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Review

Advancing biomimetic bone Scaffolds: From electrospun 2D membranes to functional 3D nanofiber constructs

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ABSTRACT

Advancing beyond traditional electrospun two-dimensional (2D) membranes, functional three-dimensional (3D) nanofiber constructs represent a transformative approach. Unlike planar 2D structures, these advanced 3D constructs uniquely integrate essential biomimetic nanotopography with hierarchical porosity, offering mechanical adaptability and spatial guidance for cell infiltration, proliferation, and extracellular matrix (ECM) remodeling—critical for functional bone regeneration. This review systematically examines fabrication strategies enabling the transition from 2D electrospun membranes to 3D architectures, including gas foaming, short nanofiber assembly, and 3D printing. It emphasizes the synergistic advantages of organic/inorganic composites achieved through electrospinning's material versatility, effectively replicating native bone's collagen (COL)/hydroxyapatite (HAp) composition. Furthermore, the interconnected porous networks inherent to these 3D constructs enhance their functionality as carriers for bioactive molecules and stem cells, enabling spatiotemporally controlled osteogenesis. Targeted modification with osteoinductive and angioinductive functionalization further augments their efficacy in promoting bone tissue regeneration. In conclusion, this review provides valuable insights into the development and clinical potential of these advanced biomimetic scaffolds.

1. Introduction

As a vital load-bearing and metabolic 3D organ, bone poses complex regeneration challenges when defects occur due to trauma, tumors, or degenerative diseases—conditions affecting over two million patients globally each year [1]. While autologous bone grafts remain the clinical gold standard, donor site limitations, secondary trauma, and immune rejection hinder their widespread application [2]. Metal implants, though mechanically robust, face biocompatibility issues such as stress shielding and poor osseointegration, often leading to bone resorption and implant failure. To address these limitations, bone tissue engineering has emerged as a transformative approach by developing biomimetic scaffolds that recapitulate the native ECM microenvironment and aim to mimic the 3D structure and function of the original bone. These tissue engineering scaffolds dynamically support osteogenic differentiation, vascularization, and tissue remodeling, offering a breakthrough in bone defect treatment [3,4].

The natural bone ECM is composed of COL nanofibers and HAp crystals, where the nanoscale topography guides osteoblast adhesion and mineralization, while 3D porous networks facilitate cell migration, nutrient exchange, and vascular ingrowth [5]. Early studies primarily focused on electrospun nanofiber 2D membranes. However, their dense layered architecture resulted in suboptimal porosity and permeability, limiting utility for volumetric bone regeneration [6]. Consequently, the synergistic effect of 3D structure and nanofiber morphology has raised significant attention in the design of bone tissue engineering scaffolds

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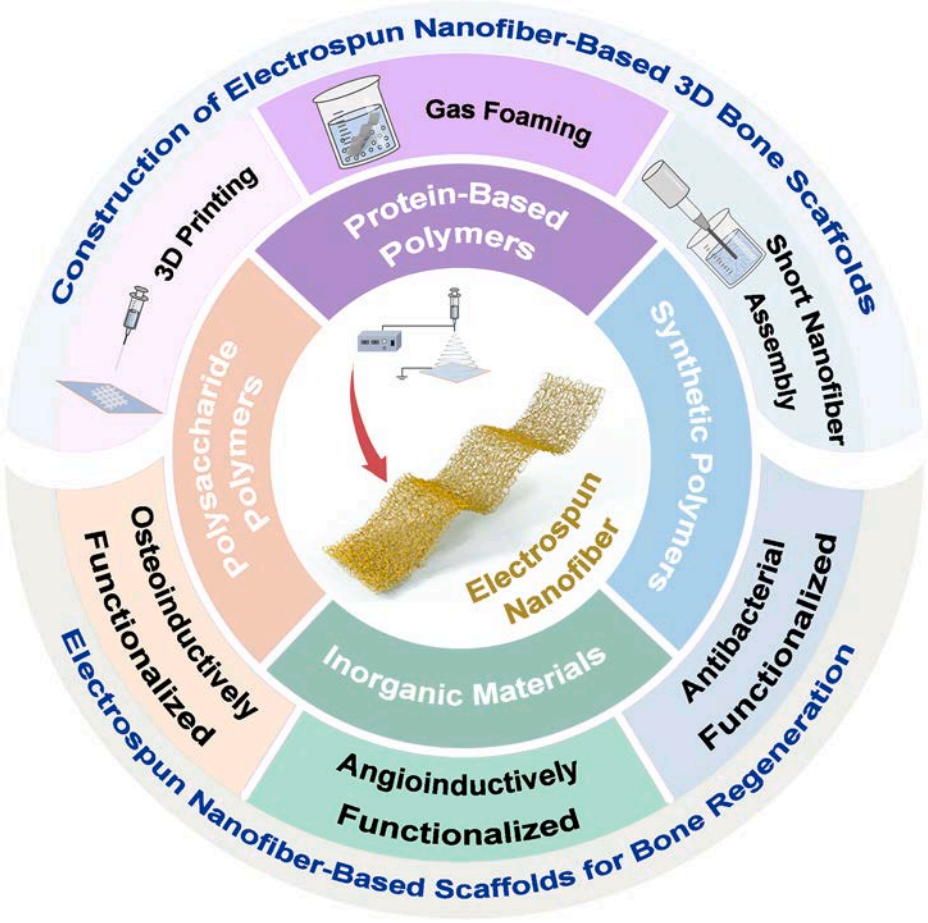
[7]. 3D nanofiber network can effectively simulate the topological characteristics of bone ECM and promote the directional differentiation of osteoblasts [8]. The development of fabrication technologies such as 3D printing, short nanofiber assembly, and gas foaming has enabled the electrospun nanofiber-based scaffolds from "planar biomimicry" to "3D regulation". These innovations allow simultaneous optimization of mechanical properties, pore geometry, and bioactive functionalization for tailored therapeutic outcomes.

Currently, research on electrospun nanofiber-based 3D scaffolds focuses on two strategics: material innovation and structure-function integration. Material innovation focus on hybrid systems combining synthetic polymers with natural biopolymers and inorganic phases, balancing tunable degradation rates with enhanced osteoconductivity [9]. For structure-function integration, multiscale bionic designs aim to emulate bone's heterogeneous composition and adaptive mechanical behavior. This review critically evaluates progress in electrospun nanofiber-based 3D scaffolds development through four aspects: material hybridization strategies, fabrication technology advancements, preclinical efficacy in bone regeneration, and translational challenges (Scheme 1). By synthesizing current successes and limitations, we provide a roadmap for designing next-generation scaffolds that bridge the gap between laboratory innovation and clinical implementation.

2. Bone tissue engineering and electrospun nanofiber-based 3D scaffolds

Bone serves as a vital structural and metabolic organ in vertebrates, performing essential physiological functions including hematopoiesis, mineral ion homeostasis, and mechanical protection of internal organs [10]. At the tissue level, bone comprises osteoblasts embedded within a calcified ECM, where nano HAp crystals are periodically deposited within COL fibrils to form an organic-inorganic nanocomposite (Fig. 1). This matrix constitutes over 90 % of bone volume, with minor contributions from glycosaminoglycans and regulatory proteins [5]. The inherent heterogeneity of this nanocomposite—characterized by coexisting ordered (HAp alignment) and disordered (COL fibril networks) domains across multiple length scales—confers unique mechanical resilience and enables dynamic self-remodeling through coupled osteoblast-osteoclast activity [11].

Following injury, bone defects trigger the recruitment of mesenchymal stem cells (MSCs) to the damaged site, initiating a tightly regulated repair cascade involving neovascularization, provisional cartilage formation, mineralization, and eventual remodeling into mature bone [3,4]. This prolonged healing process underscores the critical role of structural hierarchy and biochemical signaling in achieving functional restoration. Inspired by these biological principles, bone tissue engineering strategies aim to replicate both the **multiscale architecture** and **self-adaptive properties** of native bone. As shown in Fig. 2, tissue engineering scaffolds—fabricated from polymers, ceramics, or composites—are designed to mimic the ECM's mechanical and biochemical microenvironment, thereby supporting cell adhesion, spatial organization, and differentiation [5]. For instance, 2D electrospun membranes and 3D printed scaffolds can emulate COL-HAp interactions at the nanoscale while providing macroscale structural guidance. By integrating materials science with developmental biology, bone tissue engineering bridges the gap between synthetic constructs and living tissues. Current innovations focus on optimizing scaffold designs to synchronize with the temporal dynamics of bone healing, ultimately advancing toward clinically viable solutions for large-scale defect repair.



Scheme 1. Schematic illustration of the application of electrospun nanofiber-based 3D scaffolds in bone regeneration.

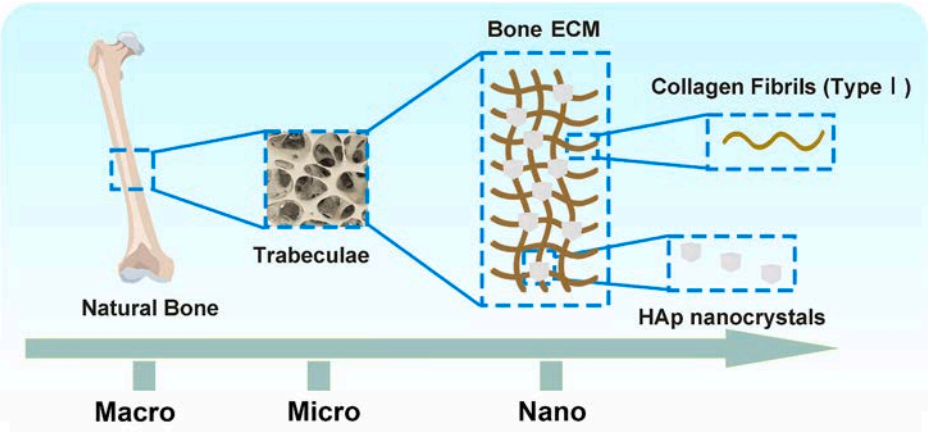


Fig. 1. Structure and composition of natural bone.

