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Review

Emerging advances in hydrogel-based therapeutic strategies for tissue regeneration

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ABSTRACT

Significant developments in cell therapy and biomaterial science have broadened the therapeutic landscape of tissue regeneration. Tissue damage is a complex biological process in which different types of cells play a specific role in repairing damaged tissues and growth factors strictly regulate the activity of these cells. Hydrogels have become promising biomaterials for tissue regeneration if appropriate materials are selected and the hydrogel properties are well-regulated. Importantly, they can be used as carriers for living cells and growth factors due to the high water-holding capacity, high permeability, and good biocompatibility of hydrogels. Cell-loaded hydrogels can play an essential role in treating damaged tissues and open new avenues for cell therapy. There is ample evidence substantiating the ability of hydrogels to facilitate the delivery of cells (stem cell, macrophage, chondrocyte, and osteoblast) and growth factors (bone morphogenetic protein, transforming growth factor, vascular endothelial growth factor and fibroblast growth factor). This paper reviewed the latest advances in hydrogels loaded with cells or growth factors to promote the reconstruction of tissues. Furthermore, we discussed the shortcomings of the application of hydrogels in tissue engineering to promote their further development.

Contents

Abbreviations: 3D, three-dimensional; TGF, transforming growth factor; BMP, bone morphogenetic protein; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; EGF, epidermal growth factor; EVs, Extracellular vesicles; MSCs, mesenchymal stem cells; ECM, extracellular matrix; hBMSCs, human bone marrow mesenchymal stem cells; IL-4, interleukin-4; BMMs, bone marrow-derived macrophages; GG, gellan gum; SF, silk fiber.

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1. Introduction

Tissue engineering involves harnessing cells, engineering, materials, and biochemical and physiochemical factors to replace biological tissues [23]. The implementation of tissue engineering requires appropriate cells, scaffolds supporting cell attachment and growth, and bioactive molecules that regulate cell growth, proliferation, and differentiation, such as growth factors. And materials used to prepare scaffold preparation can be divided into natural and synthetic polymers, ceramics, and glasses [1]. In particular, natural polymers are suitable for fabrication processes such as hydrogelation and photopolymerization [117]. Hydrogels prepared by polymers are soft high-water-content materials with many advantages, including good biocompatibility, soft mechanical strength, low cytotoxicity, *in vivo* enzyme degradability, and a microenvironment similar to natural tissue providing an appropriate environment for cell adhesion and proliferation[25,37,47,69].

Despite the dominance of small-molecule drugs and protein therapeutics in treatment, we can engineer our own body's cells to treat disease [94]. Interestingly, hydrogels can serve as an active matrix to maintain cell growth, proliferation, and differentiation [124]. Cell therapy achieve more complex functions than small molecule drugs or biologics, resulting in more effective disease treatments and a promising approach for treating refractory diseases [15]. Growth factors are widely acknowledged as essential in repairing tissue due to their influence on cell signaling pathways through extracellular and intracellular mechanisms [102]. Thus, it is generally believed that hydrogels containing cells and growth factors have great potential. Based on the natural three-dimensional (3D) environment in hydrogels, cells can proliferate and form tissues with specialized configurations and morphologies [97].

Currently, various hydrogels have been considered to regenerate tissue by delivery cells (stem cells, macrophages, chondrocytes, osteoblasts), growth factors (bone morphogenetic protein (BMP), insulin-like growth factors, transforming growth factor (TGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) etc.) and hormones [48]. In this article, we discussed the extensive applications of hydrogels in tissue repair providing a foothold for further research on hydrogels.

2. Applications of the hydrogels

Trauma is one of the most common injuries, and it is the damage to human tissues caused by mechanical factors [86]. Normal wound healing is a dynamic, complex and multi-stage process involving synergistic interactions between various cells, cytokines and growth factors [85]. Although traditional dressings such as gauze [80,129] and bandage [82] are widely used because of their simple manufacture, low cost and strong absorbency, the weakness of their antimicrobial effects, hemostatic ability and mechanical performance still exists. Besides, in the process of wound healing, traditional dressings would cause secondary damage because of the adhesion of new tissues [3,31]. To date, many wound dressings have been explored, such as hydrogel, film, nanofiber, hydrocolloids, xerogels and hydrofibers. Within them, hydrogels could clean up the matabolites produced from the damaged tissue, effectively reduce the probability of wound bacterial infection and provide a moist environment with antioxidant and free radical scavenging capability, which can be highly beneficial for wound healing [134].

As complex biopsies, cartilage and bone play several key roles in the body. However, they are difficult to heal in view of the poor self-healing ability. And without adequate treatment, bone and cartilage loss will conducive to deleterious long-term effects. Many therapeutic strategies such as microfracture [49], autologous chondrocyte implantation [63,70], xenografts, allografts and autologous bone grafts are indicated for cartilage repair and bone regeneration [107]. However, there are various defects such as poor mechanical properties of cartilage, cell death, limited bone mass, disease transmission, contamination, and immune response. Given that current treatment methods have limitations, much emphasis has been placed on finding new and effective methods to treat bone and cartilage defects. Tissue engineering is a prospective strategy to repair damaged cartilage and promote bone regeneration, with hydrogel being used as a suitable scaffold material [21]. This paper reviewed the latest advances in hydrogels embedded with cells or growth factors to promote the reconstruction of wound, bone and cartilage (Table 1 and Fig. 1).

2.1. Types of functional cells encapsulated in hydrogels

Cell therapy refer to that treatment of diseases by introduce new cells into an organism or tissue and cell-based therapies have recently been studied. Hydrogels have the capability of 3D cell cultures, which can overcome the abnormal polarization of cells in 2D culture. And because of the *in vivo* tissue stroma matrix-mimicked property, hydrogels support cell-cell and cell-extracellular matrix interactions, enabling the growth and proliferation of cells [9,127]. Various cells are encapsulated in hydrogels to reproduce *in vitro* while maintaining functional characteristics and to sustainably promote tissue reconstruction [9]. There are many studies on the application of hydrogel delivery cells for tissue engineering.

2.1.1. Stem cell

As is known to all, stem cells can self-renew and differentiate into many cell types, which are essential for the renewal and

Table 1
Materials and methods of cell/growth factors delivery in tissue regeneration.

Application	Materials	Delivery methods	Cell/growth factors types	References
Bone regeneration	Graphene oxide-modified silk fibroin/nanohydroxyapatite	3D-printed scaffold	Urine-derived stem cells	[103]
	Methacryloylated gelatin/nanohydroxyapatite/nanosilicate	Injectable hydrogels	MSCs	[99]
	Gelatin	Injectable hydrogels	BMP-2	[17]
	ECM/oleoyl chitosan	Implanted constructs	ALN/BMP-2	[27]
Cartilage repair	Silk fibroin and tyramine-substituted gelatin	3D-printed scaffold	Stem cell	[66]
	Methacrylated hyaluronic acid/polycaprolactone	3D-printed scaffold	BMSC	[71]
	Chitosan/poly(ε-caprolactone)	3D-printed scaffold	Synovial MSCs	[65]
	Catechol-modified chitosan	Injectable hydrogels	BMSC	[137]
	Silk and methacrylated silk fibroin	3D-printed scaffold and injectable hydrogels	BMP-2 and TGF-β3	[116]
Wound healing	Silk fibroin	Patches	MSCs	[79]
	Silk fibroin	Injectable hydrogels	BMSCs	[64]
	Microporous annealed particle	Scaffold	Epidermal growth factor	[91]

regeneration of injured physiologic tissue [85]. At present, new methods of combining stem cells with hydrogels have been widely studied and applied to tissue engineering (Fig. 2).

