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Advanced construction strategies to obtain nanocomposite hydrogels for bone repair and regeneration

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Abstract

Bone tissue engineering is pivotal in facilitating bone reconstruction by promoting persistent angiogenesis and osteogenesis. Initially, the hot gel composite hydrogel scaffold technique was employed. However, to address various limitations, numerous gel structures have since been developed, including osteogenic gellan gels, semi-interpenetrating network hydrogels, photoinduced crosslinking methacrylate gels, and supramolecular hydrogels. This review examines the mechanisms, formation principles, and medical benefits of these gel structures. In addition, novel bioengineering techniques to regulate human bone growth are expected to emerge in the future. This work is expected to significantly expedite the advancement of hydrogel membranes in the field of bone repair.

Introduction

A hydrogel is a three-dimensional (3D) network structure composed of hydrophilic polymer chains with a high content ranging from 90% to 99%, which facilitates efficient oxygen and substance exchange[1]. In recent decades, a variety of natural hydrogels (e.g., alginate (Alg)/gelatin) and synthetic hydrogels (e.g., gelatin-PEG and PAAm/Dex-U) have undergone unprecedented development in biomedical fields due to their high porosity, satisfactory nutritional permeability, high biocompatibility, low immunogenicity, and tunable physical and chemical properties[2–4]. Compared to other organic molecules or polymers, the multimolecular structure of hydrogels can provide a suitable matrix for cell transplantation and differentiation, endogenous regeneration, biorepair, wound healing and continuous drug delivery[5–8]. Moreover, the 3D network system of hydrogels can simulate the microstructure of the extracellular matrix (ECM) and provide a suitable environment for cell survival[9–12].

In contemporary society, diseased or damaged bone tissue is a common clinical problem in orthopedic medicine, and bone has become the second most frequently transplanted tissue after blood[13–15]. Although both non-surgical (e.g., casting, electrical stimulation, and ultrasound therapy) and surgical approaches (e.g., internal fixation, external fixation, bone grafting and bone regeneration) have been applied for bone repair, these existing treatments may not be suitable for all types of bone diseases[16]. For example, autologous or allogeneic bone transplantation is commonly used for treating bone defects; however, this therapy can cause damage at the donor site, and acquiring suitable donors can be challenging[17,18]. To address the aforementioned problems, bone tissue engineering utilizing hydrogels or hydrogel membranes as scaffolds has emerged as a promising solution. To the best of our knowledge, hydrogels composed of crosslinked polymer chains represent a unique class of scaffold materials characterized by a 3D hydrophilic network structure that can maintain its stability

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even after absorbing several times its own volume of water[19–21]. Therefore, hydrogels can mimic the natural tissue environment and provide structural support to defect sites, allowing bone defects to be repaired by intrinsic healing mechanisms[22].

Despite years of exploration, there are still many unsolved problems regarding the use of hydrogels or hydrogel membranes for bone repair. The greatest challenges are as follows: (1) During the fabrication of synthetic hydrogels, potentially toxic crosslinkers may be utilized. (2) Most synthetic procedures are intricate and laborious. (3) Although natural hydrogels are considered ideal for bone repair, their poor mechanical properties often hinder their application in this field. Therefore, effective strategies for constructing suitable gels that promote cell adhesion and growth are urgently needed.

In this review, we first present a fundamental overview of bone repair, encompassing nonsurgical modalities. (casting, electrical stimulation, ultrasound therapy) and surgical approaches (internal fixation, external fixation, bone grafting and bone regeneration). The present study provides a comprehensive overview of the recent advances and challenges in the application of hydrogels for bone repair. Various hydrogel structures, including osteogenic gellan gel, semi-interpenetrating network hydrogels (semi-IPNs), interpenetrating network hydrogels (IPNs), and photoinduced crosslinking methacrylate gelatin (MAGel), are highlighted. The functional, mechanistic, and medical advantages of these hydrogel structures are thoroughly examined (Fig. 1). The findings of this study suggest that further research will lead to the development of more advanced hydrogel materials and bioengineering techniques for bone repair.

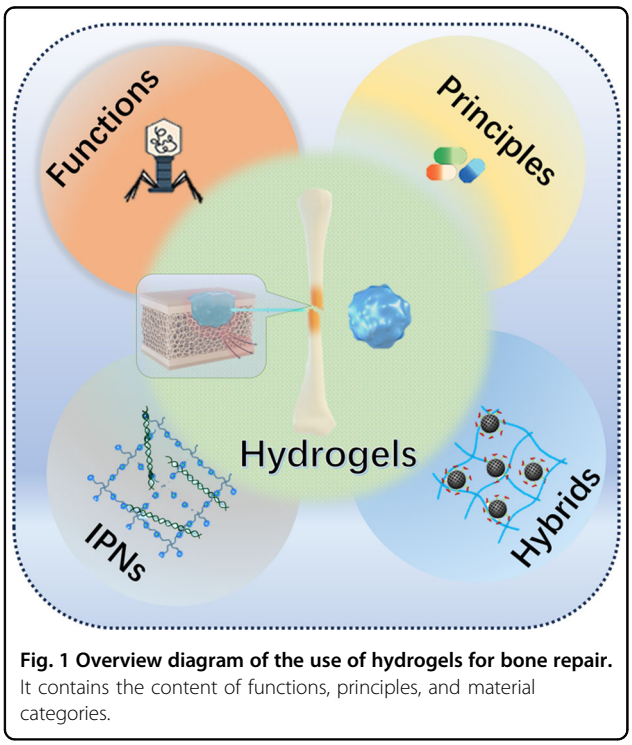

Fig. 1 Overview diagram of the use of hydrogels for bone repair. It contains the content of functions, principles, and material categories.

Profiles of bone repair

Before discussing the role of hydrogels in bone repair, we first describe and categorize several commonly used techniques for bone repair. Basically, techniques for bone repair can be broadly classified into nonsurgical and surgical approaches. The nonsurgical approaches include casting, electrical stimulation, and ultrasound therapy, and the surgical approaches include internal fixation, external fixation, bone grafting and bone regeneration (Fig. 2). Notably, existing nonsurgical or surgical approaches may not be suitable for all types of bone fractures. The severity of the fracture, the age and overall health of the patient, and other factors determine the most appropriate treatment plan. Detailed descriptions are provided below.

Nonsurgical approaches

Casting

Casting involves using a cast or brace to immobilize the broken bone and allow it to heal naturally. A cast is commonly made of rigid material, such as plaster or fiberglass, which is wrapped around the affected limb to keep the bone in place. The cast is usually worn for several weeks to months, depending on the severity of the fracture and the individual's healing progress[23–28]. Generally, casting is a nonsurgical approach that is commonly used for bone fractures[29–34] and typically involves the following steps: initial evaluation, reduction, and immobilization[35–38].

Electrical stimulation

Electrical stimulation is a noninvasive approach that promotes bone healing by stimulating the activity of bone cells. Electrical stimulation can be administered in several ways, including direct current stimulation (DCS), pulsed electromagnetic field (PEF) stimulation, or capacitive coupling (CC)[39–41]. DCS involves the application of a small electrical current to the skin or directly to the bone, which is thought to stimulate the activity of bone cells and promote the growth of new bone tissue[42]. PEF and CC involve the use of low-frequency electromagnetic waves around the affected area[43–48].

Ultrasound therapy

Ultrasound therapy is a noninvasive approach in which high-frequency sound waves are used to stimulate bone healing. The sound waves penetrate deep into the tissue and stimulate the activity of bone cells, thereby promoting the growth of new bone tissue[49–52]. There are two types of

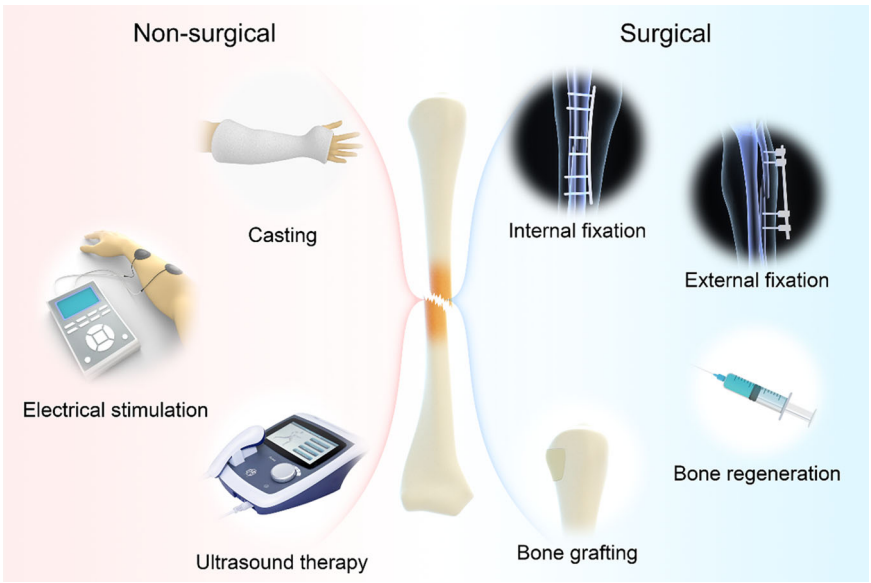

Fig. 2 Commonly used nonsurgical and surgical approaches for bone repair.

ultrasound therapy: low-intensity pulsed ultrasound (LIPUS) and high-intensity focused ultrasound (HIFU). LIPUS uses low-intensity sound waves to promote bone healing, while HIFU uses high-intensity sound waves to destroy damaged tissue and stimulate new tissue growth[53].

