabbit muscle-derived stem cells (rMDSCs) onto the scaffold, ozone-treated scaffold materials exhibited a higher concentration of type II collagen. *In vivo* animal experiments also demonstrated the ability of ozone-treated scaffold materials to promote cartilage repair [Figure 4A][89]. Moreover, inspired by mussel chemistry, Zhou *et al.* developed a hydrogel using catechol-modified chitosan (CS-C) treated with horseradish peroxidase/hydrogen peroxide (HRP/H_2O_2)[90]. *In vitro* cell experiments demonstrated that the CS-C hydrogel effectively maintained the morphology of bone marrow stem cells (BMSCs). After four days of continued culture, there was no significant difference in cell numbers on the CS-C material compared to the control group. We further explored the potential of stem cells to differentiate into chondrocytes within the hydrogel. The results revealed a significant increase in the expression of Sox9, Col2a1, and ACAN at days 7 and 21 compared to day 1. Furthermore, BMSCs loaded into the CS-C hydrogel with a chondrogenic medium exhibited superior chondrogenic differentiation compared to the control group. Importantly, encapsulating BMSCs in the CS-C hydrogel outperformed both untreated and CS-C alone, promoting hyaline cartilage reconstruction [Figure 4B][90]. The current satisfactory *in vivo* cartilage regeneration has been mainly achieved due to the microscopic properties of the scaffold, such as hydrophilicity[91] and strong adhesive force[92], which endows the materials with multiple properties and regulates the microenvironment. This regulation facilitates cell-cell and cell-matrix communications, thereby improving tissue regeneration.

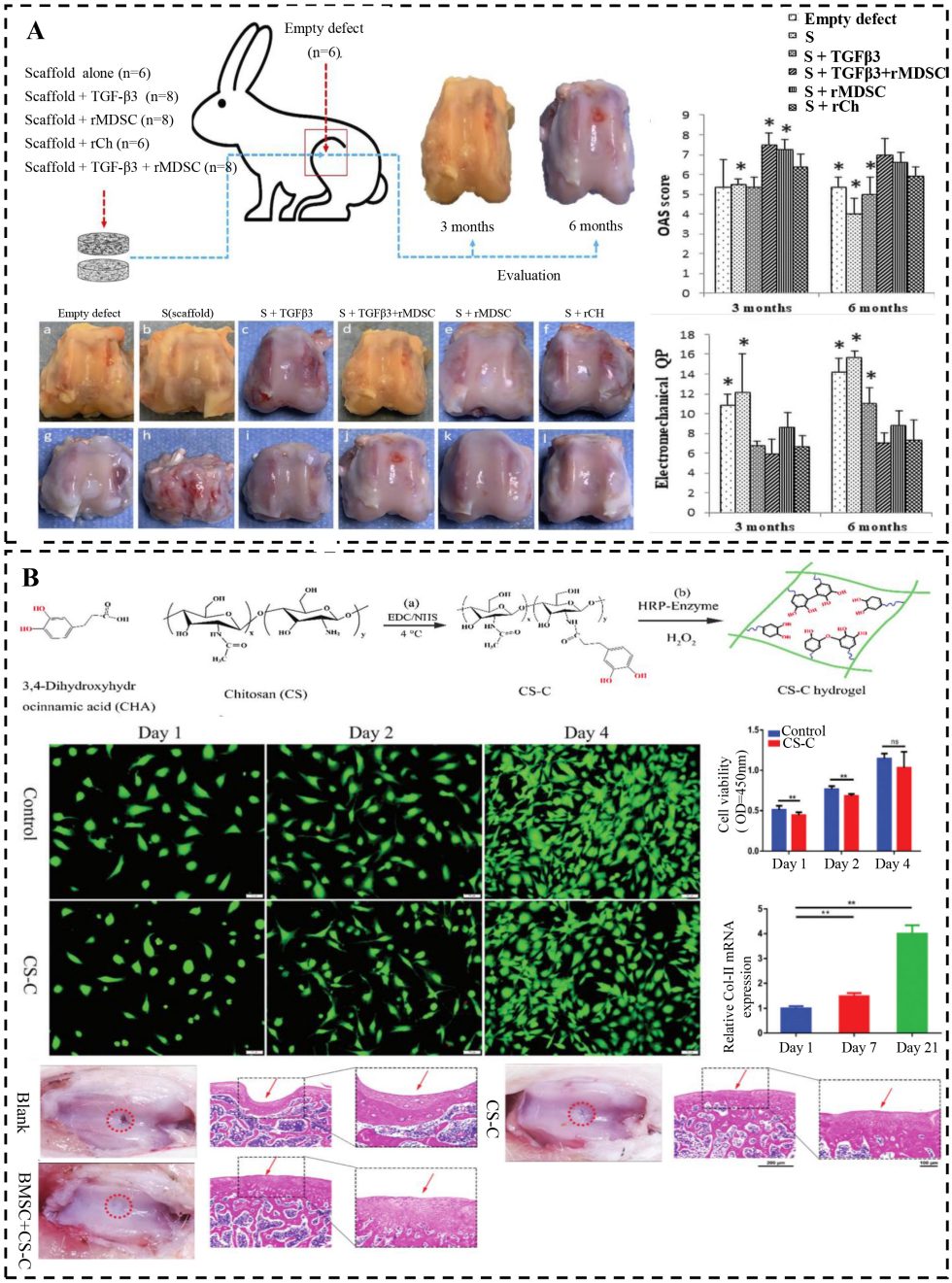

Figure 4. The modification of biomaterials for osteochondral repair. (A) Modify electroscope PCL scaffolds loaded with TGF-3 and stem cells for cartilage regeneration[89].(Open access). (B) A catechol-modified chitosan (CSC) hydrogel is modified by horseradish peroxidase/hydrogen peroxide (HRP/H_2O_2) for osteochondral repair. (Reproduced with permission[90].Copyright 2022, *Journal of Materials Chemistry B*).*$P < 0.05$, **$P < 0.01$, ***$P < 0.0001$.

