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Review

Polydopamine-Modified Polycaprolactone Scaffolds Loading Metal Nanoparticles for Bone Tissue Engineering

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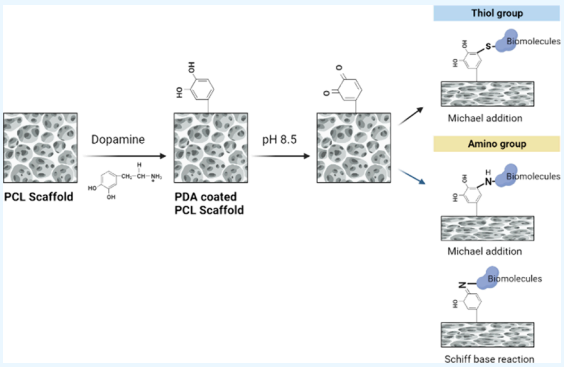
ABSTRACT: Recent advancements in materials synthesis and processing technology, coupled with a deeper understanding of bone nanoscale structure and biology, have provided new avenues for designing bioactive materials in bone tissue regenerative medicine. This Review focuses on the design and application of polydopamine-modified polycaprolactone scaffolds loading metal nanoparticles for bone tissue engineering. We explore their antibacterial properties and their ability to guide cell behavior. Specifically, we discuss the synthesis techniques, protein deposition, morphology variations, and interactions with the extracellular matrix of these scaffolds and biocompatibility and efficacy in promoting bone tissue regeneration in vitro and in vivo. Challenges and unmet needs are reviewed in the development of polymer- and metal-based materials for bone tissue engineering.



1. INTRODUCTION

Nowadays, the rapid development of materials synthesis, processing technology, and our deeper understanding of bone nanoscale structure and biology provide new insights for the design of bioactive materials in bone tissue regenerative medicine. Scaffolds composing multifunctional materials have been explored using polymers, medical metal materials, bioceramics, and carbon nanomaterials.[1−4]

Polydopamine (PDA) has garnered increasing attention since 2007 in the field of bioimaging, antibacterial, cancer, and regenerative medicine.[4−12] Different shapes of PDA-based materials, such as nanoparticles, mesoporous structure, and nanocapsules, have been successfully synthesized and applied for bone repair and regeneration.[8,13,14] PDA shows robust adhesion to almost all solid surfaces, facilitating the development of PDA-based scaffolds in targeted bone-injured areas.[15] Polycaprolactone (PCL) is a widely used bone tissue engineering synthetic polymer approved by the US Food and Drug Administration (FDA). However, PCL is not highly efficient in improving cell adhesion, maintaining low and hydrolytic degradation under acidic circumstances and potential thermoplastic behavior due to the hydrophobic property.[16−19] Researchers have modified PCL's hydrophobic surface with biomolecules like peptide hydrogels and PDA to enhance cell adhesion.[17,18] With the application of a PDA surface coating, PCL−PDA can function as a scaffold for hydroxyapatite nucleation and mineralization.[18] Concurrently, metal ions, which demonstrate antibacterial properties and biological functions such as promoting angiogenesis and inducing osteogenic differentiation, have emerged as promising agents for guiding cell behavior and modifying the biophysical properties of scaffold materials. Owing to these advantages, PCL−PDA and metal-based bioactive scaffolds have been extensively designed and studied, with several representative examples enumerated in Table 1.

This Review focuses on the design and application of polymer- and metal-based materials for bone tissue engineering. First, we introduce the biomaterials that use PDA-modified PCL polymers as the scaffold and metal ions as the antibacterial component for bone tissue engineering. The protein deposition, morphology variation, and interplays between scaffold and extracellular matrix (ECM) within a period of time are described. Furthermore, the biocompatibility and bone tissue regeneration results of scaffolds are evaluated both in vitro and in vivo. Finally, we review the biomedical unmet needs and challenges in the development of polymer- and metal-based materials for bone tissue engineering.