Summary

The nonsurgical approaches of casting, electrical stimulation, and ultrasound therapy all possess potential risks and limitations (Table 1). For instance, the cast may need to be removed or replaced if it becomes too tight or if the skin underneath becomes irritated or infected. Electrical stimulation and ultrasound therapy are often used in conjunction with other bone repair techniques, such as casting or bone grafting, to help accelerate the healing process[54]. However, these approaches may not be suitable for all types of bone fractures or medical conditions. A qualified health care professional should be consulted to determine the best course of action for a particular individual.

Surgical approaches

Internal fixation

Internal fixation is a surgical technique in which bone fractures are repaired by implanting metal screws, plates, or rods inside the body to hold the broken bone in place. These implants are typically made of titanium or stainless steel and are designed to remain in the body permanently or temporarily[55–57]. Internal fixation is usually recommended for complex fractures or for fractures that cannot be treated with nonsurgical approaches. The procedure involves making an incision at the site of the fracture and using specialized tools to position the implants accurately[58,59].

External fixation

External fixation is a surgical technique in which bone fractures are repaired by implanting metal pins or screws into the bone and attaching them to an external metal frame that holds the bone in place. The pins or screws are inserted through the skin and into the bone on either side of the fracture, and the external frame is attached to the pins or screws[60]. External fixation is typically recommended for complex fractures that cannot be treated with nonsurgical approaches such as casting or internal fixation[61].

Bone grafting

Bone grafting is a surgical technique in which bone fractures are repaired by transplanting bone tissue from one area of the body (called the donor site) to the area of the fracture (called the recipient site). Bone grafting is typically used when a fracture is severe, has failed to heal properly, or is located in an area with poor blood supply[62–64]. There are several types of bone grafts, including autografts (bone tissue from the patient's own body), allografts (bone tissue from a donor), and synthetic grafts (artificial materials)[65]. During the procedure, a surgeon makes an incision at the site of the fracture and removes all damaged or dead tissue, then transplants the bone tissue from the donor site to the recipient site and secures it using pins, screws, or plates[66–68].

Table 1 Comparisons among nonsurgical and surgical approaches for bone repair.

Categories	Approach	Medium	Advantages	Disadvantages
Nonsurgical approaches	**Casting**	Plaster or fiberglass	Easy availability and effectiveness	Potential muscle atrophy and stiffness
	Electrical stimulation	Electricity and magnetism	Safety	Assistive technology
	Ultrasound therapy	Sound waves	Convenience	Skin irritation or mild pain; assistive technology
Surgical approaches	**Internal fixation**	Metal screws, plates, or rods	Ability to enable early mobilization and weight-bearing activities	Potential for infection, implant failure, and nerve damage; low pain and swelling
	External fixation	Metal pins or screws	Stable fixation	Potential for infection, pin loosening, and pin tract infection
	Bone grafting	Bone tissue and metal pins or screws	Rapid recovery	Potential for graft rejection
	Bone regeneration	Biological agents; scaffolds or matrices	Abundant materials with different functions	Potential for infection, inflammation, and rejection of the biologic agents or scaffolds

Bone regeneration

Bone regeneration is the process by which new bone tissue is formed to replace damaged or missing bone tissue. This process is stimulated by growth factors and other biological agents, which can be applied directly to the site of a bone injury or defect[69–71]. Bone regeneration can occur naturally, but it can also be enhanced through the use of biological agents such as bone morphogenetic proteins (BMPs), growth factors, and stem cells. BMPs are naturally occurring proteins that stimulate the formation of new bone tissue. Growth factors are proteins that promote cell growth and differentiation and can help stimulate the growth of new bone tissue. Stem cells are undifferentiated cells that can differentiate into bone cells and thereby help to regenerate bone tissue[72–74]. In addition to biological agents, scaffolds or matrices can be used to facilitate bone regeneration. These 3D structures provide a template on which new bone tissue can grow. They can be made from natural materials (e.g., collagen) or synthetic materials (e.g., hydrogels)[75–79]. Polymeric hydrogels with a structure analogous to the extracellular matrix (ECM) have been recognized as promising platforms for loading various biological agents to promote bone regeneration.

Summary

Surgical approaches for bone repair involve physically manipulating the bones to realign them and/or using implants to hold them in place while they heal. Surgery may be necessary to treat severe bone fractures or fractures for which nonsurgical approaches are ineffective. In surgical treatment, the multimolecular system of hydrogels exhibits promise as an appropriate matrix for cell transplantation and differentiation, endogenous regeneration, biorepair, wound healing, and continuous drug delivery, which is attributed to the 3D microstructures that closely resemble the original ECM network system. It should be noted that surgical approaches to bone repair also carry some risks, such as infection, bleeding, inflammation, nerve damage and rejection reactions (Table 1). The recovery time after surgery can also depend on various factors, such as the extent of the injury, the overall health status of the patient, and the quality of the bone tissue at the injury site.

Functions and underlying mechanisms of hydrogels in bone repair

Hydrogels, water-swollen crosslinked polymer networks, have attracted increasing interest in the field of bone repair due to their biocompatibility, biodegradability, and tunable mechanical and physicochemical properties[80]. On the basis of previous reports, we divide the functions and mechanisms of hydrogels in bone repair into several categories, as hydrogels or hydrogel membranes can serve as scaffolds for cell delivery, drug delivery systems, tissue engineering materials, bone substitutes, and implant coatings.

Scaffolds for cell delivery

Hydrogels can be used as scaffolds for cell delivery in bone repair, providing a 3D environment that supports cell growth and proliferation. The hydrogel scaffold can be loaded with bone-forming cells, such as mesenchymal stem cells (MSCs), and implanted at the site of the bone injury or defect[81–84]. There are several ways in which hydrogels can be used as scaffolds for cell delivery. (a) Encapsulation of cells: Hydrogels can be used to encapsulate bone-forming cells, protecting them from the harsh

environment at the injury site and increasing their survival. Hydrogels can also regulate the release of nutrients and growth factors, providing a controlled environment for cells to grow and proliferate[85,86]. (b) Promotion of cell adhesion and migration: Hydrogels that promote cell adhesion and migration can be designed by incorporating cell-adhesive peptides or other molecules into the hydrogel structure. These molecules can help to increase cell attachment and spreading within the hydrogel, leading to more effective tissue regeneration[87–89]. (c) Control of cell differentiation: Hydrogels that control the differentiation of bone-forming cells can also be designed by incorporating growth factors or other signaling molecules into the hydrogel structure. This type of hydrogel can promote the differentiation of cells into bone-forming cells, leading to more effective bone regeneration[90]. (d) Combination with other biomaterials: Hydrogels can be combined with other biomaterials, such as ceramics or metals, to create composite scaffolds with improved mechanical properties and bioactivity. Combining hydrogels with other biomaterials can also help promote bone regeneration by providing a favorable environment for bone-forming cells to grow and proliferate[91–93].

Overall, hydrogels offer a versatile platform for cell delivery in bone repair by providing a 3D environment that supports cell growth and proliferation. The ability of hydrogels or their composites to encapsulate cells, promote cell adhesion and migration, and control cell differentiation makes hydrogels a promising vehicle for improving bone regeneration in various clinical situations. For instance, Chen et al. developed a porous hydrogel based on calcium silicate ($CaSiO_3$) incorporating human umbilical vein endothelial cells (HUVECs) and Wharton's jelly mesenchymal stem cells (WJMSCs), named PMGH[94]. The composite scaffold not only significantly enhanced cell proliferation and viability but also elevated the levels of angiogenic markers and bone formation proteins. Therefore, this method is believed to be highly effective for regenerating complex bone defects in deep areas.