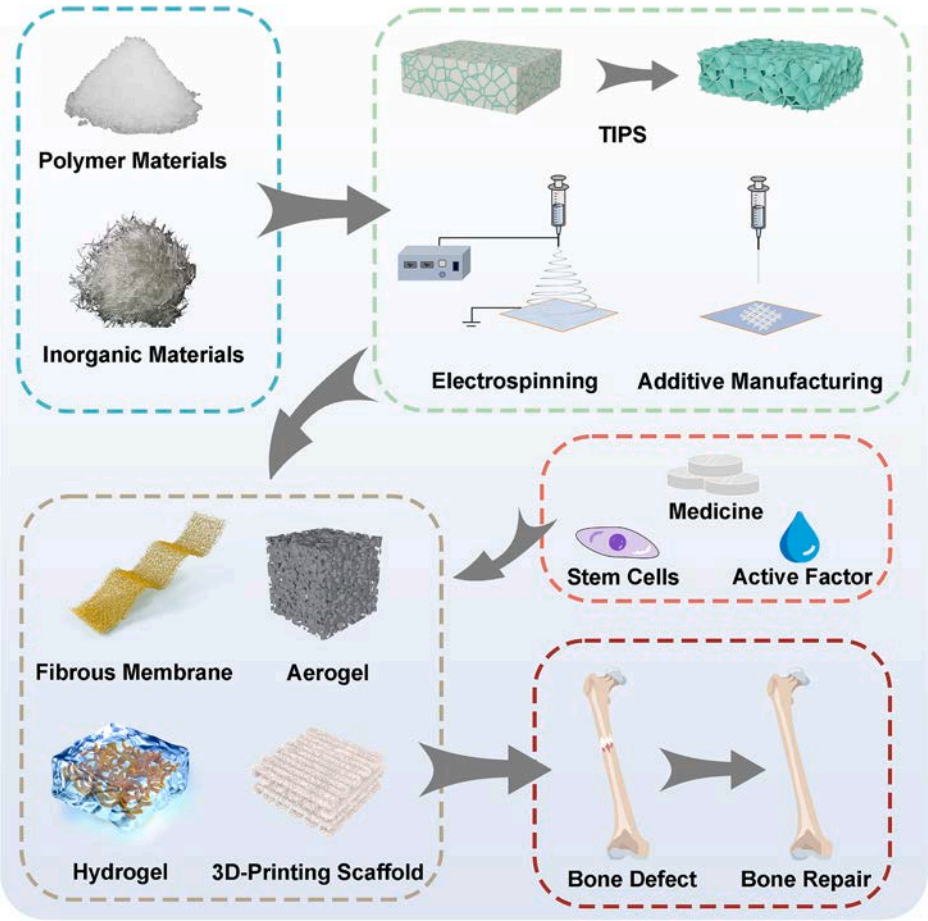


Fig. 2. The general design process of bone tissue engineering scaffolds.

Thanks to the richness of material choices and the diversity of construction methods, electrospun nanofiber-based 3D scaffolds can play an active role in bone tissue engineering [5]. Electrospun nanofiber-based 3D scaffolds not only reconfigure the fiber network characteristics of natural bone matrix on the microscopic scale but also can introduce a variety of biologically active components through component design, which realizes effective support for cell adhesion, migration, infiltration, and nutrient transport, and provides a favorable structural foundation for the formation and functional reconstruction of newly formed bone tissue.

3. Fabrication of electrospun nanofiber-based 3D bone scaffolds

3.1. Electrospun 3D nanofiber scaffolds: from 2D limitations to 3D innovation

Nanofibers have garnered significant attention in biomedical research due to their high surface-to-volume ratio, tunable surface chemistry, and structural similarity to the native ECM [12]. Nanofibers show good potential application in many biomedical fields, such as tissue engineering [3,4], drug delivery [13,14], and biosensors [15,16]. There are various methods to prepare nanofibers, mainly including

phase separation [17], template synthesis [18], self-assembly [19] and electrospinning [20]. Electrospinning stands out as the most versatile and scalable technique. By adjusting parameters such as voltage, flow rate, and polymer concentration, electrospinning enables precise control over fiber diameter (50–1000 nm) and morphology (e.g., smooth, porous, or core-shell structures). Furthermore, its compatibility with diverse materials—including synthetic polymers, natural biopolymers, and inorganic nanoparticles—allows the creation of composite fibers that mimic the organic-inorganic composition of natural bone [21]. Due to its diversity in material selection and flexibility in functional modulation, the electrospinning technology becomes a promising method for nanofiber preparation, which is particularly suitable for biomedical applications, such as the construction of tissue engineering scaffolds, the delivery of precise drugs, and the development of highly sensitive biosensors.

Electrospinning is a technique based on the principles of electrohydrodynamics to prepare micro-to nanoscale nanofiber materials using polymer solutions [22]. Conventional electrospinning, produces densely packed 2D membranes with restricted thickness and poor pore interconnectivity, resulting in limited cell infiltration and uneven nutrient diffusion [6]. To address these shortcomings, recent advances have shifted focus toward electrospun nanofiber-based 3D scaffolds that replicate the hierarchical porosity and spatial complexity of native bone ECM. Unlike their 2D counterparts, 3D nanofiber networks exhibit better properties, such as enhanced cellular infiltration, dynamic mechanical cues, bioactive functionalization [8,23]. These innovations position electrospun nanofiber-based 3D scaffolds as a transformative platform for recapitulating the bone regeneration microenvironment, bridging the gap between nanoscale biomimicry and volumetric defect repair.

3.2. Selection of biomaterials for electrospun nanofiber-based 3D bone scaffolds

Biomaterials must meet the basic requirements of appropriate mechanical properties, biocompatibility, and stability in physiological environments in their applications [24]. When designing electrospun nanofiber-based 3D scaffolds for promoting the formation of new tissues, the following factors should be considered comprehensively based on the specific application requirements: host response to biomaterials (i.e., biocompatibility), physicochemical surface properties of the materials, and their cost-effectiveness with respect to practical clinical applications [22]. Currently, a variety of biomaterials are able to fulfill the needs of electrospinning preparation, including biopolymers and inorganic ceramic materials [12]. Among them, biopolymers usually refer to biodegradable polymers that can be completely broken down into simple molecules under the action of biological enzymes within a certain period of time [25]. Biopolymers can be categorized into two main groups: natural polymers and synthetic polymers. The main advantages of natural polymers are their excellent biocompatibility and wide accessibility [26], while synthetic polymers can exhibit better mechanical properties and thermal stability [27]. In addition, numerous bioactive inorganic materials are widely used in the electrostatic spinning process. In this subsection, several types of typical biopolymers and inorganic materials suitable for the preparation of nanofibers by electrospinning are described in detail.

3.2.1. Natural polymers

3.2.1.1. Natural polysaccharide polymers.

(1) Chitosan (CS)

CS is a naturally occurring polysaccharide prepared by partial or complete deacetylation of chitin and has a rich source [28]. Due to its excellent biodegradability, biocompatibility, and biofunctionalization, CS is widely used in the fields of tissue engineering and drug delivery [29,30]. Compared with other natural biomaterials, CS also possesses unique antibacterial properties [31] and anti-inflammatory effects [32], which make it show unique advantages in biomedical applications. Despite the many excellent biological properties of CS, there are some limitations in its physicochemical properties. For example, CS is mostly soluble only in acidic solvents, which leads to its low solubility in water or other biological fluids [28]. In addition, the mechanical properties of CS are poor and its thermal stability is insufficient [33]. In order to solve these problems, the preparation of chemically modified CS derivatives can effectively improve its properties, thus expanding the application of CS [34].

(2) Hyaluronic Acid (HA)

HA is a glycosaminoglycan, a polyanionic substance, formed by the alternating polymerization of D-glucuronic acid with *N*-acetylglucosamine [35]. It is widely found in epithelial, neural, and connective tissues of vertebrates and is one of the major components of the ECM and intercellular matrix. HA can be obtained through large-scale production, provides the osmotic swelling pressure of articular cartilage, and plays an important role in physiological processes such osteoarticular lubrication, maintenance of water homeostasis, and promotion of wound healing. In addition, HA has excellent physicochemical properties, and its inherent biocompatibility and viscosity and elasticity make it an important biomaterial in the fields of drug delivery and tissue engineering [36,37]. However, HA has a rapid degradation rate, which may affect the timeliness of its action as a scaffold or drug carrier *in vivo*.

(3) Sodium Alginate (SA)

SA, mainly derived from brown algae, is a naturally occurring polysaccharide formed by linear polymerization of monoglycuronic acids [38]. It has the advantages of being non-toxic and harmless, inexpensive, and abundantly available. A significant feature of SA is its ability to cross-link with divalent or trivalent cations to form a gel network structure, and this hydrogel has good stability [38]. In the field of tissue engineering, SA-based hydrogels can effectively simulate the ECM environment and promote the generation of new tissues [38,39]. In addition, SA-based hydrogels possess high hydrophilicity and moisturizing properties, making them valuable for applications in areas such as drug carriers and wound dressings [38,39]. However, the limitation of sodium alginate is the poor mechanical properties of its hydrogel structure, which limits its application in the field of tissue engineering.

(4) Gellan Gum (GG)

Gellan gum (GG) is a linear anionic extracellular polysaccharide with a tetrasaccharide repeating unit consisting of L-rhamnose, D-glucuronic acid, and two D-glucans [40]. The gel strength of GG is insensitive to ambient pH variations, and it has unique gelation and rheological properties. Its most characteristic feature is that it dissolves at high temperatures, while it is able to form gels again at low temperatures [41]. GG is usually of high acyl structure, and the high content of acyl group will make the gel easy to be hydrolyzed, therefore, in practice, GG is usually subjected to deacylation treatment to obtain low acyl GG [42,43]. Low acyl CG has good stability and the gel formed by it has high mechanical strength. In addition, GG possesses good biocompatibility and biodegradability, which makes it excellent in areas such as drug delivery and tissue engineering [44,45]. However, the limitations of GG are that the hydrogels it forms have poor mechanical properties, are fragile, and lack effective interaction sites with cells [46]. Therefore, a series of physical or chemical modification methods are usually employed to enhance their biofunctionality and thus expand their application areas [46–48].

3.2.1.2. Natural protein-based polymers.

(1) COL

COL, a natural protein material, is distributed in almost all multicellular organisms, and it accounts for about 30 % of the total proteins in the human body [49]. COL forms a highly organized 3D system *in vivo,* which surrounds the cells to form the main structure of the ECM and plays a crucial role in regulating cellular behavior and maintaining the structural homeostasis of the ECM [50]. COL has excellent biocompatibility and biodegradability. Compared with other natural biomaterials, endogenous COL materials have a large number of high-affinity ligand sites, through which the bionic scaffold structures formed by COL can significantly promote cell adhesion and proliferation [51]. In the field of tissue engineering, COL scaffold structures can be multifunctionalized by a variety of processing methods. However, the major drawbacks of COL in applications are its poor mechanical strength and inherent immunogenicity, which have limited its wide application in biomedical fields [52].

(2) Gelatin (GEL)

GEL is a denaturation product formed through the COL hydrolysis under acid, alkali or high temperature conditions [53]. It retains some of the advantages of COL, such as biodegradability and biocompatibility. Compared with COL, GEL can be obtained in a more accessible manner and at a much lower cost than COL. In addition, since the immunogenicity of hydrolytically denatured GEL is significantly lower than that of COL, this significantly enhances its safety for biomedical applications [54]. GEL is capable of reversible transformations between gels and sols. Specifically, GEL solutions exhibit low viscosity at high temperatures while transforming into elastic gels at low temperatures. This property makes GEL promising for a wide range of applications in fields such as tissue engineering and drug delivery [55,56]. However, the main limitations of GEL are its poor mechanical properties and its excessive degradation rate *in vivo*, which may affect its long-term effects [57].

