Engineered Science
DOI: http://dx.doi.org/10.30919/es1819

The Role of Bioactive Glass in Osteoarthritis Treatment and Cartilage Regeneration

Ruiguo Chen,[1,*] Ling Pen,[1,2] Rana Ahmed Tauseen,[3] Sajid ur Rehman,[1,*] Fu Zhang,[4,5] Kun Ma[1,*] and Junfeng Wang[1,2,6]

Abstract

Osteoarthritis (OA) is a progressive degenerative joint disease primarily affecting older adults, characterized by cartilage degradation, abnormal bone growth, and joint dysfunction. Despite various treatments available, there is currently no cure for OA, and existing therapies often lead to adverse side effects. Bioactive glass (BG), recognized for its biocompatibility and osteoconductive properties, has emerged as a promising therapeutic approach for OA management. This review article discusses the mechanisms through which BG promotes cartilage regeneration, including the stimulation of chondrocyte proliferation and differentiation. It also explores BG's role as an effective drug delivery system for targeted, localized release of anti-inflammatory agents and growth factors to reduce inflammation and restore joint function. Additionally, the review highlights the formation of hydroxyapatite layers upon BG degradation, enhancing bone integration, and the positive effects of released ions on cellular responses. The article also addresses the challenges faced in the clinical application of BG, such as individual variability, long-term stability, and the need for personalized treatments. Finally, future directions in optimizing BG material properties, developing intelligent bioglass composites, and advancing 3D or 4D printing technologies for personalized OA therapies are proposed.

Keywords: Osteoarthritis; Bioactive glass; Anti-inflammatory; Bioactive glass composites.
Received: 20 July 2025; Revised: 21 September 2025; Accepted: 21 October 2025.
Article type: Review article.

1. Introduction

OA is a chronic degenerative joint disease with significant implications, prevalent worldwide, especially among the middle-aged and elderly populations. The pathological characteristics of OA are primarily manifested as the gradual degeneration of articular cartilage, which is the main cause of joint dysfunction and pain.[1-3] This degeneration not only involves the loss of chondrocytes and destruction of the extracellular matrix but is also accompanied by osteophyte formation at the joint margins. These changes collectively lead to a progressive loss of joint function.[3] Although OA is fundamentally a non-inflammatory disease, it is often associated with low-grade chronic inflammation during its progression, which further exacerbates joint damage.[4] As cartilage is an avascular tissue with limited self-repair capabilities, the search for effective treatments to promote cartilage repair and regeneration holds significant clinical importance.

Currently, the treatment of OA primarily aims to alleviate symptoms and slow disease progression. Nonsteroidal anti-inflammatory drugs (NSAIDs) can relieve pain; however, long-term use may lead to gastrointestinal and cardiovascular complications.[5-7] For patients with severe OA, joint replacement surgery can significantly improve joint function,

[1] *High Magnetic Field Laboratory, Key Laboratory of High Magnetic Field and Ion Beam Physical Biology, Hefei Institutes of Physical Science, Chinese Academy of Sciences, Hefei, 230031, China*
[2] *University of Science and Technology China (USTC), Hefei, 230026, China*
[3] *Internal Medicine department, SSM Health St. Joseph Hospital–St. Charles, 300 1st Capitol, St. Charles MO, 63301, USA*
[4] *Library and Journal Center, Hefei Institutes of Physical Science, Chinese Academy of Sciences, Hefei, 230031, China*
[5] *College of Information Management, Nanjing Agricultural University, Nanjing, 210095, China*
[6] *Institutes of Physical Science and Information Technology, Anhui University, Hefei, 230601, China*
**E-mail*: rgchen@hmfl.ac.cn (R. Chen); sajidrehman@hmfl.ac.cn (S. Rehman); makun@hmfl.ac.cn (K. Ma)

but the associated surgical risks and lengthy recovery period can severely impact patients' quality of life.[8,9] Therefore, developing new therapeutic strategies to address unmet clinical needs, particularly those that promote cartilage repair and regeneration, is of utmost importance. Over the years, researchers have explored various biomaterials for OA and cartilage repair, but the limitations of these materials can compromise therapeutic outcomes. Hydrogels and collagen scaffolds provide a supportive 3D microenvironment for cells but often lack mechanical strength and long-term stability.[10,11] Synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) offer tunable degradation rates but may produce acidic byproducts that impair local tissue regeneration.[12] Ceramic materials like hydroxyapatite (HA) and tricalcium phosphate (TCP) demonstrate excellent biocompatibility and bone integration but are brittle and lack the ability to actively modulate cellular behavior. Compared to these systems, BG exhibits unique advantages: it can bond directly to bone through hydroxyapatite formation, release therapeutic ions such as silicon (Si^{4+}), calcium(Ca^{2+}), Phosphate (PO_4^{3-}), Magnesium (Mg^{2+}), Boron (B^{5+}), Copper (Cu^{2+}), Zinc (Zn^{2+}) , strontium(Sr^{2+}) and Vanadium (V^{5+}) that stimulate chondrocyte proliferation and differentiation, promote angiogenesis, and act as a drug delivery carrier for anti-inflammatory agents and growth factors.[13] These properties position BG as a superior and versatile candidate for OA treatment.

Biomaterials can not only provide structural support for cells but also deliver growth factors and gradually be replaced by new tissue during biodegradation, demonstrating significant potential for application.[14-16] Among various biomaterials, BG has become a focal point in the field of arthritis repair due to its unique biocompatibility and bone-binding capabilities.[17] BG is an inorganic material that can react with physiological fluids to form a layer of hydroxyapatite, similar to the primary components of human bone, thereby promoting the integration and growth of bone tissue. BG can release ions, which stimulate the proliferation and differentiation of chondrocytes, thereby facilitating tissue regeneration.[18] Additionally, BG can serve as a drug delivery vehicle for the localized administration of anti-inflammatory drugs or growth factors, aiding in the alleviation of joint inflammation and promoting functional recovery.[19] These characteristics render BG a promising candidate for OA treatment, providing possibilities for the development of novel therapeutic approaches.

This review aims to generalize the latest research progress on BG in arthritis repair, focusing on its mechanisms of action and clinical application prospects. Through an in-depth exploration of BG, we hope to provide a novel and effective therapeutic solution for patients with arthritis, thereby improving their quality of life. Furthermore, this article will discuss the challenges faced by BG in practical applications and its future development directions, intending to offer valuable insights for researchers in the field.

2. Structural features and pathogenesis of synovial joints

The synovial joint is the most complex and highly mobile type of joint in the human body, with intricate structure and diverse functions. It is primarily composed of the articular ends of bones, articular cartilage, the joint capsule, synovial membrane, synovial fluid, ligaments, tendons, and bursae as shown in Fig. 1. The articular ends of the bones are formed by the bone surfaces of two or more adjacent bones, which are covered by a layer of transparent cartilage known as articular cartilage. This cartilage is mainly composed of type II collagen and aggrecan, which effectively reduce friction, distribute load, and provide cushioning and protection during joint movement.[20]

Externally, the joint is encapsulated by a connective tissue structure called the joint capsule, which is lined by the synovial membrane. The synovial membrane secretes synovial fluid that lubricates the joint surfaces, while also facilitating the diffusion of nutrients to the cartilage and the removal of metabolic waste products. Synovial fluid is rich in hyaluronic acid and lubricin, playing a key role in joint lubrication, nutritional support, and anti-inflammatory defense.[21] Ligaments, as essential connective structures between bones, limit the range of joint movement and maintain joint stability. Tendons, connecting muscles to bones, transmit the force generated by muscle contraction, thereby driving joint motion. Some joints also contain structures such as menisci or articular discs, which enhance the congruence and stability of the bone surfaces and further absorb shock.[22]

Secondly, the articular cartilage is a specialized connective tissue in human joints, primarily composed of chondrocytes, extracellular matrix, collagen fibers, and polysaccharides. Chondrocytes are located within lacunae and vary from flat to oval or round in shape from superficial to deep layers, maintaining normal cartilage metabolism. Chondrocytes are the only cell type within articular cartilage, responsible for maintaining the balance of the extracellular matrix (ECM) and supporting the cartilage's function. They regulate the mechanical and biological properties of cartilage by synthesizing and degrading matrix components such as proteoglycans and collagen, thus preserving cartilage integrity.[23] The cartilage matrix consists of extracellular

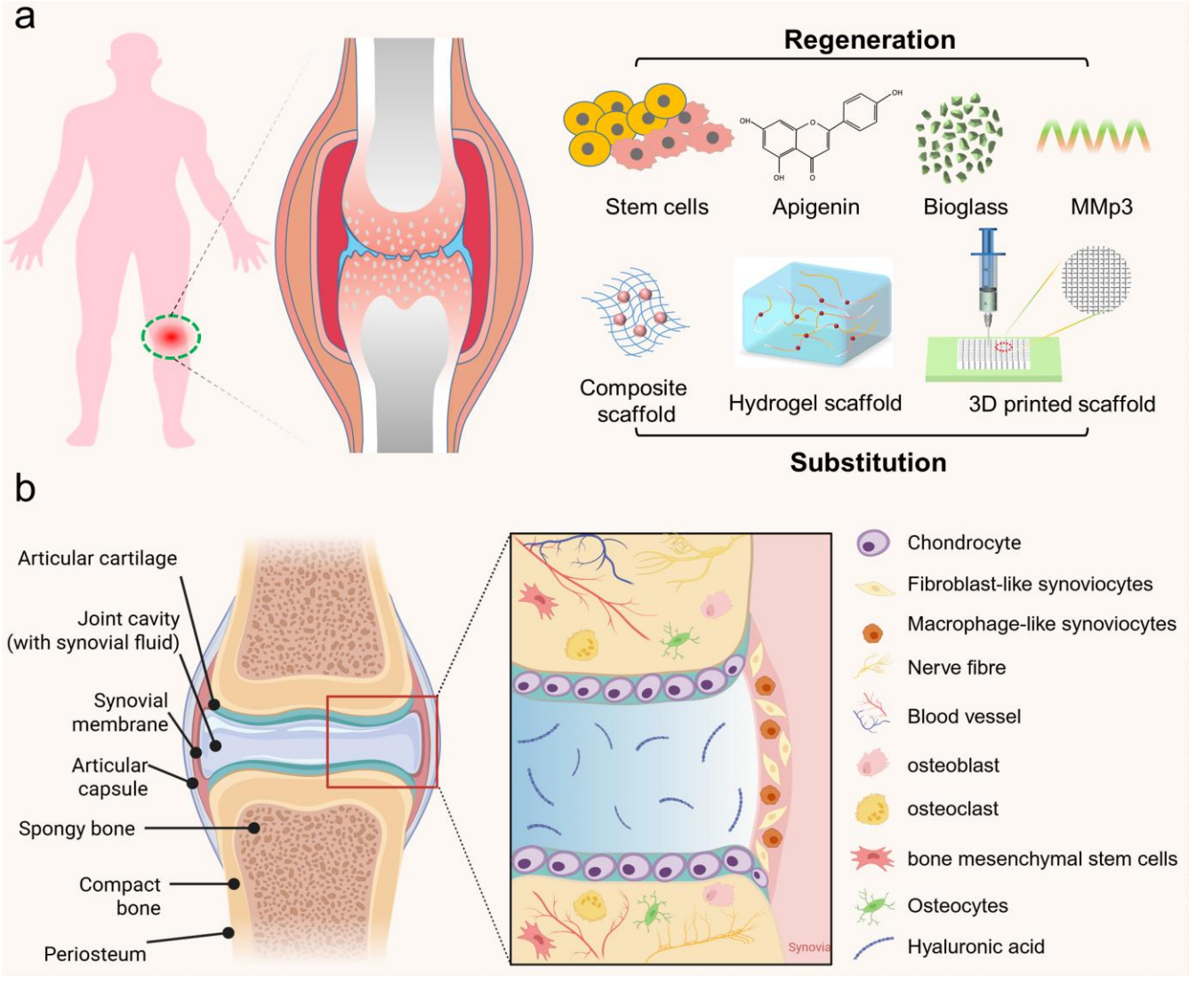

Fig. 1: (a) Schematic diagram of strategies for treating OA, including promoting cartilage regeneration and cartilage replacement. (b) Composition and structure of the synovial joint. Chondrocyte: maintain the structure and function of cartilage; Fibroblast-like synoviocytes: synthesize hyaluronic acid, lubricin, and other molecules; Macrophage-like synoviocytes: engulf debris and secrete inflammatory factors; Nerve fibre: perceive stimuli; Blood vessel: provide oxygen and nutrients; Osteoblast: synthesize and mineralize bone matrix, regulate bone formation; Osteoclast: multinucleated macrophage cell line, involved in bone resorption; Bone mesenchymal stem cells: differentiate into osteoblasts, chondrocytes, adipocytes; Osteocytes: sensitize to mechanical loading and participate in the regulation of bone remodeling; Hyaluronic acid and lubricin: lubricate the cartilage surface to prevent friction.

substances, mainly collagen fibers and large proteoglycans (*e.g.*, chondroitin sulfate). Collagen fibers provide strength and resilience to cartilage, while proteoglycans help maintain the elasticity and compressive resistance of the tissue. The predominant type of collagen in cartilage is type II collagen, which constitutes the majority of the collagen fibers.[24] The basic structure of articular cartilage can be divided into three layers: the superficial layer, middle layer, and deep layer. The superficial layer is the outermost layer in contact with synovial fluid, characterized by a smooth and elastic surface. The middle layer contains more densely packed collagen fibers and glycosaminoglycans, reducing moisture permeability. The deep layer, the innermost layer of the cartilage, is primarily composed of loosely arranged collagen fibers.[24] Osteoblasts are primarily located in the subchondral bone beneath the cartilage and are responsible for new bone formation, mineralization, and bone remodeling. Under normal circumstances, osteoblasts work in conjunction with osteoclasts to maintain the stability and functionality of the joint through bone remodeling and metabolic regulation.

The primary function of articular cartilage is to bear and distribute mechanical loads, ensuring even distribution of external forces and enlarging the weight-bearing surface to maximize resistance to mechanical stress and protect the

cartilage from damage. The smooth surface of articular cartilage reduces friction during joint movement, allowing for flexibility and minimizing wear. Cartilage's elasticity effectively absorbs and cushions external impacts.[25] However, once cartilage is damaged, its ability to absorb and buffer stress diminishes, leading to progressive joint injury and degenerative changes. The smoothness of the cartilage surface facilitates smooth movement between bones, significantly reducing friction. As cartilage is avascular and lacks nerves, its nutrition primarily relies on the diffusion of synovial fluid during joint movement and the supply from the arterial branches surrounding the synovial membrane, which are critical for maintaining cartilage integrity.[26,27]

In OA, subchondral bone exhibits abnormal remodeling, with increased osteoblast activity leading to thickening of the subchondral bone and an increase in trabecular bone density. Signals released by osteoblasts (*e.g.*, TGF-β and osteoprotegerin) can influence cartilage metabolism through osteoclasts and stimulate abnormal differentiation of chondrocytes.[28] Excessive mineralization and thickening of the subchondral bone alter the microenvironment of the cartilage, potentially further aggravating cartilage degeneration. Osteophytes, a typical pathological feature of OA, arise from the proliferation and mineralization of subchondral osteoblasts.[29] Osteophytes can alter joint mechanics and induce pain, thereby limiting joint function. In the inflammatory environment of OA, osteoblasts may exhibit enhanced mineralization activity in response to inflammatory factors (*e.g.*, TNF-α and IL-6) as shown in Fig. 2. Although osteoblasts do not directly participate in cartilage degradation, their abnormal activity and imbalance in bone remodeling significantly affect the progression of OA.