Drug delivery systems

Hydrogels can also be used as drug delivery systems for bone repair, providing sustained release of therapeutic agents to the injury site[95]. There are several ways in which hydrogels can be used for drug delivery in bone repair: (a) Incorporation of drugs into the hydrogel: Drugs or other therapeutic agents can be incorporated into the hydrogel structure and then released from the hydrogel over time, sustaining the release of the therapeutic agent at the injury site. This approach can help increase the efficacy of the drug and reduce the risk of side effects[96–98]. (b) Targeting of specific cells or tissues: Hydrogels can be designed to target specific cells or tissues by incorporating cell-targeting molecules or tissue-specific ligands into the hydrogel structure. This design can help increase the drug's localization to the injury site, leading to more effective therapy[99]. (c) Response to environmental stimuli: Hydrogels can be designed to respond to environmental stimuli, such as changes in pH or temperature, to release a drug in a controlled manner. This type of hydrogel can help increase the efficacy of drugs by releasing them in response to specific environmental cues[100–102].

Hence, hydrogels offer a versatile platform for drug delivery in bone repair, providing sustained release of therapeutic agents to the injured site. As shown in Fig. 3, Wang et al. developed a thermosensitive hydrogel based on mesoporous silica nanoparticles (MSNs), which was utilized for the controlled release of stromal cell-derived factor-1 (SDF-1) and metformin to promote bone regeneration in diabetic patients. The proposed strategy involves scavenging the reactive oxygen species (ROS) generated by the disrupted glucose metabolism, thereby facilitating the recruitment of bone marrow mesenchymal stem cells (BMSCs) to promote osteogenesis[103]. In conclusion, the ability to incorporate drugs into hydrogels, introduce targeting to specific cells or tissues, and design hydrogels to respond to environmental stimuli makes hydrogels promising vehicles for improving bone regeneration in a variety of clinical situations. It should also be noted that improper drug loading may result in rapid release due to the high water content and porous nanostructure of hydrogels. The search for an appropriate strategy has thus emerged as a prominent and urgent research topic.

Tissue engineering

Tissue engineering is a field of research that focuses on creating new tissues and organs to replace or repair damaged or diseased tissues. In bone repair, tissue engineering approaches aim to create new bone tissue using a combination of cells, biomaterials, and signaling molecules[104–107]. Tissue engineering can be used in bone repair in several ways. (a) Cell-based therapies: Cell-based therapies involve the use of bone-forming cells, such as MSCs, to promote bone regeneration. MSCs can be isolated from a patient's own bone marrow or adipose tissue and then expanded in the laboratory before transplantation back into the patient at the site of the bone injury. MSCs have been shown to promote bone formation and remodeling and can also differentiate into other cell types, such as cartilage and fat cells[108–115]. (b) Biomaterials: Biomaterials can be used to provide a scaffold for cell growth to promote bone regeneration. Synthetic biomaterials, such as polycaprolactone (PCL) and poly(lactic-co-glycolic acid) (PLGA), can be used to create 3D scaffolds that mimic the structure of natural bone tissue. These scaffolds can then be seeded with bone-forming cells and implanted at the site of bone injury to promote bone regeneration[116–120]. (c) Signaling molecules: Signaling

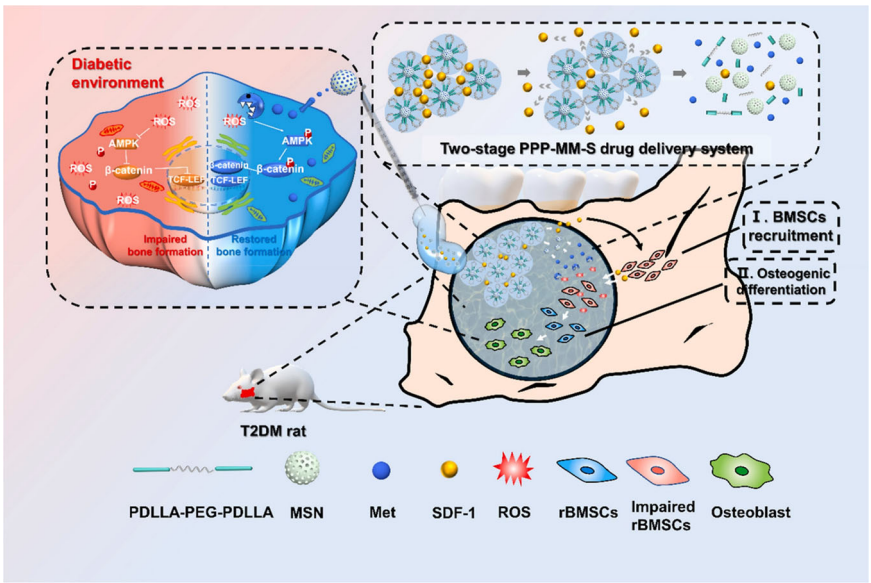

Fig. 3 Hydrogels for drug delivery systsems. Schematic illustration of the design principles and drug delivery mechanisms of hydrogels. Reproduced with permission[103]. Copyright 2023, Elsevier.

molecules, such as growth factors and cytokines, can be used to promote bone regeneration by stimulating the growth and differentiation of bone-forming cells[121]. For example, bone morphogenetic protein-2 (BMP-2) has been shown to stimulate bone formation and is commonly used in bone tissue engineering. (d) Combination therapies: Tissue engineering approaches can be combined with multiple other therapies to promote bone regeneration. A scaffold can be seeded with bone-forming cells and then treated with growth factors to promote cell differentiation and bone formation. Alternatively, a scaffold can be precoated with signaling molecules that can promote bone formation and then seeded with bone-forming cells[122,123].

In brief, tissue engineering approaches offer a promising strategy for bone repair, with the potential to create new bone tissue that is biocompatible and structurally similar to natural bone tissue. Zheng et al. developed a biocompatible hydrogel composite scaffold by combining natural silk, organic sodium alginate (SA) and inorganic calcium silicate (CS). The resulting hydrogel scaffolds strongly stimulated the proliferation of BMSCs, which can be effectively applied in tissue engineering applications[124]. Ongoing research in tissue engineering is focused on increasing the efficiency and safety of these approaches, with the ultimate goal of developing effective bone repair therapies for use in a clinical setting.

Bone substitutes

Bone substitutes are biomaterials that can be used to replace or supplement bone tissue when the body is unable to heal itself or to aid in bone regeneration. They can be used in a variety of applications, including the repair of bone defects resulting from trauma, disease, or surgical intervention[125,126]. There are several types of inorganic and organic bone substitutes. (a) Ceramics: Ceramic bone substitutes, such as calcium phosphate and hydroxyapatite, are biocompatible and can stimulate bone growth. They are often used in dental implants, as well as in the repair of bone defects. (b) Polymers: Polymer bone substitutes, such as PCL, PLGA and some hydrogels, can serve as scaffolds for cell growth and bone regeneration. They can also be used to release growth factors or other signaling molecules to promote bone healing. (c) Metals: Metal bone substitutes, such as titanium and its alloys, are commonly used in orthopedic applications. These materials are solid and durable and can be designed to closely match the mechanical properties of natural bone tissue. (d) Composite materials: In composite bone substitutes, two or more materials, such as ceramics and polymers, are combined to achieve the desired properties for bone repair. For example, a composite material may be designed both to provide mechanical support and to promote bone growth.

Bone substitutes can also be categorized as either synthetic or natural matrices. Synthetic bone substitutes are usually made from materials such as ceramics, polymers, or metals, while natural bone substitutes are derived from biological sources such as human or animal tissue. Morais et al. synthesized injectable hydrogel bone substitutes by combining Alg, chitosan, and hyaluronate (HA) with glass-reinforced hydroxyapatite (GR-HAP). At pH 7.4, the

Alg/HA hydrogel exhibited 80% degradation, which lasted for three days. The results indicated that all the hydrogels exhibited non-Newtonian viscoelastic fluid characteristics with low maximum extrusion forces, making them suitable as carriers for bone substitutes. Although the use of bone substitutes is a promising approach for bone repair, these approaches are not without limitations[127–131]. For example, they may not be able to mimic the complex structure and mechanical properties of natural bone tissue. Additionally, there is a risk of immune response or rejection if the material is not biocompatible or is derived from an animal source. Ongoing research in this area has focused on improving the properties of bone substitutes and developing more effective strategies for bone repair.