As multipotent stromal cells capable of migration, differentiation, and immunomodulation, mesenchymal stem cells (MSCs) representing an alternative treatment method in tissue regeneration are involved in the continuous maintenance and repair of many tissues (Fig. 2 B, C, D) [5,39,109].

In recent years, MSC therapy has shown great potential to promote bone healing [109]. It has been shown that MSCs can directly differentiate into osteoblasts and osteocytes, secrete various bioactive substances and acquire similar functions to bone tissue [52]. For example, Sayanti Datta et al. obtained an io-hybrid hydrogel by crosslinking oleoyl chitosan and acellular bone extracellular matrix (ECM); the human amnion-derived mesenchymal stem cells were embedded in the hydrogel to promote bone

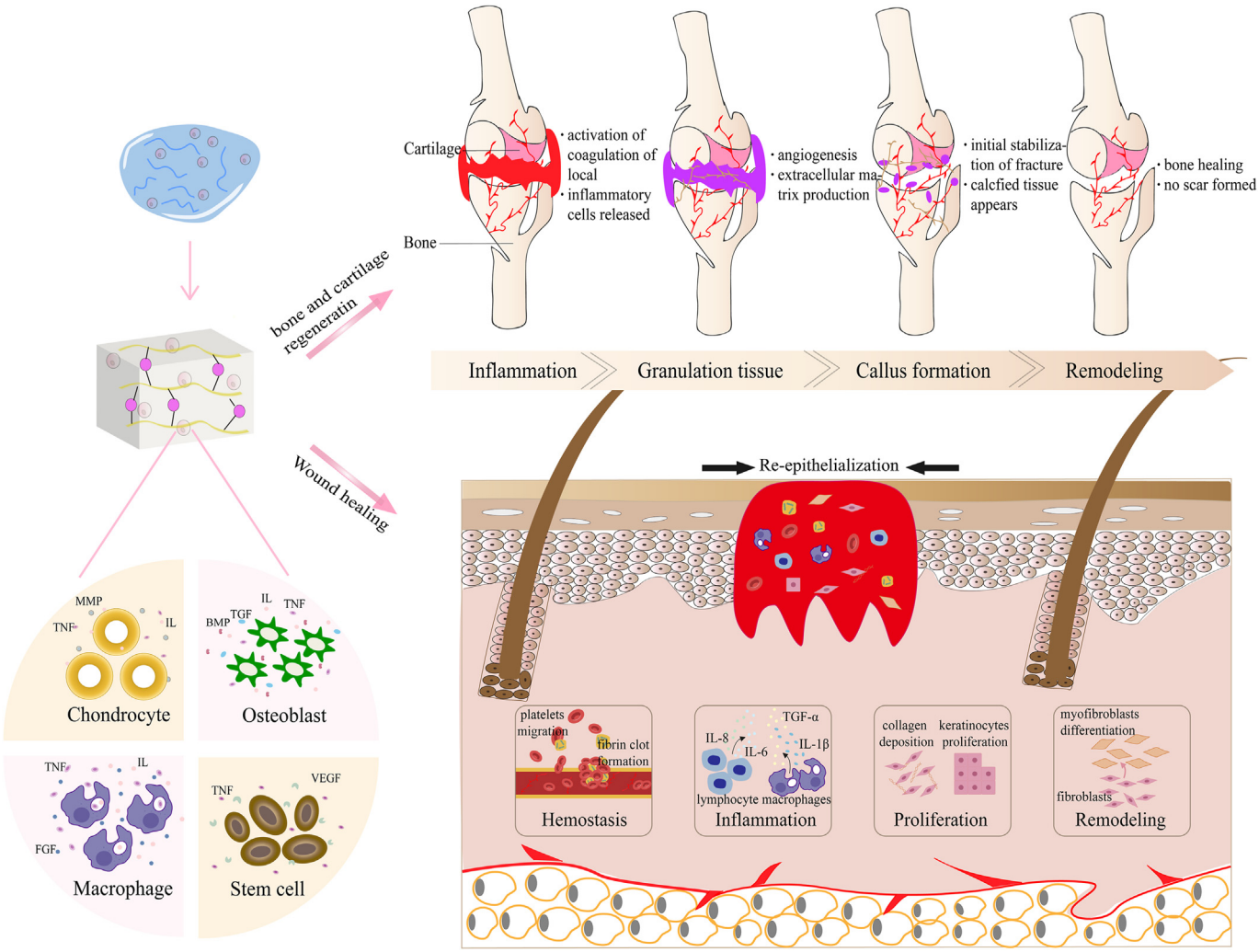

Fig. 1. Biomedical applications of hydrogel constructs loaded with cells and growth factors for healing wounds and treating bone and cartilage defects.