2. MATERIALS FOR BONE TISSUE ENGINEERING

Various kinds of materials and material combinations have exhibited potential for bone tissue engineering. Generally,

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Table 1. Representative PCL−PDA Scaffold Applications for Bone and Tissue Engineering

biomaterials selection	scaffold fabrication technology	PDA functions	evaluations	therapeutic area	ref
PCL−PDA−HA scaffolds	electrospinning	facilitate the coating of HA	enhanced bone regeneration, increased regenerated collagen at the defect site, enhanced osteogenesis	bone tissue engineering, calvarial bone defect model	28
PCL/PDA membrane	electrospinning	promote the adhesion of therapeutic proteins and cells	promoted the regeneration of periodontal tissue and bone repair	periodontal tissue engineering	29
PCL/bioactive glass PDA/CS scaffolds	high-pressure molding/salt leaching technique	facilitate the modification of chitosan	enhanced protein adsorption, cell adhesion, and osteogenic differentiation, promoted cranial bone regeneration	bone regeneration	30
PCL/PDA/GNPs scaffolds	3D printing	reduce gold ions into gold NPs	3D porous structure provided substrate interconnectivity, PDA coating enhanced GNP growth and may accelerate bone differentiation, good osteogenic activity	bone tissue engineering	31
PLGA/PCL−PDA−Ag scaffolds	electrospinning	facilitate the loading of Ag NPs and collagen	antimicrobial, osteogenic properties	orofacial tissue regeneration	32

choosing the appropriate material for bone tissue engineering is determined by some key factors, including but not limited to the advancement of fabrication technology and implementation methods. The most common biomaterials used for bone tissue engineering applications are natural polymers, synthetic polymers, biodegradable metals, bioceramics, carbon-based materials, and composite materials.[20,21]

2.1. PCL−PDA-Based Materials. *2.1.1. PCL—Properties and Applications.* PCL is a synthetic polymer produced via ring-opening polymerization of ε-caprolactone. PCL possesses excellent chain flexibility and can be synthesized at variable chain lengths. The properties of PCL are highly dependent on its molecular weight; PCL is a semicrystalline polymer in nature with a melting temperature of 59−64 °C and behaves like an elastic material with high toughness and excellent mechanical properties at physiological temperatures.[22−24] PCL is a biocompatible inert polymer with low toxicity, low immunogenicity, and good tissue compatibility. PCL can be degraded by hydrolysis of aliphatic ester linkages, and it usually takes more than 2−3 years to be fully degraded in vivo.[25] These properties perfectly meet the needs of bone tissue engineering, for the bone resorption and remodeling process usually takes a long period of time. The design of PCL scaffolds for bone tissue engineering is also guided by the properties and functions of healthy bone tissue. For example, the porous structure of PCL is prone to conduct cell adhesion, proliferation, nutrients transportation, and vascular infiltration and to mimic the multiscale organization and hierarchy of the bone matrix.[26] Hence, PCL is widely used as a suture and scaffold material for bone tissue engineering.[27]

2.1.2. PDA—Properties and Applications. PDA is a versatile polymer derived from the self-polymerization of dopamine. It has unique adhesive and surface modification properties, making it an attractive material for various applications in bone and tissue regeneration.[33] Dopa (3,4-dihydroxyphenylalanine) is a very crucial component of adhesive proteins secreted by mollusks. The ortho-benzenediol groups endow the excellent chelation and reduction capabilities of Dopa. When oxidized to quinone under alkaline aerobic conditions, Dopa can react with chemical groups of substrate materials covalently, bringing in strong adhesion to inorganic materials such as metals and poly(tetrafluoroethylene). Dopamine, a derivative of Dopa, shares similar structures and properties with those of Dopa. Typically, dopamine monomer undergoes oxidative self-polymerization in weakly alkaline conditions to form PDA.[34−36] PDA is a melanin resembling polymer that exhibits outstanding adhesion and hydrophilicity properties.