Recently, a new concept based on the organoid technology has radically changed the idea of osteochondral repair. Research has shown that organoids can induce differentiation from a single cell type through time-dependent sequential activation of growth and differentiation factors (e.g., TGF-β3, BMP-2/4, TGF-β1, fibroblast growth factor (FGF)-2, and growth differentiation factor (GDF)-5) [Figure 5A][93-95]. For example, Crispim *et al.* developed a new suspension expansion protocol and encapsulated chondrocytes into alginate hydrogels to prepare cartilage organoids[96]. This approach promoted cell proliferation and facilitated the self-assembly of organoids with significantly higher levels of collagen II, VI, and glycosaminoglycans

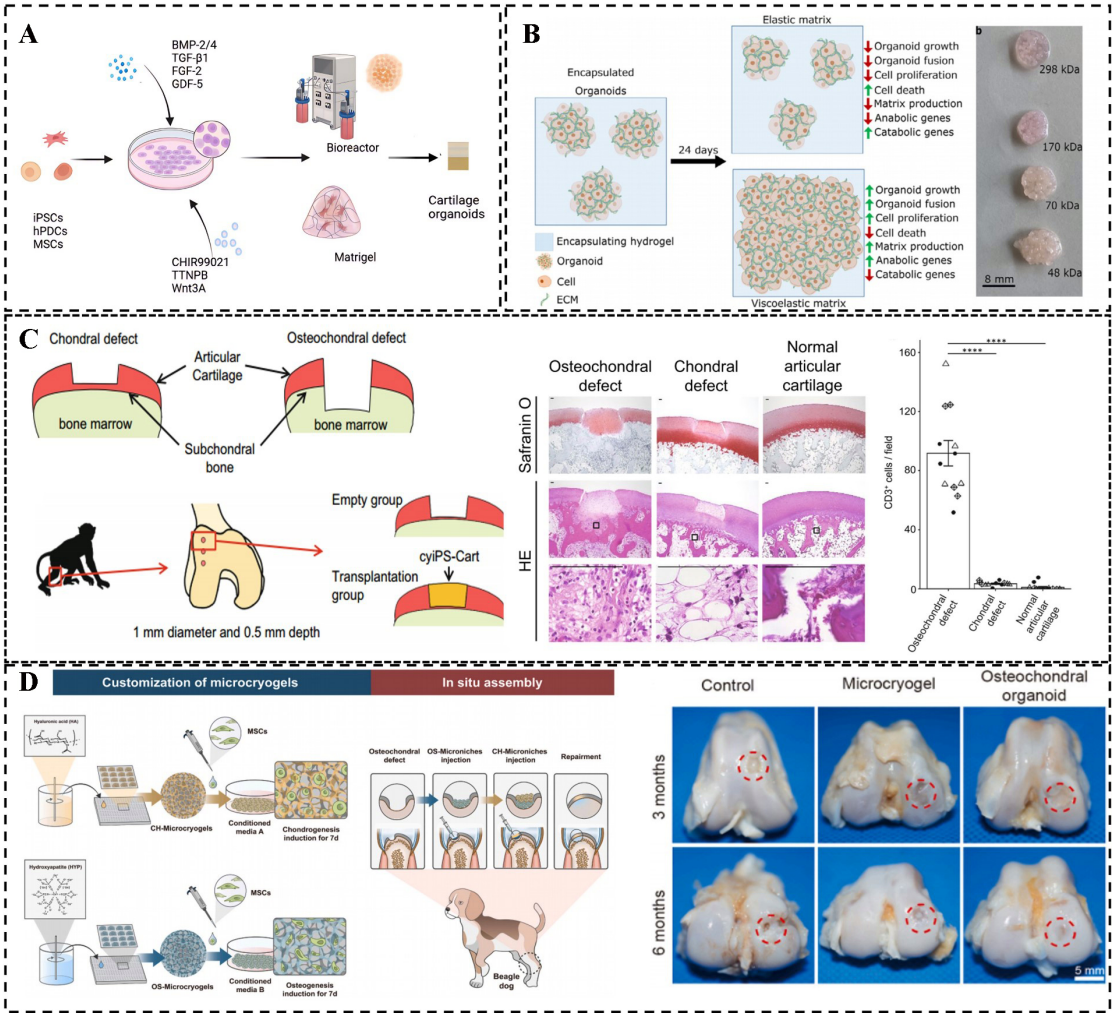

Figure 5. Cartilage organoids and regeneration repair. (A) Preparation process of cartilage organoids and cartilage repair[95]. (Open access). (B) Illustrating the effect of viscoelasticity on organoid growth and fusion, along with the gross morphology of various alginate hydrogel formulations containing organoids after 24 days of culture (Scale bar: 8 mm)[96]. (Open access). (C) The evaluation of cyiPS-Cart transplantation on cartilage and osteochondral defects[97]. (Open access). (D) The generation and repair of canine osteochondral defects with biphasic self-assembling osteochondral organoids[98]. (Open access). *$P < 0.05$, **$P < 0.01$, ***$P < 0.0001$.

[Figure 5B]. Similarly, Abe *et al.* implanted allogeneic induced pluripotent stem cells (iPSC)-derived cartilage organoids into primate cartilage defects; the result showed that cartilage organoids survived *in vivo* without eliciting an immune reaction and were integrated with host native cartilage [Figure 5C][97]. Subsequent studies have indicated that organoids with biphasic structures are more conducive to tissue regeneration and repair. Yang *et al.* developed biphasic gelatin-based microcryogels containing HA and HYP to promote cartilage, bone regeneration and repair (denoted as CH-Microcryogels and OS-Microcryogels)[98]. These materials exhibited excellent cellular compatibility in canine cartilage defects, inducing chondrogenesis and osteogenic differentiation of MSCs, and potential for generating self-assembling osteochondral organoids, providing a highly promising avenue for osteochondral repair [Figure 5D][98]. Despite variations in the methods for preparing cartilage organoids, the efficacy of cartilage repair still falls short of clinical demands. In the future, exploring how to fully utilize the inherent advantages of materials, develop processes for obtaining stable cellular states, and combine both aspects to prepare osteochondral organoids will remain crucial research directions.