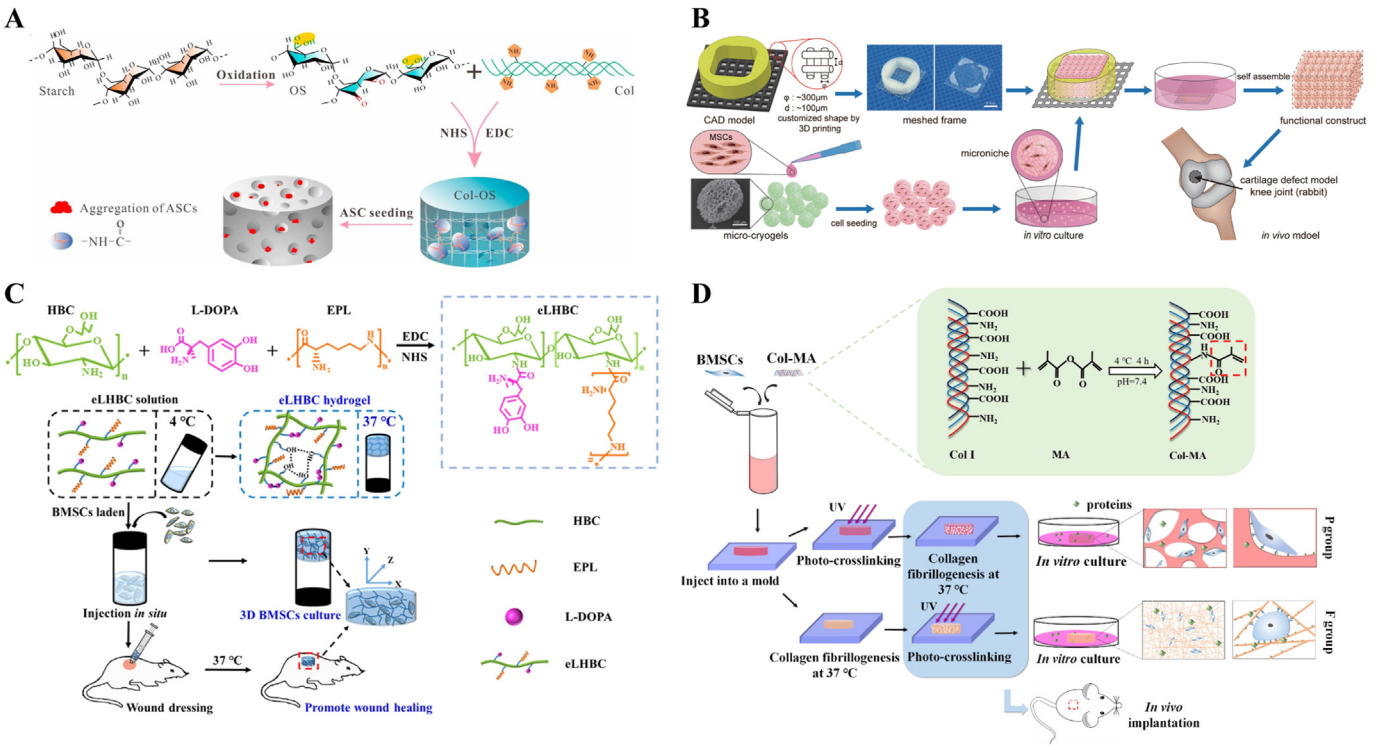

Fig. 2. (A) O xidized starch crosslinked collagen hydrogel inoculated with ASCs [118]. Copyright 2020, Elsevier B.V. (B) 3D functional tissue constructs using a unique gelatin-based microscopic hydrogel [119]. Copyright 2020, Elsevier. (C) Preparation of eLHBC injectable hydrogel encapsulating BMSCs as wound dressing [105]. Copyright 2021, Elsevier. (D) Fabrication of two collagen hydrogels with different network microstructures and chondrogenic differentiation of BMSCs in the hydrogels [123]. Copyright 2019, Elsevier.

regeneration [28]. Mesenchymal stem cells can also treat cartilage defects. Jay M Patel et al. designed a hyaluronic acid hydrogel system to interdigitate with and stimulate sealing of degenerated cartilage to protect damaged cartilage. Moreover, hyaluronic acid therapy was further functionalized to improve MSC attachment to the injured regions by combining hyaluronic acid modifications with a current palliative treatment for osteoarthritis, MSC injection, which led to the deposition of extracellular matrix to "seal" damaged cartilage. The novel therapeutic strategy not only restored cartilage biomechanics but also potentially prevented subsequent wear and degeneration [87].

MSC can secrete trophic factors playing important roles in tissue engineering. Studies have shown that MSC spheres secrete more trophic factors than individual MSC, which are beneficial to promoting angiogenesis, reducing local inflammation and finally accelerating wound healing. Therefore, a kind of fibrin gel delivery system was designed for simultaneously enhancing the proangiogenic and anti-inflammatory potential of entrapped MSC spheroids [83]. Similarly, an electrospray encapsulation device was developed, in which single or spherical MSCs were encapsulated into micron-sized alginate beads, and then embedded in an injectable thermosensitive hydrogel matrix. This study achieved increased immunomodulatory effects of MSC without expansion, and promoted tissue regeneration by significantly improving the MSC paracrine action in spheroid forms with an optimized three-dimensional MSC culture [84]. However, scar formation during wound healing is unavoidable. To this end, microgels composed of aligned silk nanofibers were developed to load bone marrow mesenchymal stem cells and disperse them into injectable silk nanofiber hydrogels. The synergistic effect of silk-based composite hydrogel and mesenchymal stem cells stimulated angiogenesis and transformation of pro-inflammatory and anti-inflammatory phenotypes of macrophages, and when applied to the wound, scarless tissues with hair follicles could be formed [136].

In addition to mesenchymal stem cells, researchers have attempted to use other stem cells in tissue engineering. For example, Kan Yue et al. designed a visible light *in-situ* crosslinked tyramine-methacrylamide gelatin encapsulating the articular chondroprogenitor cells and corroborated that tyramine-methacrylamide gelatin hydrogel significantly improved the expression of type II collagen and facilitated the generation of cartilage [113]. A novel biodegradable Schiff base crosslinker difunctional polyurethane and glycol chitosan were used as raw materials to prepare hydrogels, inoculating adipose-derived adult stem cells on the gel and combining with acupuncture to promote the re-epithelization process and achieve skin regeneration [16]. Results from these studies evidence supporting the therapeutic benefits of stem cells, and in recent years MSCs have become a hot topic. But it is still not clear to identify the self-renewal ability and molecular mechanism of MSCs and how culture expansion changes the cell composition and population function [85].

2.1.2. Macrophage

Macrophages play essential roles in tissue engineering. It has been established that permanent tissue macrophages and other cells trigger an inflammatory cascade, which polarizes macrophages to pro-inflammatory phenotypes which produce cytokines to recruit MSCs. After the acute inflammatory response subsides, anti-inflammatory macrophages rise, and tissue regeneration is stimulated, facilitating MSC and vascular differentiation [108]. Accordingly, an adequate transition of macrophages from pro-inflammatory to anti-inflammatory phenotypes is critical for tissue regeneration [108,113]. There are a variety of means to promote the polarization of macrophages to anti-inflammatory phenotypes.

Haoyu Wang et al. engineered a biomimetic and photo-responsive hyaluronan-alkoxylphenacyl-based polycarbonate hydrogel nanocomposite that could control 3D cell-ECM interactions to regulate macrophage polarization [110]. Based on this, a new type of glycopeptide hydrogel was developed to simulate glycoprotein components and nanofiber structures of the skin ECM and polarize macrophages into anti-inflammatory phenotype by inducing mannose receptors activation through ERK/STAT6 pathway, which can accelerate wound healing [36]. It was also found that the stiffness of the ECM plays a vital role in regulating the polarization of macrophages. After mouse bone marrow-derived macrophages (BMMs) were embedded in polyacrylamide hydrogels with different substrate stiffness, low and medium substrate stiffness promoted the shift of BMMs to pro-inflammatory and anti-inflammatory, respectively [14].

Except these methods mentioned before, novel double network hydrogels were prepared basing on hyaluronic acid and type II collagen in squid cartilage, which directly or indirectly regulated the dynamic immune response of neutrophils/macrophages, induced the activation of anti-inflammatory macrophages by inhibiting pro-inflammatory macrophage-mediated inflammatory response [24].

Besides. Interleukin-4 is a common immune cytokine that can induce the anti-inflammatory macrophage phenotype to reduce the immune-inflammatory response and accelerate tissue repair after implantation. So, the double hydrogel layers system on titania nanotubes is designed as a reservoir for regulating the release of IL-4 and interferon-γ. It was found that interferon-γ released from the hydrogel system stimulated the switching of macrophages to pro-inflammatory phenotypes, whereas IL-4 polarized macrophages to anti-inflammatory phenotypes [11]. Similarly, graphene oxide-carboxymethyl chitosan/poly diacrylate interpenetrating network hydrogels was prepared. After IL-4 was loaded and released in a controlled manner, macrophage differentiation into the anti-inflammatory type was observed. The hydrogel scaffolds promoted new bone formation and tissue repair through immune regulation of the local microenvironment [139].