In the early stages of OA, chondrocytes typically exhibit increased metabolic activity and proliferation. However, as the disease progresses, they gradually display characteristics of apoptosis and senescence, resulting in further degradation of the extracellular matrix. Changes in osteoblast function also impact the biomechanical properties of the joint, potentially leading to osteoporosis or osteophyte formation, exacerbating pain and discomfort.[30] Additionally, metabolic factors significantly contribute to OA pathogenesis. Adipose tissue not only stores energy but also participates in systemic inflammatory responses by secreting various cytokines. The chronic inflammatory state induced by obesity increases the concentration of pro-inflammatory factors in the joint, accelerating cartilage degradation and bone remodeling.[31]

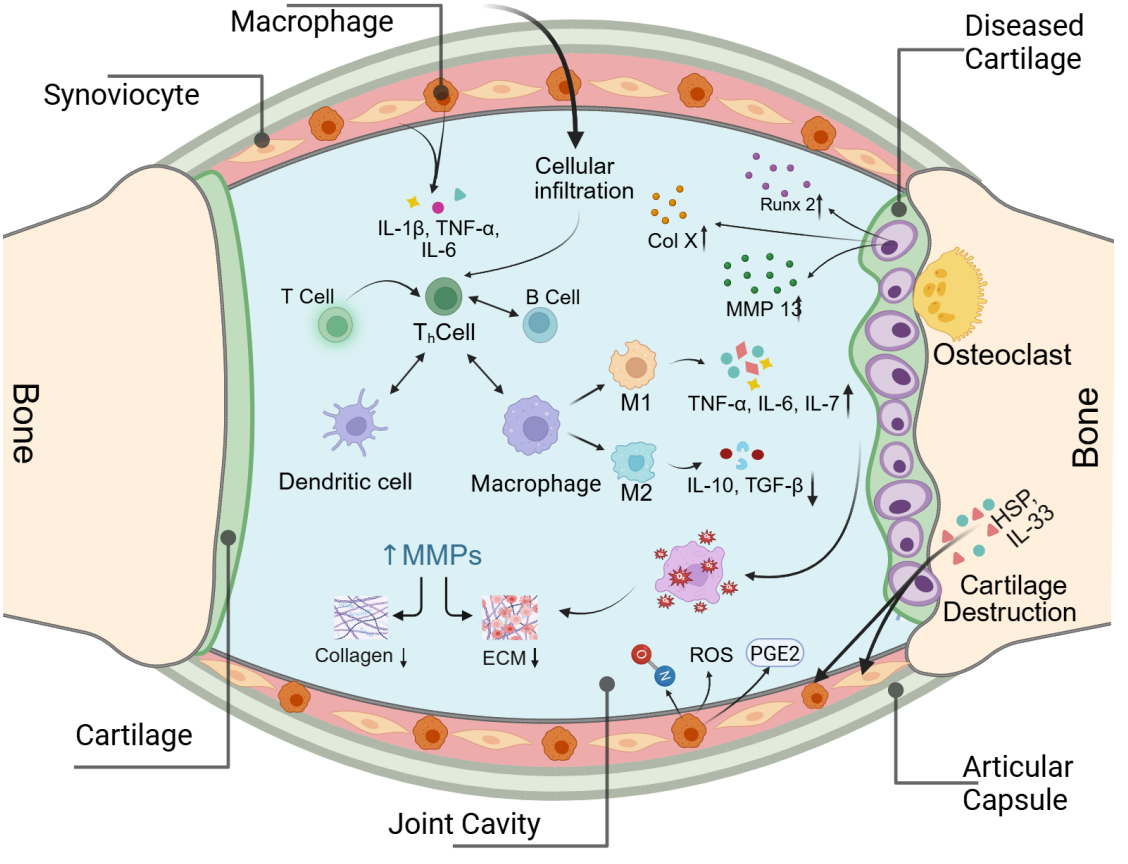

Fig. 2: Schematic diagram of the biological mechanisms involved in the pathogenesis of OA.

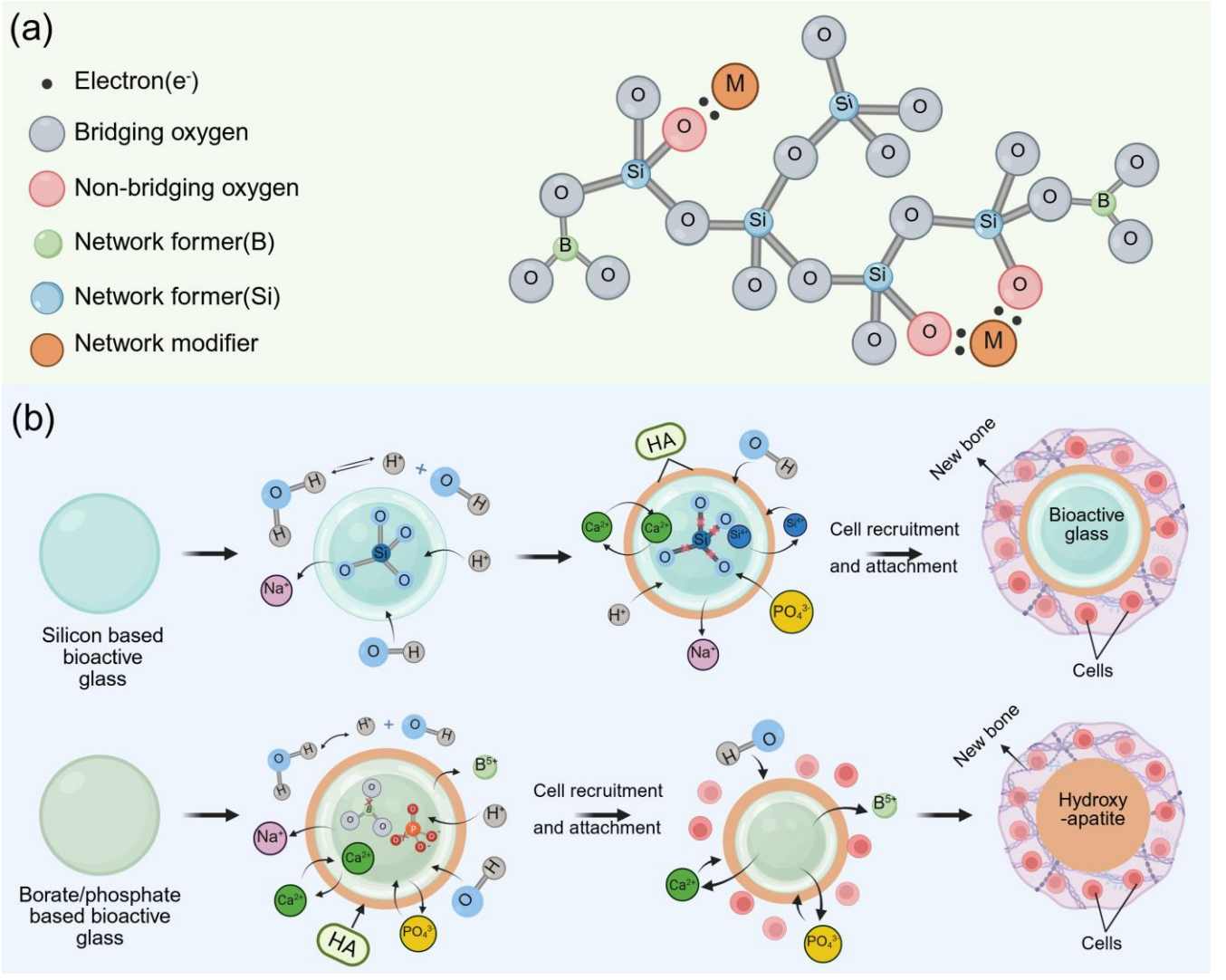

Fig. 3: (a) Schematic representation of the network structure of SBG; (b) Surface reaction stages of different kinds of BG in hard tissue healing.

3. BG in promoting cartilage repairing

BG is a class of glass materials capable of achieving specific biological and physiological functions, first discovered by L. L. Hench in 1969. Its main components include silica (SiO_2), sodium oxide (Na_2O), calcium oxide (CaO), and phosphorus pentoxide (P_2O_5).[32] Based on their chemical composition, BG can be classified into silicate, borate, and phosphate.

Silicate BG (SBG) primarily consist of SiO_2, Na_2O, CaO, and P_2O_5, with SiO_2 being the predominant component.[33] The fundamental structural unit is the "SiO_4 tetrahedron", formed by a Si atom surrounded by four oxygen atoms as shown in Fig. 3(a). These tetrahedra can connect through bridging oxygens, forming covalent bonds (Si-O-Si) that contribute to the glass network's continuity.[34] Network modifiers, such as alkali-metal cations K^+, Ca^{2+}, and Mg^{2+} disrupt the Si-O-Si bonds, resulting in a modified structure (Si-O-M). The presence of non-bridging oxygens increases with the addition structural properties.[38] PBG can degrade rapidly in biological of network modifiers, leading to reduced structural continuity and enhanced degradation properties. The bioactivity and solubility can be adjusted through its composition.[35]

When SBG is implanted in the body, it gradually degrades over time, forming hydroxyapatite (HA) on its surface. As the implantation time increases, the hydroxyapatite layer tightly bonds with both the bone tissue and surrounding soft tissues as shown in Fig. 3(b). The degradation rate of SBG in vivo is relatively slow, and during this degradation process, a silica-rich layer forms on the surface, further reducing the degradation rate of the glass. As this silica-rich layer thickens, it hinders the degradation of the internal glass structure.[36] Phosphate-BG (PBG), characterized by its P_2O_5 content, features P-O tetrahedra as the basic structural unit.[37] In this structure, phosphorus (P) has a valence of 5^+, forming single and double bonds with oxygen atoms. The different stoichiometry of P compared to Si leads to distinct structural systems, PBG undergoes the following reactions:[39]

i. Hydration reaction: The network-modifying ions in the glass structure, such as Na^+ and Ca^{2+}, exchange with H^+ ions in the water, forming a hydrated layer on the glass surface.

ii. Hydrolysis reaction: Under the action of water molecules and H^+, the P-O-P covalent bonds in the glass network break, leading to structural degradation and dissolution of the glass.

Currently, PBG is less commonly used for hard tissue repair; however, it may possess additional clinical potential as an absorbable material.[40] Borate BG (BBG) refers to primarily composed of boron trioxide (B_2O_3), along with oxides of essential metallic elements required for human growth, such as CaO, Na_2O, and magnesium oxide (MgO). In this composition, B_2O_3 serves as the glass network former, primarily existing in the forms of [BO_3] and [BO_4] within the glass structure. The coexistence of the two structures ensures that the glass shows good dopability.[41] The degradation mechanism of BBG in bodily fluids resembles that of SBG. Compared to SBG, BBG does not develop a boron-rich surface layer during degradation, and the hydroxyapatite (HA) that forms on its surface is porous, allowing for better ion exchange.[42] As a result, it more readily and completely converts to hydroxyapatite. The transformation of BBG to HA can be described through a series of dissolution-precipitation.[36] 1) Ligand ions within the glass network, such as Na^+ and K^+, exchange with H^+ ions in solution. 2) The glass network structure begins to degrade, with B–O–B bonds breaking and $[BO_3]^{3-}$ ions released into the solution to form H_3BO_3. 3) Ca^{2+} ions within the glass migrate to the surface, where they combine with PO_4^{3-} to form an amorphous CaO–P2O5 layer that accumulates on the glass surface. 4) This CaO–P_2O_5 layer gradually accumulates and eventually crystallizes into hydroxyapatite (HA).

Compared to other bioactive materials, BG offers notable advantages, primarily due to its exceptional biocompatibility.[37] This biocompatibility arises from two main factors: (1) upon interaction with biological fluids, BG forms a biomimetic hydroxyapatite (HA) layer on its surface; (2) the dissolution products and released ions of BG have osteogenic capabilities.[43] Therefore, BG is a highly promising implant material for bone tissue repair and regeneration.

3.1 The role of BG in promoting chondrocyte proliferation and differentiation

Studies have shown that BG gradually dissolves in vivo, releasing various bioactive ions. These ions play important roles in cellular signaling, promoting the proliferation and differentiation of chondrocytes and mesenchymal stem cells (MSCs), which is critical for the repair of articular cartilage as shown in Fig. 4. Table 1 provides a summary of the biological responses of cells to different ions released from bioactive glass. In a physiological environment, BG releases essential ions, particularly Si^{4+}, Ca^{2+}, Mg^{2+}, B^{5+}, and Sr^{2+}, which significantly aid cartilage tissue repair. The therapeutic effects of BG in OA are largely attributed to the specific biological activities of these individual ions. In the following sections, the roles of key metal ions are discussed in detail with respect to their mechanisms in supporting cartilage repair and modulating inflammatory responses.

Si^{4+}: These ions are essential for chondrocyte proliferation and extracellular matrix production. It stimulates chondrocyte proliferation and metabolic activity, promoting collagen and proteoglycan synthesis, thereby enhancing cartilage matrix formation.[44] Si^{4+} further support chondrocyte proliferation and differentiation by enhancing extracellular matrix (ECM) synthesis. Additionally, Si^{4+} stimulate the production of collagen and glycosaminoglycans (GAGs), which are key components of the cartilage matrix, thereby strengthening the structure and function of cartilage.[45,46]

Ca^{2+}: BG releases a large amount of Ca^{2+} ions in tissue fluid, which are crucial in cellular signaling. Ca^{2+} play key roles in intracellular and extracellular signaling pathways, activating pathways within chondrocytes to promote cell adhesion, migration, and differentiation, thereby aiding functional recovery and regeneration of chondrocytes.[47] Ca^{2+} also support ECM mineralization, enhancing chondrocyte differentiation and matrix deposition, thereby increasing the hardness and stability of cartilage tissue. Studies have also found that Ca^{2+} stimulate the synthesis of matrix metalloproteinases (MMPs), which play a critical role in cartilage matrix remodelings.[47]

PO_4^{3-}: These ions participate in the formation of chondrocyte extracellular matrix and are essential for mineralization, combining with Ca^{2+} to form apatite, thus promoting chondrocyte mineralization and differentiation and enhancing the mechanical properties of cartilage.