Smart materials

Osteochondral regeneration and repair generally involve a complex interplay of cellular and molecular actions within the microenvironment, including MSC differentiation, ECM production, inflammatory response, biomechanical stimulation, and genetic and signaling pathways[99]. In this context, smart materials as drug delivery systems play a crucial role in microenvironmental regulation during osteochondral regeneration[100]. These materials, as vehicles or scaffolds, offer the controlled release and targeted delivery of therapeutic agents, ultimately promoting repair and regeneration of the damaged tissue. This section summarizes the recently developed delivery/stimuli-responsive systems designed to enhance osteochondral regeneration.

Stimuli-responsive systems

Stimuli-responsive drug delivery systems are designed for enhanced drug retention, controlled release, and target delivery of therapeutics, thereby improving efficacy while minimizing potential side effects[101]. The stimuli selection depends on the specific requirements of the therapy, characteristics of the drug, and the nature of osteochondral injury or disease. In the context of cartilage injury, abnormal changes occur in the tissue microenvironment due to the inflammatory response, including elevated temperature in the joint cavity, increased levels of ROS, and decreased pH. These alterations can inhibit the regeneration and repair of cartilage[50,102].

(1) Exogenous stimulation

To tackle and normalize the abnormal tissue microenvironment, various drug delivery systems that respond to exogenous stimulation have been extensively investigated. Recently, Liu *et al.* developed a nanomedicine delivery system with multiple responsive characteristics (KGN-PCM@mPBs) [Figure 6A], which includes temperature-sensitive phase-change materials (PCM) loaded with kartogenin (KGN) and mesoporous Prussian blue nanoparticles (mPB) responsive to near-infrared (NIR) light[103]. The results suggested that the nanocomposite effectively promoted chondrogenic differentiation, inhibited hypertrophic differentiation of MSCs, and achieved satisfactory cartilage repair in a rat model through intra-articular injection of KGN-PCM@mPBs with NIR-triggered controlled KGN release. Similarly, stimuli-responsive hydrogel has also been used for osteochondral repair. Lin *et al.* developed an injectable thermoresponsive chitosan graft copolymer (chitosan-graft-poly(N-isopropylacrylamide) (CS-g-PNIPAAm or CSPN)) hydrogel, incorporating infrapatellar fat pad-derived MSCs (IFPSC) and platelet-rich plasma (PRP) to assess its potential in cartilage formation, osteogenesis, and regeneration [Figure 6B][104]. The results demonstrated that CSPN05-PRP hydrogel significantly upregulated chondrogenic and osteogenic gene expression in IFPSCs, substantially increasing sulfated glycosaminoglycan content, alkaline phosphatase activity and mineralization. Initial *in vivo* investigations indicated that rIFPSC-CSPN05-PRP effectively promoted bone-cartilage defect regeneration within four weeks.

(2) Endogenous stimulation

Unlike materials that release drugs in response to exogenous stimuli, smart drug delivery materials with endogenous responses (e.g., temperature, pH, enzyme, and ROS) can fully leverage the unique microenvironment following cartilage injury to exert therapeutic effects. For instance, Ji *et al.* developed a "building block" drug delivery system using natural stimuli such as inflammatory response and increased joint cavity temperature [Figure 7A][105]. The system, comprising porous chitosan microspheres and hydroxypropyl chitin thermosensitive hydrogel, created a 3D network supporting water absorption and retention. By encapsulating dimethylallyl glycine in hydrogel and attaching KGN to porous microspheres,