2.1.3. Chondrocytes

Importantly, chondrocytes have been embedded in various hydrogels to treat cartilage defects. The glucuronide acid residues in the repeat units of gellan gum (GG) have a similar structure to native articular cartilage glycosaminoglycans and hyaluronic acid has characteristics of cartilage protection and cartilage induction and lubricate cartilage, both of which play important roles in cartilage formation [35,106]. But GG lacks cell-binding sites for cell growth and migration, which may lead to significant cell death. The physical blending of GG with different lengths of silk fiber (SF) improved the mechanical properties and cell adhesion of GG and enhanced cell viability and growth of chondrocytes in the GG blended with SF [60].

With scientific progress achieved, injectable hydrogels have attracted considerable attention in cartilage tissue engineering in recent years. Accordingly, biomimetic, hyaluronic acid-based cryogel scaffolds produced with hyaluronic acid and glycidyl methacrylate were engineered that possessed shape-memory characteristics which contracted and restored their form after syringe injection to fill cartilage defects non-invasively and provided a beneficial microenvironment for chondrocytes to maintain live and metabolically active following injection through syringe needles [46]. However, studies have shown that although hyaluronic acid-based hydrogel supports cell-based cartilage formation, changing the concentration of hyaluronic acid usually leads to changes in biochemical signals and stiffness affecting cell actions. To this end, elastin-like protein-hyaluronic acid hydrogels were developed through dynamic hydrazone bonds by the reaction between hydrazine-modified elastin-like protein and aldehyde-modified hyaluronic acid. Chondrocytes were embedded in elastin-like protein-hyaluronic acid hydrogels, and in dose-dependent increase of cartilage-marker gene expression and improved sulfated-glycosaminoglycan deposition while minimizing unwanted fibrocartilage phenotypes due to increased concentration of hyaluronic acid [138].

2.1.4. Osteoblasts

Osteoblasts that differentiate from MSCs resident in the bone marrow can secrete various bioactive substances and have been widely studied in bone regeneration [89]. Osteoconductive hydrogels were developed via a facile one-step micellar copolymerization of acrylamide and urethane acrylate dextran, followed by the *in-situ* mineralization of hydroxyapatite nanocrystals. The mineralized hydroxyapatite improved the mechanical properties, promoted the adhesion and proliferation of osteoblasts, and stimulated osteogenic differentiation [33]. There were also silver nanoparticles-loaded hydrogels using gelatin as a stabilizing agent under sunlight. Interestingly, the survival and spread of cells were improved after the osteoblasts were fixed with hydrogels [43]. Researchers also modified the chitosan hydrogel with catechol and added zeolitic imidazolate framework-8 (ZIF-8) for further modification to obtain a catechol-functionalized chitosan nano-ZIF-8 composite hydrogel system (CA-CS/Z) with good adhesion and mechanical properties. After co-culturing with osteoblasts, the osteogenesis-related genes were upregulated, and the secretion of osteogenesis-related proteins was promoted, resulting in significant collagen secretion and a high degree of extracellular matrix mineralization [72].

2.1.5. Cell co-culture

Co-culture represents a superior model to mimic natural tissues whereby two different types of cells are simultaneously seeded onto tissue engineering scaffolds, thus avoiding the current limitation of utilizing only one cell (Fig. 3) [81]. An injectable cellular compatible double-network hydrogel was prepared to encapsulate, co-culture, and stimulate the angiogenesis/osteogenic differentiation of vascular endothelial cells and hBMSCs. The direct co-culture system was found to be capable of simultaneously enhance osteogenesis and vascularization by offering 3D cell-cell communication [122]. It was also proposed to co-transplant MSCs and fibroblasts using a Hylan-A dermal filler hydrogel containing tenascin-C and collagen I to provide augmented cellular reserve at the damaged site and apply it to the wound site to promote wound closure and reduce inflammation and cicatrix formation following wounding [126]. Co-culture systems have been shown to solve many of the problems encountered with single culture in tissue engineering, such as the gradual decrease of cell number. Although cell co-culture has the advantage of synergistic effect, the current cell co-culture mostly simply mixes two cell populations, which is prone to the uneven spatial distribution of cells. Therefore, many studies have focused on controlling cell coculture at an accurate ratio recently [18].

2.2. Types of growth factors encapsulated in hydrogels

Growth factors in the extracellular matrix regulate cellular behavior and drive different cell fates by binding to specific transmembrane receptors [8]. Importantly, growth factors can induce and enhance cell responses and promote cell differentiation into the desired lineage; the secretion of growth factors directly affects tissue development and recovery, accurate control of the dynamic