B^{5+}: B^{5+} ions promote chondrocyte and MSC proliferation by activating specific signaling pathways, such as the Wnt/β-catenin pathway, which plays a crucial role in tissue regeneration and cell differentiation, particularly in cartilage repair. Activation of the Wnt signaling pathway enhances chondrocyte proliferation and matrix formation.[48] B^{5+} also interact with signaling molecules like bone morphogenetic protein (BMP) and transforming growth factor-beta (TGF-β) to regulate the differentiation of MSCs into chondrocytes.[49] The TGF-β pathway is important for chondrocyte differentiation and matrix production, and B^{5+} enhance this pathway.[50] B^{5+} incrondrocytes, promoting the production of

type II collagen and proteoglycans-key components of cartilage tissu, thereby improving cartilage repair capacity. Since MMPs are critical enzymes in cartilage degradation, B^{5+} may inhibit MMP overexpression, protecting the ECM from excessive degradation and slowing OA progression.

Sr^{2+}: Sr^{2+} promote cartilage regeneration by regulating the proliferation and differentiation of chondrocytes and MSCs. Studies show that Sr ions activate signaling pathways such as Wnt/β-catenin and extracellular-signal-regulated kinase / mitogen-activated protein kinase (ERK/MAPK), which are closely related to chondrocyte proliferation and differentiation.[51,52] Sr^{2+} enhance chondrocyte proliferation, matrix synthesis, and inhibit apoptosis, thereby delaying OA progression. Sr ions also stimulate the production of cartilage matrix components like type II collagen and proteoglycans.[53]

Mg^{2+}: Magnesium ions promote chondrocyte proliferation and cartilage matrix production by regulating ECM mineralization, thereby enhancing chondrocyte activity and proliferation.[54,55] Magnesium incorporation has anti-inflammatory effects by modulating macrophage polarization toward the anti-inflammatory M2 phenotype, thereby reducing local inflammation. Magnesium ions inhibit the release of pro-inflammatory factors, such as tumor necrosis factor-alpha. (TNF-α) and interleukin-6 (IL-6), mitigating inflammatory damage to chondrocytes.[56] Magnesium ions also promote anti-inflammatory factor secretion, helping to restore a regenerative environment in the damaged cartilage and protecting cartilage tissue.

Cu^{2+} and Zn^{2+}: As essential trace elements, Cu^{2+} help prevent tissue infection and oxidative stress-induced cartilage damage through their antioxidant and antibacterial properties.[57] Zn^{2+} regulate the production of proteoglycans and collagen fibers, enhancing cartilage matrix synthesis and improving cartilage repair outcomesium.[58]

V^{5+}: They are emerging as functional ions with potential cartilage regeneration effects. Studies have shown that V^{5+} can promote chondrocyte differentiation and cartilage matrix formation by activating the Mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway, thereby accelerating chondrocyte proliferation and enhancing cartilage repair.[59]

3.2 Promotion of cell adhesion and proliferation

When BG materials come into contact with bodily fluids, a hydroxyapatite (HA) layer forms on their surface. This HA layer, which resembles natural bone tissue, mimics the extracellular matrix's chemical structure, thereby enhancing cell-matrix interactions and promoting cell adhesion.

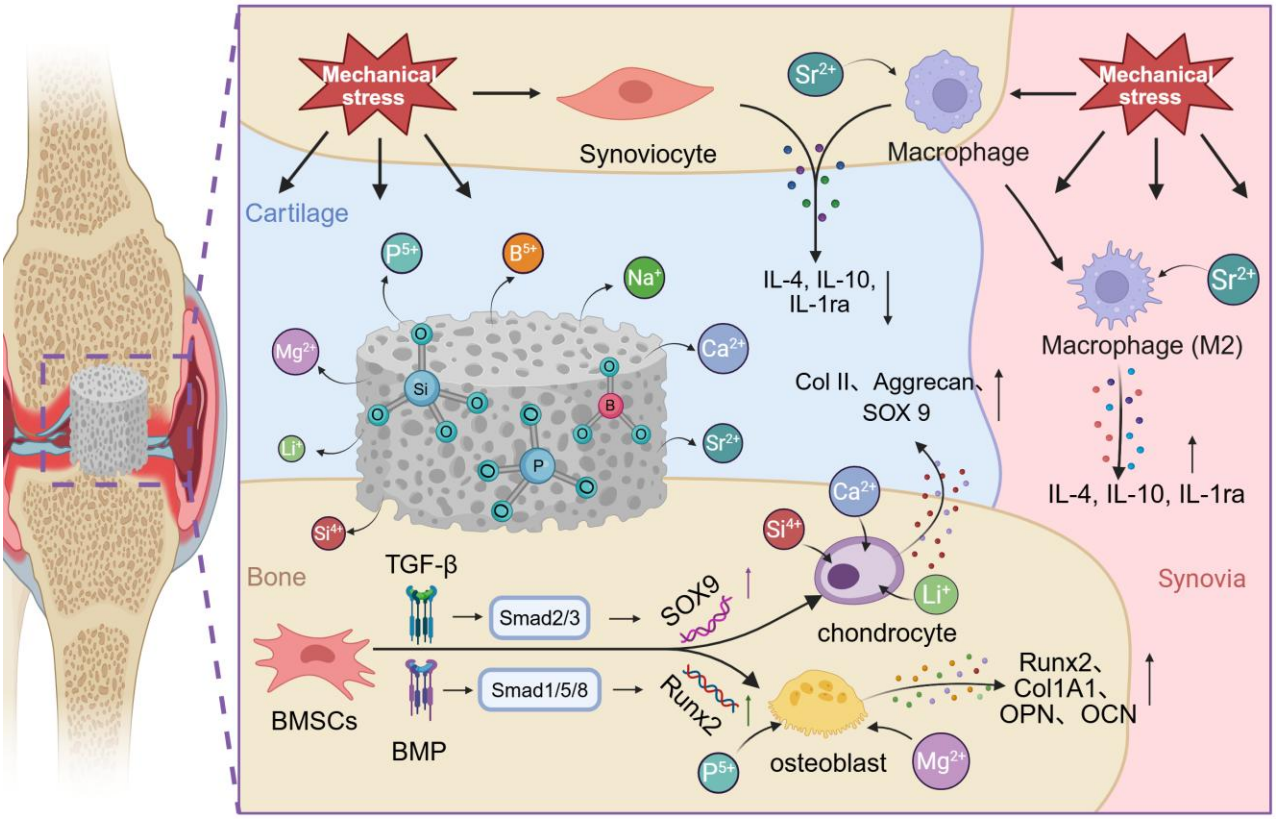

Fig. 4: Schematic diagram illustrating the mechanisms by which ions released from BG influence various cellular processes involved in cartilage repair.

Table 1: Biological responses of cells to various ions released from bioactive glass.

Ions	Biological response	Reference
Si^{4+}	Upregulate kinase insert domain receptor (KDR, vascular endothelial growth factor receptor), fibroblast growth factor receptor 1 (FGFR1, basic fibroblast growth factor receptor), and activin receptor-like kinase 1 (ACVRL1, transforming growth factor-β receptor) expression.	[60]
Si^{4+} and Li^{+}	Upregulate collagen type II (COL2A1), aggrecan (ACAN), SRY-box transcription factor 9 (SOX9), and neural cadherin (N-cadherin, CDH2) expression.	[45]
Si^{4+} 、Li^{+}、Ca^{2+}	C-C chemokine receptor type 7 (CCR7), integrin alpha X (CD11c), TNFα, IL-6, interleukin-1 beta (IL-1β), cluster of differentiation 163 (CD163), cluster of differentiation 206 (CD206, mannose receptor C type 1), interleukin-10 (IL-10)	[61]
Ca^{2+}	Up regulate COL2A1, SOX-9, ACAN、Hypoxia-inducible factor 1 (HIF-1)	[62]
P^{5+}	Regulate osteoblastic proliferation via Insulin-like growth factor 1 (IGF-1), stimulated stanniocalcin 1expression, upregulate phosphate inorganic transporter 1 (PiT1) protein expression at the plasma membrane,	[63-65]
B^{5+}	Increases cell prolifer ation and growth at low concentrations, show antioxidant properties, activate Wingless-related integration site/β-catenin signaling pathway (Wnt/β-catenin)	[66]
Sr^{2+}	Stimulate COL2A1, SOX-9, and ACAN gene expression, activated M2 macrophages.	[46, 67, 68]
Li^{+}	Activation of Wnt/β-catenin signalling pathway, elicit the expression of exosomal pro-angiogenic miR-130a in the exosomes	[69,70]
Mg^{2+}	Stimulates new bone formation; increases bone cell adhesion and stability, Upregulate Collagen type X alpha 1 chain (COL10A1) expression,	[71,72]
Cu^{2+}	activating HIF signaling pathway, suppress IL-1 activity	[62, 73, 74]
Zn^{2+}	Suppress nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) expression, increase the expression of anti-inflammatory and antiapoptotic proteins, inhibit NF-κB activation	[75-77]
V^{5+}	Activate MAPK/ERK signal path	[59]
Ag^{+}	Anti-inflammatory	[78]

Furthermore, this HA layer provides a favorable environment for chondrocytes to attach, grow, and generate new cartilage matrix.[79] BG releases ions beneficial to cell activity, which play a crucial role in promoting cell adhesion. For example, Ca^{2+} and PO_4^{3-}, are not only essential components of the HA layer but also interact with integrins on cell membranes, triggering the signaling pathways necessary for adhesions are key cell membrane receptors that interact with the extracellular matrix (such as HA or calcium-phosphorous compounds on the surface of bioactive glass) to mediate cell adhesion and signaling.[80] BG activates downstream signaling pathways, such as the focal adhesion kinase (FAK) pathway, via interactions with integrins, thereby enhancing cell adhesion.[81] The miructure of BG increases the contact area with cells, enhancing physical adsorption. By modulating the surface roughness and pore structure of bioactive glass, cell attachment and settlement can be effectively improved. The microporous structure provides cells with "anchor points" similar to the extracellular matrix, facilitating stable attachment and rapid expansion.

Ions released during the degradation of BG stimulate cell proliferation. Ca^{2+} as critical secondary messengers in cell signaling, participate in and activate various proliferation-related signaling pathways (*e.g.*, the Wnt/β-catenin pathway), thereby promoting cell growth.[82] Ca^{2+} actipression of certain genes (*e.g.*, VEGF, TGF-β), increasing the production of fibroblast growth factor (FGF), which in turn promotes chondrocyte or osteoblast proliferation.[83] Si^{4+} stimulate chod osteoblast proliferation by activating the ERK/MAPK signaling pathway, thereby enhancing tissue regeneration.[84]

BG promotes mesenchymal stem cell (MSC) differentiation into chondrocytes and enhances cartilage matrix synthesis through active ion release and the provision of a physical scaffold. Ions released by BG activate specific signaling pathways (*e.g.*, Wnt/β-catenin, MAPK) that promote stem cell differentiation into chondrocytes. Additionally, the highly active surface of BG adsorbs and concentrates growth factors (*e.g.*, TGF-β and IGF-1), which play a significant role in chondrocyte proliferation and differentiation, further promoting tissue repair and regeneration.[85]

The microstructure of BG also influences chondrocyte proliferation. Surface characteristics, such as roughness and porosity, significantly impact cell adhesion, proliferation, and differentiation. Rougher surfaces provide enhanced mechanical support and contact points, facilitating chondrocyte attachment and expansion.[86] Moreover, chemical modifications of bioactive glass, such as the addition of Polyvinyl alcohol (PVA) or poly(D,L-lactic acid) (PDLLA), can enhance its effects on chondrocytes by improving biocompatibility, thus promoting adhesion and differentiation.[87] BG also fosters chondrocyte growth and differentiation by optimizing the local microenvironment (*e.g.*, pH and ion concentrations). A stable microenvironment supports normal chondrocyte function and promotes chondrogenic differentiation.[88] Some bioactive glasses can deliver growth factors, such as bone morphogenetic proteins (BMPs) and TGF-β, which stimulate chondrocyte differentiation and tissue regeneration.

Furthermore, BG promotes the production of extracellular matrix (ECM) components, such as collagen and fibronectin, which create a conducive environment for cell proliferation and support cell adhesion and migration. Ions released by BG regulate gene expression, promoting the synthesis of these matrix proteins, thereby establishing an optimal microenvironment for cell proliferation.[89,90]

When BG dissolves, it releases ions which regulate matrix synthesis by promoting the production of type II collagen and proteoglycans the primary components of the cartilage matrix. Type II collagen is abundant in cartilage matrix and serves as a key structural protein, providing mechanical strength to cartilage tissue.[91,92] Proteoglycans are another crucial component, possessing water-retaining and buffering capacities that help cartilage maintain elasticity and shock absorption. Studies have shown that Si^{4+} can stimulate the TGF-β (transforming growth factor-β) signaling pathway, a critical regulator of matrix synthesis and ECM stability.[93] Ca^{2+} enhances the secretion of proteoglycans and collagen, increasing matrix thickness and density.[65,94,95] Sr^{2+} ions, through regulation of the Wnt/β-catenin and TGF-β pathways, further facilitate the synthesis of type II collagen and proteoglycans, accelerating cartilage matrix regeneration.[51]

Degradation products of BG can activate signaling pathways involved in ECM synthesis. The TGF-β signaling pathway is one of the primary pathways that promotes ECM synthesis in chondrocytes, with Si^{4+} and Ca^{2+} released from BG activating this pathway.[96,97] His activation enhances chondrocyte secretion of type II collagen, proteoglycans, and other ECM components, thereby supporting cartilage tissue repair and regeneration.[98] Additionally, specific ions in BG can activate the MAPK pathway, especially the ERK1/2 subtype, which plays a pivotal role in cell proliferation and differentiation and also in regulating cartilage matrix synthesis. Sr^{2+} and Si^{4+} can also stimulate matrix synthesis through modulation of the Wnt/β-catenin signaling pathway, which is essential for cartilage differentiation, development, and regeneration, inducing type II collagen synthesis and stimulating proteoglycan accumulation.[99,100]

BG is commonly used as a scaffold material in tissue engineering. Its porous structure not only provides an optimal physical environment for chondrocyte adhesion and proliferation but also promotes uniform ECM deposition and distribution, thereby supporting matrix synthesis and stability.[101] The porosity of BG is critical for its bioactivity, as its adjustable porosity allows cells to migrate and expand effectively within the scaffold.[102] This structure also supports even ECM distribution throughout the scaffold, which benefits the mechanical properties and functional restoration of newly formed cartilage.