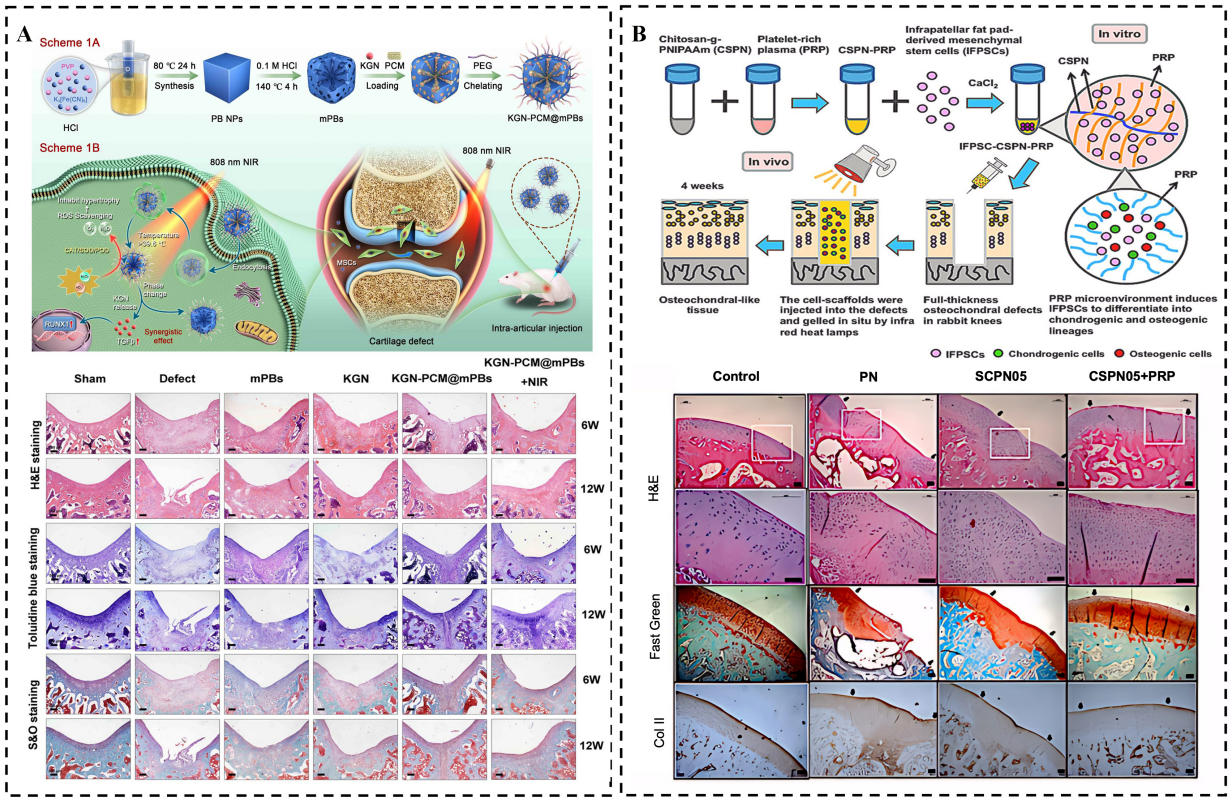

Figure 6. Exogenous stimuli-responsive systems of smart material. (A) A KGN-PCM@mPB system based on a NIR stimulus-response. (Reproduced with permission[103]. Copyright 2023, *Nanoscale*). (B) A SCPN-PRP system based on a thermosensitive stimulus-response activated by infrared heat lamps. (Reproduced with permission[104]. Copyright 2022, *Elsevier*).

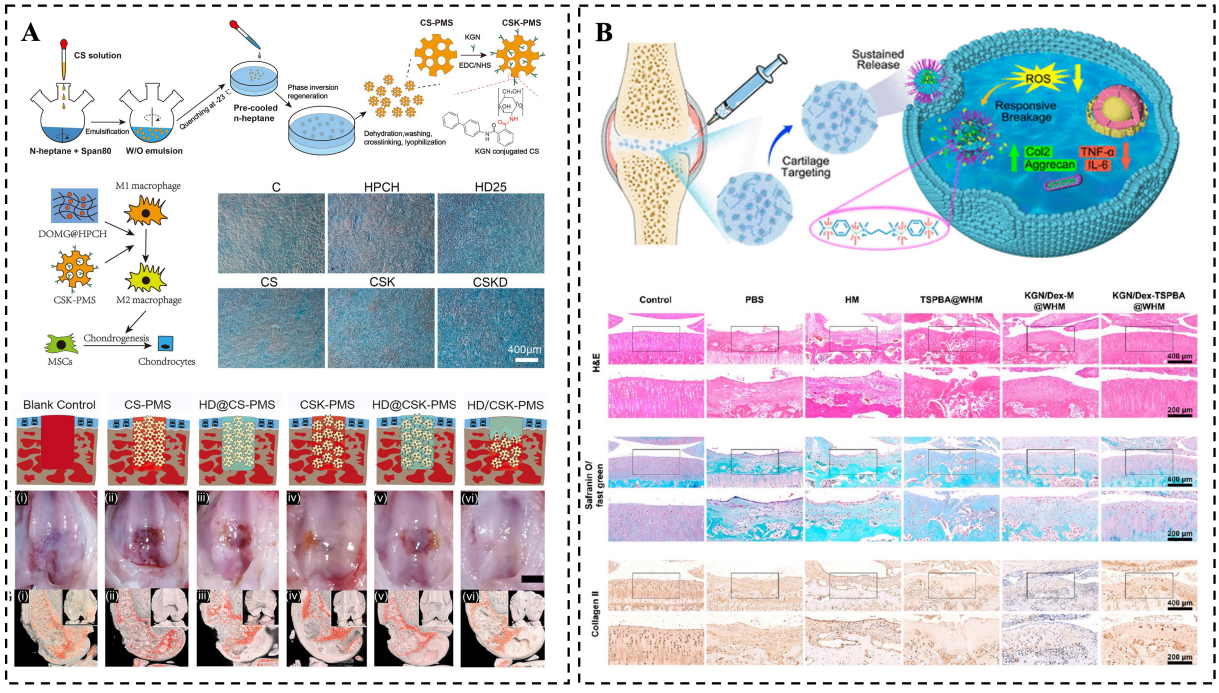

Figure 7. Endogenous responses stimulus systems of smart material. (A) A HD-SCK-PMS system based on a thermal stimulus-response (Reproduced with permission[105]. Copyright 2022, *Elsevier*). (B) A KGN/Dex-TSPBA@WHM system based on a ROS stimulus-response. (Reproduced with permission[106]. Copyright 2022, *American Chemical Society*).

the composite scaffold successfully modulated the local microenvironment, polarizing macrophages toward the M2 phenotype and promoting cartilage regeneration. Similarly, Yu *et al.* developed a functional nanoparticle with ROS responsiveness through microfluidic and photopolymerization technology [Figure 7B][106]. These materials not only eliminated excess ROS and reduced inflammation, but also promoted *in situ* release of dexamethasone and KGN, demonstrating favorable ROS responsiveness, enhanced chondrogenic differentiation, and down-regulation of pro-inflammatory factors.