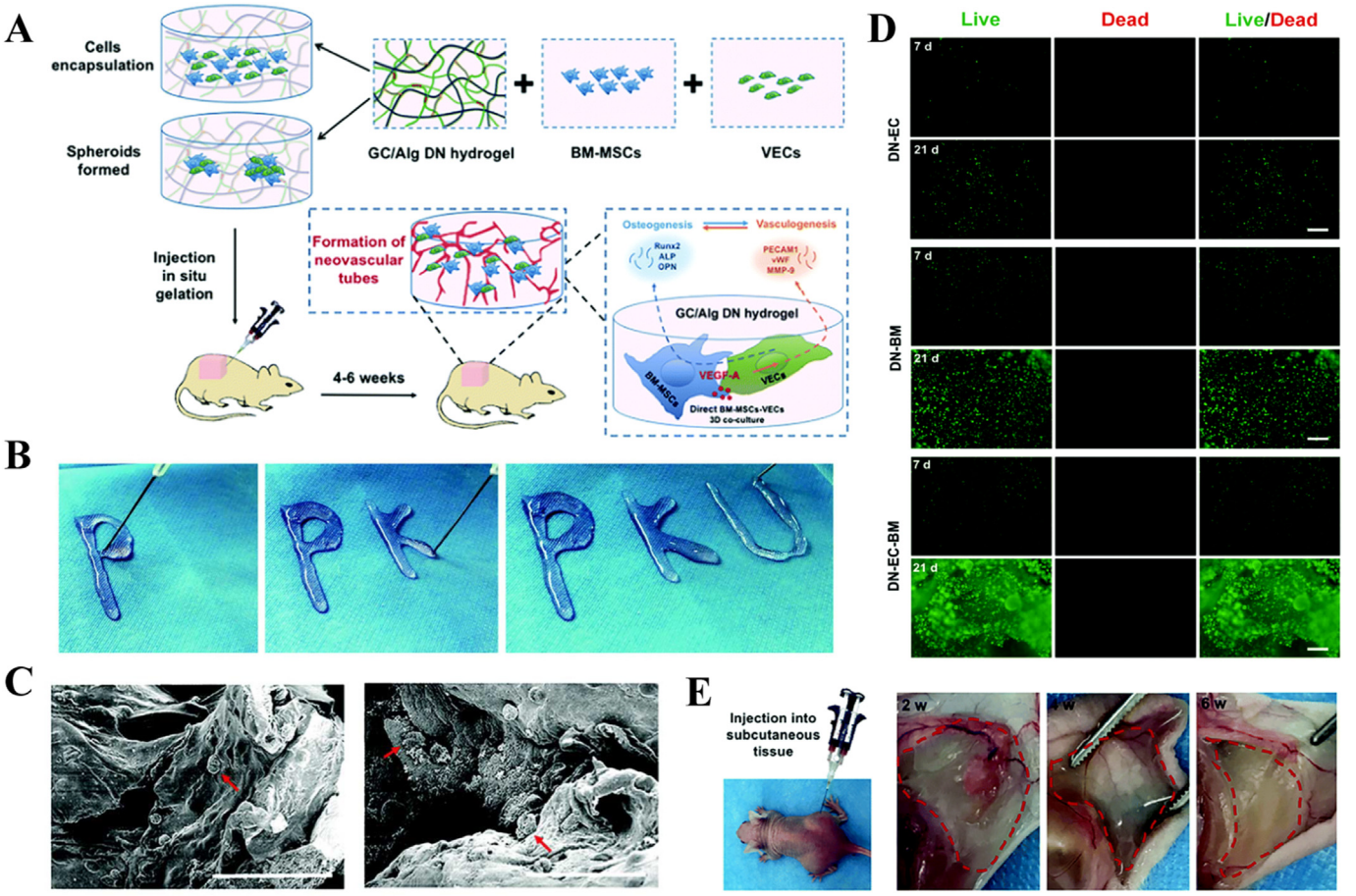

Fig. 3. (A) Preparation and utilization of a GC/Alg DN hydrogel as a 3D scaffold for the co-culture of BM-MSCs with VECs. (B) Demonstration of the injectability of GC/Alg DN hydrogel. (C) SEM images of GC/Alg DN hydrogel. Bar, 50 μm. (D) Images of Live/Dead assay staining of VECs and BM-MSCs on hydrogel. Bar, 50 μm. (E) Injectability of the GC/Alg DN hydrogel and *in vivo* injection [122]. Copyright 2018, Royal Society of Chemistry.

distribution of growth factors and may lead to control of specific regeneration processes or treatments [8,12]. Consequently, the application of hydrogels for the transport of growth factors has attracted the attention of researchers (Fig. 4).

2.2.1. Bone morphogenetic protein

Bone morphogenetic protein family members are involved in various functions in bone, predominantly promoting bone formation after injury. And bone morphogenetic protein2 (BMP-2) is reportedly the most important regulator of bone that promotes the differentiation of osteoblast precursor cells into mature osteoblasts and improves their early enrichment at bone injury site [19]. However, due to the lack of an effective means of delivery, BMP-2 needs to be applied at a supraphysiological dose to achieve clinical effect. In addition to economic costs, supraphysiological doses significantly raise the hazard of side effects, such as swelling, osteolysis and heterotopic ossification [104]. Therefore, many studies have considered embedding them in hydrogels to repair bone, focusing on increasing the transportation of BMP-2 while remaining bioactivity. One study developed functionalized nanoclay which was used as a physical crosslinking agent to crosslink hyaluronic acid. The hydrogel prolonged the *in vivo* local activity of BMP-2 [61]. Moreover, highly osteoconductive hydrogel composites which could slowly release BMP-2 for a long time were prepared by mixing inorganic minerals, whitlockite, or hydroxyapatite, in pyrogallol-conjugated hyaluronic acid [22].

2.2.2. Transforming growth factor

Among the secretory growth factors, the transforming growth factor-β (TGF-β) family has received much attention, given its functions at the cell level and in the development of many diseases [32]. TGF-β is an evolutionarily conserved secreted protein, widely expression in embryo and adult tissues, and controls many basic aspects of cell behavior [133]. Therefore, most methods involve incorporating TGF-β into scaffolds to achieve long-term cartilage regeneration. For example, adipose-derived stem cells and TGF-β3 were embedded in photocrosslinkable methacrylated gelatin hydrogels to form 3D structure [96]. Moreover, it is also a feasible way to load TGF-β3 onto the surface of graphene oxide nanosheets, encapsulate it in a photo-sensitive poly-D, L-lactic acid/polyethylene glycol hydrogel, and mix it with hBMSCs during photocrosslinking [98]. Similarly, in a study, TGF-β3 with human bone marrow-derived mesenchymal stem cells were directly loaded into poly-D, L-lactic acid/polyethylene glycol/poly-D, L-lactic acid hydrogels, or this hydrogels with the addition of hyaluronic acid, and *in vitro* cultured. The construct exhibited controlled release of TGF-β3 without using extra TGF-β3 in the culture medium [30].