The applications of PDA in regenerative medicine can be categories into two forms: as a surface coating material or framework material.[35,37−39] As a coating material, PDA has a sufficient amount of amine, imine, and catechol groups to react with thiol and amino ligands of PCL via Michael addition reaction and/or Schiff base reaction (Figure 1).[40,41] Biomolecules with thiol and amino ligands can be modified with PDA covalently. Meanwhile, noncovalent forces such as $\pi-\pi$ stacking or hydrogen bonding also allow the loading of bioactive molecules onto PDA-based scaffolds.[40,42] In addition, the reducibility of catechol groups on PDA make it possible for the reduction of metal nanoparticles (NPs) onto scaffolds.[43,44] This "add-layer" modification method facilitates substrate functionalization without affecting their intrinsic properties. As a framework material, PDA is able to improve adhesion and

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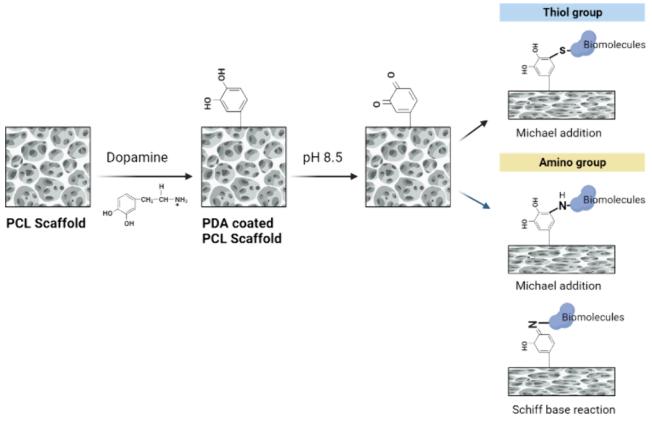

Figure 1. Schematic illustration of PCL−PDA scaffold modification with thiol and amino group containing biomolecules.

mechanical strength of the scaffold and facilitate cell attachment, proliferation, and differentiation simultaneously.[45−47] Hence, the application of PDA in regenerative bone and tissue engineering has attracted a huge amount of scientific interests.

2.1.3. PDA Coating for Enhanced Bone Regeneration. Surface modification plays a crucial role in the biofunctions of porous polymeric scaffolds. Researchers utilize the highly bioactive chitosan (CS)-immobilized porous composite scaffolds for enhanced bone regeneration.[30] To achieve this, the porous PCL/bioactive glass (BG) (PB) composite scaffolds were created using PDA as a bridging layer to anchor CS. Briefly, the PB scaffold was synthesized via a high-pressure molding/salt leaching method, taking advantage of the high-pressure molding squeeze effect. This porous PB scaffold was endowed with excellent mechanical capabilities, such as a compressive modulus to enhance bone repair. Sequentially, the PDA coating layer and CS components were introduced onto the porous surface of PB scaffolds using solution soaking (Figure 2a).

Early cell attachment plays a pivotal role in cell adhesion and bone osseointegration. As showed, a small number of ellipsoidal cells are observed on PB, whereas a larger amount of bone marrow stromal cells (BMSCs) spread among PB−CS, PB−PDA, and PB−PDA−CS, indicating that porous PB−PDA−CS is more efficient for cell attachment and possesses high F-actin expression. The cell images and quantitative cell area and density results suggest that PB−PDA−CS scaffolds have good biocompatibility and can be used for cell proliferation (Figure 2b). It is proven that PDA coating is beneficial for cell attachment and the covalent immobilization of CS onto PCL/BG−PDA (PB−PDA) scaffolds significantly improves protein adsorption, cell adhesion, and osteogenic differentiation when compared to CS physically absorbed scaffolds. Osteogenic differentiation of BMSCs was further assessed via osteogenesis-related gene mRNA expression. The expression of collagen type I (Col-I) and osteopontin (OPN) indicates that CS promotes the osteogenic differentiation of BMSCs significantly.

Furthermore, the PB−PDA−CS scaffolds notably enhanced cranial bone regeneration and offer a practical and efficient method to fabricate artificial bioactive scaffolds for bone tissue engineering (Figure 2c). There is barely new bone formed in the control group, whereas a large amount of regenerative bone can be spotted in PB around the defect areas. By contrast, the neobone almost fulfills the entire defects after the treatment of PB−CS, PB−PDA, and PB−PDA−CS and displays a comparatively higher bone volume per total sample volume (BV/TV) of defects on the basis of qualitative micro-CT analysis ($p < 0.05$). Moreover, PB−PDA−CS presents a compact trabecular bone structure with the highest trabecular number (Tb.N) and lowest trabecular separation (Tb.Sp) ($p < 0.05$), indicating that PDA and CS modification could improve the bioactivity of scaffolds and facilitate bone regeneration.