(3) Exo-endogenous stimulation

Recently, a novel smart material based on applied mechanical force or combined exogenous stimuli has been employed for osteochondral regeneration and repair. For instance, Liu *et al.* developed a piezoelectric nanofiber using biodegradable poly(L-lactic acid) to generate controlled piezoelectric charges through mechanical stress[107]. This nanofiber enhanced extracellular protein absorption and triggered endogenous TGF- release via the calcium signaling pathway, stimulating chondrocyte proliferation and promoting cartilage formation and regeneration. Based on the theory that piezoelectric stimulation can influence chondrocyte behaviors and facilitate cartilage regeneration, Vinikoor *et al.* utilized the principle of electric generation through ultrasound stimulation to develop a biodegradable, injectable hydrogel with piezoelectric properties [Figure 8A][108]. Activated by ultrasound, this hydrogel produced local electrical signals, stimulating cell migration and inducing stem cells to release TGF-. The *in vivo* studies that involved rabbits with severe osteochondral injuries treated with piezoelectric hydrogel and ultrasound demonstrated enhanced subchondral bone formation, improved hyaline-cartilage structure and mechanical qualities comparable to healthy natural cartilage.

Interestingly, materials responsive to external ultrasound and internal enzymes and ROS have also been developed. Wu *et al.* constructed a novel ROS-responsive *in-situ* nanocomposite hydrogel based on fibronectin and thrombin-catalyzed enzymatic reactions[109]. This hydrogel was loaded with BMSCs, KGN, ROS-responsive thiolated ketone (TK) liposomes, bio-enzyme thrombin, and ultrasound-sensitive PpIX [Figure 8B][109]. Under ultrasound, enzyme and ROS stimulation, the sustained release of KGN significantly promoted the chondrogenic differentiation of BMSCs through the Smad5/mTOR signaling pathway, effectively improving cartilage regeneration in a rat model of articular cartilage defects. Although combining exogenous with endogenous stimuli has certain advantages, the combination introduces greater complexity in the material structure. Current stimulus-responsive materials still require further in-depth investigation in terms of sensitivity and outcomes in cartilage treatment.

Multifunctional systems

Multifunctional systems, comprising organic and inorganic phases containing ions such as magnesium (Mg) and zinc (Zn), have emerged as promising candidates for ion delivery in osteochondral regeneration[110,111]. Metal-organic frameworks (MOFs), which consist of metal ions/clusters and organic ligands, can scavenge ROS across a broad spectrum by combining specific metal cations/clusters with organic ligands. They show superior performance to natural enzymes, including exceptional stability, compatibility with biological systems, natural degradation under physiological conditions, and gradual release of bioactive substances in response to oxidative stress and inflammation. For example, Shu *et al.* developed bioceramic scaffolds functionalized with a Zn-Co bimetallic organic framework (Zn/Co-MOF) for repairing osteochondral defects by OA[112]. The research indicates that the Zn/Co-MOF scaffold, by sequentially releasing Zn^{2+} and Co^{2+} ions, alleviates excessive ROS production under acute inflammatory conditions, promotes MSC differentiation into both bone and cartilage cells, and further enhances the regeneration of cartilage and subchondral bone [Figure 9A][112]. Similarly, previous studies have shown the

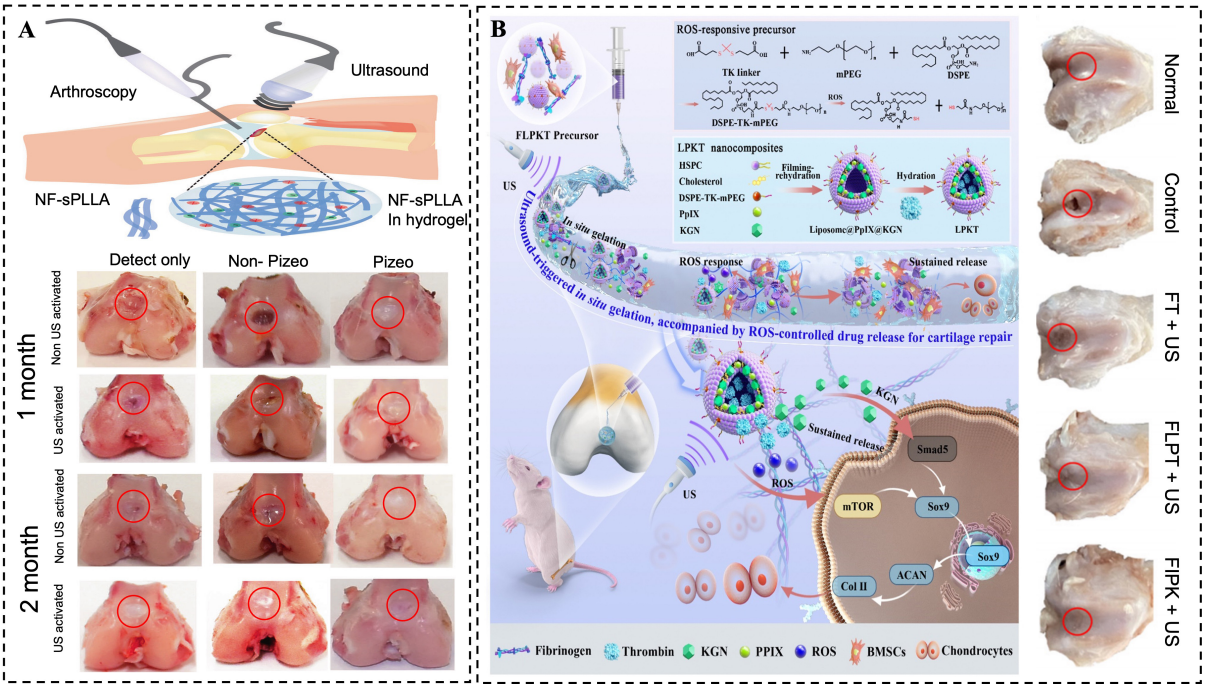

Figure 8. Multifunctional-stimulus responsive systems. (A) A NF-sPLLA hydrogels system based on a piezoelectric and ultrasound stimulus-response[108]. (Open access). (B) A LPKT hydrogels system based on an ultrasound, enzyme and ROS stimulus-response. (Reproduced with permission[109]. Copyright 2023, *Materials Horizons*).