3.2.2. Synthetic polymers

(1) Polycaprolactone (PCL)

PCL is a semi-crystalline synthetic polymer made by polymerization of hexanoate repeating units [58]. It has biodegradability, good biocompatibility, and mechanical properties, and thus has been widely used in biomedical fields, especially in bone tissue engineering [59]. The most notable advantage of PCL is its excellent flexibility and chemical stability, which makes it highly adaptable to processing and modification, and able to satisfy the physicochemical property requirements of different application needs [60]. In addition, the blending compatibility of PCL is quite excellent, which allows it to be compounded with other biomaterials, such as gelatin and chitosan, in order to broaden its application range [60]. However, the major drawbacks of PCL include its slow degradation rate and its hydrophobicity, which limits its effectiveness in cell attachment and protein adsorption [28]. Therefore, despite the obvious advantages of PCL in bone tissue engineering, its limitations such as degradation rate and hydrophobicity still need to be overcome by further physicochemical modifications.

(2) Polylactic Acid (PLA)

PLA is a linear aliphatic synthetic polyester produced from lactic acid by polymerization reaction, which is widely used in biomedical applications [61]. PLA has excellent biodegradability and biocompatibility, and it is abundantly available, inexpensive, and non-toxic and non-hazardous to humans. In addition, PLA has high mechanical strength, which makes it excellent for bone tissue engineering with high stress loads [62]. Its melting point is between 170 and 230 °C, and its better thermal stability allows PLA to undergo various heat treatment processes to further enhance its physicochemical properties [63]. Despite the excellent physicochemical properties of PLA, its rapid degradation process may lead to the accumulation of lactic acid, which may cause inflammatory reactions [64]. In addition, PLA is poorly hydrophilic due to its inherent hydrophobicity, which makes its interaction with cells and protein adsorption weak [63]. While scaffolds prepared from PLA materials possess high strength and high modulus, they also have limitations due to their inherent fragility.

3.2.3. Inorganic materials

(1) HAp

HAp is the main inorganic component of human bone and its chemical structure is highly similar to that of natural bone mineral [65]. As a bioactive material, HAp can effectively promote osseointegration, i.e., the bonding of the implant with the surrounding bone tissue, thereby accelerating the bone healing and repair process. When being compounded into nanofibers, HAp can significantly enhance the mechanical properties of nanofibers. Currently, HAp has become an ideal material for use in orthopedic surgery, joint replacement, and dental implants, and is widely used in bone tissue engineering scaffolds and drug delivery systems [66]. These applications take full advantage of the biofunctionality of HAp, which can effectively overcome the limitations of traditional materials and meet the growing clinical needs [67].

(2) Silicon Dioxide (SiO_2)

SiO_2, a biomaterial widely available in nature, is highly hydrophilic, thermally stable and biocompatible [68]. It has important applications in the biomedical field especially in imaging, drug delivery, and tissue engineering. SiO_2 nanomicrospheres have become an important material in biomedical imaging and drug delivery due to their controllable particle size, ease of synthesis, and cost-effectiveness [69,70]. In addition, SiO_2-based composite scaffolds exhibit significant advantages in promoting biomineralization and protein adsorption, and thus show good potential for application in tissue engineering [71,72]. Notably, the preparation and application of SiO_2 flexible nanofibers have also received extensive attention. Such flexible nanofibers overcame the limitation of brittleness of traditional inorganic materials and greatly broadened their application in bone tissue engineering [30,73].

3.3. Construction of electrospun nanofiber-based 3D bone scaffolds

The choice of material determines the biochemical properties of the scaffold, while the fabrication strategy determines the structural hierarchy of the scaffold, which is critical to mimic native bone [74]. Currently, a variety of methods have been developed for the construction of electrospun nanofiber-based 3D scaffolds, but many of them still have obvious deficiencies in terms of structural controllability and scale consistency [74]. For example, centrifugal spinning technology can produce electrospun nanofiber-based 3D scaffolds with high efficiency, but the resulting 3D nanofiber structures are mostly randomly stacked, their pore structures are difficult to be precisely controlled, and they lack the ability to construct macroscopic geometries [75]. The combination of electrospinning and templates to build 3D structures (e.g., roller collection, stacking method), on the other hand, generally suffers from poor reproducibility, insufficient mechanical stability, and limited structural scales [76]. Compared with these methods, gas foaming, short fiber assembly and 3D printing technologies have more advantages in terms of structure regulation, spatial construction and process controllability, and are currently the key directions for constructing nanofiber-based 3D scaffolds. Therefore, this section will describe these techniques in detail for electrospun nanofiber-based 3D bone scaffolds

construction (Fig. 3).

Therefore, the construction of electrospun nanofiber-based 3D scaffolds, with properties closer to the natural ECM microenvironment, has shown great promise for applications in the biomedical field. In this section, several representative technological tools are selected for the 3D construction method of electrospun nanofiber-based 3D scaffolds.

3.3.1. Gas foaming

The gas foaming technique constructs 3D porous scaffolds by introducing gas bubbles into electrospun nanofiber membranes, followed by controlled expansion to create an interconnected macroporous architectures [77]. Based on bubble generation mechanisms, gas foaming can be classified into physical and chemical methods [78]. This technique effectively creates electrospun nanofiber-based 3D scaffolds with a highly interconnected porous structure with significantly increased porosity and a multilayered structure through post-processing. This 3D porous structure can significantly promote cell infiltration and proliferation and enhance the performance of the scaffolds in tissue engineering [79]. Kim et al. [80] developed a modified gas foaming process to fabricate hierarchical scaffolds with dual-scale porosity. The resulting scaffolds exhibited enhanced mechanical stability and promoted osteogenic differentiation of MSCs through improved biomineralization. These advances demonstrate gas foaming as a versatile and scalable method for converting 2D electrospun membranes into functional electrospun nanofiber-based 3D scaffolds.

3.3.2. Short nanofiber assembly

The short nanofiber assembly scaffolds are typically constructed by cutting nanofiber membranes into small pieces and uniformly dispersing them in a liquid medium using high-speed homogenization techniques. Subsequently, the dispersed short nanofibers are cast into predetermined molds and freeze-dried to remove the liquid medium and form a preliminary fiber network. Finally, the bonding between the fibers is further enhanced by chemical or physical cross-linking methods to obtain 3D scaffolds with a continuous fiber network structure [81]. This process can significantly enhance the structural stability of the scaffold and provide a suitable microenvironment for cell growth and proliferation. In recent years, researchers have developed a variety of 3D scaffold construction strategies based on short nanofibers. For example, Chen et al. [82] designed a porous 3D scaffold prepared from GEL/PLA short nanofibers, and the scaffold significantly promoted cell infiltration and proliferation. In addition, Wang et al. [30] prepared a highly elastic 3D scaffold using SiO_2 short nanofibers composite with CS, which provided a new idea for the treatment of complex irregular bone defects. The electrospun nanofiber-based 3D scaffolds constructed by short nanofibers can precisely regulate physicochemical and mechanical properties, which has a wide potential for application in the field of bone tissue engineering. This approach provides a new direction for the development of higher performance bone tissue engineering scaffolds.

3.3.3. 3D printing

The 3D printing technology enables the construction of 3D scaffolds by stacking materials layer by layer based on a predefined digital program [83]. In the biomedical field, 3D printing has been widely used to fabricate tissue engineering scaffolds for repair and regeneration of defective tissues [84]. However, the large pore size between the microfilaments of 3D printed scaffolds usually adversely affects cell adhesion and infiltration. In contrast, electrospun nanofibers can simulate an ECM microenvironment, thereby promoting cell infiltration and tissue regeneration. Therefore, more and more studies have been devoted to combining 3D printing with nanofiber technology to design more advanced scaffolds. For example, Liu et al. [85] integrated PLA electrospun nanofibers into 3D-printed PCL grids, creating the electrospun nanofiber-based 3D scaffold that enhanced M2 macrophage polarization and vascularized bone regeneration in rat cranial defects prepared a composite scaffold combining PLA fibers prepared by electrostatic spinning with 3D printed PCL networks, which not only promoted macrophage polarization toward the M2 phenotype, but also efficiently induced vascular regeneration and bone regeneration in a cranial defect model. Zhou et al. [86] assembled short nanofibers with 3D printed PCL scaffolds and successfully achieved a tunable porous structure, which significantly promoted angiogenesis and new bone formation. More advanced construction methods are still being explored. It is foreseeable that the combination of electrospun nanofibres and 3D printing technology will open further applications in the field of bone tissue engineering.

4. Application of electrospun nanofiber-based 3D bone scaffolds

Based on the previous systematic description of the material composition and 3D structure construction strategies of electrospun nanofiber-based 3D scaffolds, this section will further focus on the research of their application in bone tissue engineering. In recent years, researchers have developed a series of structurally stable and

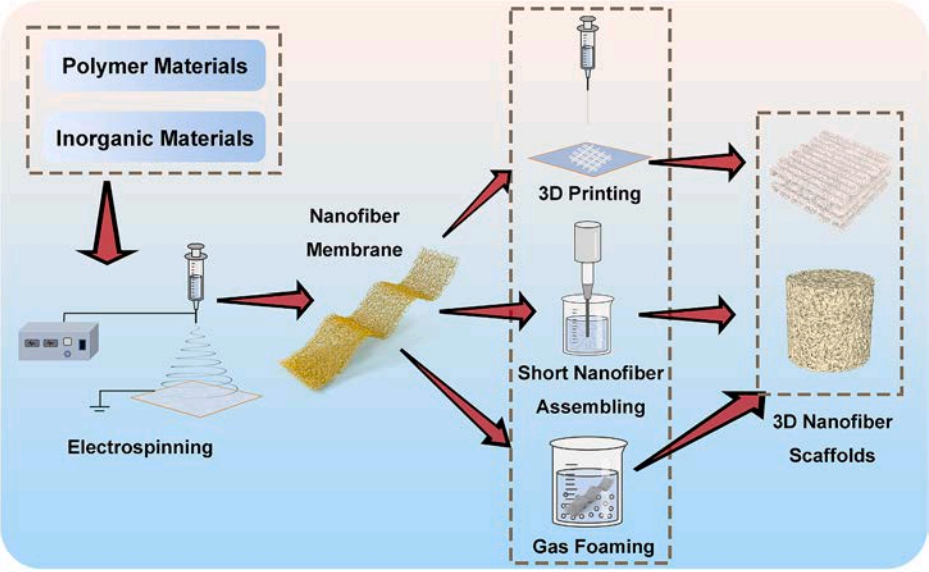


Fig. 3. Construction strategies for electrospun nanofiber-based 3D scaffolds.

functionally diverse electrospun nanofiber-based 3D scaffolds based on different material systems, construction strategies and biofunctional requirements, which are widely used in the directions of bone defect repair, collaborative regeneration of bone vasculature, and reconstruction of the complex bone microenvironment, and have made significant research progress. In this subsection, we will review the organic scaffolds, organic-inorganic composite scaffolds and their functionalization strategies, and systematically introduce their research progress and application practice in bone tissue engineering.