2.1.4. PCL−PDA Scaffold for In Situ Bone Tissue Regeneration. Classical bone tissue engineering usually utilizes culture-expanded cells and scaffolds to generate tissue constructs for transplantation, and an alternative PCL-based scaffold is applied to address these drawbacks.[28] In this approach, the PCL−PDA scaffold can redirect endogenous stem cells to the injury site and bypass ex vivo cell culture and tissue transplantation. To facilitate the endogenous stem cell survival and differentiation into osteogenic cells, PCL scaffolds were prepared by electrospinning and modified with hydroxyapatite (HA) and PDA to increase the osteoinductive potential and mechanical properties. The coating of PDA is beneficial for osteogenic differentiation and mineralization of the stem cells (Figure 3a).[49−52] Substance P (SP), a tachykinin neuropeptide, mobilizes and recruits bone marrow-derived mesenchymal stem cells (MSCs) to the defective site. SP has the potential to induce hematopoietic stem cells, CD29+ cells, and bone marrow-derived MSCs to diffuse into the circulation system and participate in the regenerative process at the injury site. In addition to the SP, bone marrow-derived CD29+ CD105+ CD45− cells are mobilized, and bone tissue regeneration is enhanced in a critical-sized calvarial bone defect model. The combination treatment of osteoinductive PCL−PDA−HA scaffolds and SP demonstrated the greatest bone regeneration (60.91 ± 15.70%; Figure 3b) and highest collagen deposition level (59.39 ± 11.00% vs 5.91 ± 1.88% (PBS); Figure 3c) after 8 weeks administration. Consequently, the synergistic effects of the PCL−PDA−HA scaffold and SP treatment recruit endogenous stem cells from bone marrow to the targeted critical-sized calvarial bone defect areas, holding great promise for in situ bone tissue regeneration.

2.1.5. PCL−PDA Membranes for Periodontal Regeneration. Periodontitis, a prevalent chronic inflammatory condition affecting tissues that support teeth, poses a significant challenge due to the limited applications of regenerative periodontal membranes. To address this limitation, Hasani-Sadrabadi et al. developed biophysiological PCL membranes via electrospinning technology and coated with biomimetic PDA to enhance therapeutic protein and cell adhesion (Figure 4a).[29] PCL was partially wet with dopamine monomer, then the catechols of dopamine monomer were oxidized to quinones groups, and subsequently it was rearranged to form the adhesive PDA layer. PCL nanofibers showed uniform shapes with average diameters of 270 ± 30 nm regardless of the PDA coating. The pore size of interconnected porous PCL−PDA is measured to be 2.1 ± 0.7 μm. Such multiscale membranes can mimic the complex periodontal tissue extracellular environment and act as functional tissue constructs for periodontal regeneration.

PDA plays a pivotal role in expediting the osteogenic differentiation of dental-derived stem cells by fostering HA mineralization. Next, PDA-coated PCL membranes were used as cell substrates. Since the PCL core is biodegradable, human periodontal ligament stem cells (PDLSCs) can interact with