Implant coatings

Implant coatings are thin layers of material that are applied to the surface of an implant to enhance its biocompatibility and promote tissue integration[132]. Coatings can be applied via a variety of methods, including physical vapor deposition (PVD), plasma spraying, electrochemical deposition, and sol-gel coating. Some examples of implant coatings are as follows. (a) Hydroxyapatite (HA): HA is a mineral component of bone that is commonly used as a coating material for orthopedic implants. HA coatings can promote bone ingrowth and integration with the surrounding tissue[133]. (b) Titanium nitride (TiN): TiN is a complex, wear-resistant coating that can be used on orthopedic implants to improve their durability and resistance to wear[134]. (c) Diamond-like carbon (DLC): DLC is a carbon-based coating that can be used on orthopedic implants to reduce wear and friction. DLC coatings can also increase the biocompatibility of implants by reducing the likelihood of inflammation and rejection[135]. (d) Antibiotic coatings: Implants can be coated with antibiotics to reduce the risk of infection after surgery. Antibiotic coatings (e.g., hydrogels) can be applied using a variety of methods, including PVD and electrochemical deposition[136].

Implant coatings can increase the long-term success of implants by promoting tissue integration and reducing complications such as wear, inflammation, and infection[137–139]. However, there are challenges associated with implant coatings, such as ensuring that the coating adheres securely to the implant surface and avoiding the risk of the coating delaminating or flaking off over time. Ongoing research in this area is focused on developing more effective and durable implant coatings to increase the success of orthopedic implants[140,141]. Hydrogels have great potential as coatings in the field of bone repair due to their unique properties and versatility[142]. As shown in Fig. 4, antibacterial hydrogels have become increasingly popular for antimicrobial and orthopedic applications. To date, a wide range of anti-infective hydrogels have been developed and utilized for orthopedic implants, encompassing natural matrices such as hyaluronic acid (HA), synthetic matrices such as polyethylene glycol (PEG), and composites such as HA + polylactic acid (PLA). These materials possess distinct properties that can effectively combat implant-associated infections. However, additional research is needed to fully explore the effectiveness and safety of these agents in clinical applications.

Summary

Overall, hydrogels have attracted substantial attention for bone repair and bone regeneration. Due to their 3D network structure and their advantageous mechanical and biological properties, hydrogels can be utilized as bone substitutes and in tissue engineering applications. Additionally, hydrogels can serve as versatile platforms for cell and drug delivery systems, enabling controlled release in response to environmental stimuli during therapeutic processes. Therefore, the precise release of bone stem cells, drugs, and antimicrobial agents supports cell growth and proliferation, promoting osteogenesis and regeneration in various clinical scenarios. The use of hydrogels as implant coatings can effectively reduce bacterial adhesion and increase long-term durability. The aforementioned

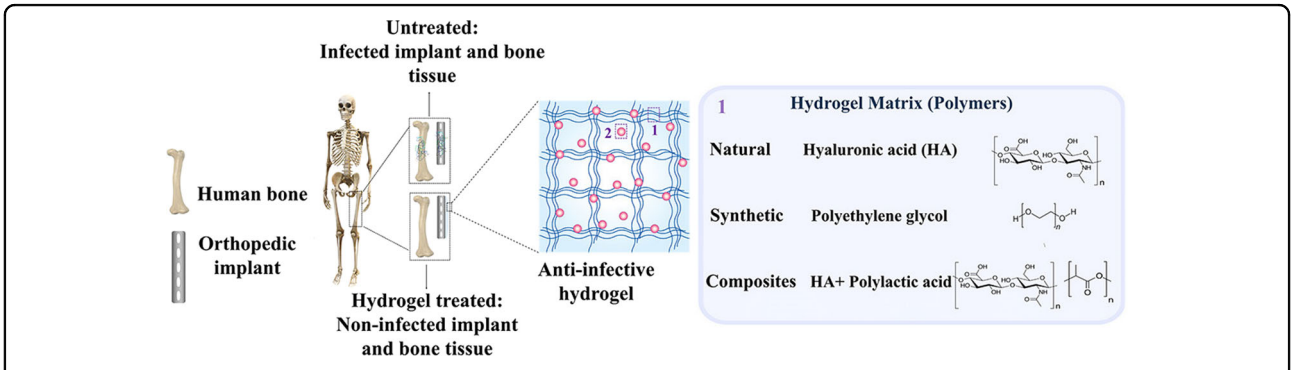

Fig. 4 Schematic images of anti-infective hydrogels for bone repair. Reproduced with permission[142]. Copyright 2021, American Chemistry Society.

Table 2 The functions and underlying mechanisms of hydrogels in bone repair.

Applications	Medium	Functions	Principles	Examples
Scaffold for cell delivery	Cell-laden hydrogels and their composites	Encapsulation of cells, promotion of cell adhesion and migration, and control of cell differentiation	Cell growth and proliferation	Ref. [94]
Drug delivery system	Drug-incorporated hydrogels	Incorporation of drugs into the hydrogel; Targeting of specific cells or tissues; Response to environmental stimuli	Molecular targeting treatment	Ref. [103]
Tissue engineering	Hydrogel composite scaffolds	Combination of cells, biomaterials, and signaling molecules	Creation of new tissues and organs	Ref. [124]
Bone substitute	Hydrogels and their composites	Mechanical support and bone growth	Replacement or supplementation of bone tissue	Ref. [127]
Implant coating	Modified hydrogels	Biocompatibility and tissue integration	Coating on the surface of an implant	Ref. [142]

studies support the potential of hydrogels as promising vehicles for enhancing bone repair and regeneration. All of these functions of hydrogels in bone repair and the underlying mechanisms are summarized in Table 2.

Construction strategy of hydrogels for bone repair

Semi-interpenetrating network hydrogels (semi-IPNs)

In semi-IPNs, specific polymer-based networks are crosslinked to other polymer chains, resulting in improved physicochemical properties, such as biocompatibility, mechanical strength and suitable rheological properties. For instance, Park et al. reported a semi-IPN structure containing cellulose nanofibers (CNFs) with a high aspect ratio of 240 and a polyacrylamide (PAM) mesh. Due to the strong interaction between the PAM network and rigid natural nanofibers, the compression strength of this semi-IPN system up to 3-fold higher than that of pure PAM[143]. Intriguingly, the PAM/BCNF composite hydrogels can be utilized for mechanical stress-responsive drug release and delivery. Similarly, this kind of hydrogel has shown great potential in the field of bone repair. For instance, Cui et al. designed semi-IPNs (OSA/Gel/CNF) through a facile one-step reaction of oxidized alginate (OSA), cellulose nanofibers, and gelatin (Gel), which mainly relied on the cooperative effects of hydrogen bonds and imine bonds[32]. As shown in detail in Fig. 5, during the synthesis of OSA/Gel/CNF from its three components, OSA acted as a natural reagent to link Gel via Schiff base reactions between amino and aldehyde groups, whereas CNFs formed hydrogen-bond interactions. The advantages of these semi-IPNs are as follows: (1) Compared to SA, OSA is more readily degraded in vivo and is more suitable for cell encapsulation. (2) The semi-IPNs exhibited both excellent mechanical properties and a high compressive modulus (>361.3 KPa). (3) As a result, the semi-IPNs showed good injectability and self-healing ability, both of which are promising for bone repair applications.

Interpenetrating network hydrogels (IPNs)

The design of IPNs, which consist of intertwining double hydrogel networks in a single system during gelation, is considered another effective strategy for bone repair. IPNs can synergistically present the advantages of both types of network, including biocompatibility and high mechanical strength. As shown in Fig. 6a, Macdougall et al. synthesized flexible poly(ethylene glycol)-only (PEG) interpenetrating meshes by the addition of unfunctionalized polysaccharides[144]. Here, the PEG-based hydrogels were first obtained in phosphate-buffered saline (PBS) through a reaction between the alkyne and thiol end groups (nucleophilic thiol-yne click reaction). Simultaneously, some unfunctionalized natural polymers (e.g., chitosan, gelatin, heparin, alginate, HA, etc.) were incorporated to form a secondary loose crosslinked network driven by electrostatic forces. This strategy endows the crosslinked IPNs with good stretchability and enhanced tensile performance (Fig. 6b), as well as self-healing capabilities (Fig. 6c). Therefore, IPN materials possess the advantages of both of their component systems and can effectively overcome the disadvantages associated with each network. Consequently, these materials have potential for further application in bone repair.