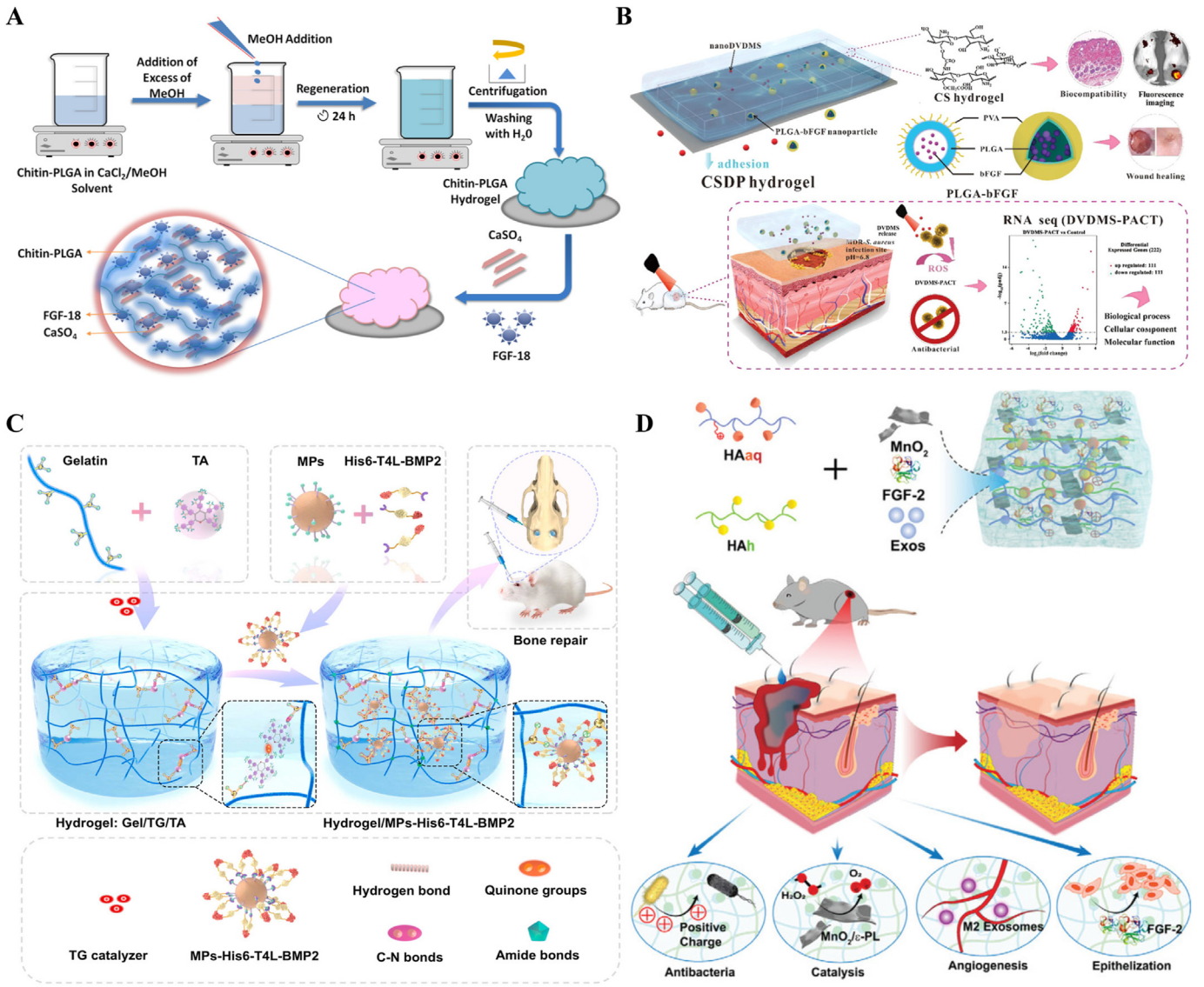

Fig. 4. (A) Preparation of Chitin-PLGA Hydrogel incorporated $CaSO_4$ and FGF-18 [100]. Copyright 2017, American Chemical Society. (B) CSDP hydrogel construction [73]. Copyright 2020, American Chemical Society. (C) The fabrication of hydrogel Gel/TG/TA-MPs-His6-T4L-BMP2 [17]. Copyright 2021, Elsevier. (D) Construction and application of the multi-functional HA@MnO2/FGF-2/Exos hydrogel [120]. Copyright 2022, Wiley.

2.2.3. *Vascular endothelial growth factor*

It is well known that impaired spontaneous vascularization is the main cause of the lack of tissue healing [10,95]. Therefore, promoting angiogenesis is a key method in tissue engineering to promote the repair of damaged tissues, while VEGF is a best-known regulator for angiogenesis [26,121]. VEGF can promote angiogenesis and blood flow recovery in damaged tissue by stimulating endothelial cell proliferation, migration, and sprouting [121]. However, due to the low activity and instability of VEGF in damaged site, the success of direct application of VEGF is limited [111]. So a growth factor delivery system was developed which was based on porous particles and a thermosensitive hydrogel, and continuously released growth factor to imitate their biological production during bone regeneration [59]. However, it is believed that monotherapy can achieve only limited and unsatisfactory results [111]. It has been proven that co-delivery of platelet derived growth factor-BB enlarges the therapeutic reach of VEGF and promotes associated arteriogenesis. Therefore, researchers prepared a highly controlled protein transport system to deliver engineered versions of platelet derived growth factor-BB proteins and VEGF, which was efficient to induce arteriogenesis and angiogenesis in diabetic mouse skin [10].

2.2.4. *Fibroblast growth factor*

The fibroblast growth factor and its receptor signaling system adjusts various biological processes, and plays roles in regulating angiogenesis, wound repair, and others by controlling survival, migration, proliferation, differentiation and metabolism of target cells [125]. Among them, FGF-18 is one of the molecules that assist in inducing endogenous BMP-2 synthesis and increases expression of BMP-2 by suppressing noggin. FGF-18 is also conducive to endothelial cell migration, which may contribute to angiogenesis [100]. An injectable chitin-poly(lactide-co-glycolide) hydrogel containing whitlockite nanoparticles or bioglass nanoparticles with FGF-18 was developed that indicated lasting discharge of FGF-18 [4]. Similarly, through the Michael addition of dithiothreitol and 4-arm acrylated polyethylene glycol a hydrogel dressing embedded with basic fibroblast growth factor and heparin was designed. Through the regulation of heparin, the hydrogel system sustainably

released FGF within 10 days [88]. Ever-increasing proof certifies that FGF participates in the modulation of the regeneration and repair process. However, there are few reports concerning the ill effects of it on tissues and its clinical curative effect [34].

2.2.5. Epidermal growth factor

Epidermal growth factor (EGF) is a small polypeptide with a molecular weight of 6 kDa, which is the first and most successfully applied growth factor for wound repair and regeneration [130]. EGF as a stimulant for fibroblasts and keratinocytes to promote the formation and re-epithelization of granulation tissue is particularly important for repairing wounds [62,91]. It was found that a growth factor solution containing EGF directly applied to wounds accelerated wound healing in a short time. However, as a bioactive protein, EGF is unstable and easily denatured, which hinders its application in tissue engineering. A viscous carry, such as a polymeric hydrogel, may moderately increase the bioavailability of growth factors and overcome the unstable, short half-life of growth factors *in vivo* [50]. Hence, a stimuli-responsive drug-loaded hydrogel wound dressing was prepared using carboxymethyl agarose and calcium ion crosslinking, followed by the loading of recombinant human epidermal growth factor to accelerate wound healing [128]. Similarly, new polysaccharide nanocomposite loaded EGF was added to chitosan-ulvan hydrogels, which continuously released epidermal growth factor and showed significantly faster-wound healing efficiency concerning considerably faster granulations tissue formation and collagen deposition [77]. However, the existing hydrogel dressings have poor stimuli-responsive properties which cannot satisfy the demands of therapy, including the sustained release of the drug and maintaining a suitable humidity and permeability environment for healing. To address the challenge, a EGF-loaded hydrogel dressing with stimuli-responsive capability using carboxymethyl agarose was synthesized that could swell and release EGF based on the change of pH and temperature [128].

2.3. Vesicles

There is great interest in the development of extracellular vesicles (EVs) and nanoparticles (NPs) for disease treatment and diagnosis. EV/NP-based therapies offer a significant advantage in the delivery of drugs to specific targets. In research, nanoparticles are useful because of their uniform size and detectability while extracellular vesicles have low toxicity and immunogenicity, and efficiently avoid endosomal pathways and lysosomal degradation [29,101]. Although recently there are so far no specific guidelines from the US Food and Drug Administration concerning requirements for approval of such products for human use and a regulatory definition of nanotechnology was not adopted, in nanomedicine field a large number of articles has been published [101].