4.1. Polymer-based electrospun nanofiber-based 3D bone scaffolds

Biodegradable polymer nanofibers are ideal materials for constructing electrospun nanofiber-based 3D bone scaffolds due to their good biocompatibility, excellent flexibility and easy functionalization. These scaffolds mimic the bone ECM, promoting cell adhesion, proliferation, and differentiation [87]. For example, Li et al. [88] developed COL I -modified poly(lactic-co-glycolic acid) (PLGA) electrospun nanofiber-based 3D scaffolds using short nanofiber assembly with a porous, rough structure that effectively mimics the natural bone ECM, enhancing adhesion and proliferation of preosteoblast MC3T3-E1 cells. Xu et al. [10] fabricated core-shell PLA/CS nanofibers via coaxial electrospinning; the surface-coated chitosan promoted (HAp mineralization and upregulated expression of osteogenic markers alkaline phosphatase (ALP) and osteocalcin (OCN).

In order to construct an excellent 3D nanofiber structure, Zhang et al. [29] prepared root-like chitosan nanofibers without organic solvents using short nanofiber assembly. These fibers exhibited superior aqueous dispersion, high positive charge density, and a wet-state tensile strength of 18.13 MPa preosteoblasts seeded on this electrospun nanofiber-based 3D scaffold showed higher adhesion efficiency and multidirectional proliferation compared to 2D nanofibrous membranes (Fig. 4). Yao et al. [89] fabricated PCL/PLA electrospun nanofiber-based 3D scaffolds using short nanofiber assembly with 95.8 % porosity and submicron-to-300 μm pore sizes. The composites exhibited enhanced stiffness, elasticity, and cell adhesion relative to pure PCL scaffolds, with *in vitro* and *in vivo* results demonstrating improved osteogenic differentiation of MSCs and new bone formation.

4.2. Inorganic/polymer composite electrospun nanofiber-based 3D bone scaffolds

In electrospun nanofiber-based 3D scaffold design, it is often difficult to balance strength and toughness [90]. Although polymer nanofibers usually have excellent toughness, their strength is low. Therefore, single polymer nanofibers have limitations in bone tissue engineering applications. In addition, when polymer nanofibers are prepared as electrospun nanofiber-based 3D scaffolds for bone tissue engineering, their highly porous structure tends to further weaken the structural strength of the scaffolds [11]. If the scaffolds are not strong enough, they may face the risk of mechanical incompatibility or collapse after implantation, which may lead to the failure of bone defect repair. Therefore, considering the highly mineralized nature of natural bone, introducing inorganic components into polymer nanofiber scaffolds to form an organic/inorganic hybrid structure has become an effective way to enhance the strength and toughness of scaffolds [91]. The inorganic component can improve the mechanical strength of the scaffold, while the organic/inorganic composite structure can significantly enhance the similarity with natural bone, which can more effectively promote the osteogenic differentiation of cells and promote the repair of bone defects.

HAp is a bone mineral with properties such as promoting osteogenic differentiation, improving the mechanical strength of composite scaffolds, and can be used as a carrier for controlled release of drugs [92,93]. Salim et al. [94] used electrostatic spinning to prepare Polyvinyl Alcohol (PVA)/HA nanofibers and verified the positive effect of the HAp

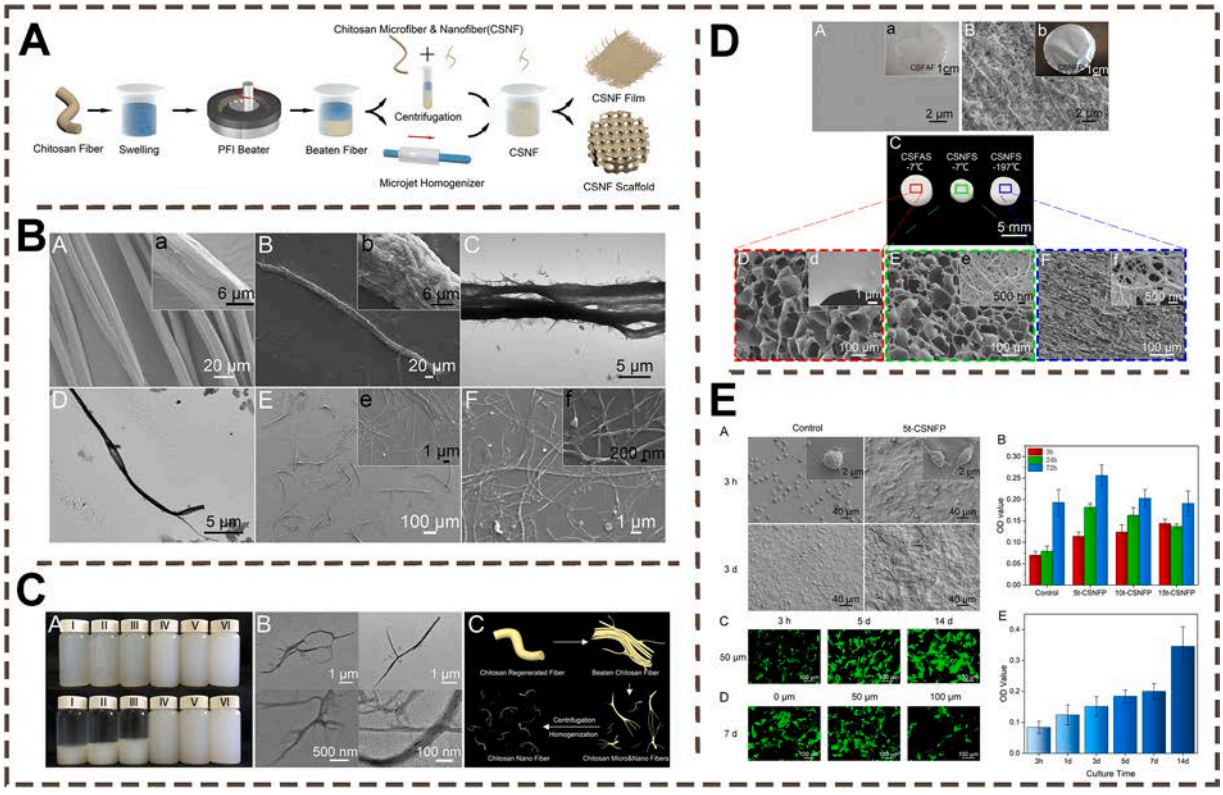


Fig. 4. (A) Preparation of CS nanofiber membranes and scaffolds. (B) Microstructures of the CS nanofibers. (C) Dispersion properties of different CS nanofibers. (D) SEM images of CS nanofiber membranes and scaffolds. (E) Growth of the cells on CS nanofiber membranes and scaffolds [29] Copyright 2021, American Chemical Society.

composite system on the generation of new bone. The results showed that the incorporation of HAp nanoparticles enhanced the mechanical stability of the fiber structure and improved the cell adhesion and proliferation behaviors on the nanofiber surface. Miszuk et al. [95] prepared PCL electrospun nanofiber-based scaffolds with high porosity using short nanofiber assembly and deposited HAp on nanofibers by two-step simulated somatic fluidic method to form a biphasic composite electrospun nanofiber-based 3D scaffold. The scaffolds maintained good porosity, the density of the HAp coating was tunable, and the elasticity was maintained while enhancing the strength of the scaffolds. *In vitro* results showed that the coating was able to bind some small molecule drugs and achieve sustained release. This functionalized electrospun nanofiber-based 3D scaffold effectively improves the bioinertness of PCL materials, increases bioactivity and scaffold strength, and provides a good strategy for bone tissue engineering.

Bioactive glass (BG) is a silicate glass composed of basic components such as SiO_2, Na_2O, CaO, and P_2O_5, which has good biocompatibility and is able to interact effectively with various types of soft and hard tissues in the human body [96]. BG promotes the production of growth factors through the release of reactive ions, thus accelerating the cell proliferation and the generation of new bone. Kim et al. [97] dispersed the BG dispersed in PLA matrix and successfully prepared electrospun nanofiber-based 3D scaffolds with large pore sizes using short nanofiber assembly. The scaffold possessed a high specific surface area and its large pore size structure contributed to the growth of bone tissue [98]. In addition, the hydrophilicity of the composite scaffold was significantly enhanced due to the presence of BG, and the charged property of BG led to the enhancement of its adsorption capacity for proteins under ionic action. On the other hand, the ionic component of BG stabilizes the release of Si and Ca ions to stimulate new osteogenesis. Under the cooperative effect of these active ions and the macroporous scaffold, the osteogenic and angiogenic ability of the scaffold was significantly improved.

The introduction of inorganic components effectively improves the deficiencies of pure polymer fiber scaffolds in terms of mechanical properties and bioactivity [6]. In addition to the aforementioned effective methods to improve the strength of scaffolds, combining bioceramic scaffolds with nanofiber coatings is also an important strategy to improve the performance of scaffolds [99]. The high strength of ceramics and the high functionality of nanofibers can act synergistically to significantly enhance bone repair. In addition, the study of inorganic electrospun nanofiber-based 3D scaffolds has gradually gained attention in recent years [100]. For example, BG nanofibers prepared using electrospinning have a composition and structure similar to that of natural bone ECM [101,102]. In addition, Sr has been shown to inhibit osteoclastogenesis and stimulate osteoblast differentiation, while Cu upregulates vascular endothelial growth factor (VEGF) expression and promotes endothelial cell proliferation [103–105]. Combining these active ions with electrospun nanofiber-based 3D scaffolds can further enhance the bioactivity and compatibility of nanofiber scaffolds, thereby improving bone repair.

Despite the potential of BGs for a wide range of applications in the field of bone repair due to their favorable bioactivity and high compatibility, their inherent fragility still limits their wide application. The emergence of flexible inorganic nanofibers provides a novel strategy for tissue engineering scaffold design [106]. For example, flexible SiO_2 short nanofibers were composited with a CS matrix to prepare a composite hydrogel with five times the compressive strength of a single CS hydrogel, which was significantly better than the reinforcement effect of organic short nanofibers [106]. This electrospun nanofiber-based 3D scaffold not only compensated for the mechanical defects of the hydrogel itself, but also immobilized the active factors and regulated the differentiation of stem cells. Wang et al. [30] designed and prepared a flexible SiO_2–CaO nanofiber and further assembled it into the electrospun nanofiber-based 3D scaffold using CS as a matrix (Fig. 5). The strong structural connectivity of SiO_2 in the amorphous state prevents the formation of cracks and fractures, while the increased CaO content promotes biomineralization. Thus SiO_2–CaO maintain flexibility while possessing good osteogenic activity. The results showed that the composite scaffold had good mechanical properties and osteoinductive activity. In the wet state, the scaffold was able to recover 80 % after 1000 compression cycles, and its stiffness and elasticity were significantly better than that of the brittle fiber-doped composite scaffold. In addition, due to the shape memory properties of CS [107,108], this elastic scaffold can be implanted by minimally invasive implantation and self-expanding postoperatively to perfectly fill irregular bone defects. After implanting the scaffold into the cranial defect site of osteoporotic rats, the results showed that the bone volume ratio (BV/TV) was significantly higher than that of the control group. This electrospun nanofiber-based 3D scaffold reinforced by flexible inorganic nanofibers has excellent elasticity and shape memory properties, which provides a strategy for the repair of irregular bone defects. The introduction of inorganic nanofibers greatly enriches the construction of electrospun nanofiber-based 3D scaffolds. Considering the presence of multiple active ions, it is expected that this organic/inorganic nanofiber composite scaffold can achieve multiple functions such as osteogenesis, anti-breakage, and vascularization at the same time, which further improves the bone repair effect.