Hybrid hydrogels

Bioactive glass composite hydrogels

The periosteum is known to play key roles in mineralization, vascularization and protection during bone tissue regeneration[145]. However, many existing artificial periosteal grafts focus only on protection and lack the functions of osteogenesis and angiogenesis. Xin et al. developed a novel inorganic reinforced gelatin hydrogel membrane as

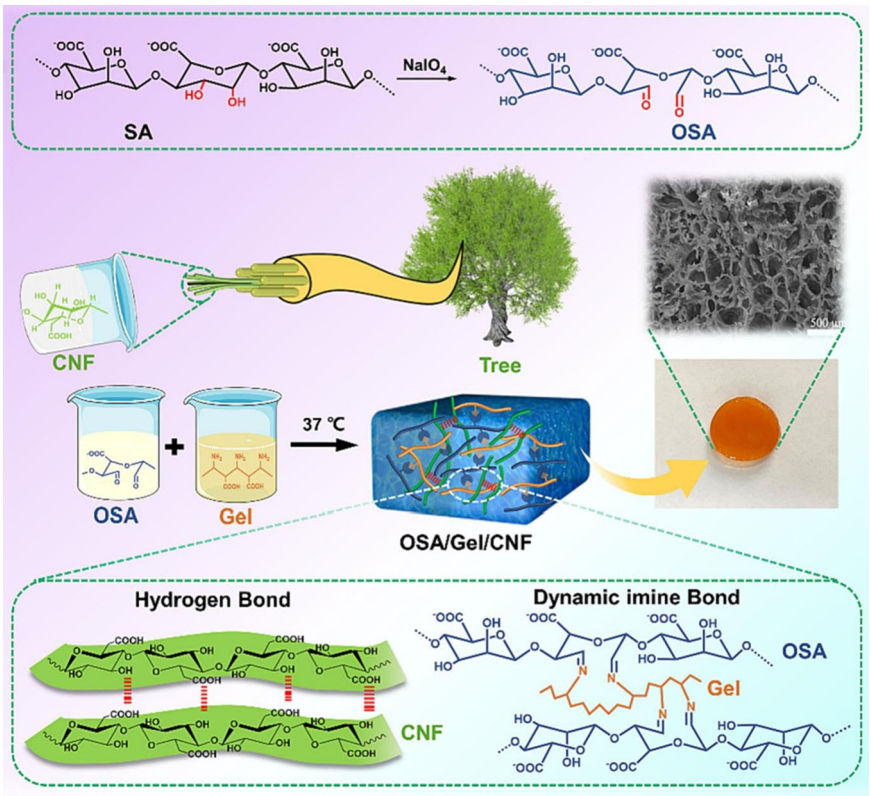

Fig. 5 Schematic image of the preparation of OSA/Gel/CNF IPNs. Reproduced with permission[32]. Copyright 2023, Elsevier.

an artificial periosteum to enhance durable angiogenesis and osteogenesis in bone reconstruction using inorganic and organic co-crosslinked dual networks[146]. As shown in Fig. 7a, mesoporous bioactive glass nanoparticles (MBGNs) were incorporated into a photo-crosslinked gelatin methacrylate (GelMA) hydrogel, affording a double-network structure with increased structural stability and improved mechanical properties (Fig. 7b). A GelMA-G-MBGN membrane enabled osteogenic differentiation both in vivo and in vitro, which is an important factor for cell differentiation and proliferation. In general, hydrogel membranes, characterized by prolonged degradation time, pH stability, biomineralization capability, and sustained ion release over an extended period of time, represent a promising approach for the development of advanced periosteal biomaterials with superior tactile sensation and bone regeneration properties.

Cell- or protein-grafted hydrogels

Xin et al. further grafted recombinant human bone morphogenetic protein-2 (rhBMP-2) onto the surface of MBGNs via amide bonds and performed photocrosslinking with GelMA[147]. As shown in Fig. 8, GelMA/MBGNS-rhBMP-2 hydrogel membranes were prepared to release RhBMP-2 in a controlled manner during the early stage of bone regeneration, followed by the release of calcium and silica ions for the long-term promotion of osteogenesis. The early release of rhBMP-2 can effectively promote local cell osteogenic differentiation in a short time. Inorganic ions can not only promote cell adhesion in the early stage but also continuously promote osteogenic differentiation in the long term. Moreover, the GelMA/MBGN-rhBMP-2 hydrogel showed excellent long-term promotion of osteogenesis and bone tissue regeneration in critical-size skull defects in rats. This presents a possible way to use bioactive factors such as rhBMP-2 in a more controlled and safe manner to accelerate bone repair.

In addition, Chen's group used 3D printing technology to fabricate polyamine-modified calcium silicate (PDACS)/polycaprolactone (PCL) scaffolds by combining WJMSCs with HUVEC-loaded hydrogels (Fig. 9a)[94]. This mixture of synthetic gel materials with cellular components not only promoted osteogenesis but also stimulated angiogenesis, leading to the development of vascular networks, which suggests that solvent-free 3D printing can be further applied to improve many aspects of bone tissue regeneration (Fig. 9b)[94]. In summary, this innovative strategy of integrating cells or proteins into hydrogels holds immense potential for the regeneration of intricate hard tissues to repair defects in deep bone structures.

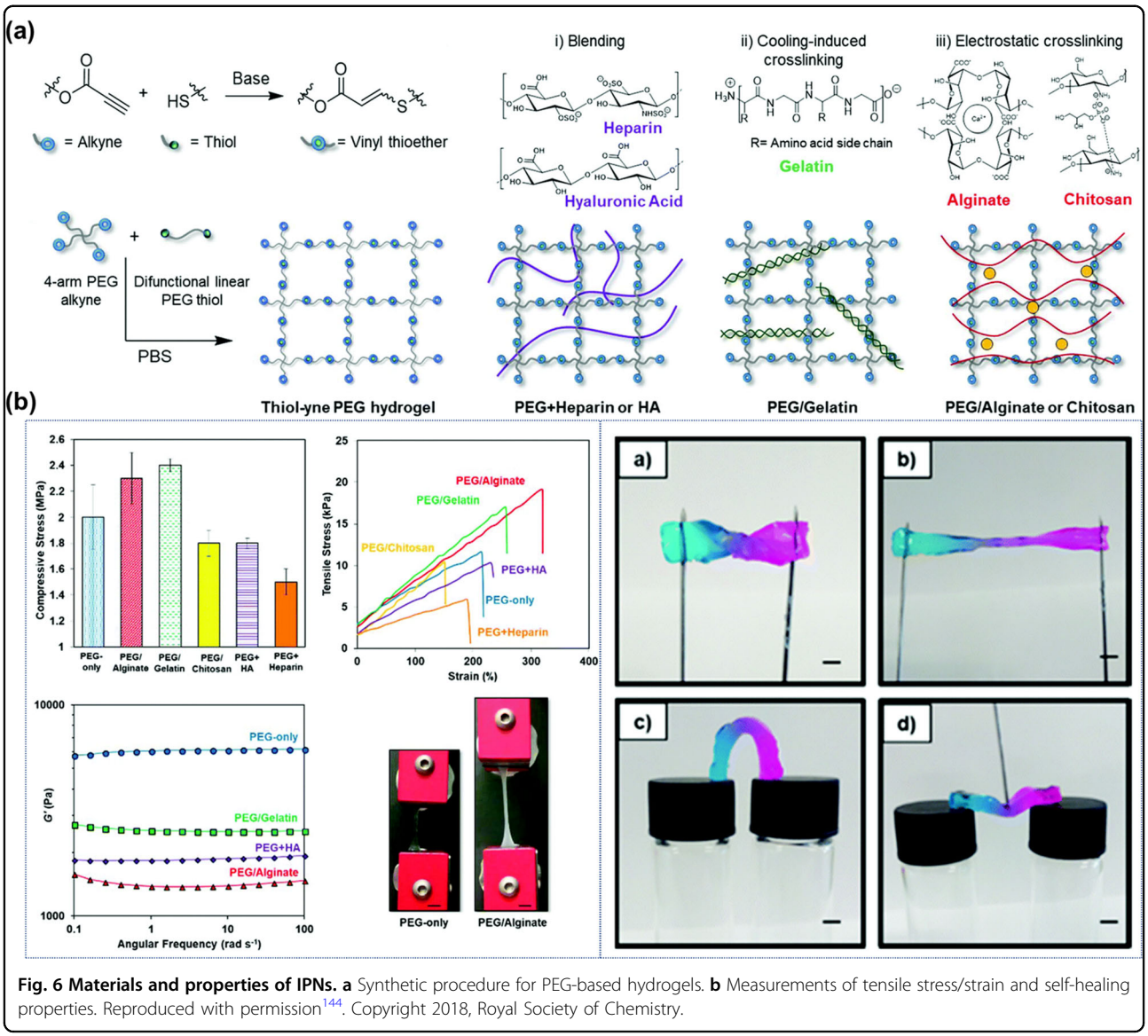

Fig. 6 Materials and properties of IPNs. a Synthetic procedure for PEG-based hydrogels. **b** Measurements of tensile stress/strain and self-healing properties. Reproduced with permission[144]. Copyright 2018, Royal Society of Chemistry.