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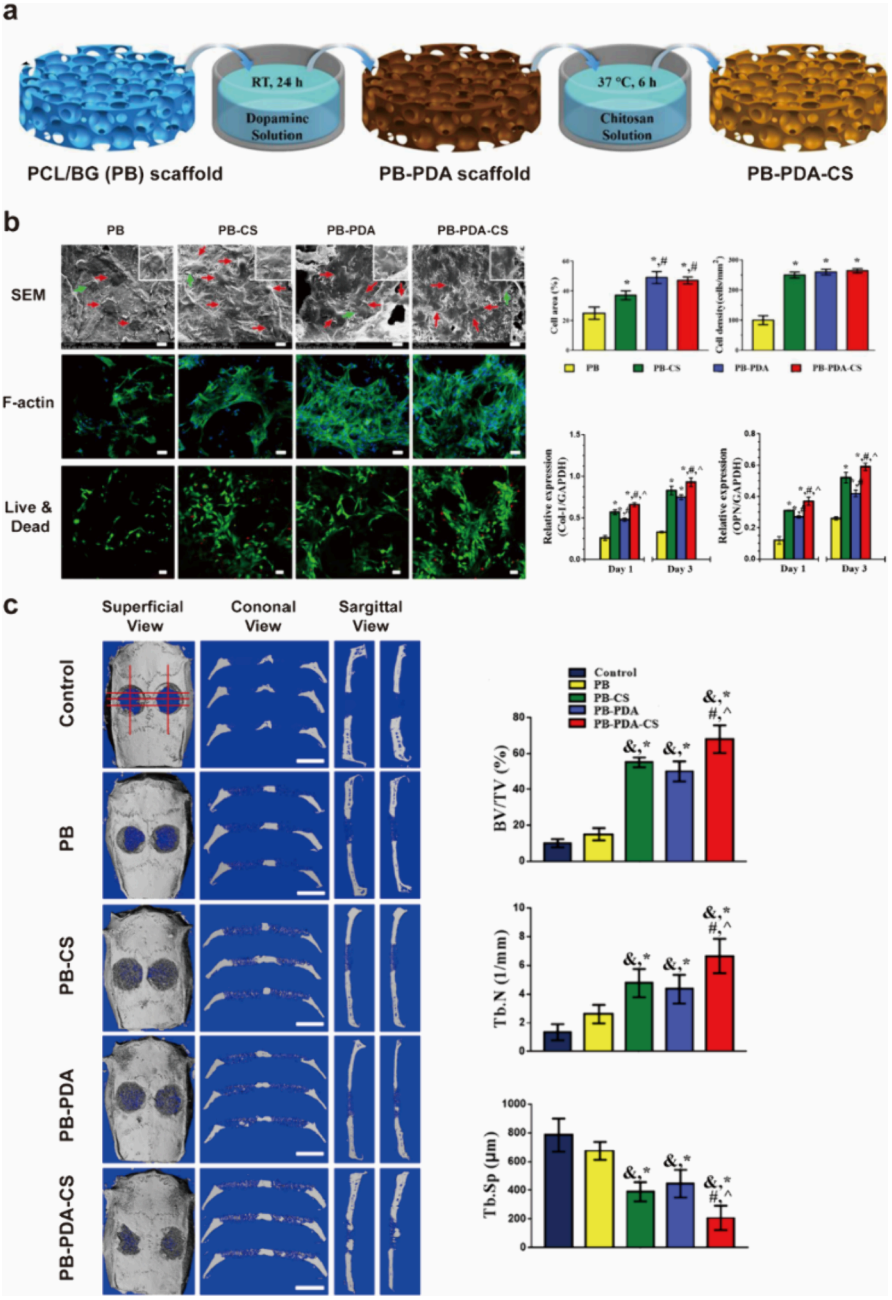

Figure 2. (a) Schematic illustration of the PCL−BG−PDA−CS scaffold. (b) SEM of scaffolds incubated with BMSCs for 6 h. Cell cytoskeleton of BMSC is noted in green and nuclei in blue. Live and dead staining of BMSCs is conducted 7 days later. The expression levels of Col-I and OPN are calculated. (c) Micro-CT images of calvarial defects are taken at 6 weeks. Qualitative bone analysis is conducted accordingly. Reproduced with permission from ref 48. Copyright 2019 ACS.

PDA-coated PCL membranes and manipulate the microenvironments accordingly. Immunofluorescent imaging and SEM images confirmed that PDA-coated PCL membranes had an active interaction with cells, and cells can remodel the membrane even after 2 weeks' culture (Figure 4b). As a result, such nanoscale scaffolds successfully mimic the intricate extracellular environment of periodontal tissue, serving as functional tissue constructs for periodontal regeneration. In a periodontal defects rat model, the engineered PCL−PDA membrane effectively facilitated regenerative periodontal tissue and bone repair, demonstrating high potential for protein and cell delivery for periodontal tissue engineering (Figure 4c).

2.2. Metal-Loaded Materials. There are surging interests pouring into the application of PCL−PDA materials to elicit osteogenesis and angiogenesis by releasing bioactive ions.[53,54] This idea has inspired an increasing design of incorporating a wide range of biologically active ions into the PCL−PDA materials, including copper, silver, gold, calcium, and magnesium. These copper, silver, and gold ion-incorporated materials provide economic and promising alternative treatments to the inclusion of bone growth factors.