Suitable mechanical strength is critical for scaffolds to successfully induce osteogenic differentiation of stem cells and promote bone tissue growth [109]. Human cortical bone has a Young's modulus of 7–30 GPa and a compressive strength of 50–151 MPa, and the mechanical properties of bone vary from site to site [110]. Therefore, ideal bone tissue engineering scaffolds should have mechanical strength similar to that of natural bone for stable load transfer. However, this is still a great challenge for electrospun nanofiber-based 3D scaffolds. On the one hand, the structural properties of nanofiber materials limit their ability to approach the mechanical properties of natural bone. On the other hand, larger pore sizes facilitate tissue growth-in and vascularization, thus promoting new bone formation. However, a 3D structure with high porosity will also inevitably weaken the overall strength of the scaffold. Therefore, how to balance high porosity with excellent mechanical properties while supporting cell adhesion and proliferation remains an urgent problem.

4.3. Functionalized electrospun nanofiber-based 3D bone scaffolds

New osteogenesis and neo tissue growth are regulated by a variety of growth factors and bioactive substances [109]. For example, whereas bone morphogenetic proteins (BMPs) are recognized as a core family of growth factors that promote bone defect repair [111]. Transforming growth factor-β1 (TGF-β1) and insulin-like growth factor 1 (IGF-1) are major factors that regulate the bone remodeling cascade response. In addition, the drug dexamethasone (DEX) assists osteogenesis by upregulating the expression of major osteogenic genes [112]. VEGF plays a key role in the process of neovascularization in bone repair, while desferrioxamine (DFO) and dimethyl oxaloacetylglycine (DMOG) promote neovascularization by inducing a hypoxic response [38,39]. The introduction of these active substances can activate multiple signaling pathways, which can significantly improve the repair of bone defects.

Typically, a single dose of growth factors is not sufficient to initiate bone formation, and supraphysiologic doses are required to produce significant results in the treatment of bone defects. This may have potential dose-dependent or toxic effects [113]. Therefore, on the basis of achieving a 3D porous structure and suitable mechanical properties, biofunctionalization of electrospun nanofiber-based 3D scaffolds through the introduction of growth factors and active drugs is an important strategy to further enhance their bone repair performance [114,115]. The combination of growth factors and drugs can effectively address the possible deficiencies of nanofiber scaffolds in terms of osteoinductivity and vascularization. Functionalized scaffolds provide a biomimetic ECM environment that reduces the dosage requirements of

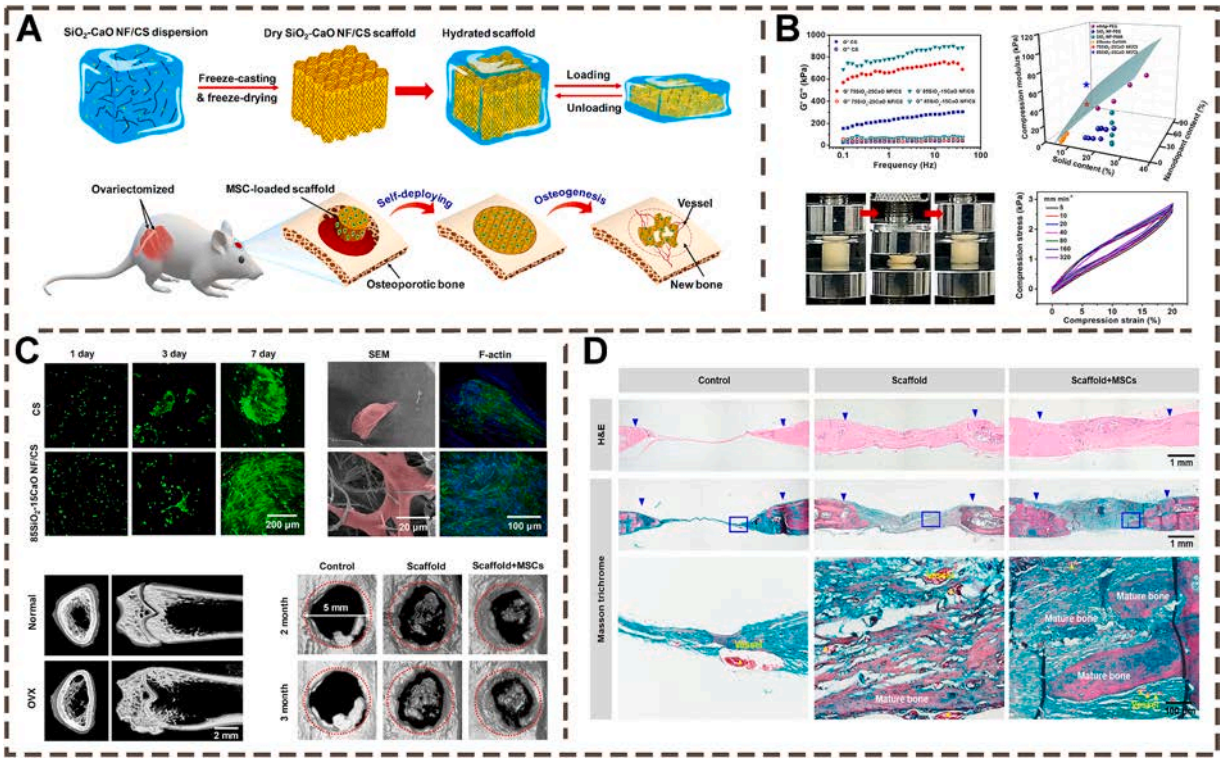


Fig. 5. (A) Schematic of the production of the elastic scaffold to improve bone repair in osteoporotic rats. (B) Elastic properties of 3D nanofiber scaffolds. (C) *In vitro* biocompatibility and *in vivo* bone regeneration capability in the rat osteoporosis model of scaffolds. (D) H&E and Masson's trichrome staining [30]. Copyright 2019, American Chemical Society.

growth factors or active agents and allows for sustained release of active substances [113–115]. For example, immobilization of active substances on the surface or inside the scaffolds by physisorption or chemical covalent binding methods can improve the stability and delivery efficiency of these factors, leading to faster and more efficient new bone generation and revascularization at bone defect locations. This multifunctional and optimized design provides an important direction for achieving superior bone repair results over non-functionalized scaffolds.

4.3.1. Osteoinductively functionalized electrospun nanofiber-based 3D bone scaffolds

Mesoporous silica nanoparticles (MSNs) exhibit a wide range of applications in the biomedical field due to their excellent biocompatibility, adjustable mesoporous structure, and highly efficient drug-carrying capacity [116–118]. DEX, as a commonly used osteoblastogenic agent, is widely used in bone repair studies because it can efficiently induce osteoclast differentiation, increase ALP activity, and enhance the level of bone mineralization [119–121]. Qiu et al. [122] prepared PLA/PCL electrospun nanofiber-based 3D scaffolds using short nanofiber assembly and immobilized DEX-loaded aminated MSNs on the surface of the nanofibers by electrophoretic deposition, constructing a composite scaffold with the function of osteogenic agent delivery. The results of *in vivo* tests showed that the scaffold was able to degrade completely *in vivo*, and the new bone generation at the defect site was significantly higher in the drug-loaded group than in the PLA/PCL group. This result fully demonstrated the osteogenesis-promoting effect of DEX, and the potential application of drug microcarriers and nanofiber composite scaffolds, which provides a novel design strategy for bone tissue engineering.

BMP, especially FDA-approved BMP-2 and BMP-7, are widely used in bone defect repair due to their powerful osteogenic induction ability [123]. However, their biomedical applications are limited by challenges such as high dosage requirements, potential side effects, and high costs [123]. Purmorphamine (Pur), a low-cost small molecule drug, can effectively activate the BMP signaling pathway, thereby promoting osteoblast differentiation and mineralization, and still exhibits a good repairing effect at low doses of BMP-2 [124,125], suggesting that combining Pur with BMP-2 is a good strategy for promoting bone repair. Miszuk et al. [126] combined short nanofiber assembly and simulated body fluid method to prepare HAp-modified polycaprolactone PCL electrospun nanofiber-based 3D scaffolds (PCL/HA-3D) and loaded Pur into the scaffolds. *In vitro* experiments showed that the PCL/HA-3D group significantly elevated the expression of osteogenic gene markers such as Runx2 and BSP compared with the unmodified PCL-3D group. The *in vivo* experiments showed that the PCL/HA-3D scaffolds had the best repair effect in combination with Pur and BMP-2, and their osteogenic capacity was significantly higher than that of all the single active ingredient control groups.

In addition, coping with the high dose requirement and potential side effect issues of BMP-2 in clinical applications, the use of BMP-2-derived peptides is an attractive alternative, as such peptides usually have higher stability and lower cost [127]. The way the peptide binds to the electrospun nanofiber-based 3D scaffold is a key factor in its stability and functional release. Physical adsorption methods suffer from immobilization instability and excessive release [128], whereas covalent modification improves the stability and sustained effect of peptides through chemical conjugation. However, the latter may interfere with direct communication between cells and peptides [129,130]. Inspired by mussel adhesion proteins, polydopamine (pDA) coatings offer a flexible and efficient solution for peptide immobilization. pDA is able to tightly attach to the surface of a variety of organic and inorganic materials through self-polymerization and act as an intermediate for covalent and non-covalent binding of active factors or drugs [131–133]. This strategy is easy to operate and not only improves the stability of active factor anchoring, but also controls its release pattern and significantly enhances the bioactivity of the electrospun nanofiber-based 3D scaffold [134].