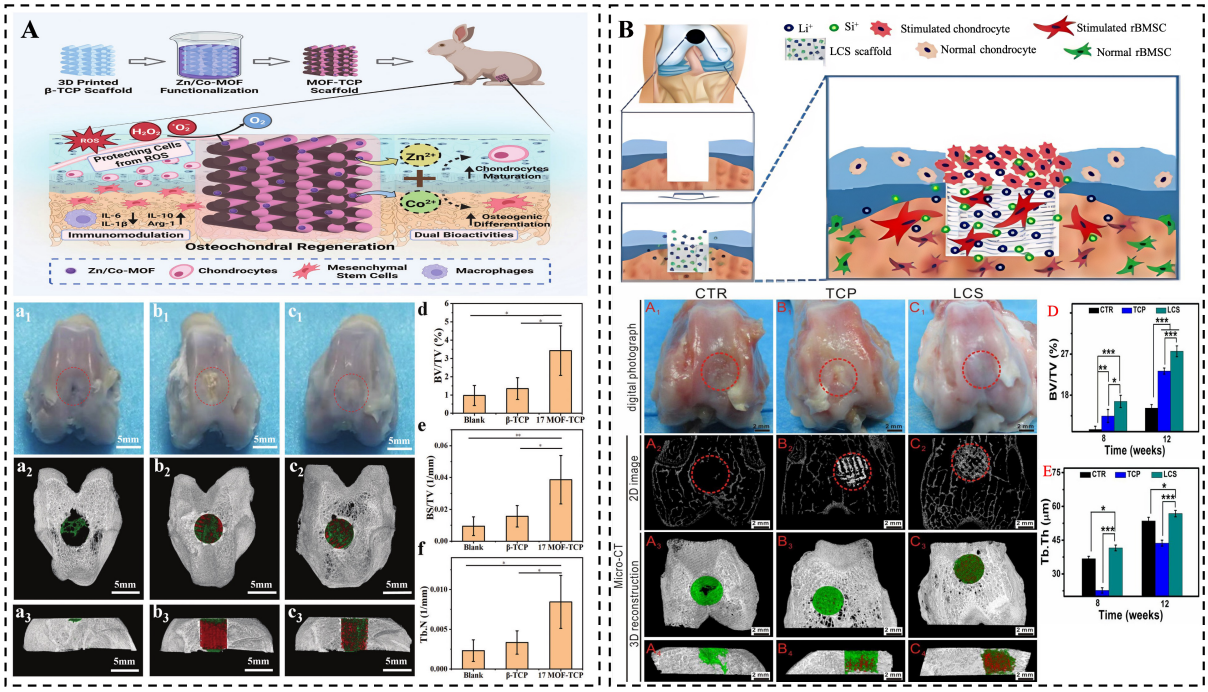

Figure 9. Hydrogel delivery system with multiple components. (A) A 3D-printed MOF-TCP scaffold with Zn^{2+} and Co^{2+} for osteochondral defects[112]. (Open access). (B) Scaffolds enriched with Li and Si ions -synergistic effects for osteochondral regeneration. (Reproduced with permission[115]. Copyright 2018, *Applied Materials Today*). $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.0001$.

positive effects of zinc and cobalt ions on promoting bone and cartilage development[113], with the latter

stimulating tissue regeneration through stimulating vascularization[114]. Scaffolds containing cations offer a promising strategy to regulate the behavior of targeted stem cells during tissue regeneration and facilitate the sequential release of diverse biomolecules. Deng *et al.* engineered a bio-inspired lamellar chitosan scaffold (LCS) enriched with lithium (Li) and silicon (Si). This system synergistically enhanced the growth and specialization of rabbit MSCs (rBMSCs), thereby promoting chondrocyte development and facilitating cartilage regeneration [Figure 9B][115]. The underlying mechanism involves the coordinated action of Li and Si, which induces chondrocyte maturation by activating the HIF pathway. Furthermore, these elements protect chondrocytes from the adverse osteoarthritic environment by inhibiting the hedgehog pathway and inducing autophagy.

Inspired by the beneficial effects of scaffold materials containing metal ions in cartilage repair, metal nanozymes have developed rapidly in recent years. Researchers have demonstrated that these nanozymes possess diverse enzymatic activities, such as that mimicking oxidoreductases including catalase (CAT)[116], superoxide dismutase (SOD)[117], and peroxidase (POD)[118]. Some metal nanozymes have already been investigated for cartilage and bone repair and regeneration. For instance, Kumar *et al.* developed a polyethylene glycol (PEG)-MnO_2 nanoparticle demonstrating excellent CAT-like activity, capable of decomposing H_2O_2 and generating oxygen *In vitro*[119]. Further animal studies revealed that the PEG-MnO_2 nanozymes effectively stayed in the joint space and scavenged ROS. Remarkably, these nanozymes protected cartilage explants from cytokine attack by decreasing glycosaminoglycan loss and nitric oxide release [Figure 10A]. Similarly, Cao *et al.* formulated a versatile silk-based hydrogel enriched with nitrogen and MOF nanozymes (CuTA@SF) that possessed multiple advantageous properties, such as anti-inflammatory, antioxidant, and antibacterial activities[120]. The CuTA@SF hydrogel demonstrated superior efficacy in promoting cell proliferation and extracellular matrix synthesis in inflammatory conditions and exhibited success in site osteochondral regeneration in rabbits [Figure 10B]. These effects may be attributed to the multiple properties of copper ions, including CAT-[121] and SOD-like activity[121,122].