2.3.1. Extracellular vesicles

Extracellular vesicles are lipid nanoparticles secreted by all cells and are involved in numerous trophic and immunomodulatory processes [76]. EVs have been shown to be heavily involved in intercellular communications and to play important roles in protecting their contents from degradation and in delivering their contents to the recipient cells needed for cellular function [114]. Because of effectively changing the physiological functions of recipient cells by delivering their cargoes [67]. And recent work has identified the protein and nucleic acid effectors of EV-mediated pro-angiogenic, anti-apoptotic and anti-inflammatory actions, which are indispensable in facilitating the tissue regeneration [7]. In addition to directly injecting the EVs into the tissue injury site to exert therapeutic effects, the EVs can be embedded into the hydraulic coagulation to functionalize the biomaterial by improving the cell-material interaction, which avoid the defects of low retention rate at the injury site and the need for repeated injection during the administration of EVs injection, thereby maintaining their stability, realizing the continuous release, and enhancing the curative effect of EVs. The use of EVs for treating bone and cartilage injuries has gained considerable attention. Synthetic nanoclay laponite-functionalized gelatin methacrylamide hydrogel for delivery of EVs was prepared. The introduction of laponite affected the release of EVs improving the potential of local retention and controlling delivery of EVs, in addition to improving the shape fidelity of the hydrogel [75]. Researchers considered that the increased retention of EVs by laponite may be due to nanoclay-protein electrostatic interactions that promote the immobilization of these EVs within the hydrogel [56]. The combined effect of co-encapsulation of hMSCs and EVs in hyaluronic-acid-based hydrogel on cartilage regeneration was studied, and the results showed that the co-encapsulation of hMSCs and EVs effectively enhanced the regeneration of cartilage tissue compared with hMSCs [20]. Presently many researchers focus on the transfer of microRNA. For example, bioglass scaffold with GelMa/nanoclay hydrogel coatings was fabricated to load EVs, and the continuously released therapeutic EVs were absorbed by BMSC and endothelial cells, promoting deposition and endothelial network formation, and inducing osteogenic differentiation and angiogenesis by transferring miR-23a-3p [51]. However, it was thought that the therapeutic actions and beneficial effects of EVs were most probably mediated by the transfer of a battery of molecules (growth factors, signaling lipids, mRNAs, regulatory miRNAs, etc.), rather than by one single molecule [41].

2.3.2. Nanoparticles

Nanoparticles are entities of any shape, ranging in size from 1 to 100 nm in any dimension, and their nanoscale size enables them to develop critical physical and chemical properties that facilitate their widespread application in tissue engineering [44]. The nanoparticles are advantageous in that their surface characteristics can be made to suit any purpose and significantly enhance the physicochemical properties of the scaffolds to facilitate their proper integration into the tissue-specific microenvironment [2,44]. Within them, the hard nanoparticles originating from carbon, silica, metal and its oxides, and quantum dots have more widespread and practical usage because of their tunable properties [92]. For instance, due to the antibacterial properties of silver nanoparticles, the superparamagnetic properties of iron oxide nanoparticles, and the high conductivity of au nanoparticles, recently they have been widely used in tissue engineering using a variety of polymer scaffolds. The bio-capped silver nanoparticles were synthesized by green route using the collagen solution as a reducing cum stabilizing agent and the aminated xanthan gum by treating xanthan gum with ethylenediamine and then a stable bio-hybrid hydrogel system was fabricated comprising aminated xanthan gum, collagen, melatonin and bio-capped silver nanoparticles for promoting effective care for various ailments by the synergistic effect of silver nanoparticles and melatonin in the hydrogel [93]. Composite injectable hydrogels were prepared by incorporating osteoinductive and osteoconductive super paramagnetic Fe_3O_4 nanoparticles and hydroxyapatite nanoparticles into di-block copolymer based thermo-responsive hydrogels. The incorporation of nanoparticles modulated bio-markers of bone differentiation and enhanced bone mineralization through magnetic field regulation [53]. Chitosan, modified with Au nanoparticles, and κ-carrageenan had been mixed with poly(NIPAM) to produce an injectable conductive hydrogel, and the results of this study showed that the addition of Au nanoparticles as a conductive component enhanced

cell growth and attachment [90]. Besides, non-metallic nanoparticles are also favored by researchers. Poly (lactic-co-glycolic acid) nanoparticles were modified with RADA16, a self-assembling peptide to encapsulate Tacrolimus, a typical immunosuppressant, and then anchored to a RADA16 hydrogel. The nanoparticle-anchoring hydrogel scaffold was capable of locally release that immunosuppressive agent enhancing the survival of transplanted cells and finally led to successful tissue regeneration [68]. Although the nanoparticles have played a good role in tissue engineering, they also have limitations, such as the lack of standard evaluation methods for biocompatibility and targeting, and the complex preparation process limiting its industrial application.

2.4. 3D bioprinting

Given the complexity of tissue structures, an appropriate 3D structure can optimally mimic the tissue repair process. The emergence of 3D bioprinting makes it possible to manufacture biological structures with hierarchical constructs analogous to their native counterparts [78]. 3D bioprinting has gained overwhelming acceptance from researchers with precisely designed cell patterns and hydrogel materials, i.e., bioinks, enabling the development of living functional tissues (Fig. 5 A, B) [45].

As a pioneering technology, 3D biological printing can prepare multicellular tissue and bionic structures with complex cell construction, tissue heterogeneity, structural and functional multiformity, and an extremely sophisticated microenvironment, which plays important roles in tissue regeneration [112]. For example, a 3D pre-vascularized skin patch was printed in skin-derived extracellular matrix bio-ink and worked with adipose-derived stem cells and endothelial progenitor cells to promote wound closure, re-epithelization, neovascularization, and blood flow [58]. And novel tissue engineering biomaterials were successfully developed that could mimic the composition of regional cartilage tissue and extracellular matrix by using microfluidic print heads with mixing units and incorporating them into extrusion-based bio-printers. Co-culture of human articular chondrocytes and human mesenchymal stem cells in hydrogel scaffolds revealed incremental chondrocyte proliferation and cartilage ECM deposition [55]. Nonetheless, achieving optimal cell distribution and cell deposition levels in 3D scaffolds remains significant challenges. For this reason, an osteoblast-laden nanocomposite hydrogel was developed on the basis of polyethylene glycol diacrylate/laponite XLG nanoclay/hyaluronic acid sodium salt bio-inks by two-channel 3D bioprinting methods, which delivered oxygen and nutrients and promoted differentiation and osteogenesis of osteoblasts and improved viability and deposition efficiency [131]. But the quality of the 3D bioprinting scaffold is affected by its biodegradability, cell response, biocompatibility, and exposed tissue microenvironment. At present, cell-free 3D printing constructs have been widely used in plastic surgery and other fields, but there has been no clinical experiment using cell-loaded 3D biological printing constructs, so continuous research is still needed in the field of 3D printing [78].