3.3 Anti-inflammatory effects of bioactive glass

The anti-inflammatory properties of BG play a critical role in treating OA, as inflammation is a key factor in the degradation of joint cartilage in OA. By modulating the inflammatory response, BG can help slow or prevent cartilage degradation, thereby promoting tissue repair and regeneration. Chronic inflammation in OA is often associated with elevated levels of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, which activate matrix metalloproteinases (MMPs) in articular cartilage, leading to matrix degradation.[103,104] BG releases ions which modulate the functions of macrophages and synovial cells, reducing the secretion of these pro-inflammatory cytokines. Studies indicate that nuclear factor-kappa B (NF-κB), a key regulator of inflammation, plays a role in the expression of IL-1β and TNF-α. Ca^{2+} and Si^{4+}, inhibit the release of pro-inflammatory cytokines by modulating the extracellular signal-regulated kinase (ERK) and NF-κB signaling pathways, thus reducing inflammatory responses.[105] Moreover, Si stimulates the transforming growth factor-beta (TGF-β) pathway, which not only aids in cartilage regeneration but also reduces pro-inflammatory cytokine production, contributing to anti-inflammatory effects.[96]

Hao *et al.*[106] outlined the dual functional states of macrophages, M1 and M2, and their relevance in pathological and healing processes. As illustrated in Fig. 5a, M1-polarized macrophages are responsible for pro-inflammatory responses through the production of cytokines and reactive oxygen/nitrogen species, which are typically associated with

tumor suppression and early inflammatory responses. Although limited in osteoarthritic models, these immune phenotypes have been identified in hepatic carcinoma, where a higher presence of M1 macrophages correlated with improved prognosis. In the context of tissue repair, Shang *et al.* demonstrated that macrophage dysregulation impairs diabetic wound healing,[108] and targeting this axis could enhance regeneration. Fig. 5b shows that treatment with fluorescence imaging and Dapi staining levels. The influence of zinc-containing mesoporous BG nanoparticles (ZnRBGNs) on macrophage behavior is analyzed by Zhu *et. al.*[107] Flow cytometric analysis in Figs. 5c and 5d-e indicated that exposure to 2h-, 8h-, and 24h-ZnRBGNs suppressed M1 polarization (CD86) and enhanced M2 marker (CD206) expression. Among these, 2h-ZnRBGN showed the most pronounced anti-inflammatory effect, suggesting that controlled Zn release plays a pivotal role in shifting macrophages toward a tissue-repair phenotype. Together, these findings demonstrate that bioactive glass-based materials, through ion-mediated immunomodulation, effectively promote the transition from pro-inflammatory M1 to anti-inflammatory M2 macrophages. This mechanism is particularly relevant in OA treatment and tissue engineering, where controlling inflammation is critical for successful regeneration. Ca^{2+} influences the ERK/MAPK pathway to suppress inflammatory responses in chondrocytes and synovial cells, thereby reducing MMP production and protecting the cartilage matrix.[47,109] B^{5+} also present in bioace anti-inflammatory effects by reducing the production of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2), both of which are pro-inflammatory mediators involved in arthritis and pain. By inhibiting COX-2 and PEG-2, B^{5+} ions

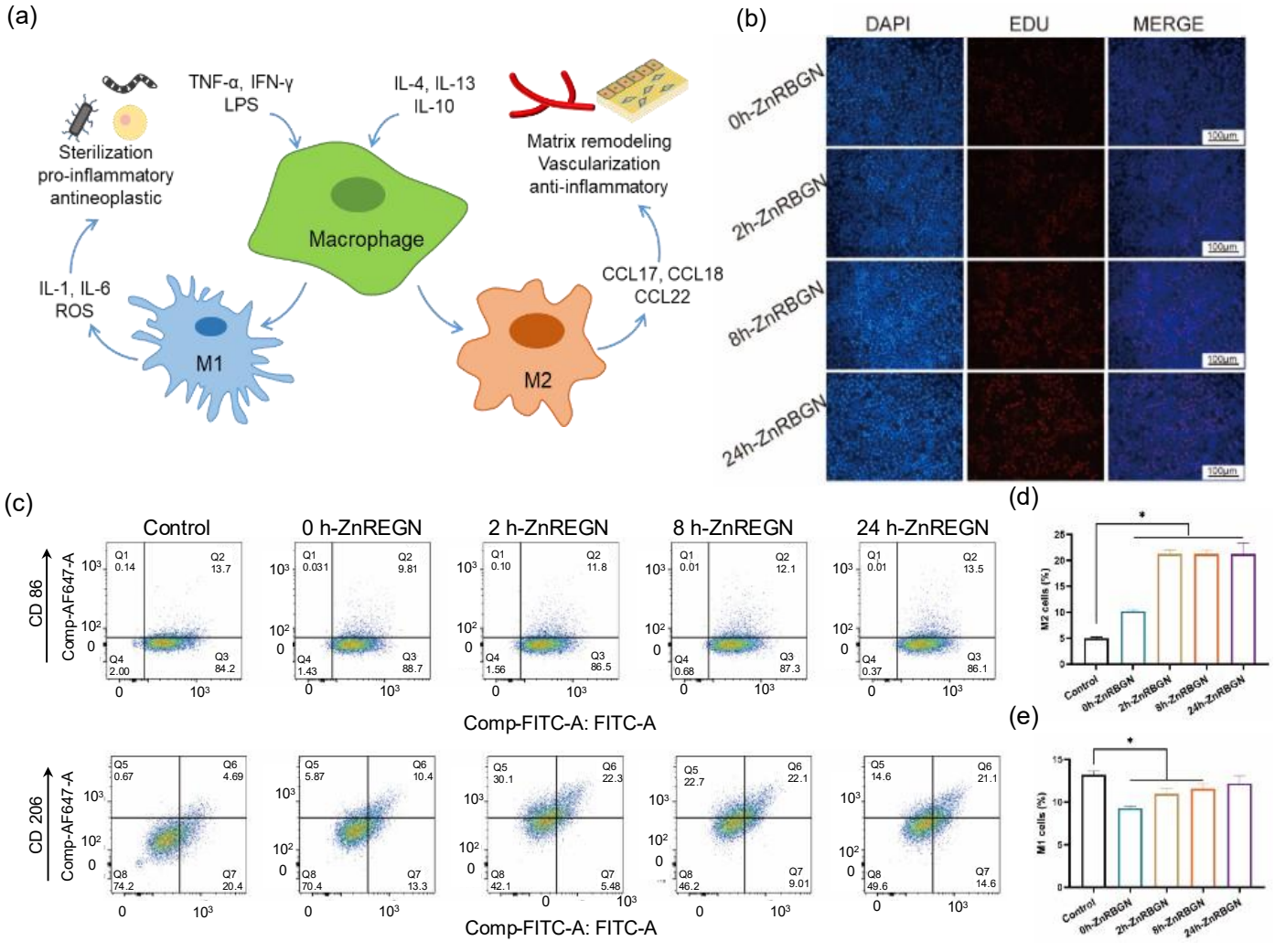

Fig. 5: Anti-inflammatory properties of BG and its composites. (a) M1/M2 macrophage activation model, Adapted from ref. [106] with permission under CC BY license. (b) Cell proliferation analysis with 0.1 mg/mL extracts of ZnRBGNs collected at 0, 2, 8, and 24 h, as shown by EdU incorporation and DAPI nuclear staining. (c-e) Influence of Zn-containing BG leachate on M1 and M2 polarization of macrophages, Adapted from ref. [107] with permission under CC BY license © 2024.

alleviate joint inflammation and pain.[110]

Macrophages can differentiate into two major phenotypes: 1) pro-inflammatory M1 and 2) anti-inflammatory M2. BG stimulates the polarization of macrophages towards the M2 phenotype, which is dependent on the activation of the STAT6 signaling pathway.[111] The active ions in BG promote STAT6 activation, enhancing the expressinflammatory genes such as IL-10 and TGF-β, which facilitate M2 macrophage generation, reduce tissue inflammation, and promote repair and regeneration.[112] BG also inhibits the NF-κB pathway, thereby reducing M1 macrophage activation ande release of pro-inflammatory cytokines such as IL-1β and TNF-α. NF-κB is a key pathway in M1 macrophage polarization, and its inhibition reduces inflammation, encouraging M2 polarization.[113]

In addition, BG improves the microenvironment of damaged tissue, promoting M2 polarization, modulates the local pH, creating a slightly alkaline environment conducive to tissue repair. This environment reduces M1 macrophage activity and promotes M2 polarization, enhancing the repair response. Additionally, $Si^{4+}$and Sr^{2+} released by BG exhibit antioxidant properties that reduce oxidative stress and reactive oxygen species (ROS) production.[114,115] ROS are critical regulators of inflammation, and by lowering ROS levels, BG reduces M1 polarization an generation.[116]

BG also stimulates the release of anti-inflammatory cytokines, such as the secretion of IL-10, a classic anti-inflammatory cytokine that inhibits the production of pro-inflammatory cytokines and encourages M2 polarization.[61] TGF-β, which plays a significant role in tissue repair and regeneration, is also modulated by bioactive glass, facilitating both chondrocyte and osteerentiation as well as M2 macrophage polarization, thereby reducing inflammatory responses.[117]

4. BG composites for cartilage repair

The materials formed by combining BG with other substances, such as polymers, ceramics, and metals, to enhance their biomedical properties. Researchers have been focusing on creating BG composites to further improve their effectiveness in cartilage repair. These composites enhance the functional and biomechanical properties of bioactive glass, offering multifaceted capabilities for tissue repair. Common BG composites include bioactive glass-polymer, bioactive glass-chitosan (CS), bioactive glass-hydrogel, bioactive glass-ceramic, and bioactive glass-metal composites.

4.1 BG-polymer composites

BG combined with poly (lactic-co-glycolic acid) (PLGA) is known for its excellent biocompatibility and effectiveness in cartilage repair. PLGA is a biodegradable polymer that supports cartilage cells, enhancing both the mechanical strength and flexibility of the material. Studies indicate that bioactive glass-PLGA scaffolds exhibit improved mechanical properties and processability, which are essential for supporting cartilage tissue.[118] Similarly, bioactive glass-polyethylene glycol (PEG) composites represent an innovative approach to cartilage repair. The bioactivity of the glass encourages cellular differentiation and matrix generation, while PEG provides an ideal environment for chondrocyte proliferation and migration. This composite has shown promising results in supporting long-term chondrocyte survival and promoting cartilage-like tissue formation in vitro and animal models.[119] Composites made with BG and 2-hydroxyethyl methacrylate (HEMA) also exhibit excellent biocompatibility, with tunable mechanical properties mimicking cartilage structure, making them especially effective in load-bearing cartilage repair applications.[120] CS is a natural polysaccharide with excellent biocompatibility, biodegradability, and antibacterial properties. Combining BG with CS to create scaffold materials significantly enhances the mechanical strength of the composite while preserving its bioactivity. CS- BG composites provide a conducive environment for chondrocyte growth, promoting the formation and deposition of cartilage matrixn, a primary component of cartilage tissue, can be combined with BG to improve cellular adhesion and proliferation while retaining the bioactivity of the material. In vitro studies of collagen- BG composite scaffolds have demonstrated high chondrocyte adhesion and cartilage matrix production capabilities, indicating their potential for supporting cartilage regeneration.[121]

4.2 Bioactive Glass-Hydrogel Composites

Hydrogels are biomimetic materials capable of replicating the soft structure of cartilage tissue, providing strong support for cellular growth. The composite of bioglass and hydrogel can significantly improve the biocompatibility of the composite material.[122,123] The incorporation of BG nanoparticles into hydrogels enhances their mechanical strength and uses the ion release properties of BG to promote chondrocyte differentiation and cartilage matrix formation. In recent years, bioactive glass-containing hydrogels have been widely applied in cartilage repair studies, showing promising results in terms of tissue integration and repair. PVA hydrogels, which offer low friction and are non-toxic to cells, have mechanical properties similar to those of cartilage, making them attractive implant materials.[124] Composite scaffolds made of BG fibers and PVA hydrogels exhibit high

mechanical performance, while the PVA matrix can control ion concentration by adjusting the release of ions from BG fibers (BGF). This biodegradable, glass fiber-reinforced hydrogel composite has shown strong cartilage repair capabilities, offering potential for medical applications.[125] A dual-network (DN) hydrogel system, comprising a layer of BG integrated with glycol-chitosan (GC) and benzaldehyde-functionalized polyepoxyethylene networks, as well as sodium alginate (Alg) and calcium chloride ($CaCl_2$), has been shown to not only promote cartilage regeneration but also support subchondral bone reconstruction.[126] Studies also demonstrate that a composite hydrogel consisting of BG/Alg injectable hydrogel combined with agarose (AG)/naringin hydrogel exhibits an adequate swelling ratio, facilitating the fusion of regenerated tissue with host cartilage. This composite hydrogel can enhance the typical chondrocyte phenotype by upregulating aggrecan, SRY-box 9, and collagen type II alpha chain. Furthermore, it may stimulate M2 macrophage polarization, reduce inflammation, and prevent ECM degradation by lowering the expression levels of inducible metalloproteinase-13 matrix, nitric oxide synthase, and metalloproteinase-1 matrix. When injected into a rat cartilage defect model, the resulting tissue is similar to normal cartilage, securely integrating with surrounding tissue while preserving the chondrocyte phenotype and controlling the host inflammatory response.

Within bioactive glass-hydrogel composites materials, design lessons from multifunctional hydrogel systems are directly applicable. For example, Yang *et. al*.[127] reported an ultra-durable, cell free hydrogel with rapid shape memory for cartilage repair. As shown in Fig. 6a, imidazolidinyl urea is incorporated into a polyurethane network based on PEG and MDI to create a hydrogen bond reinforced matrix, and co loading tannic acid and kartogenin yields PTK with high strength, stable cyclic mechanics suitable for minimally invasive delivery, tissue adhesion, and anti-inflammatory, antioxidant, and antibacterial activity. After implantation, tannic acid conditions the defect microenvironment and supports cell homing, while gradual degradation releases kartogenin to promote chondrogenic differentiation. In Figs. 6b and c, gross views show nonhealing defects in controls, minimal repair with the base PMI hydrogel, partial restoration with PKG and PTA that leaves irregular surfaces and visible margins, and smooth hyaline like cartilage that blends with adjacent tissue after PTK treatment. Fig. 6d shows Safranin O and Fast Green staining indicating a hyaline matrix of near normal thickness and a distinct cartilage to bone interface with PTK, whereas PTA exhibits calcific regions and PKG shows only partial cartilage formation. Fig. 6e demonstrates that type II collagen staining is negligible in control and PMI, intermediate with PKG and PTA, and continuous and intense with PTK. Quantitative analyses in Figs. 6f to i confirm superior outcomes for PTK, including the highest ICRS score, the lowest OARSI score, minimal defect width, and a marked increase in type II collagen intensity relative to control, PMI, PKG, and PTA. While this system does not contain bioactive glass, its modular reinforcement, multi bioactivity, and controlled release provide a useful template for BG hydrogel composites that aim to couple ion mediated bioactivity with robust mechanics and targeted biological cues. Altogether, these data demonstrate that bioactive glass-based scaffolds whether structured via 3D printing, integrated into injectable hydrogels, or engineered as bi-layered constructs promote effective osteochondral regeneration. Their ability to modulate inflammation, support chondrogenesis, and integrate structurally with native tissue underscores their promise in treating complex joint defects.