Using PCL−PDA to incorporate metal ions can achieve specific functionalization of materials, and the continuous release of metal ions, such as Ag+, via the PCL−PDA coating can significantly realize durable antibacterial activity. However,

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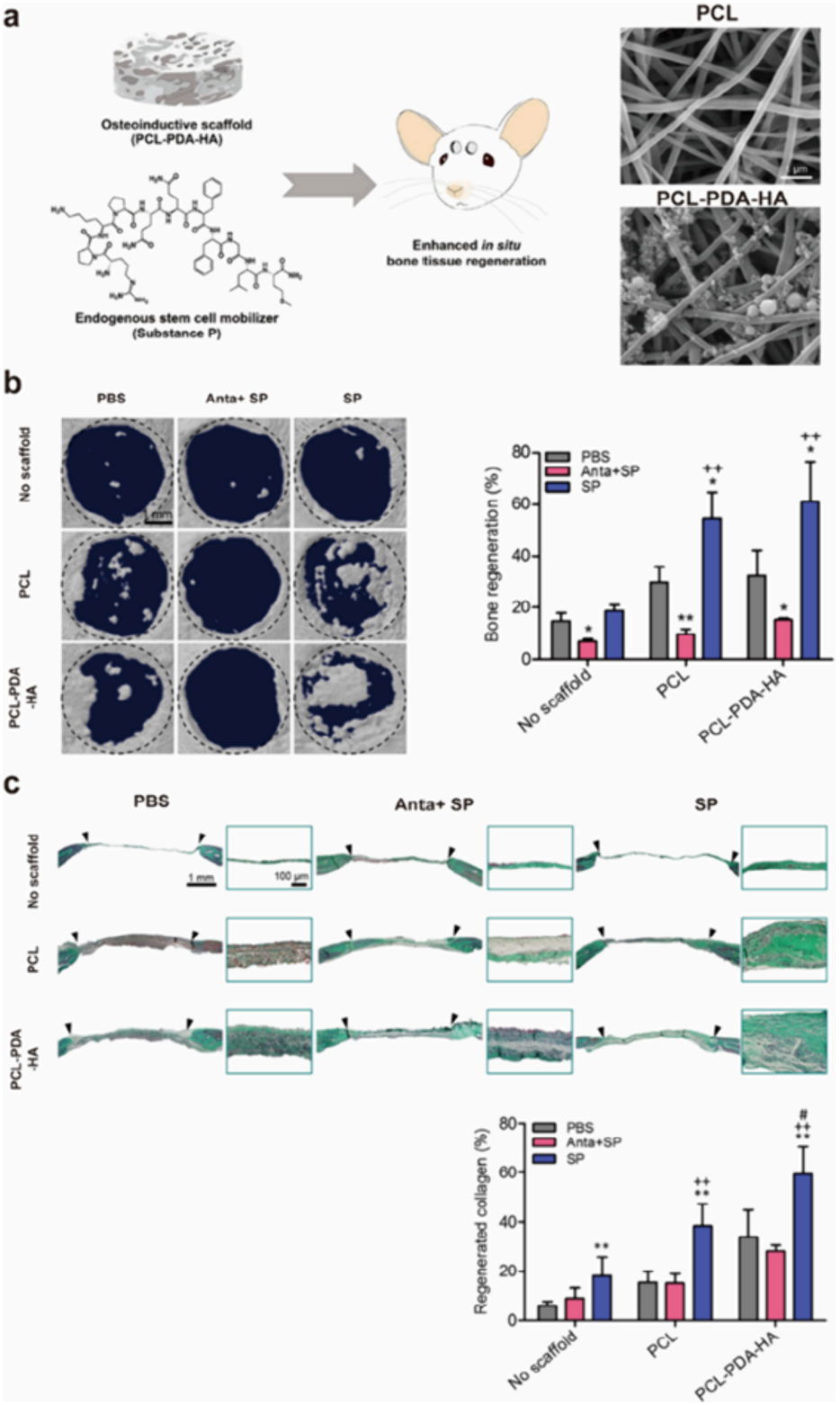