$CaCO_3$-based bioceramics and hydrogels

The utilization of composite hydrogels in bone regeneration is limited due to their inadequate ossification performance. To address this issue, a new osteoblastic gellin glue gel was designed by Abalymov et al. As shown in Fig. 10a, a calcium carbonate ($CaCO_3$)-based composite bioceramic and hydrogel were generated and used to encapsulate and immobilize the enzyme[148]. The addition of $CaCO_3$ to the hydrogel increased the stability of the particles and decreased the enzyme activity. The $CaCO_3$-incorporated alginate hydrogels remained stable for almost 13 days, much longer than calcium alginate-based hydrogels and Alg-based hydrogels (Fig. 10b). In addition, the $CaCO_3$-based hydrogels showed high protein loading capacity, reaching 37% by weight. According to the results of cell experiments, the composite hydrogels containing alkaline phosphatase (ALP) resulted in a higher concentration of hydroxyapatite, suggesting their potential in bone repair treatment. These results indicated that composite hydrogels containing Ca/Mg $CaCO_3$ submicron particles effectively optimized bone remodeling and other cell growth applications. Therefore, hydrogels can serve as highly efficient and biocompatible carriers for drug delivery in bone reconstruction applications.

2D black phosphorus nanosheet-based composite hydrogels

Many challenges in bone tissue engineering need to be solved to achieve efficient bone regeneration. To enhance stem cell function and generate a vascularized network, a novel strategy was proposed: to accelerate bone regeneration by continuously providing phosphorus (P) rather

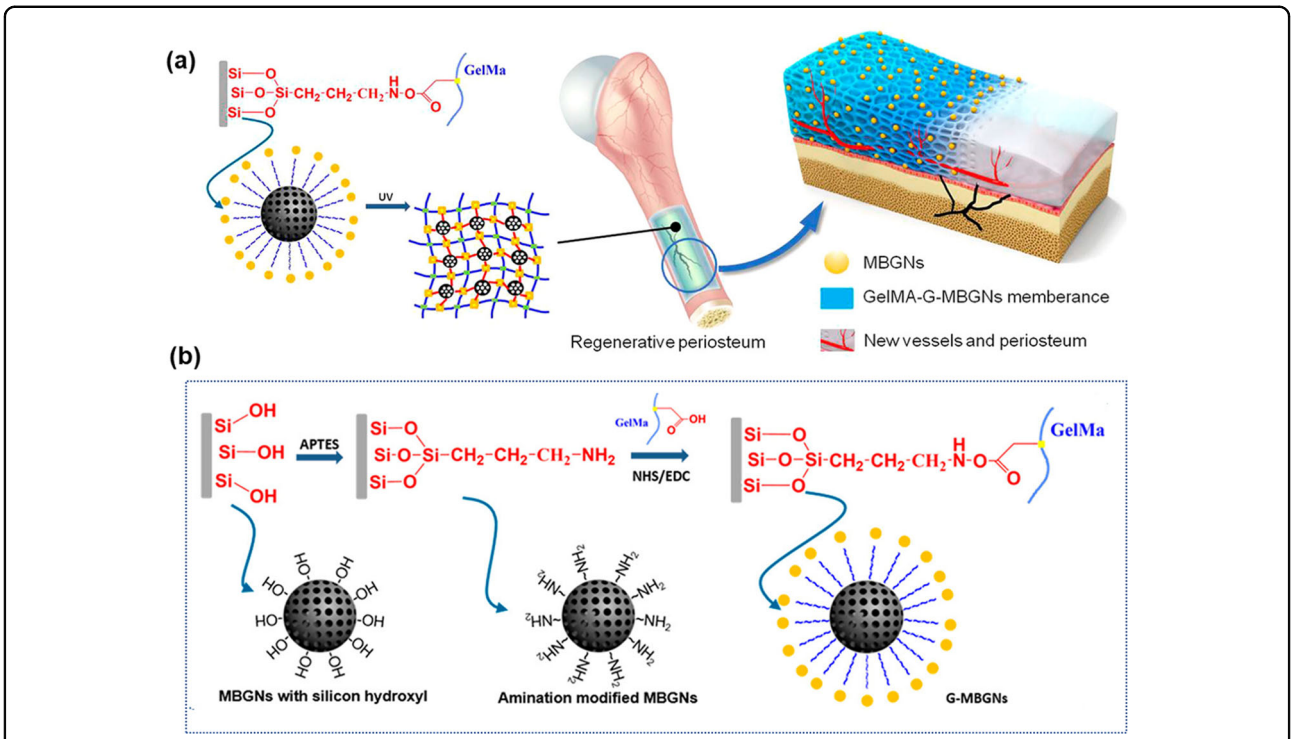

Fig. 7 Schematic diagram of the use of bioactive glass composite hydrogels for periosteal regeneration. a Inorganic strengthened hydrogel membrane for regenerative periosteum. **b** Fabricating amino modified MBGNs and GelMA-MBGNs (G-MBGNs). Reproduced with permission[146]. Copyright 2017, American Chemistry Society.

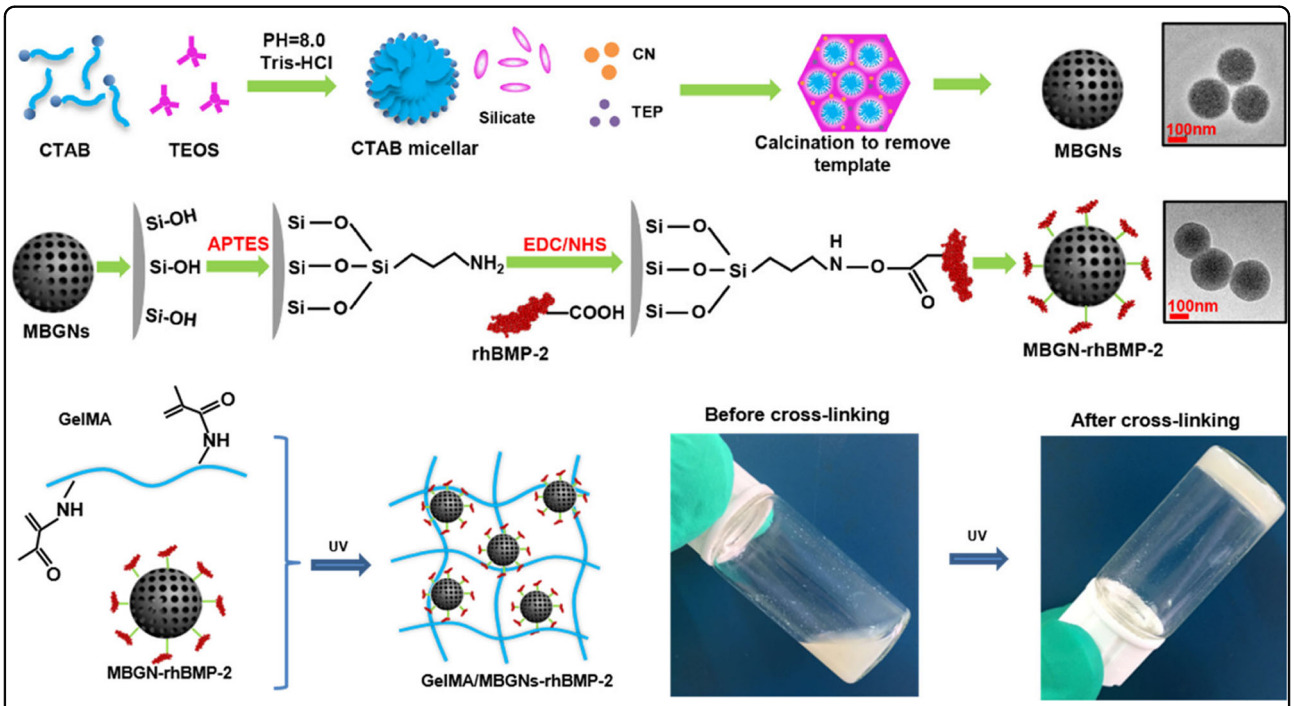

Fig. 8 The formation of GelMA/MBGNs-rhBMP-2 hydrogel. It shows excellent long-term osteogenesis and the ability to promote bone tissue regeneration in critical-size skull defects in rats. Reproduced with permission[147]. Copyright 2018, American Chemistry Society.