Currently, electrospun fibers have also gained much interest in various biomedical applications. Electrospun nanofibers can be simply prepared from synthetic polymers, natural molecules, and

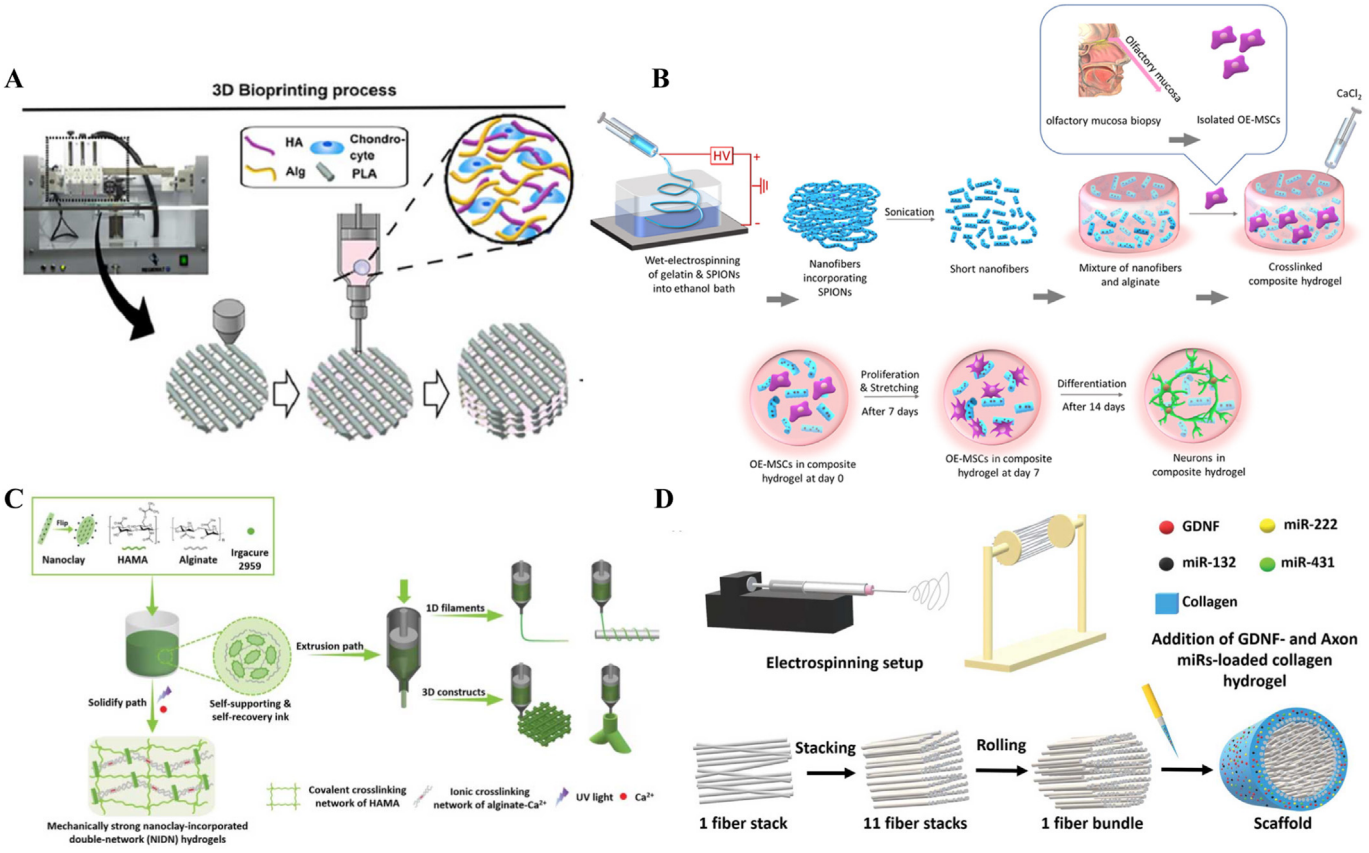

Fig. 5. Strategy of preparing composite scaffold by 3D bioprinting or electrospun. (A) Preparation of bio-inspired hydrogel composed of hyaluronic acid and alginate [6]. Adapted with permission. Copyright 2020, Elsevier. (B) Preparation of alginate-magnetic short nanofibers 3D composite hydrogel [57]. Copyright 2021, Wiley. (C) Design strategy for the fabrication of 1D filaments and 3D constructs based on the unique, mechanically strong NIDN hydrogels [42]. Copyright 2020, Elsevier. (D) A 3D fiber-hydrogel scaffold composed of aligned electrospun fibers and collagen matrix [132]. Copyright 2021, Advanced Science.

other materials [115]. Due to the high plasticity of morphology, topographical similarity to the native ECM, and good tissue compatibility, electrospun is always used as a replacement in tissue engineering [13]. Hydrophilic polymers are more popular because of their hydrophilic surfaces and good cell interaction associated with enhanced cell seeding efficiency [38].

In recent years, electrospun fibers incorporated with hydrogel have been widely explored in tissue regeneration (Fig. 5 C, D). For example, a method for developing 3D bioactive nanofiber scaffolds through coaxial cell electrospraying and concurrent emulsion electrospinning was designed. Endothelial cells are inoculated in hydrogel microspheres and deposited with nanofibers containing VEGF in the scaffold preparation process, leading to nanofibrous scaffolds with 3D encapsulated cell-embedded microspheres [135]. And the superiority provided by electrospun hydrogel fibers is the natural fibers within ECM microenvironments and of water-swollen nature of native ECM [40]. Consequently, they are unstable to maintain desirous forms and weak mechanically. For improving their biological and physical traits, chemically modified by blending or crosslinking with other biomaterials is adopted [38]. For instance, alginate/gelatin hydrogel nanofibers for 3D cell culture by exploiting wet electrospinning of in situ fast crosslinked alginate and gelatin systems were fabricated [74]. Similarly, novel L-arginine-loaded citric acid crosslinked polyvinyl alcohol-hyaluronic acid nanofibers were fabricated by electrospinning, and cellulose nanocrystals were incorporated as nanofiller significantly improving mechanical and swelling properties of nanofibers [54].

3. Conclusion

Hydrogels embedded with cells or cytokines are well characterized in highly structured and controlled *in vitro* environments, and show good therapeutic effects in animal models. However, hydrogel applications in tissue engineering have also encountered various challenges, such as complex tissues production, tissue quality, sufficient angiogenesis, functional integration between the host tissues and graft, and unexpected accidents. Understanding the fundamental interactions between multifunctional biomaterials and cell therapies can help us bridge the gap between the current state and our expectations for hydrogels. Therefore, researchers are warranted to further understand the influence of hydrogels on cell behavior, the triggering factors of cell adhesion, and the cell response to the softness of hydrogels. Biodegradability and the mechanical and morphological properties of hydrogels are also obstacles to be overcome for further development in this field. It can be further considered to adjust the degradation rate and mechanical properties of hydrogels by designing biodegradable precursors or optimizing crosslinking agents to match cell proliferation and the formation of new tissues.

Various novel hydrogels are primarily in the experimental research stage and have not yet stepped into clinical practice. Due to the complexity of the human microenvironment, the future work should focus on the pharmacological and toxicological research and clinical application of hydrogels. Indeed, although tissue engineering faces many challenges, currently developed hydrogels have shown much promise in the biomedical field. It is widely believed that the clinical application of hydrogel drug delivery systems will be feasible in the future.

Ethics statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

Author contributions

Shuling Wang, Honghua Zhang, Qingchang Tian drafted the work organized co-author to write this review, and give final approval of the version to be published. Wenqi Li, Jing Hu, Cheng Chen, XinYue Li accomplished the main text of the manuscript and abbreviations in the manuscript. Jing Hu, Cheng Chen, Xinyue Li, Yanru Xin and Qingchang Tian accomplished the figure in the manuscript.

Declaration of competing interest

The authors declare no competing financial interest.

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