4.3 Bioactive Glass-Ceramic Composites

Bioceramics, known for their biocompatibility, bioactivity, and mechanical strength, are commonly used in bone tissue reconstruction. They can also support subchondral bone regeneration when combined with bioactive glass. Common bioceramic materials include hydroxyapatite, TCP and various BG formulations. Using 3D printing, Lina and colleagues developed scaffolds by combining copper-incorporated bioactive glass-ceramics (Cu-BGC) with sodium alginate. Their studies demonstrated that these Cu-BGC scaffolds promoted cartilage regeneration and enhanced the restoration of the osteochondral interface.[62] Clemens Gögele and colleagues prepared BG within the Si-B-Na-P system using a high-temperature melting method and fabricated it into porous scaffolds to assess its effects on chondrocytes. Results indicated that both primary articular chondrocytes (pACs) and human mesenchymal stem cells (hMSCs) could adhere to and proliferate on these scaffolds. After 28 days of co-culture, the pACs exhibited sustained expression of type II collagen and cartilage-specific proteoglycans, suggesting that their chondrogenic phenotype was successfully maintained.[101] Detailed biological responses triggered by BG and its composite materials in OA treatment are summarized in Table 2.

5. Challenges and conclusion

Despite significant advancements in the application of BG for OA repair, several challenges remain. Although BG demonstrates excellent biocompatibility in vitro, individual biological responses may vary in clinical settings. Certain

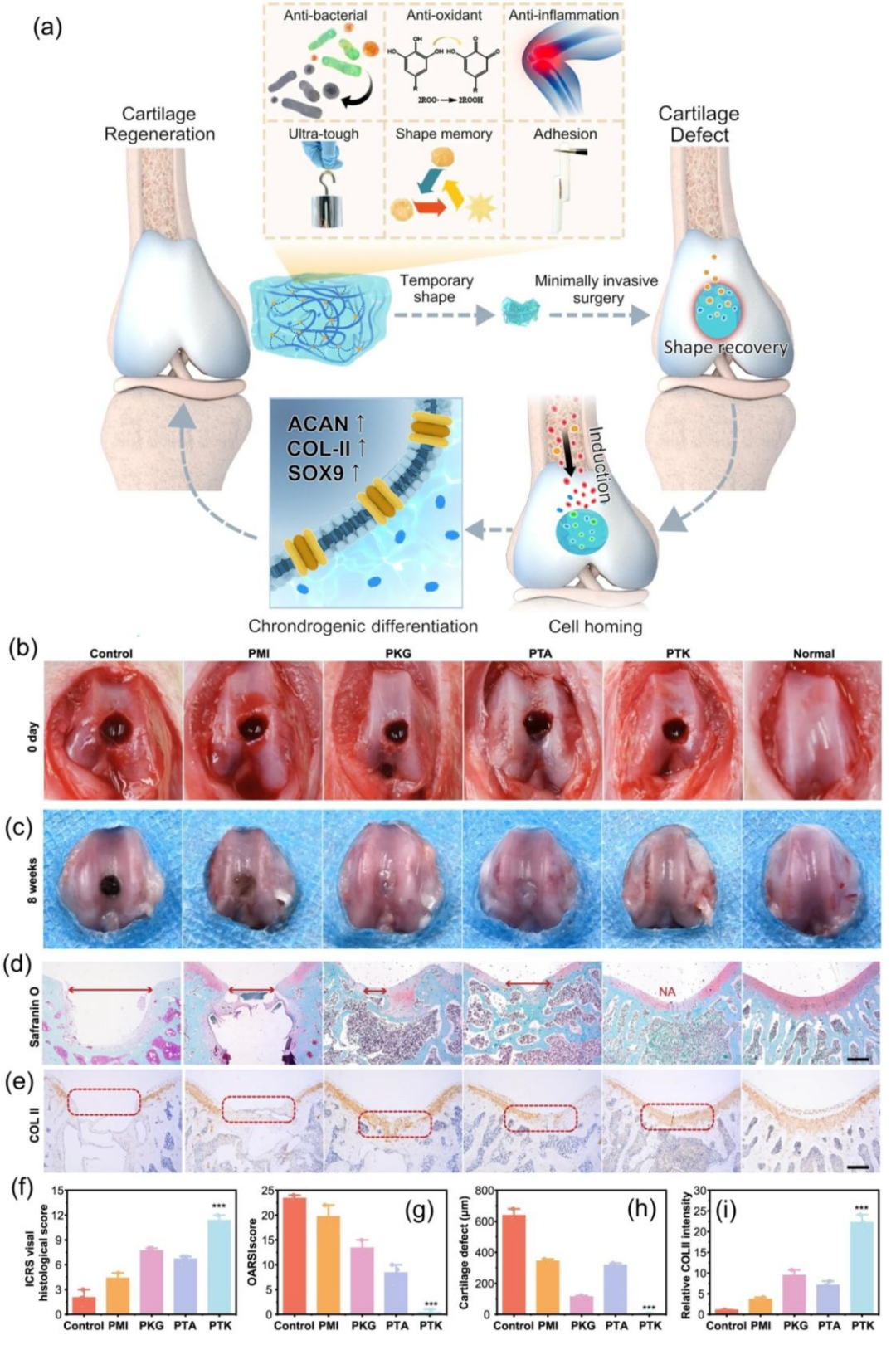

Fig. 6: (a) Illustration of Protein tyrosine kinase (PTK) hydrogel–mediated cell-free cartilage repair. The hydrogen-bonded network provides strong mechanics, adhesion, and anti-inflammatory, antioxidant, and antibacterial properties. (b, c) Gross images of rat knee joints at 0- and 8-weeks post-surgery under different treatments (scale bar: 2 mm). (d, e) Safranin O/Fast Green and COL II immunohistochemical staining of control, Phosphomannose isomerase (PMI), protein kinase G (PKG), phosphotungstic acid (PTA), and PTK groups (scale bar: 200 μm). (f–i) Quantitative analyses: ICRS and OARSI histological scores, defect width, andPKG relative COL II intensity. Adapted with permission under CC BY license. Adapted from ref. [127] with permission under CC BY license © 2023.

Table 2: Biological responses triggered by BG and composite materials in OA treatment.

Material	Major outcome	Reference
$CaO–SiO_2–P_2O_5$ combined with Polymer poly-L-lactide-co-glycolide (PLGA)	enhance hBMSC osteogenesis, modulate the osteogenic response of hBMSC	[118]
$SiO_2–CaO–P_2O_5$ combined with the viscoelastic low-crosslinked PEGS	reconstructed well-integrated articular hyaline cartilage and its subchondral bone in 12 weeks,	[119]
SiO_2-CaO-SrO-NaF mixed with HEMA to form glass ionomer cements (RMGICs)	extracts from the cements promote cell viabilit, showing desirable physical/mechanical properties with lower toxicity	[120]
$SiO_2–CaO–P_2O_5$ Complex with CS/Alg	The CSB composite cartilage scaffold requirements of cartilage tissue repair, promote the proliferation of cells	[128]
SiO_2-Na_2O-CaO-P_2O_5-SrO combined with collagen	High expression of osteocalcin, increase differentiation of stem cells to osteoblast	[129]
$8P_2O_5$-$12B_2O_3$-15MgO-14CaO-$1Na_2O$-$10Fe_2O_3$ strethened PVA hydrogel composites; $SiO2–CaO–P_2O_5$ conplexed with PVA hydrogel	Revealed a mechanical properties of human articular cartilage, support the proliferation of chondrocytes; Show better mechanical properties, support the proliferation of mice chondrocytes, upregulate the expression AGGRECAN, SOX9, COL2	[87,125]
$SiO_2–CaO–P_2O_5$mixed with DN hydrogel(included GC, dibenzaldhyde functionalized poly(ethylene oxide) and sodium alginate	promoting cartilage regeneration, better in repairing osteochondral defect	[126]
SiO_2-Na_2O-CaO-P_2O_5/Alg combined with AG/Naringin hydroge	upgrade SRY-box 9, and collagen type II alpha one chain. stimulate the polarization of M2 macrophage, lower inflammations, and decrease metalloproteinase-13 matrix, nitric oxide synthase, and metalloproteinase-1 matrix expressiom	[130]
3D printing SiO_2-CuO-CaO-P_2O_5/Alg scaffolds	improved cartilage regeneration, recovery of osteochondral interface	[62]
SiO_2-B_2O_3-CaO-P_2O_5 scaffold	pACs and hMSCs attached and proliferated on the scaffold, sustained type II collagen expression, maintained chondrogenic phenotype.	[101]
SiO_2-Na_2O-B_2O_5-P_2O_5-K_2O/ PLGA Scaffold	collagen type II, cartilage proteoglycans, the transcription factor SOX9 formed on the scafflods.	[131]
SiO_2-CaO-MgO nanospheres/DCECM	stimulate articular cartilage and subchondral bone regeneration	[132]
SiO_2-Na_2O-CaO-MgO-P_2O_5-K_2O-$L_{i2}O$ micronanofibers/hyaluronic acid	promote the chondrogenic behavior of ATDC5 cells	[132]
SiO_2-Na_2O-CaO-P_2O_5/ PHBV 3D porous scaffolds	Up regulate COL II (A), aggrecan (B), and the SOX-9 gene expression, promote cartilage matrix protein production and better biomechanical performance	[133]
PLCL/chondroitin sulfate/$SiO_2–CaO–B_2O_3–K_2O–P_2O_5–ZnO–SrO$	Promote calcified cartilage repair	[134]

patients may experience allergic reactions or immune rejection, which can compromise therapeutic outcomes.

Biocompatibility testing is a prerequisite for translating BG and BG composites into clinical use. Standard in vitro assays, such as MTT, XTT or other tetrazolium-based viability tests and Live/Dead staining, are used to evaluate cytotoxicity, cell adhesion and proliferation. According to ISO 10993-5 guidelines, a material passes cytotoxicity tests if cell viability remains at or above 70 % relative to controls. These assays are complemented by analyses of inflammatory cytokine expression and oxidative stress to determine immunological safety. In vivo studies, including subcutaneous and intra-articular implantation in small and large animal models, assess local tissue integration, degradation kinetics, immune responses and functional recovery. For devices that contact blood, hemocompatibility tests such as hemolysis and platelet activation assays are required. Evaluation criteria therefore include cell viability above 70 %, absence of chronic

inflammation or fibrotic encapsulation, and evidence of tissue regeneration. Composite systems (for example, BG–polymer or BG–ceramic) are additionally assessed for mechanical stability, sustained ion release and their ability to synergistically promote chondrogenesis and osteogenesis.

Additionally, long-term BG implants could potentially lead to chronic inflammatory responses, raising concerns about their safety. Current research predominantly addresses short-term outcomes, and data on the long-term stability and efficacy of BG in vivo are limited. Extended use may lead to degradation of products negatively impacting surrounding tissue or unexpectedly affecting joint function. Therefore, more longitudinal studies are needed to assess the long-term safety and effectiveness of BG materials.

Several other barriers currently limit the large-scale clinical use of BG. Manufacturing BG on an industrial scale is complicated by high melting temperatures and the need for strict compositional control, and producing uniform, porous scaffolds in large batches remain challenging and costly.

The intrinsic brittleness of melt-derived BG scaffolds makes them unsuitable for load-bearing sites, and tougher composites are required to achieve mechanical resilience. Biological variability also remains an obstacle: individual immune responses vary, and some patients may exhibit inflammatory reactions or delayed integration. Long term safety data are sparse, and the balance between BG degradation kinetics and tissue regeneration is not yet optimized. Regulatory hurdles add to these challenges; obtaining approval requires extensive large animal studies and costly, multicenter clinical trials, particularly because no predicate load-bearing implant exists to expedite approval.

Moreover, the heterogeneity in OA progression and patient biology demands customizable BG solutions. Most BG materials are designed as general-purpose products, lacking specificity for individualized treatment. Developing BG with tailored compositions and release profiles to accommodate different clinical needs is therefore essential for future research.

To address these challenges, future studies should focus on optimizing BG materials through artificial-intelligence–assisted design and high throughput experimentation. Machine learning can guide compositional tuning to enhance bioactivity, mechanical strength, degradation rate and immunomodulatory properties. Combining BG with polymers or ceramics can yield composites with improved flexibility and mechanical stability while maintaining ion release and bioactivity. Novel fabrication techniques such as sol–gel synthesis, electrospinning, stereolithographic three-dimensional printing and other additive manufacturing methods hold promise for scalable, cost-effective production of patient specific scaffolds. Reducing production costs by refining melting techniques, using lower-cost raw materials and optimizing manufacturing protocols will also accelerate translation. Finally, rigorous clinical evaluation including large scale, multicenter trials is needed to establish the safety, efficacy and cost effectiveness of BG-based treatments across diverse patient populations.

Bioactive glass, with its superior bioactivity and regenerative capabilities, has demonstrated great potential in OA treatment. Current research focuses on BG's ability to promote cartilage repair, suppress inflammatory responses and enhance localized drug delivery efficiency. Future research may involve further optimization of BG composition, exploring the effects of various doped ions on cartilage repair, and developing BG composites to improve mechanical performance and biocompatibility. Although most studies are currently based on animal models, BG's potential for clinical application is gradually becoming apparent.

Acknowledgements

This work was supported by the support of Postdoctoral Fellowship Program (Grade C) of China Postdoctoral Science (GZC20232719 to Ruiguo Chen). Provincial Natural Science Foundation of Anhui (2408085MC060 to Kun Ma). National Key R&D Program of China (2023YF1607500 to Junfeng Wang). Research Fund for International scientists; W2433142 to S. R. The "Foreign Youth Talent Plan" initiative of the National Bureau of Foreign Experts Affairs (QN2023061007L granted to S. R). Anhui Provincial Key Research and Development Program (2023z04020016 to Junfeng Wang). A portion of this work was performed on the Steady High Magnetic Field Facility, the High Magnetic Field Laboratory, CAS.

Further, the authors would like to acknowledge the use of artificial intelligence (AI) tools in assisting with the refinement of this manuscript and Biorender for schematic illustrations. The authors affirm that the final content, including its authenticity, accuracy, and interpretation, is entirely the responsibility of the authors. All analyses and conclusions were thoroughly reviewed, revised, and validated by the authors to ensure the manuscript meets the highest standards of scientific integrity and accuracy.

Conflict of Interest

There is no conflict of interest.

Supporting Information

Applicable.

CRediT Statement

Ruiguo Chen: Funding acquisition, conceptualization, original draft writing, data curation, editing, and revising. **Ling Pen:** Data curation, formal analysis, and investigation. **Rana Ahmed tauseen:** Analysis and support in original draft writing. **Sajid ur Rehman:** Support in data curation, investigation, and original draft writing. **Fu Zhang:** Investigation and support in original draft writing. **Junfeng Wang:** Support in funding acquisition, supervision of the original draft, and editing. **Kun Ma:** Lead in conceptualization, data curation, formal analysis, support in funding acquisition, and writing–review & editing.

References

[1] F. Motta, E. Barone, A. Sica, C. Selmi, Inflammaging and Osteoarthritis, *Clinical Reviews in Allergy & Immunology*, 2023, **64**, 222-238, doi: 10.1007/s12016-022-08941-1.

[2] A. Latourte, M. Kloppenburg, P. Richette, Emerging pharmaceutical therapies for osteoarthritis, *Nature Reviews Rheumatology*, 2020, **16**, 673-688, doi: 10.1038/s41584-020-00518-6.

[3] L. Sharma, Osteoarthritis of the knee, *New England Journal of Medicine*, 2021**, 384**, 51-59, doi: 10.1056/NEJMcp1903768.