Figure 3. Enhanced in situ bone tissue engineering with nanofibrous PCL−PDA−HA scaffolds. (a) Illustration and SEM images of electrospun nanofibrous PCL modified with HA and PDA. Scale bar is 1 μm. (b) Enhanced bone regeneration of stem cell-mobilized Substance P and engineered scaffolds for 8 weeks. (c) Enhanced regenerative bone collagen deposition with SP and PCL−PDA−HA scaffold combination treatment in calvarial bone defects models for 8 weeks. Reproduced with permission from ref 28. Copyright 2017 John Wiley and Sons.

metal ions incorporated into the PCL−PDA scaffold via electrospinning can be easily agglomerated due to the strong conductivity during electrochemical deposition, affecting distribution and uniformity of metal ions.[55] Utilizing rapid prototyped PCL scaffold and further coated PDA onto the PCL scaffold to grow metal ions, such as gold nanoparticles, on the surface can eliminate chemical treatment and improve biocompatibility. These gold nanoparticle-coated 3D PCL−

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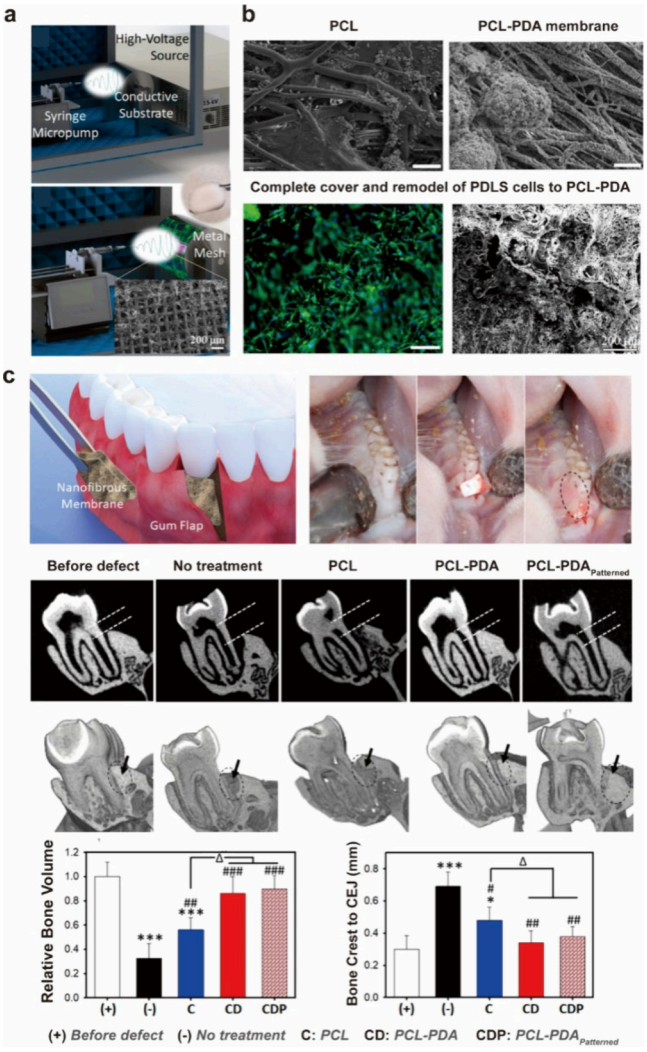

Figure 4. (a) Synthesis process of periodontal membranes via electrospinning. SEM images of PCL−PDA membranes cultured with osteogenic media for 4 weeks. Scale bars are 2 μm. (b) Immunofluorescent images of PDLSCs cocultured with membranes show full coverage of PCL−PDA structures. β-Actin is indicated in green and DAPI in blue; scale bars are 100 μm. SEM images of PCL−PDA membranes cocultured with cells for 2 weeks. (c) Periodontal defect model setup in rat. (c) Micro-CT imaging and quantative analyses of rat maxilla with PCL, PCL−PDA, or PCL−PDA$_{Patterned}$ scaffolds. Reproduced with permission from ref 29. Copyright 2019 ACS.