The synthetic peptide KIPKASSVPTELSAISTLYL (P24), as a derivative peptide of BMP-2 residue, has been shown to significantly enhance

ALP activity and effectively promote stem cell osteogenic differentiation and new bone formation in *in vivo* and *in vitro* experiments [135–137]. Ye et al. [138] demonstrated that P24 peptide could significantly enhance the activity of ALP and effectively promote stem cell osteogenic differentiation and new bone formation in ex vivo experiments by combining nHAp/PLA/GEL electrospun nanofibers and pDA coating, immobilizing P24 peptide on the surface of the scaffold to obtain the electrospun nanofiber-based 3D scaffold (Fig. 6). The experimental results showed that the pDA coating significantly improved the immobilization efficiency of P24 and was able to achieve 21 days of sustained peptide release, which was significantly better than the efficiency of the physical immobilization method. In *in vitro* cellular assays, the composite scaffolds significantly increased ALP activity and expression levels of osteogenesis-related genes. *In vivo* experiments demonstrated that the composite scaffold effectively promoted new bone generation in a critical bone defect model. By combining electrospun nanofiber-based 3D scaffolds and pDA-assisted delivery system, this method not only mimicked the ECM environment of natural bone, but also achieved efficient and sustained release of the peptide. In addition to the excellent performance of P24 peptide in combining with electrospun nanofiber-based 3D scaffolds to achieve bone repair, various other BMP-derived peptides have also been developed and shown promising applications. For example, BMP-2-derived peptides with seven glutamate structural domains (E7) were able to efficiently bind to the surface of HAp via calcium coupling and achieve sustained release for up to two months *in vivo* [139]. In addition, Sun et al. [140] designed a P28 peptide based on the P24 peptide, which not only enhanced the controlled release performance of the peptide, but also further enhanced the bone affinity of the scaffold.

In conclusion, these chemical peptides can effectively avoid side effects such as immune response and ectopic osteogenesis that may be triggered by high doses of BMP in clinical applications due to their advantages of short structure, precise action and low cost. Therefore, in many specific application scenarios, BMP-derived peptides can give full play to their characteristics as an excellent alternative to BMP in electrospun nanofiber-based 3D scaffolds and provide new solutions for bone tissue engineering.

4.3.2. *Angioinductively functionalized electrospun nanofiber-based 3D bone scaffolds*

Bone is a highly vascularized hard tissue that requires a supply of oxygen, minerals, and other nutrients to function properly [111]. When a bone defect occurs, the vascular network surrounding the bone tissue is consequently disrupted, and growth factors are then required to revascularize the damaged area to restore energy metabolism at the defect site to promote new bone formation. Hypoxia is the predominant

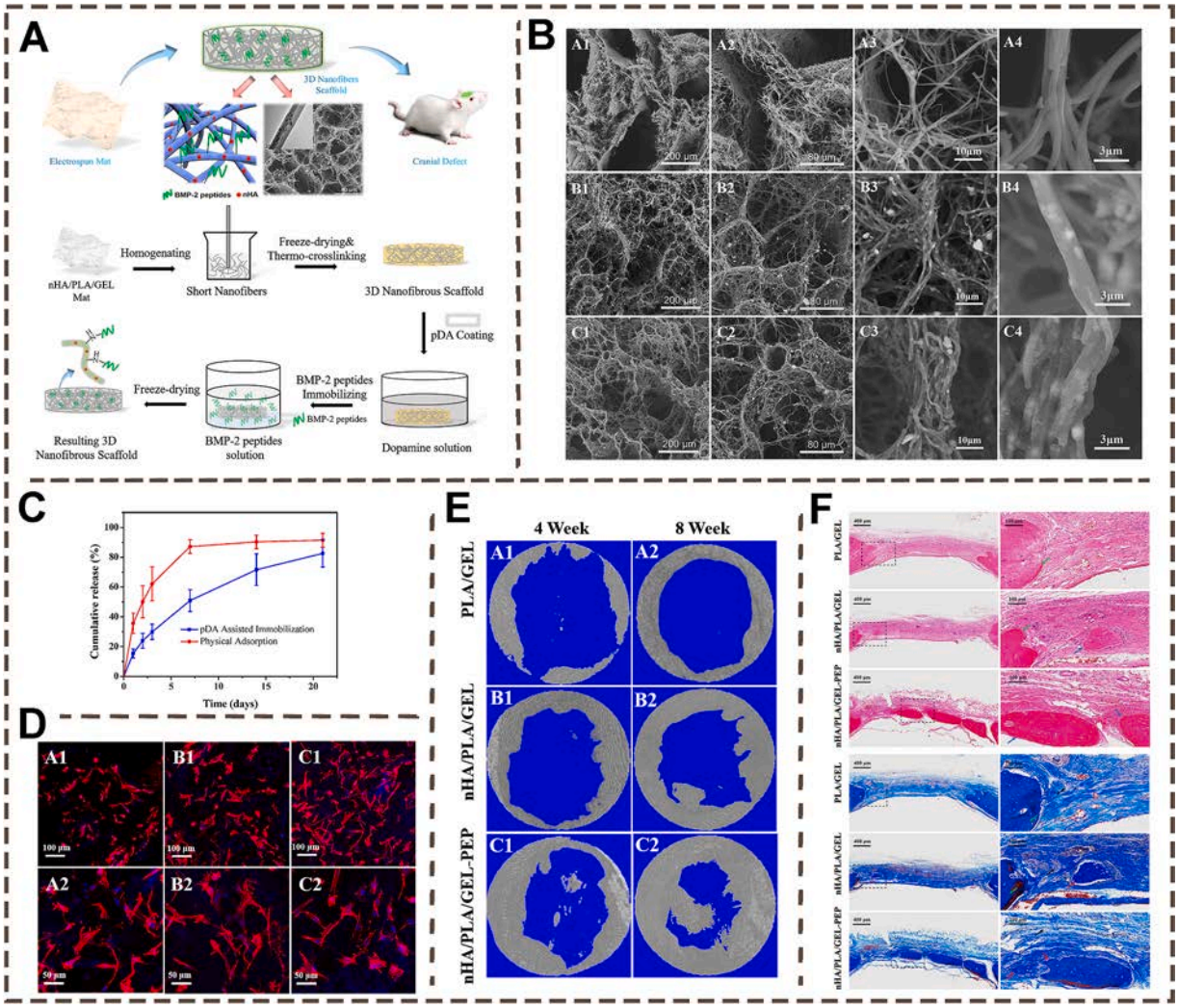


Fig. 6. (A) Schematic of electrospun nanofiber-based 3D scaffold preparation. (B) SEM images of the internal morphological structures. (C) Release kinetics of P24 peptide from scaffolds. (D) CLSM images of BMSCs cultured on scaffolds. (E) Micro-CT images of rat cranial bones defects. (F) H&E and Masson's trichrome stained images [138].

physiological stimulus that induces angiogenesis, and the expression of key vascular growth factors such as VEGF, placental growth factor (PGF), and platelet-derived growth factor-B (PDGF-B) is induced under hypoxic conditions by the transcriptional activity of hypoxia-inducible factor (HIF-1) [141]. Thus, HIF-1 is a major regulator of oxygen homeostasis and plays an important role in physiological activities such as hypoxic vascularization [142]. Small molecule inhibitors of prolyl hydroxylase (PHD: an enzyme responsible for the degradation of HIF-1) have been shown to activate HIF-1 to promote vascular regeneration.

DFO is effective in PHD inhibition due to its excellent iron chelating ability, so it can be used to promote vascular regeneration to enhance bone repair [143,144]. However, with high toxicity and short half-life, DFO is still not very effective in specific applications [145]. Yao et al. [146] prepared GEL electrospun nanofiber-based 3D scaffolds (GF) by combining short nanofiber assembly and particle leaching techniques. Cross-linking was achieved by covalent bonding between the carboxyl group of GEL and the amino group of DFO, and DFO was immobilized on the highly porous nanofiber scaffolds, which not only effectively reduced its toxicity but also significantly extended its half-life. *In vitro* data showed that the toxicity of the nanofiber scaffold (GF-DFO) on hMSCs and HUVECs was significantly reduced compared with free DFO, and the VEGF expression of both cells was significantly elevated. The *in vivo* data demonstrated that the composite scaffolds could significantly promote new bone generation at the site of bone defects. The above results suggest that constructing composite nanofiber scaffolds for hypoxia-induced angiogenesis is a good strategy in the field of bone repair. Gu et al. [147] combined 3D printing caramel sacrificial templates with thermotropic phase separation to prepare PLA/PCL nanofiber scaffolds (IPMs) with interconnected perfusable microchannel networks. The rh-VEGF 165 factor was then introduced into the IPMs in a non-covalent form to form composite nanofiber scaffolds (VEGF@IPMs). *In vitro* and *in vivo* results showed that the nanofiber scaffolds induced abundant angiogenesis. This composite nanofiber scaffold combining microchannel networks with angiogenic factors to induce angiogenesis is a promising approach in bone repair.

DMOG, a small molecule drug that simulates hypoxia, induces angiogenesis and promotes bone repair by inhibiting PHD activity in order to stabilize HIF-1 [148,149]. Ha et al. [150] formed composite scaffolds with interconnected microchannels by constructing PCL 3D printing scaffolds and GEL-SiO_2 nanofibers with interconnecting microchannels, and using electrostatic interactions to load DMOG and bone-forming peptides onto the scaffold surface, forming a composite scaffold with temporal release properties (Fig. 7). The microchannel structure of the scaffolds facilitated nutrient delivery, and the highly porous nanofiber matrix provided a favorable environment for cell attachment. In addition, the combined release of DMOG and bone-forming peptides promoted early angiogenesis and late bone tissue formation, respectively. *In vitro* and *in vivo* experiments showed that the composite scaffolds exhibited superior performance in both angiogenesis and bone regeneration. Combining the hypoxia-induced angiogenesis strategy with electrospun nanofiber-based 3D scaffolds effectively promoted bone.

In summary, electrospun nanofiber-based 3D scaffolds that meet the requirements of 3D porous structure, excellent mechanical properties, and biofunctionalities show a broad application prospect in the field of bone defect repair. Although there are still some technical challenges for electrospun nanofiber-based 3D scaffolds, such as the stability of the organic/inorganic material binding interface. However, electrospun nanofiber-based 3D scaffolds have demonstrated significant progress in the functional realization of bone tissue engineering. Through fine material design and advanced preparation techniques, electrospun nanofiber-based 3D scaffolds have been able to meet the basic functional requirements needed for bone repair, such as good biocompatibility and a microenvironment that supports cell attachment and proliferation. In the future, the development of complex scaffolds with multifunctional properties by combining biodegradable multiple fibers with metal ions, ceramics, growth factors, etc., will further expand the application areas and is expected to become one of the important trends and dominant technologies in the field of bone repair.

4.3.3. Antibacterial functionalized electrospun nanofiber-based 3D bone scaffolds

In bone tissue engineering, bacterial infection remains a major cause of implant failure, impaired osseointegration, and delayed functional recovery [151]. Although various drug-loaded scaffolds have been developed to address infection-related bone defects, challenges persist in balancing antibacterial efficacy with regenerative performance [152]. Electrospun nanofiber-based 3D scaffolds offer unique advantages due to their high surface area and tunable porous architecture, enabling efficient loading and homogeneous distribution of antimicrobial agents. The flexibility in fiber orientation and 3D structural design enhances biocompatibility and supports the establishment of a microenvironment conducive to both antibacterial activity and osteogenesis [152]. Compared to conventional scaffold materials, electrospun nanofiber-based 3D scaffolds exhibit superior antibacterial efficiency, controlled drug release, and regenerative integration, making them a promising direction for the development of functional bone repair systems.