[4] H. Lorenz, W. Richter, Osteoarthritis: Cellular and molecular changes in degenerating cartilage, *Progress in Histochemistry and Cytochemistry*, 2006, **40**, 135-163, doi: 10.1016/j.proghi.2006.02.003.

[5] D. Sok, S. Raval, J. McKinney, H. Drissi, A. Mason, K. Mautner, J. M. Kaiser, N. J. Willett, NSAIDs reduce therapeutic efficacy of mesenchymal stromal cell therapy in a rodent model of posttraumatic osteoarthritis, *The American Journal of Sports Medicine*, 2022, **50**, 1389-1398, doi: 10.1177/03635465221083610.

[6] G. O. Cioroianu, A. Florescu, C. E. Simionescu, T. N. Sas, D. N. Tarniță, O. C. Rogoveanu, The therapeutic benefits of NSAIDs and physical therapy in knee osteoarthritis, *Romanian Journal of Morphology and Embryology*, 2024, **65**, 217-224, doi: 10.47162/RJME.65.2.08.

[7] E. Tajik, Z. Vaezi, M. Tabarsa, A. Hekmat, H. Naderi-Manesh, Grafting of sinapic acid onto glucosamine nanoparticle as a potential therapeutic drug with enhanced anti-inflammatory activities in osteoarthritis treatment, *International Journal of Biological Macromolecules*, 2023, **253**, 127454, doi: 10.1016/j.ijbiomac.2023.127454.

[8] S. Muthu, J. V. Korpershoek, E. J. Novais, G. F. Tawy, A. P. Hollander, I. Martin, Failure of cartilage regeneration: emerging hypotheses and related therapeutic strategies, *Nature Reviews Rheumatology*, 2023, **19**, 403-416, doi: 10.1038/s41584-023-00979-5.

[9] A. Emami, H. Namdari, F. Parvizpour, Z. Arabpour, Challenges in osteoarthritis treatment, *Tissue and Cell*, 2023, **80**, 101992, doi: 10.1016/j.tice.2022.101992.

[10] C. S. Li, Y. Xu, J. Li, S. H. Qin, S. W. Huang, X. M. Chen, Y. Luo, C. T.Gao, J. H. Xiao, Ultramodern natural and synthetic polymer hydrogel scaffolds for articular cartilage repair and regeneration, *BioMedical Engineering OnLine*, 2025**, 24**, 1-26, doi: 10.1186/s12938-025-01342-3.

[11] R. D.Prasad, R. S. Prasad, R. B. Prasad, S. R. Prasad, S. B. Singha, D. Singha, R. J. Prasad, P. Sinha, S. Saxena, A. K. Vaidya, B T. Shivanand, R. S. Umapati, H. Avinash, M. B. Deshmukh, M. N. Padvi, G. J. Navathe, A Review on Modern Characterization Techniques for Analysis of Nanomaterials and Biomaterials, *ES Energy & Environment*, 2024, **23**, 1087, doi: 10.30919/esee1087.

[12] M. Ansari, A. Darvishi, A. Sabzevari, A review of advanced hydrogels for cartilage tissue engineering, *Frontiers in Bioengineering and Biotechnology*, 2024, **12**, 1340893, doi: 10.3389/fbioe.2024.1340893.

[13] Z. Guo, J. Han, Z. Li, Y. Sun, R. Chen, S. ur Rehman, H. Xia, J. Zhang, K. Ma, J. Wang, Borate bioactive glass enhances 3D bioprinting precision and biocompatibility on a sodium alginate platform via Ca2+ controlled self-solidification, *International Journal of Biological Macromolecules*, 2024, **277**, 134338, doi: 10.1016/j.ijbiomac.2024.134338.

[14] M. Ansari, M. Eshghanmalek, Biomaterials for repair and regeneration of the cartilage tissue, *Bio-Design and Manufacturing*, 2019, **2**, 41-49, doi: 10.1007/s42242-018-0031-0.

[15] J. Zhu, Y. Zhao, W. Zhang, X. Gu, T. Gao, J. Kong, D. Quan, Bio-inspired feature-driven topology optimization for rudder structure design, *Engineered Science*, 2019, **5**, 46-55, doi: 10.30919/es8d716.

[16] P. P. Bag, G. P. Singh, S. Singha, G. Roymahapatra, Synthesis of metal-organic frameworks (MOFs) and their biological, catalytic and energetic application: a mini review, *Engineered Science*, 2021, **13**, 1-10, doi: 10.30919/es8d1166.

[17] Y. Zhu, X. Zhang, G. Chang, S. Deng, H. F. Chan, Bioactive glass in tissue regeneration: unveiling recent advances in regenerative strategies and applications, *Advanced Materials*, 2025, **37**, 2312964, doi: 10.1002/adma.202312964.

[18] V. M. Schatkoski, T. Larissa do Amaral Montanheiro, B. R. Canuto de Menezes, R. M. Pereira, K. F. Rodrigues, R. G. Ribas, D. Morais da Silva, G. P. Thim, Current advances concerning the most cited metal ions doped bioceramics and silicate-based bioactive glasses for bone tissue engineering, *Ceramics International*, 2021, **47**, 2999-3012, doi: 10.1016/j.ceramint.2020.09.213.

[19] T. Tao, S. ur Rehman, S. Xu, J. Zhang, H. Xia, Z. Guo, Z. Li, K. Ma, J. Wang, A biomimetic camouflaged metal organic

framework for enhanced siRNA delivery in the tumor environment, *Journal of Materials Chemistry B*, 2024, **12**, 4080-4096, doi: 10.1039/D3TB02827E.

[20] N. Yildirim, A. Amanzhanova, G. Kulzhanova, F. Mukasheva, C. Erisken, Osteochondral interface: regenerative engineering and challenges, *ACS Biomaterials Science & Engineering*, 2023, **9**, 1205-1223, doi: 10.1021/acsbiomaterials.2c01321.

[21] R. Chijimatsu, T. Saito, Mechanisms of synovial joint and articular cartilage development, *Cellular and Molecular Life Sciences*, 2019, **76**, 3939-3952, doi: 10.1007/s00018-019-03191-5.

[22] C. T. Thorpe, H. R. Screen, Tendon structure and composition, *Metabolic influences on risk for tendon disorders*, 2016, **920**, 3-10, doi: 10.1007/978-3-319-33943-6_1.

[23] H. Akkiraju, A. Nohe, Role of chondrocytes in cartilage formation, progression of osteoarthritis and cartilage regeneration, *Journal of Developmental Biology*, 2015, **3**, 177-192, doi: 10.3390/jdb3040177.

[24] A. J. Sophia Fox, A. Bedi, S. A. Rodeo, The basic science of articular cartilage: structure, composition, and function, *Sports Health*, 2009, **1**, 461-468, doi: 10.1177/1941738109350438.

[25] Z. Chen, F. Yan, Y. Lu, The function of mechanical loading on chondrogenesis, *Front Biosci (Landmark Ed)*, 2016, **21**, 1222-1232, doi: 10.2741/4452.

[26] H. K. Gahunia, K. P. H. Pritzker, Effect of exercise on articular cartilage, *Orthopedic Clinics of North America*, 2012, **43**, 187-199, doi: 10.1016/j.ocl.2012.03.001.

[27] S. R. Tew, A. P. L. Kwan, A. Hann, B. M. Thomson, C. W. Archer, The reactions of articular cartilage to experimental wounding: role of apoptosis, *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 2000, **43**, 215-225, doi: 10.1002/1529-0131(200001)43:1<215::AID-ANR26>3.0.CO;2-X.

[28] N. Maruotti, A. Corrado, F. P. Cantatore, Osteoblast role in osteoarthritis pathogenesis, *Journal of Cellular Physiology*, 2017, **232**, 2957-2963, doi: 10.1002/jcp.25969.

[29] S. Junker, G. Krumbholz, K. W. Frommer, S. Rehart, J. Steinmeyer, M. Rickert, G. Schett, U. Müller-Ladner, E. Neumann, Differentiation of osteophyte types in osteoarthritis–proposal of a histological classification, *Joint Bone Spine*, 2016, **83**, 63-67, doi: 10.1016/j.jbspin.2015.04.008.

[30] R. F. Loeser, J. A. Collins, B. O. Diekman, Ageing and the pathogenesis of osteoarthritis, *Nature Reviews Rheumatology*, 2016, **12**, 412-420, doi: 10.1038/nrrheum.2016.65.

[31] A. T. Toivanen, M. Heliovaara, O. Impivaara, J. P. A. Arokoski, P. Knekt, H. Lauren, H. Kroger, Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis: a population-based study with a follow-up of 22 years, *Rheumatology*, 2010, **49**, 308-314, doi: 10.1093/rheumatology/kep388.

[32] L. L. Hench, The story of Bioglass®, *Journal of Materials Science: Materials in Medicine*, 2006**,** **17**, 967-978, doi: 10.1007/s10856-006-0432-z.

[33] Q. Fu, M. N. Rahaman, B. S. Bal, R. F. Brown, D. E. Day, Mechanical and in vitro performance of 13–93 bioactive glass scaffolds prepared by a polymer foam replication technique, *Acta Biomaterialia*, 2008, **4**, 1854-1864, doi: 10.1016/j.actbio.2008.04.019.

[34] J. R. Jones, Review of bioactive glass: from Hench to hybrids, *Acta biomaterialia*, 2013, **9**, 4457-4486, doi: 10.1016/j.actbio.2012.08.023.

[35] S. Sen, R. E. Youngman, NMR study of Q-speciation and connectivity in K2O–SiO2 glasses with high silica content, *Journal of non-crystalline solids*, 2003, **331**, 100-107, doi:10.1016/j.jnoncrysol.2003.08.071.

[36] W. Huang, D. E. Day, K. Kittiratanapiboon, M. N. Rahaman, Kinetics and mechanisms of the conversion of silicate (45S5), borate, and borosilicate glasses to hydroxyapatite in dilute phosphate solutions, *Journal of Materials Science: Materials in Medicine*, 2006, **17**, 583-596, doi: 10.1007/s10856-006-9220-z .

[37] S. ur Rehman, S. Xu, H. Xu, T. Tao, Y. Li, Z. Yu, K. Ma, W. Xu, J. Wang, The Role of NMR in Metal Organic Frameworks: Deep Insights into Dynamics, Structure and Mapping of Functional Groups, *Materials Today Advances*, 2022, **16**, 100287, doi: 10.1016/j.mtadv.2022.100287.

[38] J. C. Knowles, Phosphate based glasses for biomedical applications, *Journal of Materials Chemistry*, 2003, **13**, 2395-2401, doi: 10.1039/B307119G.

[39] B. C. Bunker, G. W. Arnold, J. A. Wilder, Phosphate glass dissolution in aqueous solutions, *Journal of Non-Crystalline Solids*, 1984, **64**, 291-316, doi: 10.1016/0022-3093(84)90184-4.

[40] H. Gao, T. Tan, D. Wang, Dissolution mechanism and release kinetics of phosphate controlled release glasses in aqueous medium, *Journal of controlled release*, 2004, **96**, 29-36, doi: 10.1016/j.jconrel.2003.12.031 .

[41] R. Chen, L. Sun, R. Tan, S. Xu, H. Xu, X. Zhao, T. Tao, Q. Zhang, H. Xia, J. Han, C. Liu, Z. Yu, H. Zhan, K. Ma, J. Wang, Mechanistic study of the bioactivity improvement of Al_2O_3-doped BBG after dynamic flow treatment, *Ceramics International*, 2023, **49**, 773-782, doi: 10.1016/j.ceramint.2022.09.049.

[42] R. Chen, Q. Li, Q. zhang, S. Xu, J. Han, P. Huang, Z. Yu, D. Jia, J. Liu, H. Jia, M. Shen, B. Hu, H. Wang, H. Zhan, T. Zhang, K. Ma, J. Wang, Nanosized HCA-coated borate bioactive glass with improved wound healing effects on rodent model, *Chemical Engineering Journal*, 2021, **426**, 130299, doi: 10.1016/j.cej.2021.130299.

[43] S. I. Schmitz, B. Widholz, C. Essers, M. Becker, D. U. Tulyaganov, A. Moghaddam, I. Gonzalo de Juan, F. Westhauser, Superior biocompatibility and comparable osteoinductive properties: Sodium-reduced fluoride-containing bioactive glass belonging to the CaO–MgO–SiO_2 system as a promising alternative to 45S5 bioactive glass, *Bioactive Materials*, 2020, **5**, 55-65, doi: 10.1016/j.bioactmat.2019.12.005.

[44] V. Bunpetch, X. Zhang, T. Li, J. Lin, E. P. Maswikiti, Y. Wu, H. Ouyang, Silicate-based bioceramic scaffolds for dual-lineage regeneration of osteochondral defect, *Biomaterials*, 2019, **192**, 323-333, doi: 10.1016/j.biomaterials.2018.11.025 .

[45] C. Deng, Q. Yang, X. Sun, L. Chen, C. Feng, J. Chang, C.Wu, Bioactive scaffolds with Li and Si ions-synergistic effects for osteochondral defects regeneration, *Applied Materials Today*, 2018, **10**, 203-216 doi: 10.1016/j.apmt.2018.04.003.

[46] Z. Cai, Y. Li, W. Song, Y. He, H. Li, X. Liu, Anti-inflammatory and prochondrogenic in situ-formed injectable hydrogel crosslinked by strontium-doped bioglass for cartilage regeneration, *ACS applied materials & interfaces*, 2021, **13**, 59772-59786, doi: 10.1021/acsami.1c20565.

[47] C. Matta, R. Zakany, Calcium signalling in chondrogenesis: implications for cartilage repair, *Front Biosci (Schol Ed)*, 2013, **5**, 305-324 doi: 10.2741/S374.

[48] C.Yin, X. Jia, Q. Zhao, Z. Zhao, J. Wang, Y. Zhang, Z. Li, Transcription factor 7-like 2 promotes osteogenic differentiation and boron-induced bone repair via lipocalin 2, *Materials Science and Engineering: C*, 2020, **110**, 110671.doi: 10.1016/j.msec.2020.110671.

[49] Zhu D, Ansari AR, Xiao K, Wang W, Wang L, Qiu W, Peng K. B, Boron supplementation promotes osteogenesis of tibia by regulating the bone morphogenetic protein-2 expression in African ostrich chicks, *Biological Trace Element Research*, 2021, **199**, 1544-1555. doi: 10.1007/s12011-020-02258-w

[50] G. Erdem Koc, A. Gokcimen, F. Sahin, The effect of boric acid and sodium pentaborate pentahydrate-treated foreskin derived mesenchymal stem cells on liver fibrosis, *Biological Trace Element Research*, 2023, **201**, 4834-4849, doi: 10.1007/s12011-023-03565-8.

[51] H. Yu, Y. Liu, X. Yang, J. He, F. Zhang, Q. Zhong, X. Guo, Strontium ranelate promotes chondrogenesis through inhibition of the Wnt/β-catenin pathway, *Stem Cell Research & Therapy*, 2021, **12**, 296, doi: 10.1186/s13287-021-02372-z.