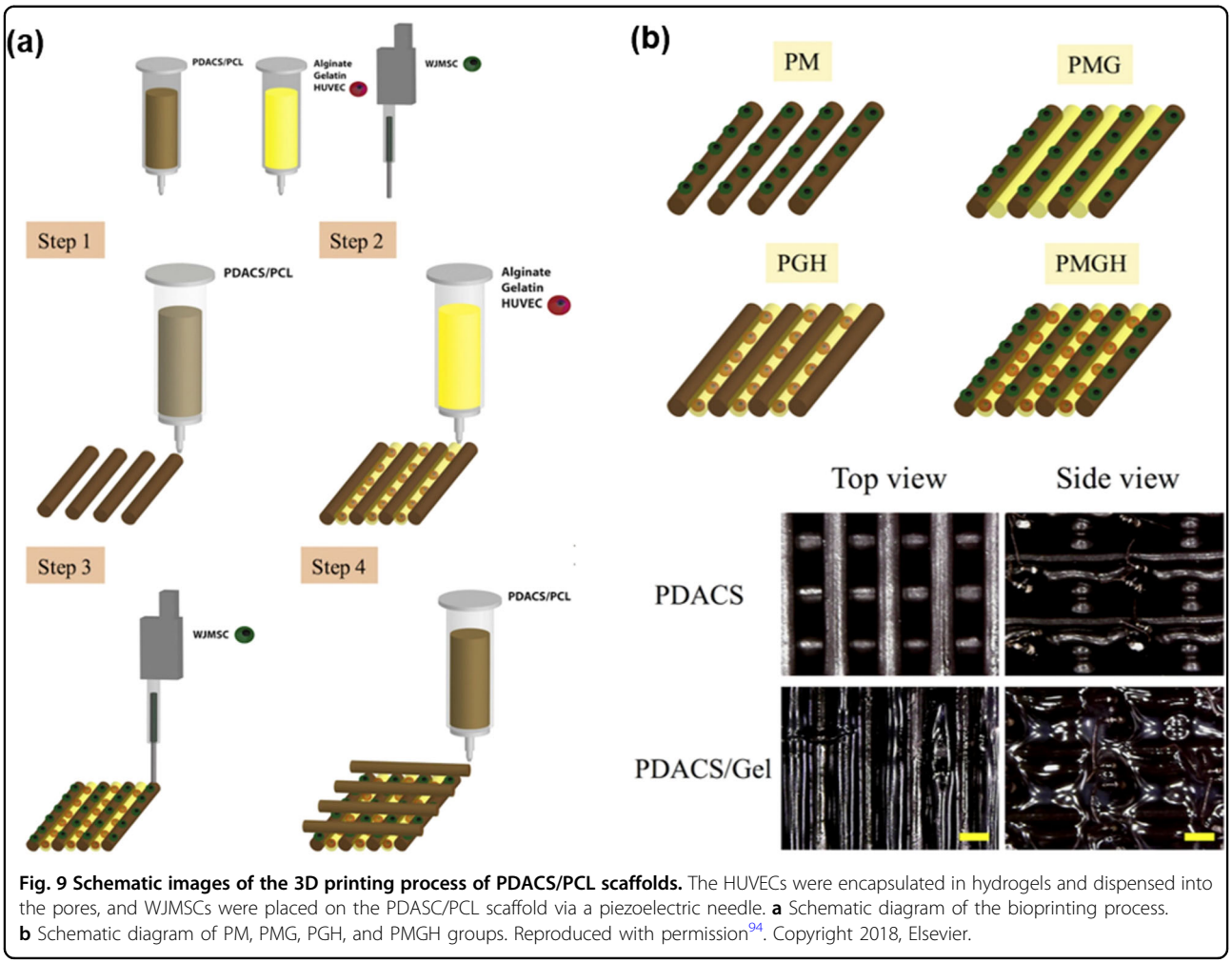

Fig. 9 Schematic images of the 3D printing process of PDACS/PCL scaffolds. The HUVECs were encapsulated in hydrogels and dispensed into the pores, and WJMSCs were placed on the PDASC/PCL scaffold via a piezoelectric needle. **a** Schematic diagram of the bioprinting process. **b** Schematic diagram of PM, PMG, PGH, and PMGH groups. Reproduced with permission[94]. Copyright 2018, Elsevier.

than exogenous calcium (Ca). Huang's group developed a hydrogel platform based on two-dimensional black phosphorus nanosheets (BPNs), which can provide slow and sustained release of P[149]. Hydrogels were prepared by the photoinduced crosslinking of GelMA, BPNs, and cationic arginine-based unsaturated polyester amides. The incorporated BPNs were shown to be encapsulated inside the hydrogel scaffold (Fig. 11), which acted as ECM for bone reconstruction. Moreover, the introduction of BPNs helped to improve the mechanical properties of the hydrogels, which can also release P in response to light and accelerate mineralization in vitro. In vivo results in a rabbit bone defect model confirmed the biocompatibility of the BPNs and showed that the BPNs helped to accelerate bone regeneration. In addition, the addition of BPNs promoted the osteogenic differentiation of human dental pulp stem cells (hDPSCs) via the BMP-RUNX2 pathway. These results strongly suggest that a strategy of continuously supplying Ca/P from BPN-containing hydrogel platforms is promising for efficient bone regeneration.

ChS-NP-based composite hydrogels

Numerous research teams are exploring the application of hydrogels in bone regeneration through the incorporation of nanoparticle. As a representative work, Radhakrishnan's group developed an injectable semi-IPN network hydrogel structure using chondroitin sulfate nanoparticles (ChS-NPs) and nano-HA (~30–90 nm) in the cartilage and subchondral hydrogel regions, respectively[150]. The results showed that the mineralized subchondral hydrogel significantly promoted osteoblast proliferation and ALP activity ($p < 0.05$), and the nanoengineered gradient hydrogel increased cartilage regeneration with subchondral bone formation and side-to-side host tissue integration. Therefore, composite hydrogels incorporating nanoparticles have become a simple but important tool due to their remarkable ability to promote osteogenic differentiation.

Summary

Hydrogel materials possess distinct structural characteristics and physical properties, including a 3D