Natural polysaccharides and polyphenols are widely used in biomedical materials due to their abundant sources, good biocompatibility, and multiple antimicrobial mechanisms [153]. Polysaccharides usually act by disrupting bacterial membranes through electrostatic interactions between their positively charged groups and the negatively charged bacterial surfaces. In comparison, polyphenols can bind to proteins or metal ions in bacterial cell walls, interfering with normal cellular activity. CS, a cationic polysaccharide rich in amino groups, can be protonated to $-NH_3^+$ under acidic conditions. These groups interact with bacterial membranes, increasing their permeability and leading to cell death, which gives CS broad-spectrum antibacterial properties [154]. Patel et al. [154] developed an antibacterial nanofibrous scaffold based on CS and cellulose nanocrystals. This scaffold exhibited a porous structure similar to the ECM and showed good mechanical strength, supporting the adhesion, proliferation, and osteogenic differentiation of BMSCs. In addition, the cationic CS component significantly inhibited the growth of Bacillus subtilis. Tannic acid, a natural plant-derived polyphenol, contains abundant phenolic hydroxyl groups that can form coordination networks with ferric ions (Fe^{3+}). Under near-infrared light, these networks generate a mild photothermal effect, which damages bacterial membranes and enhances antibacterial performance. Abie et al. [155] developed electrospun nanofiber-based 3D scaffolds by assembling BG nanofibers with tannic acid and ferric ions into a shear-thinning hydrogel ink. The scaffold exhibited favorable mechanical stability and biodegradability, enabling sustained release of bioactive ions in simulated body fluid. In vitro studies demonstrated that the scaffold effectively promoted the osteogenic differentiation of BMSCs over 21 days, as evidenced by enhanced ALP activity and upregulated expression of COL I, indicating strong osteoinductive potential. Regarding antimicrobial properties, the scaffold showed significant photothermal responsiveness under 808 nm near-infrared (NIR) light, achieving efficient bacterial eradication against Staphylococcus aureus and Escherichia coli. Genipin, a natural crosslinker derived from Gardenia jasminoides fruit, has low cytotoxicity and can generate localized heat under NIR irradiation to kill bacteria and tumor cells [156]. Wang et al. [156] fabricated an electrospun nanofiber-based 3D scaffold by combining BG nanofibers with GEL and Genipin by using short nanofiber assembly. In vitro results confirmed good cytocompatibility with osteoblasts, while NIR exposure rapidly elevated the local temperature, achieving antibacterial rates of 92–93 % against S. aureus and E. coli. Mineralization assays revealed sustained release of Ca^{2+} and PO_4^{3-}, inducing substantial hydroxyapatite deposition. In vivo studies further validated the scaffold's bone regenerative capability in a rat calvarial defect model, with significantly higher BV/TV and BMD values

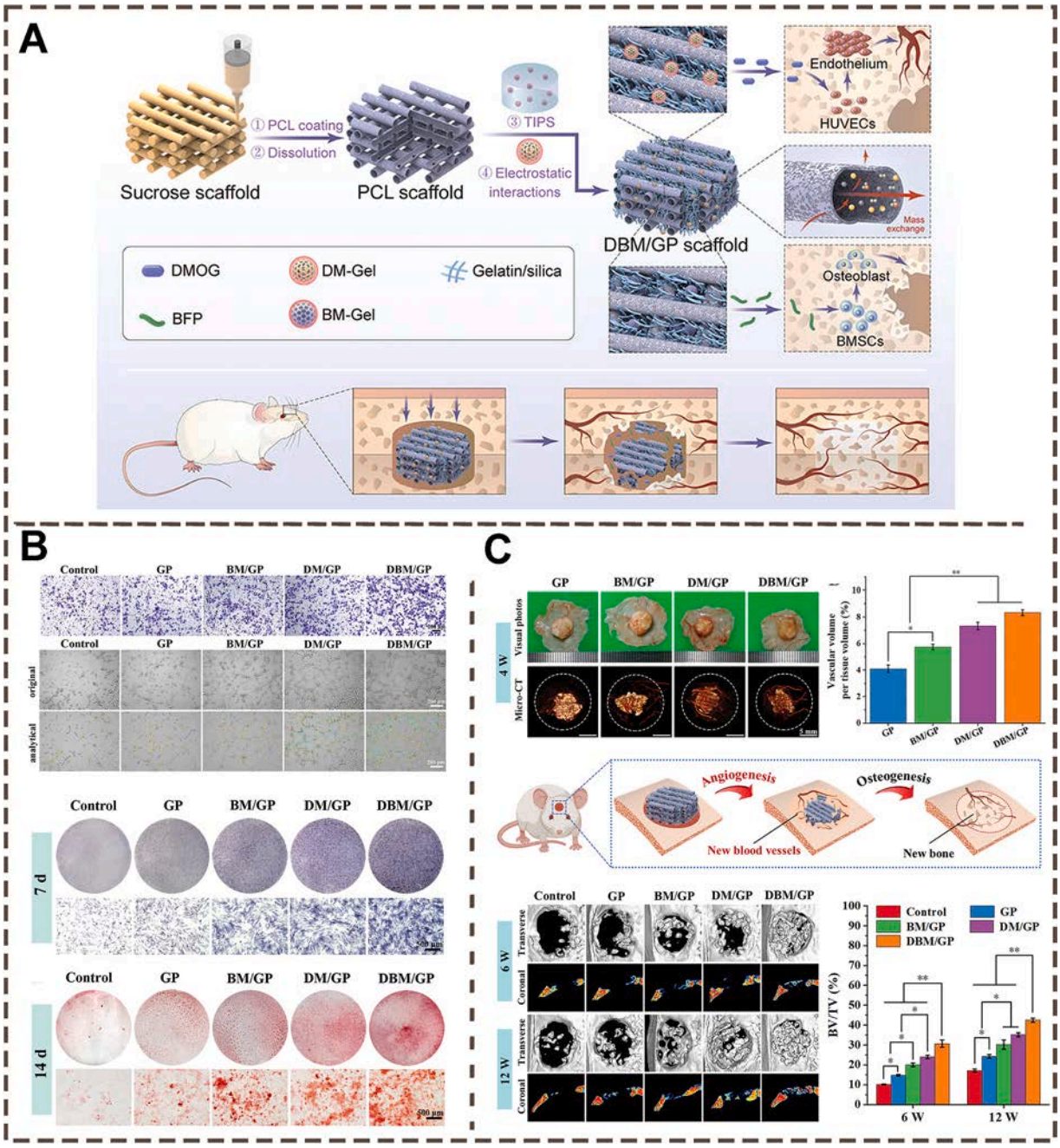


Fig. 7. (A) Schematic illustration for the preparation of scaffold. (B) Scaffolds on HUVECs migration and tubular network formation and *in vitro* osteogenesis abilities. (C) *In vivo* vascularization and bone regeneration of scaffolds [150]. Copyright 2022, Wiley.

observed after 12 weeks compared to the control group.

In contrast to natural polysaccharides and polyphenols, which mainly act through non-specific electrostatic interactions or membrane disruption, small-molecule antibiotics possess well-defined molecular targets, resulting in higher antibacterial efficacy and faster response. Electrospun nanofiber-based 3D scaffolds loaded with small-molecule antibiotics are typically fabricated by incorporating broad-spectrum antimicrobial agents into the electrospinning solution, enabling efficient encapsulation and controlled release within the nanofiber network [156]. Owing to the high surface area and interconnected porous architecture of electrospun nanofibers, these scaffolds can create a localized high-concentration antimicrobial environment at the surgical site, rapidly eliminating bacteria and preventing biofilm formation—thereby offering effective early-stage intervention for infection-associated bone defects. Amoxicillin, a widely used β-lactam broad-spectrum antibiotic, is effective against both Gram-positive and Gram-negative bacteria. Chou et al. [157] developed an electrospun nanofiber-based 3D scaffold by incorporating amoxicillin and BMP-2 into nanofibers, which were then integrated into a 3D printing PLA scaffold. In vitro release studies demonstrated sustained amoxicillin release for over 28 days, with concentrations consistently above the minimum inhibitory concentration. BMP-2 was released over a 30-day period, effectively stimulating osteogenic cellular responses. In an alveolar cleft defect rat model, animals implanted with the composite scaffold showed improved postoperative mobility and exhibited significantly enhanced new bone formation and tissue regeneration at days 7 and 14, confirming its potential for simultaneous antibacterial action and osteoinductive bone repair. Ciprofloxacin (CIP), a second-generation fluoroquinolone antibiotic,

exhibits broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria. However, its poor water solubility limits its effectiveness in localized applications. Zhang et al. [158] addressed this limitation by first forming an amorphous nanocomplex (CIP-DEX) through ionic interaction with DEX, followed by complexation with CS to obtain stable CIP-DEX-CS (CDC) nanoparticles (Fig. 8). This system enabled rapid drug release, with 95 % of CIP released within 7 h, effectively targeting postoperative infections. Its 3D porous architecture—with a porosity of 94 % and abundant nanoporosity—offered a favorable microenvironment for cell adhesion, proliferation, and drug diffusion. Antibacterial assays showed pronounced inhibition zones against Escherichia coli and Staphylococcus aureus, significantly outperforming blank controls. In vitro cell studies confirmed that the presence of BMP-2 nanoparticles significantly enhanced osteogenic differentiation of mesenchymal stem cells, as indicated by elevated ALP activity and upregulated expression of osteogenic markers including ALP, COL 1, Runx2, and OCN.

In summary, electrospun nanofiber-based 3D scaffolds offer an ideal platform for the integration of antibacterial and osteogenic functions in bone tissue engineering. By tailoring material composition and drug-loading strategies, various types of antimicrobial agents can be incorporated with good biocompatibility and functional synergy. Natural polysaccharides and polyphenols provide mild and low-toxicity antibacterial effects, while small-molecule antibiotics offer rapid and effective bacterial eradication. These approaches not only enhance local infection control but also contribute to the establishment of a favorable osteogenic microenvironment, laying a solid foundation for the multifaceted requirements of bone defect repair.

5. Translational challenges of electrospun nanofiber-based 3D bone scaffolds

Electrospun nanofiber-based 3D bone scaffolds are considered to be important candidates for next-generation bone repair materials due to their advantages in microstructure, biofunctionality and mechanical properties. However, with the deepening of the research, several core bottlenecks have gradually emerged, including the incompatibility between biodegradation and osteogenesis rate, and the unclear interaction mechanism with the immune microenvironment, all of which have limited the clinical translation and scale-up of its application to different degrees. In this regard, the following presents a systematic review and analysis of these key challenges, addressing current research progress, existing issues, and future development direction (Table 1).