[52] X. Cui, Y. Zhang, J. Wang, C. Huang, Y. Wang, H. Yang, W. Liu, T. Wang, D. Wang, G. Wang, C. Ruan, D. Chen, W. W. Lu, W. Huang, M. N. Rahaman, H. Pan, Strontium modulates osteogenic activity of bone cement composed of bioactive borosilicate glass particles by activating Wnt/β-catenin signaling pathway, *Bioactive Materials*, 2020, **5**, 334-347, doi: 10.1016/j.bioactmat.2020.02.016.

[53] B. Kołodziejska, N. Stępień, J. Kolmas, The influence of strontium on bone tissue metabolism and its application in osteoporosis treatment, *International Journal of Molecular Sciences*, 2021, **22**, 6564, doi: 10.3390/ijms22126564.

[54] J. Zhao, H. Wu, L. Wang, D. Jiang, W. Wang, G. Yuan, J. Pei, W. Jia, The beneficial potential of magnesium-based scaffolds to promote chondrogenesis through controlled Mg^{2+} release in eliminating the destructive effect of activated macrophages on chondrocytes, *Biomaterials Advances*, 2022, **134**, 112719, doi: 10.1016/j.msec.2022.112719.

[55] Z. Liao, L. Fu, P. Li, J. Wu, X. Yuan, C. Ning, Z. Ding, X. Sui, S. Liu, Q. Guo, Incorporation of magnesium ions into an aptamer-functionalized ECM bioactive scaffold for articular cartilage regeneration, *ACS Applied Materials & Interfaces,* 2023, **15**, 22944-22958, doi: 10.1021/acsami.3c02317.

[56] B. Chen, Y. Liang, J. Zhang, L. Bai, M. Xu, Q. Han, X. Han, J. Xiu, M. Li, X. Zhou, B. Guo, Z. Yin, Synergistic enhancement of tendon-to-bone healing *via* anti-inflammatory and pro-differentiation effects caused by sustained release of Mg^{2+}/curcumin from injectable self-healing hydrogels, *Theranostics*, 2021, **11**, 5911-5925, doi: 10.7150/thno.56266.

[57] L. Ma, Y. Tan, Q. Tong, X. Cao, D. Liu, X. Ma, X. Jiang, X. Li, Collagen scaffolds functionalized by Cu^{2+}-chelated EGCG nanoparticles with anti-inflammatory, anti-oxidation, vascularization, and anti-bacterial activities for accelerating wound healing, *Advanced Healthcare Materials*, 2024, **13**, 2303297, doi: 10.1002/adhm.202303297.

[58] B. Salesa, R. S. I. Serra, Á. Serrano-Aroca, Zinc chloride: time-dependent cytotoxicity, proliferation and promotion of glycoprotein synthesis and antioxidant gene expression in human keratinocytes, *Biology*, 2021, **10**, 1072, doi: 10.3390/biology10111072.

[59] S. D. Schussler, K. Uske, P. Marwah, F. W. Kemp, J. D. Bogden, S. S. Lin, T. Livingston Arinzeh, Controlled release of vanadium from a composite scaffold stimulates mesenchymal stem cell osteochondrogenesis, *The AAPS Journal*, 2017, **19**, 1017-1028, doi: 10.1208/s12248-017-0073-9.

[60] W. Zhai, H. Lu, C. Wu, L. Chen, X. Lin, K. Naoki, G. Chen, J. Chang, Stimulatory effects of the ionic products from Ca–Mg–Si bioceramics on both osteogenesis and angiogenesis *in vitro*, *Acta Biomaterialia*, 2013, **9**, 8004-8014, doi: 10.1016/j.actbio.2013.04.024.

[61] D. Zhai, L. Chen, Y. Chen, Y. Zhu, Y. Xiao, C. Wu, Lithium silicate-based bioceramics promoting chondrocyte maturation by immunomodulating M2 macrophage polarization, *Biomaterials Science*, 2020, **8**, 4521-4534, doi: 10.1039/D0BM00450B.

[62] R. Lin, C. Deng, X. Li, Y. Liu, M. Zhang, C. Qin, Q. Yao, L. Wang, C. Wu, Copper-incorporated bioactive glass-ceramics inducing anti-inflammatory phenotype and regeneration of

cartilage/bone interface, *Theranostics*, 2019, **9**, 6300-6313, doi: 10.7150/thno.36120.

[63] D. J. Baylink, R. D. Finkelman, S. Mohan, Journal of bone and mineral research, *Journal of Bone and Mineral Research*, 1993, **8**, S565-S572, doi: 10.1002/jbmr.5650081326.

[64] Y. Yoshiko, G. A. Candeliere, N. Maeda, J. E. Aubin, Osteoblast autonomous P_i regulation *via* Pit1 plays a role in bone mineralization, *Molecular and Cellular Biology*, 2007, **27**, 4465-4474, doi: 10.1128/mcb.00104-07.

[65] D. Wang, L. Canaff, D. Davidson, A. Corluka, H. Liu, G. N. Hendy, J. E. Henderson, Alterations in the sensing and transport of phosphate and calcium by differentiating chondrocytes, *Journal of Biological Chemistry*, 2001, **276**, 33995-34005, doi: 10.1074/jbc.m007757200.

[66] M. Korkmaz, R. Turkmen, H. H. Demirel, Z. K. Saritas, Effect of boron on the repair of osteochondral defect and oxidative stress in rats: an experimental study, *Biological Trace Element Research*, 2019, **187**, 425-433, doi: 10.1007/s12011-018-1381-3.

[67] C. Wang, B. Chen, W. Wang, X. Zhang, T. Hu, Y. He, K. Lin, X. Liu, Strontium released bi-lineage scaffolds with immunomodulatory properties induce a pro-regenerative environment for osteochondral regeneration, *Materials Science and Engineering: C*, 2019, **103**, 109833, doi: 10.1016/j.msec.2019.109833.

[68] F. Zhao, B. Lei, X. Li, Y. Mo, R. Wang, D. Chen, X. Chen, Promoting *in vivo* early angiogenesis with sub-micrometer strontium-contained bioactive microspheres through modulating macrophage phenotypes, *Biomaterials*, 2018, **178**, 36-47, doi: 10.1016/j.biomaterials.2018.06.004.

[69] P. Han, C. Wu, J. Chang, Y. Xiao, The cementogenic differentiation of periodontal ligament cells *via* the activation of Wnt/β-catenin signalling pathway by Li+ ions released from bioactive scaffolds, *Biomaterials*, 2012, **33**, 6370-6379, doi: 10.1016/j.biomaterials.2012.05.061.

[70] L. Liu, Y. Liu, C. Feng, J. Chang, R. Fu, T. Wu, F. Yu, X. Wang, L. Xia, C. Wu, B. Fang, Lithium-containing biomaterials stimulate bone marrow stromal cell-derived exosomal miR-130a secretion to promote angiogenesis, *Biomaterials*, 2019, **192**, 523-536, doi: 10.1016/j.biomaterials.2018.11.007.

[71] S. Yoshizawa, A. Brown, A. Barchowsky, C. Sfeir, Magnesium ion stimulation of bone marrow stromal cells enhances osteogenic activity, simulating the effect of magnesium alloy degradation, *Acta Biomaterialia*, 2014, **10**, 2834-2842, doi: 10.1016/j.actbio.2014.02.002.

[72] L. Wu, F. Feyerabend, A. F. Schilling, R. Willumeit-Römer, B. J. C. Luthringer, Effects of extracellular magnesium extract on the proliferation and differentiation of human osteoblasts and osteoclasts in coculture, *Acta Biomaterialia*, 2015, **27**, 294-304, doi: 10.1016/j.actbio.2015.08.042.

[73] C. Vinci, V. Caltabiano, A. M. Santoro, A. M. Rabuazzo, M. Buscema, R. Purrello, E. Rizzarelli, R. Vigneri, F. Purrello, Copper addition prevents the inhibitory effects of interleukin 1-b on rat pancreatic islets, *Diabetologia*, 1995, **38**, 39-45, doi: 10.1007/s001250050251.

[74] V. Ciaffaglione, E. Rizzarelli, Carnosine, zinc and copper: a menage a trois in bone and cartilage protection, *International Journal of Molecular Sciences*, 2023, **24**, 16209, doi: 10.3390/ijms242216209.

[75] M. Foster, S. Samman, Zinc and regulation of inflammatory cytokines: implications for cardiometabolic disease, *Nutrients*, 2012, **4**, 676-694, doi: 10.3390/nu4070676.

[76] Y.-W. Yan, J. Fan, S.-L. Bai, W.-J. Hou, X. Li, H. Tong, Zinc prevents abdominal aortic aneurysm formation by induction of A20-mediated suppression of NF-κB pathway, *PLoS One*, 2016, **11**, e0148536, doi: 10.1371/journal.pone.0148536.

[77] M. Yamaguchi, M. N. Weitzmann, Zinc stimulates osteoblastogenesis and suppresses osteoclastogenesis by antagonizing NF-κB activation, *Molecular and Cellular Biochemistry*, 2011, **355**, 179-186, doi: 10.1007/s11010-011-0852-z.

[78] M. Dutra-Correa, A. A. B. V. Leite, S. P. H. M. de Cara, I. M. A. Diniz, M. M. Marques, I. B. Suffredini, M. S. Fernandes, S. H. Toma, K. Araki, I. S. Medeiros, Antibacterial effects and cytotoxicity of an adhesive containing low concentration of silver nanoparticles, *Journal of Dentistry*, 2018, **77**, 66-71, doi: 10.1016/j.jdent.2018.07.010.

[79] L. Jia, Z. Duan, D. Fan, Y. Mi, J. Hui, L. Chang, Human-like collagen/nano-hydroxyapatite scaffolds for the culture of chondrocytes, *Materials Science and Engineering: C*, 2013, **33**, 727-734, doi: 10.1016/j.msec.2012.10.025.

[80] D. D. Hu, J. R. Hoyer, J. W. Smith, Phosphatidylinositol 4,5-bisphosphate is a key component in the activation of cytosolic phospholipase A_2 by store-operated calcium entry in human monocytes, *Journal of Biological Chemistry*, 1995, ***270***, 9917-9925. doi: 10.1074/jbc.270.17.9917.

[81] J. Li, J. Li, Y. Wei, N. Xu, J. Li, X. Pu, J. Wang, Z. Huang, X. Liao, G. Yin, Ion release behavior of vanadium-doped mesoporous bioactive glass particles and the effect of the released ions on osteogenic differentiation of BMSCs *via* the FAK/MAPK signaling pathway, *Journal of Materials Chemistry. B*, 2021, **9**, 7848-7865, doi: 10.1039/d1tb01479j.

[82] A. D. Kohn, R. T. Moon, Wnt and calcium signaling: β-catenin-independent pathways, *Cell Calcium*, 2005, **38**, 439-446, doi: 10.1016/j.ceca.2005.06.022.

[83] R. Detsch, P. Stoor, A. Grünewald, J. A. Roether, N. C. Lindfors, A. R. Boccaccini, Increase in VEGF secretion from human fibroblast cells by bioactive glass S53P4 to stimulate

angiogenesis in bone, *Journal of Biomedical Materials Research Part A*, 2014, **102**, 4055-4061, doi: 10.1002/jbm.a.35069.

[84] V. Christen, M. Camenzind, K. Fent, Silica nanoparticles induce endoplasmic reticulum stress response, oxidative stress and activate the mitogen-activated protein kinase (MAPK) signaling pathway, *Toxicology Reports*, 2014, **1**, 1143-1151, doi: 10.1016/j.toxrep.2014.10.023.

[85] J. Chen, Y. Wang, T. Tang, B. Li, B. Kundu, S. C. Kundu, R. L. Reis, X. Lin, H. Li, Enhanced effects of slowly co-released TGF-β3 and BMP-2 from biomimetic calcium phosphate-coated silk fibroin scaffolds in the repair of osteochondral defects, *Journal of Nanobiotechnology*, 2024, **22**, 453, doi: 10.1186/s12951-024-02712-0.

[86] M. Sarmast Sh, A. B. Dayang Radiah, D. A. Hoey, N. Abdullah, H. S. Zainuddin, S. Kamarudin, The structural, mechanical, and biological variation of silica bioglasses obtained by different sintering temperatures, *Journal of Sol-Gel Science and Technology*, 2024, **112**, 289-310, doi: 10.1007/s10971-024-06480-z.

[87] B. Lin, H. Hu, Z. Deng, L. Pang, H. Jiang, D. Wang, J. Li, Z. Liu, H. Wang, X. Zeng, Novel bioactive glass cross-linked PVA hydrogel with enhanced chondrogenesis properties and application in mice chondrocytes for cartilage repair, *Journal of Non-Crystalline Solids*, 2020, **529**, 119594, doi: 10.1016/j.jnoncrysol.2019.119594.

[88] Y. Mu, Z. Du, L. Xiao, W. Gao, R. Crawford, Y. Xiao, The localized ionic microenvironment in bone modelling/remodelling: a potential guide for the design of biomaterials for bone tissue engineering, *Journal of Functional Biomaterials*, 2023, **14**, 56, doi: 10.3390/jfb14020056.

[89] M. Setayeshmehr, E. Esfandiari, M. Rafieinia, B. Hashemibeni, A. Taheri-Kafrani, A. Samadikuchaksaraei, D. L. Kaplan, L. Moroni, M. T. Joghataei, Hybrid and composite scaffolds based on extracellular matrices for cartilage tissue engineering, *Tissue Engineering Part B: Reviews*, 2019, **25**, 202-224, doi: 10.1089/ten.teb.2018.0245.

[90] M. S. Carvalho, J. M. Cabral, C. L. da Silva, D. Vashishth, Bone Matrix Non-Collagenous Proteins in Tissue Engineering: Creating New Bone by Mimicking the Extracellular Matrix, *Polymers,* 2021, **13**, 1095, doi: 10.3390/polym13071095.

[91] R. E. Wilusz, J. Sanchez-Adams, F. Guilak, The structure and function of the pericellular matrix of articular cartilage, *Matrix Biology*, 2014, **39**, 25-32, doi: 10.1016/j.matbio.2014.08.009.

[92] H. Muir, The chondrocyte, architect of cartilage. Biomechanics, structure, function and molecular biology of cartilage matrix macromolecules, *BioEssays*, 1995, **17**, 1039-1048, doi: 10.1002/bies.950171208.

[93] H. Madry, A. Rey-Rico, J. K. Venkatesan, B. Johnstone, M. Cucchiarini, Transforming growth factor beta-releasing scaffolds for cartilage tissue engineering, *Tissue Engineering Part B: Reviews*, 2014, **20**, 106-125, doi: 10.1089/ten.teb.2013.0271.

[94] S. Asada, K. Fukuda, F. Nishisaka, M. Matsukawa, C. Hamanisi, Hydrogen peroxide induces apoptosis of chondrocytes; involvement of calcium ion and extracellular signal-regulated protein kinase, *Inflammation Research*, 2001, **50**, 19-23, doi: 10.1007/s000110050719.