Based on the multiphase composite structure of osteochondral tissue and the differential chemical composition and biological lineage in its various layers, an ideal osteochondral repair scaffold material should possess multiple biomimetic properties. It should also exhibit specific control over cell proliferation and differentiation in different regions, thereby promoting the regeneration and repair of osteochondral tissue. Liu *et al.* developed a biomimetic biphasic osteochondral scaffold with layer-specific stem cell differentiation inducers [Figure 11A][123]. This scaffold consisted of two layers, including the cartilage layer of HA hydrogel, to mimic cartilage composition. Controlled release of KGN was achieved by reinforcing CS with host-guest supramolecular units. The bone-regeneration layer, a 3D-printed HAP scaffold, released alendronate (ALN). Semi-immersed binding of the layers regulated stem cell differentiation, promoting hierarchical control for targeted differentiation into osteoblasts and chondrocytes. Simultaneously, Zheng *et al.* devised a hydrogel synthesized through the chemical reaction of gelatin, silk fibroin, and oxidized dextran, while the subchondral layer was fashioned using a nanofibrous scaffold with a porous structure. This scaffold was created by blending poly(l-lactic acid), poly(lactic-co-glycolic acid), and PCL polymers using the dual phase separation method. Subsequently, a polydopamine coating was applied to the subchondral layer to immobilize osteogenic factors [Figure 11B][124]. To facilitate the differentiation of MSCs into both chondrocytes and osteoblasts on the bilayer scaffold, the cartilage-inducing drug KGN and osteogenic-inducing factor bone morphogenetic protein-2-derived peptides (P24 peptides) were loaded into the layers, respectively. The release of KGN and P24 peptide from their respective layers was monitored, with both substances being continuously released for a minimum of 28 days. *In vitro* results indicated that the cartilage layer loaded with KGN and the subchondral layer loaded with P24 peptide effectively promoted cell growth and stimulated chondrogenic and osteogenic differentiation, respectively[124].

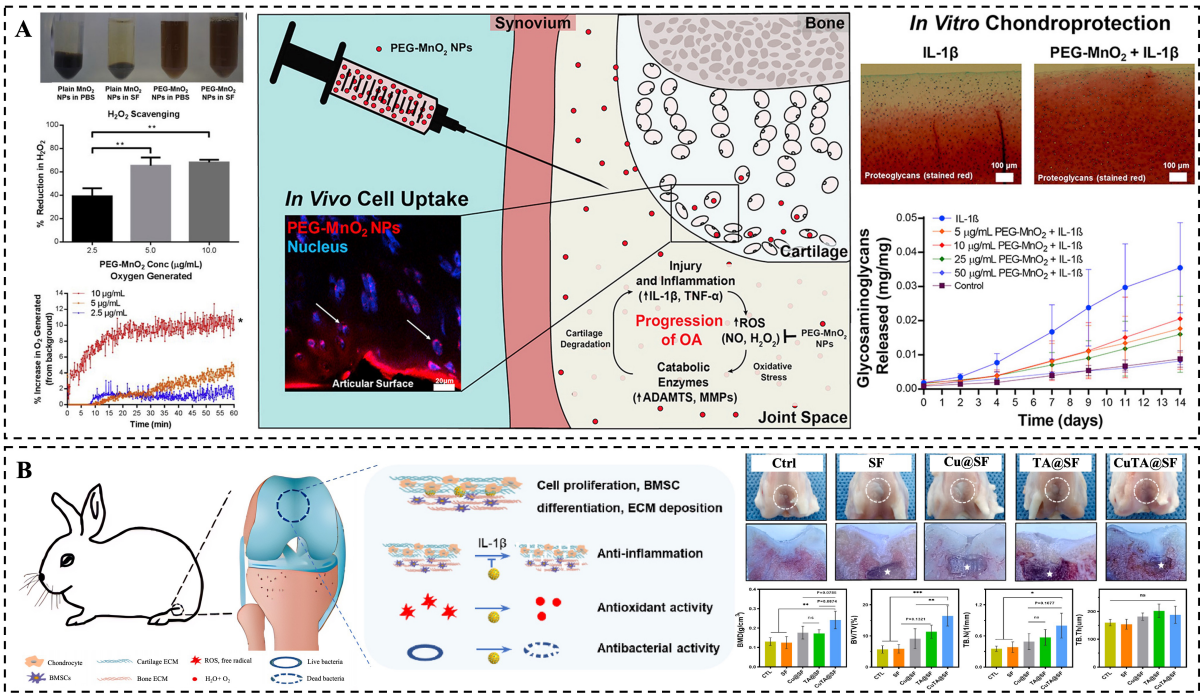

Figure 10. Metal nanozyme-mediated osteochondral regeneration and repair (A) MnO_2 nanoparticles protect cartilage during inflammation-induced oxidative stress. (Reproduced with permission[119]. Copyright 2019, *Biomaterials*). (B) A CuTA@SF hydrogel with Cu^{2+} and silk fibroin for osteochondral regeneration[120]. (Open access). $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.0001$.