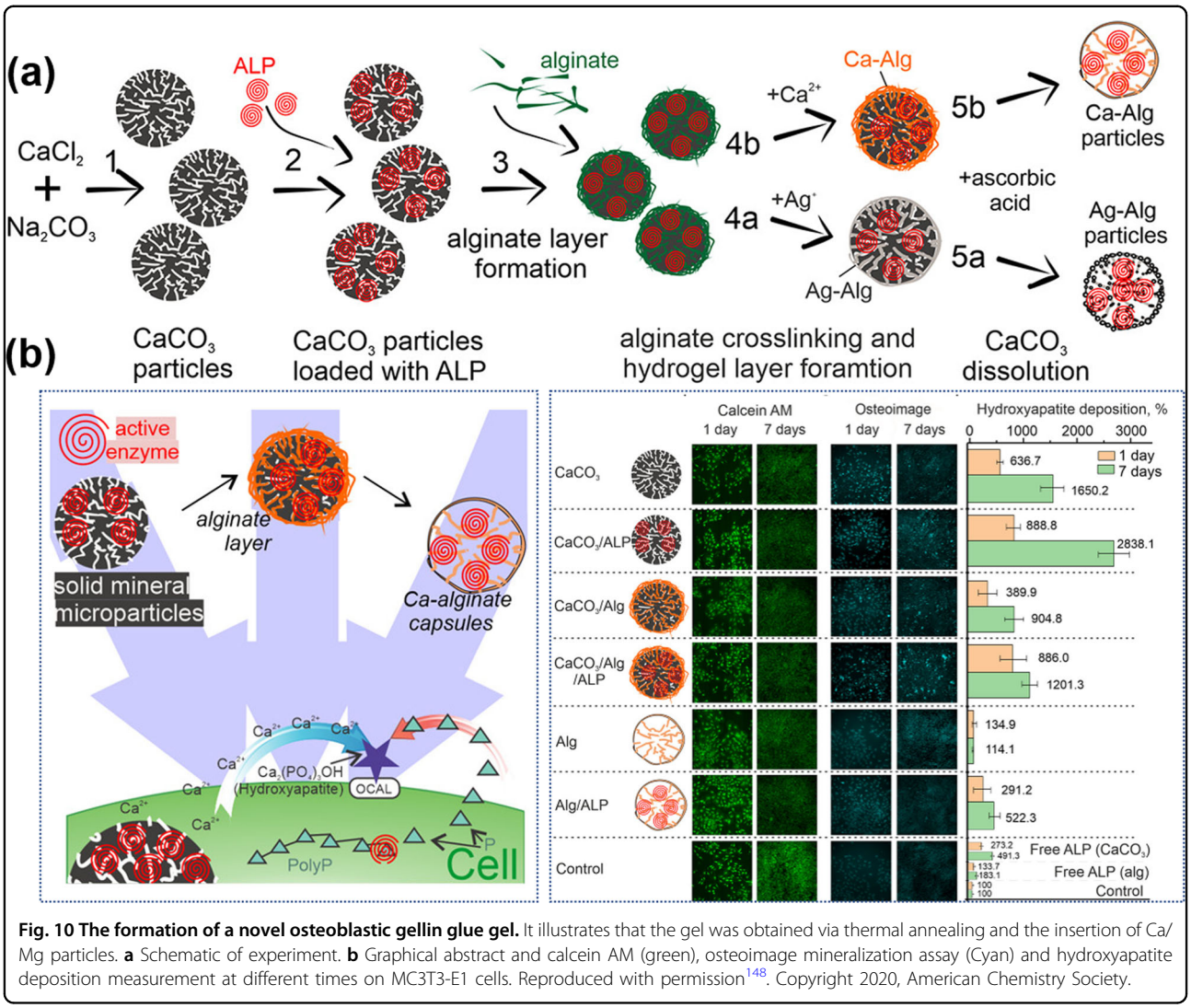

Fig. 10 The formation of a novel osteoblastic gellin glue gel. It illustrates that the gel was obtained via thermal annealing and the insertion of Ca/Mg particles. **a** Schematic of experiment. **b** Graphical abstract and calcein AM (green), osteoimage mineralization assay (Cyan) and hydroxyapatite deposition measurement at different times on MC3T3-E1 cells. Reproduced with permission[148]. Copyright 2020, American Chemistry Society.

network structure, implantability, favorable mechanical and degradation properties, and exceptional biological effects[151–153]. Various preparation techniques, such as chemical crosslinking and physical doping, have been employed to construct hydrogel materials (i.e., semi-IPNs, IPNs and hybrid hydrogels), which hold promise for fulfilling the material requirements for the clinical treatment of bone defects. In particular, different factors, including bioactive glass, cells or proteins, inorganic matrices (e.g., $CaCO_3$), 2D nanosheets (e.g., black phosphorus) and nanoparticles (e.g., CdS NPs), have been incorporated into conventional hydrogel systems to investigate their effects in the treatment of bone defects. Accordingly, a synergistic treatment strategy has become crucial for the development of high-performance hydrogel systems whose osteogenic properties can increase therapeutic efficacy.

Conclusion and outlook

To effectively address bone defects, various therapeutic strategies, encompassing nonsurgical approaches such as casting, electrical stimulation, and ultrasound therapy as well as surgical interventions such as internal fixation, external fixation, bone grafting, and bone regeneration, are commonly employed in clinical practice. The limitations of these traditional treatment modalities, such as the risks associated with immune rejection, donor site injury, and transmission of infectious diseases, emphasize the urgency and challenge of the development of high-performance biomaterials.

The development of high-performance and multifunctional biomaterials for the treatment of bone defects is essential. At present, three types of materials are used in bone tissue engineering: naturally derived biomaterials, synthetic biomaterials, and metal materials. The earliest application of bone tissue engineering involved mainly

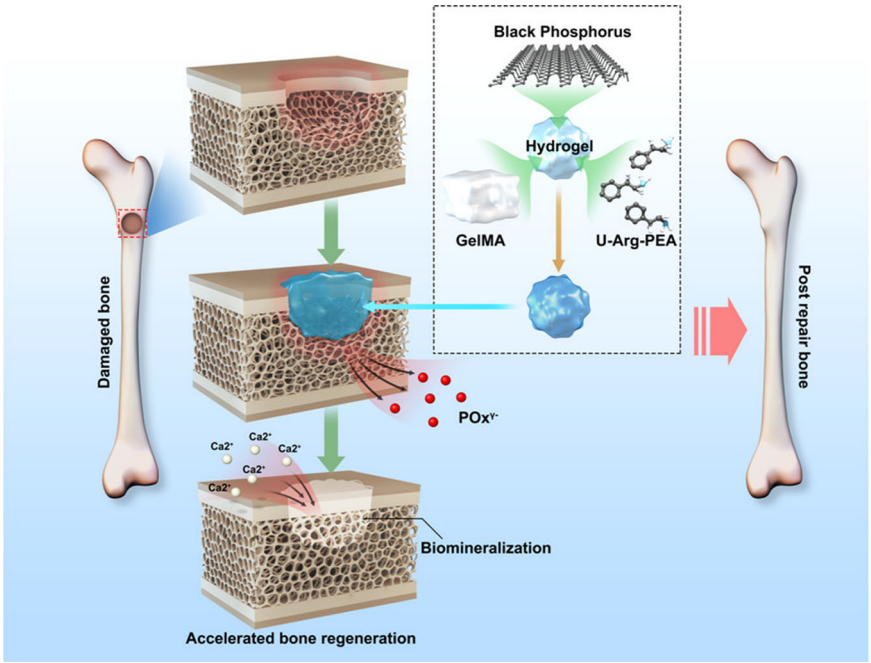

Fig. 11 Illustration of a 3D hydrogel platform containing GelMA, BPNs and U-Arg-PEA. It supplies P rather than Ca to promote biomineralization and bone regeneration. Reproduced with permission[149]. Copyright 2019, American Chemistry Society.

thermal-composite hydrogels, but the ossification performance of this method was poor, so osteogenic hydrogels were developed by thermal annealing[154,155]. At that time, the main goal was to study the biomechanics of embryonic cartilage. Later, scientists used a solvent-free process to combine glial mesenchymal stem cells with human umbilical vein endothelial cell (HUVEC)-loaded hydrogels to prepare polyamine-modified calcium silicate/polycaprolactone scaffolds. The gelatin was modified with methacrylic anhydride to obtain photo crosslinked methacrylic gelatin. By photocrosslinking with methacrylate gelatin, the hydrogel films were prepared to release Ca and Si ions in a controlled manner at the early stage of bone regeneration for the long-term promotion of osteogenesis[156–158]. Since then, great breakthroughs have been made in bone tissue engineering, and a tough and flexible amphoteric copolymer-based hydrogel with bioactive groups has been created for bone regeneration. In 2019, Hasani's group developed a unique bioinspired adhesive hydrogel with tunable mechanical properties and biodegradability that has been applied in dental clinical medicine. Subsequently, Wojda et al. developed a biomaterial system for the delivery of hydrogels to significant bone defects to promote bone regeneration[159].

With the ongoing development of materials science, numerous multifunctional materials have emerged and been applied in various aspects of biomedicine. In recent years, hydrogels have been considered promising candidate materials for tissue engineering and bone repair research due to their structural and compositional similarity to the ECM, high water content, satisfactory biocompatibility, and tunable biophysical and biochemical properties[160,161]. In addition, some hydrogels also have the advantages of low cost, multifunctionality, renewability, degradability, and excellent biocompatibility[159,162,163]. Therefore, the present study offers a comprehensive overview of the recent advances and challenges in the utilization of hydrogels for bone repair and regeneration. The application of hydrogels in the field of orthopedics has focused mainly on tissue engineering, wound healing, and drug delivery. Excitingly, some research results have been applied in clinical practice. A variety of hydrogel structures, including osteogenic gellan gel, semi-interpenetrating network hydrogels (semi-IPNs), interpenetrating network hydrogels (IPNs), and photo-induced crosslinking methacrylate gelatin (MAGel), have been described. The functional, mechanistic, and medical advantages of these hydrogel structures are thoroughly examined in this review. With the development of hydrogels and bone repair techniques and further understanding of the cellular signaling mechanisms involved in tissue repair, hydrogels will be able to mimic the natural ECM more accurately and play a more effective role in bone and soft tissue engineering.

According to previous reports, conventional synthetic hydrogels still present several disadvantages and challenges, such as an isotropic network structure, insufficient mechanical properties, weak tissue adhesion and lack of

bone conductivity. Most hydrogels serve as carriers rather than promoters of bone healing. The development of dual-functional or multifunctional hydrogels and their composites represents an intriguing research topic. Considering the diverse structures of hydrogels, it is essential to elucidate structure-property relationships to better understand the principles and mechanisms involved in bone repair. Furthermore, research on microfabrication techniques, including 3D printing, is necessary to achieve controllable nanostructures and large-scale production[164–168]. Therefore, collaborative research efforts are still needed to enhance the performance of these materials in the field of bone healing. The development of novel and highly efficient hydrogel systems could revolutionize bone defect treatment.

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Author contributions
W. Ding and Y.X. Ge contributed equally to this work. All the authors contributed to the writing, review, and editing of the manuscript.

Conflict of interest
The authors declare no competing interests.

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