[95] A. Shimazaki, M. O. Wright, K. Elliot, D. M. Salter, S. J. Millward-Sadler, Calcium/calmodulin-dependent protein kinase II in human articular chondrocytes, *Biorheology*, 2006, **43**, 223-233, doi: 10.1177/0006355x2006043003004007.

[96] J. Li, L. Wei, J. Sun, G. Guan, Effect of ionic products of dicalcium silicate coating on osteoblast differentiation and collagen production *via* TGF-β1 pathway, *Journal of Biomaterials Applications*, 2013, **27**, 595-604, doi: 10.1177/0885328211416393.

[97] S. Mukherjee, M. R. Kolb, F. Duan, L. J. Janssen, Transforming growth factor-β evokes Ca^{2+} waves and enhances gene expression in human pulmonary fibroblasts, *American Journal of Respiratory Cell and Molecular Biology*, 2012, **46**, 757-764, doi: 10.1165/rcmb.2011-0223OC.

[98] S. Li, A. L. Maçon, M. Jacquemin, M. M. Stevens, J. R. Jones, Sol–gel derived lithium-releasing glass for cartilage regeneration, *Journal of Biomaterials Applications*, 2017, **32**, 104-113, doi: 10.1177/0885328217706640.

[99] T. Rharass, H. Lemcke, M. Lantow, S. A. Kuznetsov, D. G. Weiss, D. Panáková, Ca^{2+}-mediated mitochondrial reactive oxygen species metabolism augments Wnt/β-catenin pathway activation to facilitate cell differentiation, *Journal of Biological Chemistry*, 2014, **289**, 27937-27951, doi: 10.1074/jbc.m114.573519.

[100] J. Guan, J. Zhang, S. Guo, H. Zhu, Z. Zhu, H. Li, Y. Wang, C. Zhang, J. Chang, Human urine-derived stem cells can be induced into osteogenic lineage by silicate bioceramics *via* activation of the Wnt/β-catenin signaling pathway, *Biomaterials*, 2015, **55**, 1-11, doi: 10.1016/j.biomaterials.2015.03.029.

[101] C. Gögele, S. Wiltzsch, A. Lenhart, A. Civilleri, T. M. Weiger, K. Schäfer-Eckart, B. Minnich, L. Forchheimer, M. Hornfeck, G. Schulze-Tanzil, Highly porous novel chondro-instructive bioactive glass scaffolds tailored for cartilage tissue engineering, *Materials Science and Engineering: C*, 2021, **130**, 112421, doi: 10.1016/j.msec.2021.112421.

[102] A. Cheng, Z. Schwartz, A. Kahn, X. Li, Z. Shao, M. Sun, Y. Ao, B. D. Boyan, H. Chen, Advances in porous scaffold design for bone and cartilage tissue engineering and regeneration, *Tissue Engineering Part B: Reviews*, 2019, **25**, 14-29, doi: 10.1089/ten.TEB.2018.0119.

[103] S. Liu, Z. Deng, K. Chen, S. Jian, F. Zhou, Y. Yang, Z. Fu, H. Xie, J. Xiong, W. Zhu, Cartilage tissue engineering: From pro-

inflammatory and anti-inflammatory cytokines to osteoarthritis treatments (Review), *Molecular Medicine Reports*, 2022, **25**, 99, doi: 10.3892/mmr.2022.12615.

[104] A. Mukherjee, B. Das, The role of inflammatory mediators and matrix metalloproteinases (MMPs) in the progression of osteoarthritis, *Biomaterials and Biosystems*, 2024, **13**, 100090, doi: 10.1016/j.bbiosy.2024.100090.

[105] A. Kumar, J. Mahendra, L. Mahendra, H. H. Abdulkarim, M. Sayed, M. H. Mugri, Z. H. Ahmad, A. K. Bhati, H. H. Faqehi, W. O. Algregri, S. Varadarajan, T. M. Balaji, H. Ali Baeshen, S. Patil, Synergistic effect of biphasic calcium phosphate and platelet-rich fibrin attenuate markers for inflammation and osteoclast differentiation by suppressing NF-κB/MAPK signaling pathway in chronic periodontitis, *Molecules*, 2021, **26**, 6578, doi: 10.3390/molecules26216578.

[106] X. Hao, G. Sun, Y. Zhang, X. Kong, D. Rong, J. Song, W. Tang, X. Wang, Targeting immune cells in the tumor microenvironment of HCC: new opportunities and challenges, *Frontiers in Cell and Developmental Biology*, 2021, **9**, 775462, doi: 10.3389/fcell.2021.775462.

[107] X. Zhu, W. Wen, J. Yan, Y. Wang, R. Wang, X. Ma, D. Ren, K. Zheng, C. Deng, J. Zhang, Rod-shaped mesoporous zinc-containing bioactive glass nanoparticles: structural, physico-chemical, antioxidant, and immuno-regulation properties, *Antioxidants*, 2024, **13**, 875, doi: 10.3390/antiox13070875.

[108] S. Shang, K. Zhuang, J. Chen, M. Zhang, S. Jiang, W. Li, A bioactive composite hydrogel dressing that promotes healing of both acute and chronic diabetic skin wounds, *Bioactive Materials*, 2024, **34**, 298-310, doi: 10.1016/j.bioactmat.2023.12.026.

[109] I. Raizman, J. N. A. De Croos, R. Pilliar, R. A. Kandel, Calcium regulates cyclic compression-induced early changes in chondrocytes during *in vitro* cartilage tissue formation, *Cell Calcium*, 2010, **48**, 232-242, doi: 10.1016/j.ceca.2010.09.006.

[110] K. Gundogdu, G. Gundogdu, F. Demirkaya Miloglu, T. Demirci, S. Y. Tascı, A. M. Abd El-Aty, Anti-inflammatory effects of boric acid in treating knee osteoarthritis: biochemical and histopathological evaluation in rat model, *Biological Trace Element Research*, 2024, **202**, 2744-2754, doi: 10.1007/s12011-023-03872-0.

[111] H. Xu, Y. Zhu, A. W. T. Hsiao, J. Xu, W. Tong, L. Chang, X. Zhang, Y. F. Chen, J. Li, W. Chen, Bioactive glass-elicited stem cell-derived extracellular vesicles regulate M2 macrophage polarization and angiogenesis to improve tendon regeneration and functional recovery, *Journal of Biomaterials*, 2023, **294**, 121998, doi: 10.1016/j.biomaterials.2023.121998.

[112] R. B. P. da Silva, C. C. Biguetti, M. S. Munerato, R. L. Siqueira, E. D. Zanotto, G. H. Abu Kudo, G. B. Simionato, A. C. Z. Bacelar, R. C. Ortiz, J. S. Ferreira-Junior, I. G. Rangel-Junior, M. A. Matsumoto, Effects of glass–ceramic produced by the Sol–gel route in macrophages recruitment and polarization into bone tissue regeneration, *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, 2024, **112**, e35340, doi: 10.1002/jbm.b.35340.

[113] W. Wang, S. Jia, G. Miao, Z. Sun, F. Yu, Z. Gao, Y. Li, Bioactive glass-based scaffold enhances osteochondral regeneration via dual modulation of cartilage and sub-chondral bone regions**,** *Biomaterials Advances,* 2023, **152**, 213520, doi: 10.1016/j.bioadv.2023.213520.

[114] S. E. Lehman, A. S. Morris, P. S. Mueller, A. K. Salem, V. H. Grassian, S. C. Larsen, Silica nanoparticle-generated reactive oxygen species as a predictor of cellular toxicity: mechanistic insights and safety by design, *Environmental Science: Nano*, 2016, **3**, 56-66, doi: 10.1039/C5EN00179J.

[115] H. Li, J. He, H. Yu, C. R. Green, J. Chang, Bioglass promotes wound healing by affecting gap junction connexin 43 mediated endothelial cell behavior, *Biomaterials*, 2016, **84**, 64-75, doi: 10.1016/j.biomaterials.2016.01.033.

[116] H. Y. Tan, N. Wang, S. Li, M. Hong, X. Wang, Y. Feng, Reactive oxygen species: the "-omics" role in skeletal muscle atrophy and osteoporosis, *Oxidative Medicine and Cellular Longevity*, 2016, **1**, 2795090, doi: 10.1155/2016/2795090.

[117] X. Dong, J. Chang, H. Li, Bioglass promotes wound healing through modulating the paracrine effects between macrophages and repairing cells, *Journal of Materials Chemistry B*, 2017, **5**, 5240-5250, doi: 10.1039/C7TB01211J.

[118] J. Filipowska, J. Pawlik, K. Cholewa-Kowalska, G. Tylko, E. Pamula, L. Niedzwiedzki, M. Szuta, M. Laczka, A. M. Osyczka, Incorporation of Sol–gel bioactive glass into PLGA improves mechanical properties and bioactivity of composite scaffolds and results in their osteoinductive properties, *Biomedical Materials*, 2014, **9**, 065001, doi: 10.1088/1748-6041/9/6/065001.

[119] D. Lin, B. Cai, L. Wang, L. Cai, Z. Wang, J. Xie, Q. X. Lv, Y. Yuan, C. Liu, S. G. Shen, A viscoelastic PEGylated poly(glycerol sebacate)-based bilayer scaffold for cartilage regeneration in full-thickness osteochondral defect, *Biomaterials*, 2020, **253**, 120095, doi: 10.1016/j.biomaterials.2020.120095.

[120] W. Potiprapanpong, P. Naruphontjirakul, C. Khamsuk, S. Channasanon, A. Toneluck, S. Tanodekaew, N. Monmaturapoj, A. M. Young, P. Panpisut, Assessment of mechanical/chemical properties and cytotoxicity of resin-modified glass ionomer cements containing Sr/F-bioactive glass nanoparticles and methacrylate functionalized polyacids, *International Journal of Molecular Sciences*, 2023, **24**, 10231, doi: 10.3390/ijms241210231.

[121] X. Yu, H. Zhang, Y. Miao, S. Xiong, Y. Hu, Recent strategies of collagen-based biomaterials for cartilage repair: from structure cognition to function endowment, *Journal of*

Leather Science and Engineering, 2022, **4**, 11, doi: 10.1186/s42825-022-00085-4.
[122] R. Tan, R. Chen, L. Sun, S. Xu, Z. Ji, S. Ji, C. Liu, X. Zhao, H. Xu, H. Xia, Y. Wang, J. Wang, K. Ma, From nanoscale to microscale hierarchical multifunctional nano borate bioactive glass for efficient wound healing, *Ceramics International*, 2023, **49**, 25908-25919, doi: 10.1016/j.ceramint.2023.05.140.
[123] F. Zhao, Z. Yang, H. Xiong, Y. Yan, X. Chen, L. Shao, A bioactive glass functional hydrogel enhances bone augmentation *via* synergistic angiogenesis, self-swelling and osteogenesis, *Bioactive Materials*, 2023, **22**, 201-210, doi: 10.1016/j.bioactmat.2022.09.007.
[124] S. R. Prasad, S. B. Teli, J. Ghosh, N. R. Prasad, V. S. Shaikh, G. M. Nazeruddin, A. G. Al-Sehemi, I. Patel, Y. I. Shaikh, A review on bio-inspired synthesis of silver nanoparticles: their antimicrobial efficacy and toxicity, *Engineered Science*, 2021, **16**, 90-128, doi: 10.30919/es8d479.
[125] C. Zhu, C. Huang, W. Zhang, X. Ding, Y. Yang, Biodegradable-glass-fiber reinforced hydrogel composite with enhanced mechanical performance and cell proliferation for potential cartilage repair, *International Journal of Molecular Sciences*, 2022, **23**, 8717, doi: 10.3390/ijms23158717.
[126] B. Liu, Y. Zhao, T. Zhu, S. Gao, K. Ye, F. Zhou, D. Qiu, X. Wang, Y. Tian, X. Qu, Biphasic double-network hydrogel with compartmentalized loading of bioactive glass for osteochondral defect repair, *Frontiers in Bioengineering and Biotechnology*, 2020, **8**, 752, doi: 10.3389/fbioe.2020.00752.
[127] Y. Yang, X. Zhao, S. Wang, Y. Zhang, A. Yang, Y. Cheng, X. Chen, Ultra-durable Cell-Free Bioactive Hydrogel with Fast Shape Memory and On-Demand Drug Release for Cartilage Regeneration, *Nature Communications*, 2023, **14**, 7771, doi: 10.1038/s41467-023-43334-8.
[128] D. Vukajlovic, J. Parker, O. Bretcanu, K. Novakovic, Chitosan based polymer/bioglass composites for tissue engineering applications, *Materials Science and Engineering: C*, 2019, **96**, 955-967, doi: 10.1016/j.msec.2018.12.026.
[129] G. Gharati, S. Shirian, S. Sharifi, E. Mirzaei, B. Bakhtirimoghadam, I. Karimi, H. Nazari, Comparison capacity of collagen hydrogel and collagen/strontium bioglass nanocomposite scaffolds with and without mesenchymal stem cells in regeneration of critical sized bone defect in a rabbit animal model, *Biological Trace Element Research*, 2022, **200**, 3176-3186, doi: 10.1007/s12011-021-02909-6.
[130] X. Li, Y. Lu, Y. Wang, S. Zhou, L. Li, F. Zhao, Nano-particle systems for intra-articular drug delivery in articular cartilage treatment, *Journal of Biomaterials Applications*, 2021, **28**, 1290-1300, doi: 10.1177/0885328219897591.
[131] C. Gögele, S. Müller, S. Belov, A. Pradel, S. Wiltzsch, A. Lenhart, M. Hornfeck, V. Kerling, A. Rübling, H. Kühl, K. Schäfer-Eckart, B. Minnich, T. M. Weiger, G. Schulze-Tanzil, Biodegradable poly(D-L-lactide-co-glycolide) (PLGA)-infiltrated bioactive glass (CAR12N) scaffolds maintain mesenchymal stem cell chondrogenesis for cartilage tissue engineering, *Cells*, 2022, **11**, 1577, doi: 10.3390/cells11091577.
[132] Z. Yuan, Z. Lyu, X. Liu, J. Zhang, Y. Wang, Mg-BGNs/DCECM composite scaffold for cartilage regeneration: a preliminary *in vitro* study, *Pharmaceutics*, 2021, **13**, 1550, doi: 10.3390/pharmaceutics13101550.
[133] K. Xue, S. Zhang, J. Ge, Q. Wang, L. Qi, K. Liu, Integration of bioglass into PHBV-constructed tissue-engineered cartilages to improve chondrogenic properties of cartilage progenitor cells, *Frontiers in Bioengineering and Biotechnology*, 2022, **10**, 868719, doi: 10.3389/fbioe.2022.868719.
[134] M. Liu, X. Ke, Y. Yao, F. Wu, S. Ye, L. Zhang, G. Yang, M. Shen, Y. Li, X. Yang, C. Zhong, C. Gao, Z. Gou, Artificial osteochondral interface of bioactive fibrous membranes mediating calcified cartilage reconstruction, *Journal of Materials Chemistry B*, 2021, **9**, 7782-7792, doi: 10.1039/D1TB01238J.