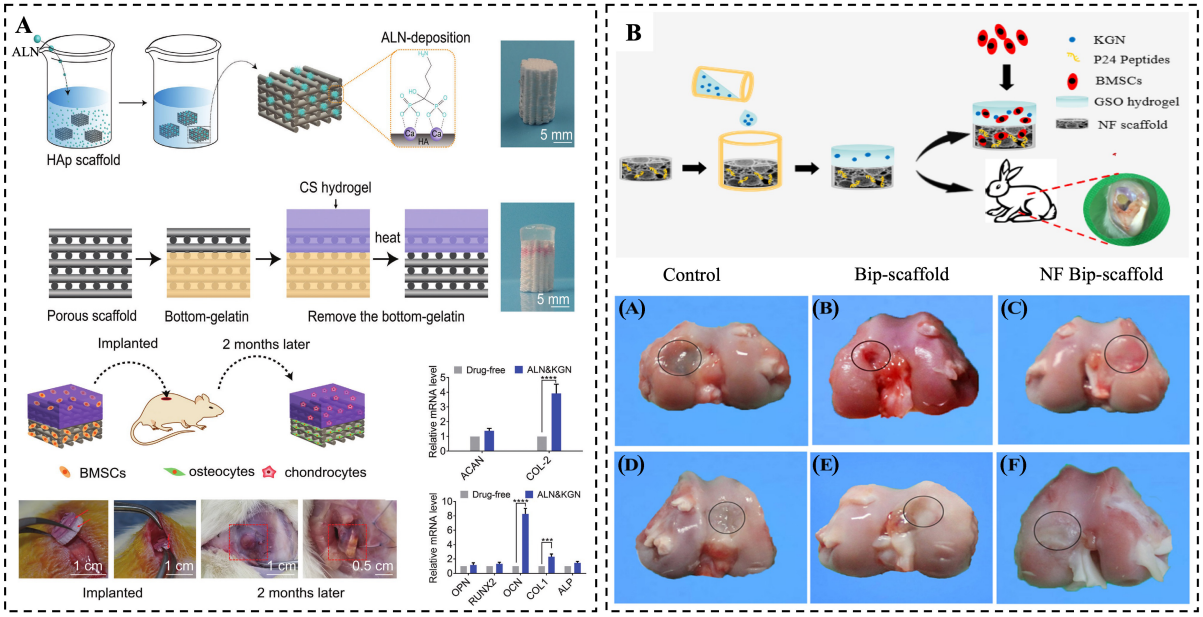

Figure 11. Double-layer biomimetic smart materials for osteochondral regeneration and repair. (A) Fabrication of biomimetic and biphasic osteochondral scaffold and *in vivo* subcutaneous assay. (Reproduced with permission[123]. Copyright 2020, *Advanced Healthcare Materials*). (B) Double-layer scaffold material with KGN and BMP-2 in osteochondral repair. (Reproduced with permission[124]. Copyright 2019, *ACS Biomaterials Science and Engineering*).

In summary, the biomimetic smart materials are currently being developed to possess the optimal physical and chemical properties, including macroscopic (e.g., multiphase) and microscopic (e.g., pore size, pore

spacing, hardness, and piezoelectric stimulation) features, and material composition (e.g., peptides, KGN, metal ions, bioactive factors, and nanoenzymes) to construct the physiological environment required for tissue repair (e.g., anti-inflammatory and antioxidant). These materials spatiotemporally guide cell migration, proliferation, and differentiation by regulating signaling pathways involving cell-cell and cell-extracellular matrix interactions, thereby influencing tissue regeneration and repair. Notably, some exhibit diverse structures and complex functionalities and demonstrate good osteochondral regeneration and repair in animals. Furthermore, they can be prepared cost-effectively through various methods.

CONCLUSION AND PERSPECTIVES

Cartilage and osteochondral repair encounter several challenges in clinical practice. In recent years, tissue engineering techniques have shown potential in regeneration and repair of cartilage/osteochondral tissues and have made significant progress. This review summarizes recent advancements in the biomimetic and smart materials for osteochondral regeneration and repair. For the biomimetic materials, current research mainly focuses on constructing functional biomimetic scaffolds with different components (e.g., cells, growth factors, and metal ions) and structures (e.g., monophasic, biphasic, triphasic, and gradient scaffolds) using various techniques such as freeze-drying, cross-linking, and 3D printing. These materials simulate the biological structure and function of natural cartilage, providing physicochemical and signaling factors to promote and trigger the regeneration and repair of cartilage tissues. As for smart materials, current research primarily involves constructing the endogenous (e.g., ROS, pH, enzyme and temperature) and exogenous (e.g., light, ultrasound, and mechanical force) stimuli-responsive systems for drug/bioactive controlled release. Through timed and targeted drug release, long-term regulation of cartilage regeneration and repair is achieved.

Biomimetic smart materials, as a promising therapeutic agent, can respond to specific stimuli and provide a conducive environment or specific structure for cells to guide cartilage tissue regeneration. However, few products have been successfully applied to cartilage regeneration and repair in clinical settings due to challenges in several aspects. First, the abnormal microenvironment during cartilage repair affects the behaviors of key cells, leading to increased M1/M2 polarization, abnormal differentiation of MSCs, decreased chondrocyte activity, and exacerbating the pathology of cartilage tissue and subchondral bone. Secondly, the dynamic control mechanism of the key physicochemical properties of biomimetic materials on cell behaviors remains unclear, making it difficult to precisely control cell-cell and cell-matrix interactions at different stages of tissue regeneration and repair, resulting in newly formed tissue being inadequately anchored to surrounding normal tissue and subchondral bone. Finally, the design of smart materials is relatively complex, with low sensitivity to exogenous/endogenous stimuli, making it challenging to release drugs at critical time points and regulate tissue microenvironments and cell behavior timely.

Osteochondral regeneration and repair are complex processes involving physicochemical and biological factors, requiring systematic strategies for developing new generation biomimetic-smart materials. These strategies should include: (1) development of highly sensitive materials that can correct and restore the tissue repair microenvironment in real time for long-term use based on the pathological characteristics after bone cartilage defects; (2) understanding of the mechanisms of scaffold material physicochemical properties on the directional regulation of cell behaviors, optimizing material composition and physical parameters; and (3) integration of interdisciplinary theories and technologies (e.g., multi-omics, cell atlas, bioinformatics, and artificial intelligence) to explore new strategies for activating endogenous regeneration capability and promoting tissue regeneration *in situ*, structural remodeling, and functional reconstruction of tissue by targeting key points in the cartilage regeneration control network. As materials development and clinical translation progress, biomimetic smart materials will play a crucial role in bone cartilage

regeneration and repair.

DECLARATIONS

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Authors' contributions

Conceptualization, investigation, and writing-original draft: Jia QP, Li QF
Writing, review & editing: Boucetta H
Writing-review & editing, supervision, and funding acquisition: Zhang LX, Xu ZP

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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