(1) Challenge of coordinating degradation rate with osteogenesis rate. Ideal electrospun nanofiber-based 3D bone scaffolds should have good mechanical support, biodegradability, and osteoinductive activity, and the polymers commonly used in

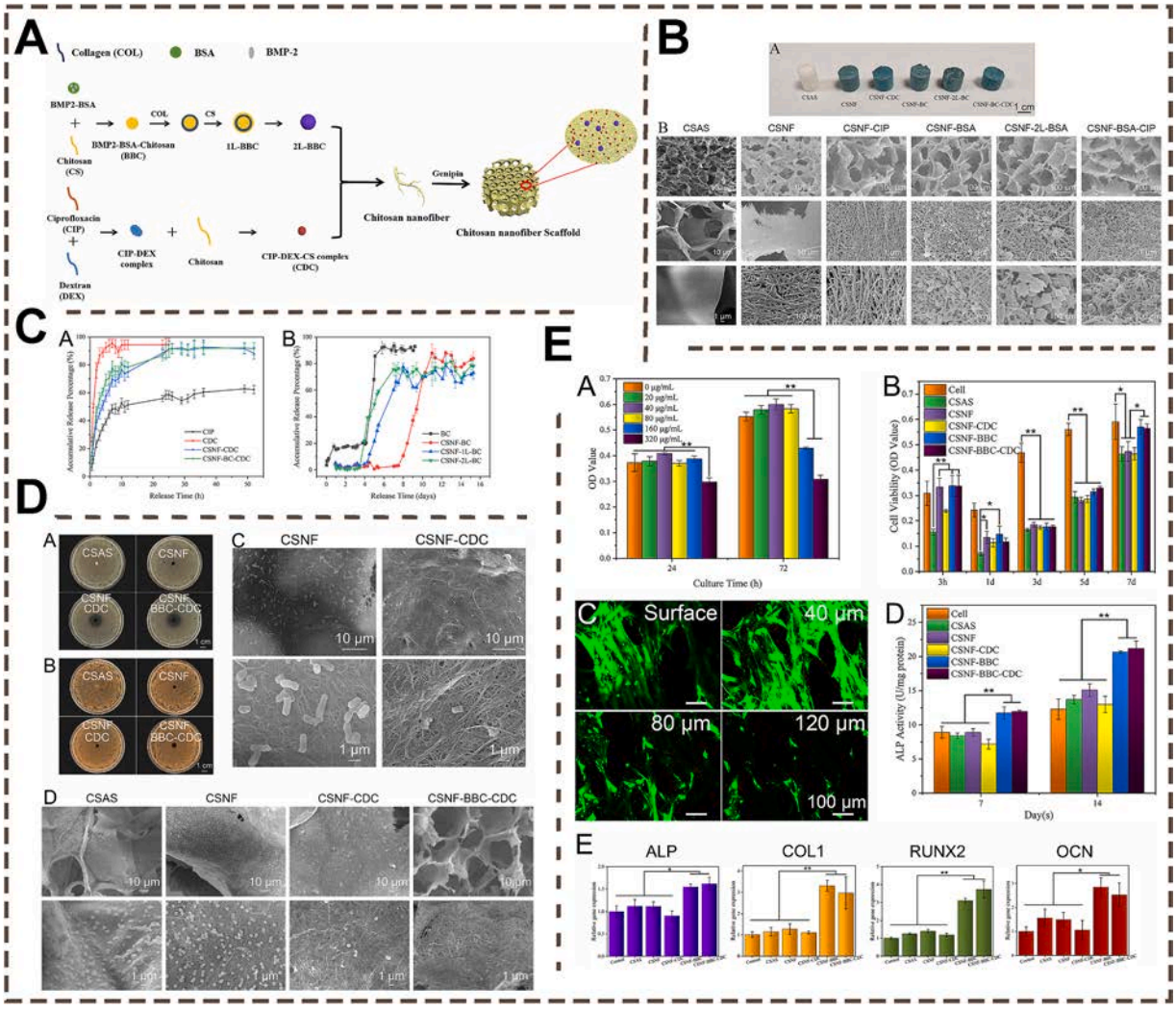


Fig. 8. (A) Preparation of electrospun nanofiber-based 3D bone scaffolds. (B) Macro and micro pictures of the composite scaffolds. (C) Drug release from composite scaffolds. (D) Antibacterial properties of composite scaffolds. (E) Cytocompatibility and osteogenic differentiation of different scaffold materials [158].

Table 1
Key challenges and emerging strategies in electrospun nanofiber-based 3D bone scaffolds.

Challenge	Key Issues	Emerging Solutions
Mismatch Between Degradation and Osteogenesis	Difficult to balance scaffold strength, degradation, and bioactivity. Degradation byproducts may negatively affect regeneration.	Use of responsive polymers (pH, enzyme, heat) and dynamic structures (4D printing) to align degradation with healing.
Instability of Functionalization	Bioactive agents may be inactivated during spinning or cause inflammation if improperly purified or dosed.	Encapsulation, coaxial spinning, and smart carriers improve stability and targeted delivery of functional factors.
Unclear Immunomodulation	Limited understanding of how scaffold properties affect immune response, especially macrophage behavior and its link to bone healing.	Smart scaffolds with cue-responsive release of immunomodulators actively shape pro-regenerative immune environments.
Scalability and Standardization	Lack of consistent fabrication parameters and evaluation standards; clinical needs require customizable, reproducible scaffolds.	Automated 3D electrospinning and modular platforms enable scalable, standardized production for clinical translation.

electrospinning currently have difficulty in balancing between these properties. In addition, the effects of scaffold degradation products on the surrounding tissue microenvironment have lacked systematic assessment. Therefore, the precise matching between material composition, structural stability and tissue repair speed is a key direction for future material design, especially in composite systems, which should take into account the triple synergy of mechanics-degradation-biology. A range of emerging strategies are now being proposed to enable more precise degradation modulation. For example, the development of pH-, temperature-, or enzyme-responsive polymers allows scaffolds to degrade on-demand in specific pathologies or repair microenvironments, thereby better matching the bone regeneration process. In addition, dynamically tunable scaffold structures have been proposed, such as 4D printing technology or stress-induced deformable fiber mesh, to achieve adaptive changes in scaffold structure or performance *in vivo* and extend the effective support period. These new approaches are expected to break through the limitations of traditional electrospun nanofiber-based 3D bone scaffolds in terms of degradation controllability, and promote their translation to the clinic even further.

(2) Stability and biosafety challenges of functionalization strategies. In order to enhance the bioactivity of electrospun nanofiber-based 3D bone scaffolds, researchers often introduce various functional factors into electrospun nanofibers. However, these factors may suffer from inactivation induced by organic solvents, electrostatic fields, or high voltages during the electrospinning process. In addition, some functional factors may cause inflammatory reactions, ectopic ossification, or cytotoxicity if they are not sufficiently purified or if the dose is not properly controlled. Currently, microencapsulation technology, coaxial electrospinning, and smart response carriers (pH, temperature, and mechanical stress response) have been proposed to improve delivery, but systematic data support is still lacking in terms of long-term *in vivo* stability, delivery precision, and biosafety. How to achieve controlled release, safe delivery and synergistic effects of functionalized components is one of the main challenges in the translation of electrospun nanofiber-based 3D bone scaffolds functionalization to clinical applications.

(3) Often, the mechanistic effects of certain scaffolds and host immune response are not fully known. Electrospun nanofiber-based 3D bone scaffolds inevitably interact with the host immune system after implantation, and in particular, the polarization state of macrophages plays an important role in scaffold integration and bone regeneration. Although it has been shown that factors such as scaffold material composition, fiber diameter, surface charge, and roughness can influence immune cell behavior, there is still a lack of systematic understanding of how scaffold physicochemical properties modulate the immune microenvironment, and thus influence the osteogenic cascade response. In addition, functionalization strategies (e.g., addition of anti-inflammatory drugs or cytokines) have shown promising results in modulating inflammation, but the spatial and temporal links between long-term immune dynamics and bone regeneration have not yet been established. Currently, smart-responsive electrospun nanofiber-based 3D bone scaffolds are capable of dynamically releasing immunomodulators in response to local microenvironmental changes (e.g., pH or enzyme activity), enabling on-demand modulation of the immune microenvironment. These synergistic strategies shift the scaffold from passively adapting to the immune system to actively shaping the favorable regenerative microenvironment, providing an innovative solution for immunocompatibility in bone tissue engineering.

(4) The large-scale preparation and standardization of electrospun nanofiber-based 3D bone scaffolds are not yet mature. The material formulations, electrospinning parameters, functionalization methods and post-treatment processes used by different research groups are highly inconsistent, and the lack of industry norms and evaluation standards limits the horizontal comparison between results and the systematic advancement of preclinical translational research. In addition, in actual clinical applications, there are highly individual differences in the site, size and physiological environment of bone defects, which impose highly customized requirements on scaffolds in terms of structure, performance and biological function. Therefore, in the future, we should accelerate the development of modular and automated 3D electrospinning manufacturing platforms, and promote the transition of electrospun nanofiber-based 3D bone scaffolds from “laboratory formulations” to “standardized products”, to achieve multi-dimensional unification of material composition, spatial configuration, biological function and quality control, thus providing a technical basis and regulatory guarantee for clinical promotion.

In conclusion, the clinical translation of electrospun nanofiber-based 3D bone scaffolds not only requires continuous optimization in material design and process development, but also requires interdisciplinary and systematic research in combination with multidimensional factors, such as tissue immunomodulation, biofunctional stability, and regulatory standards, to achieve a real breakthrough from experimental validation to clinical application.

6. Conclusion

In conclusion, electrospun nanofiber-based 3D bone scaffolds offer distinct advantages for bone regeneration. Although key challenges remain for their clinical translation, these scaffolds demonstrate considerable potential in bone tissue engineering. Their unique biomimetic microstructure, excellent mechanical properties, and capacity for multifunctional modification position them as important candidates for next generation bone repair materials. Future research should focus on the in-depth integration of material design and biological mechanisms to accelerate the transition of electrospun nanofiber-based 3D

bone scaffolds from laboratory to clinic. For example, research on electrospun nanofiber-based 3D bone scaffolds can focus more on the development of multifunctional smart materials, such as composite scaffold systems with responsive release, visual monitoring and personalized regulation capabilities. At the same time, 3D printing technology will be combined to build multi-scale structures and integrate stem cell and gene delivery functions. Through interdisciplinary collaboration and systematic evaluation, electrospun nanofiber-based 3D bone scaffolds are expected to advance personalized tissue repair and clinical translation.

CRediT authorship contribution statement

Pengfei Cai: Writing – review & editing, Writing – original draft. **Yangfan Ding:** Writing – original draft. **Chengqiang Wang:** Writing – review & editing. **Jinglei Wu:** Writing – review & editing. **Melanie L. Hart:** Writing – review & editing. **Bernd Rolauffs:** Writing – review & editing. **Xiumei Mo:** Writing – review & editing, Writing – original draft. **Binbin Sun:** Writing – review & editing, Writing – original draft, Funding acquisition, Data curation.

Consent to participate

This review article did not involve any human participants, animal experiments, or primary data collection. Therefore, no ethical approval or consent was required.

Ethical approval

Our review did not require further ethics committee approval as it did not involve animal or human clinical trials and was not unethical.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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