PDA scaffolds showed potent bone tissue regeneration in vitro and in vivo.[31]

2.2.1. Copper-Loaded Materials. Copper is one of the protective trace elements of bone that maintains the optimal status of the bone matrix. Copper is important for the growth and maturation of bone tissue and protein, especially for bone collagen.[56,57] Copper can promote bone growth and maintain bone mass through the catalytic metabolic process.[58,59] Studies have shown that copper contributes to the bone mineralization and osteoblasts.[60,61] When doped with copper, scaffolds can inhibit proinflammatory cytokine release and promote osteogenesis. Mixing PCL with bioactive glass and copper nanoparticles can generate biocompatible nanofiber scaffold and induce osteogenic potential.[62] Karuppannan et al. incorporate CuO nanoparticles into PCL/gel fibers to form CuO nanofiber with diameters ranging from 130 to 160 nm.[63] The prepared CuO nanofiber had good mechanical properties and hydrophilicity and sustained in vitro drug release for 48 h (Figure 5a). Meanwhile, CuO nanofiber has an antibacterial effect on pathogenic bacteria and supports the growth of fiber cells for tissue engineering application. The inhibition zone of CuO nanofiber against *Staphylococcus aureus*, multidrug-resistant *S. aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* was measured to be 51 ± 1.2, 40 ± 1.7, 31 ± 0.5, and 30.5 ± 0.3 mm, respectively. The FESEM image of fibroblast cell growth on CuO nanofiber for 5 days demonstrates a good compatibility and facilitates fibroblast cell attachment, proliferation, and spreading (Figure 5b, c).

2.2.2. Gold Nanoparticles (GNPs)-Loaded Materials. Gold nanoparticles (GNPs) have been widely studied in bone tissue engineering for GNPs and can promote osteogenic differentiation.[64−68] Lee et al. immobilized GNPs on the surface of PDA-coated 3D-printed PCLs to fabricate a hybrid 3D bone tissue-engineered scaffold under mild aqueous conditions (Figure 6a).[31] In this study, 3D porous scaffolds with a diameter of 400 μm were well manufactured. The open and uniform interconnected pores are convenient for nutrients, minerals, oxygen, and biomolecules to enter the inner regions of PCL−PDA (PCLD) scaffolds and facilitate cell growth. Various concentrations of $HAuCl_4$ (0.1, 0.5, 1, and 2 mM) were reduced with PCLDs to find out the optimal GNP growth conditions. As the results show, GNPs with reducing concentration of 1 mM exhibit the most uniform coverage of PCLD and aggregate obviously at 2 mM (Figure 6b). As such, PCLD1 is chosen for bone differentiation for in vitro and in vivo further study.

In micro-CT imaging, the PCLDG1 scaffold potentiates a higher amount of mineralized tissue than PCL and PCLD. Effective tissue infiltration was found in fibrous connective tissue areas around PCL, PCLD, and PCLDG1 scaffold, while inflammatory cell infiltrations were not spotted in hematoxylin and eosin (H&E) staining. This could be ascribed to the good biocompatibility of PCL which does not generate inflammatory byproducts when decomposing. The PCLDG1 scaffold was bridged via denser and thicker layer of fibrous connective tissue than other materials. Masson's trichrome (MT) staining verified the existence of newly mineralized collagenous tissues and bones. The PCLDG1 scaffold contributes to a much higher amount of new bone formation than other scaffolds, which is consistent with an in vitro study (Figure 6c).

2.2.3. Silver Ion-Loaded Materials. Oral and craniofacial environments are very challenging for regenerative medicine. The oral cavity is full of bacterial pathogens, and our natural structures are encased or supported by mineralized tissues. As a result, scaffolds with antimicrobial and osteogenic properties are highly demanded for craniofacial tissue engineering.[32]

Silver ions are well-known for their antibacterial properties and have been applied in a myriad of biomaterials with antibacterial properties for oral and craniofacial-guided tissue regeneration and bone regeneration.[69] Researchers developed a silver ion-modified poly lactic-*co*-glycolic acid/PCL (PLGA/PCL, PP) scaffold, and further coated it with collagen (PP-pDA-Ag-COL) to improve its antimicrobial and osteogenic properties.[32] To be specific, this scaffold was first synthesized by electrospinning PLGA/PCL as the matrix, then reduced with silver nanoparticles (AgNPs) in situ, and further coated with PDA and collagen I. SEM images show that the PP-pDA-Ag-COL scaffold has a highly interconnected porous and

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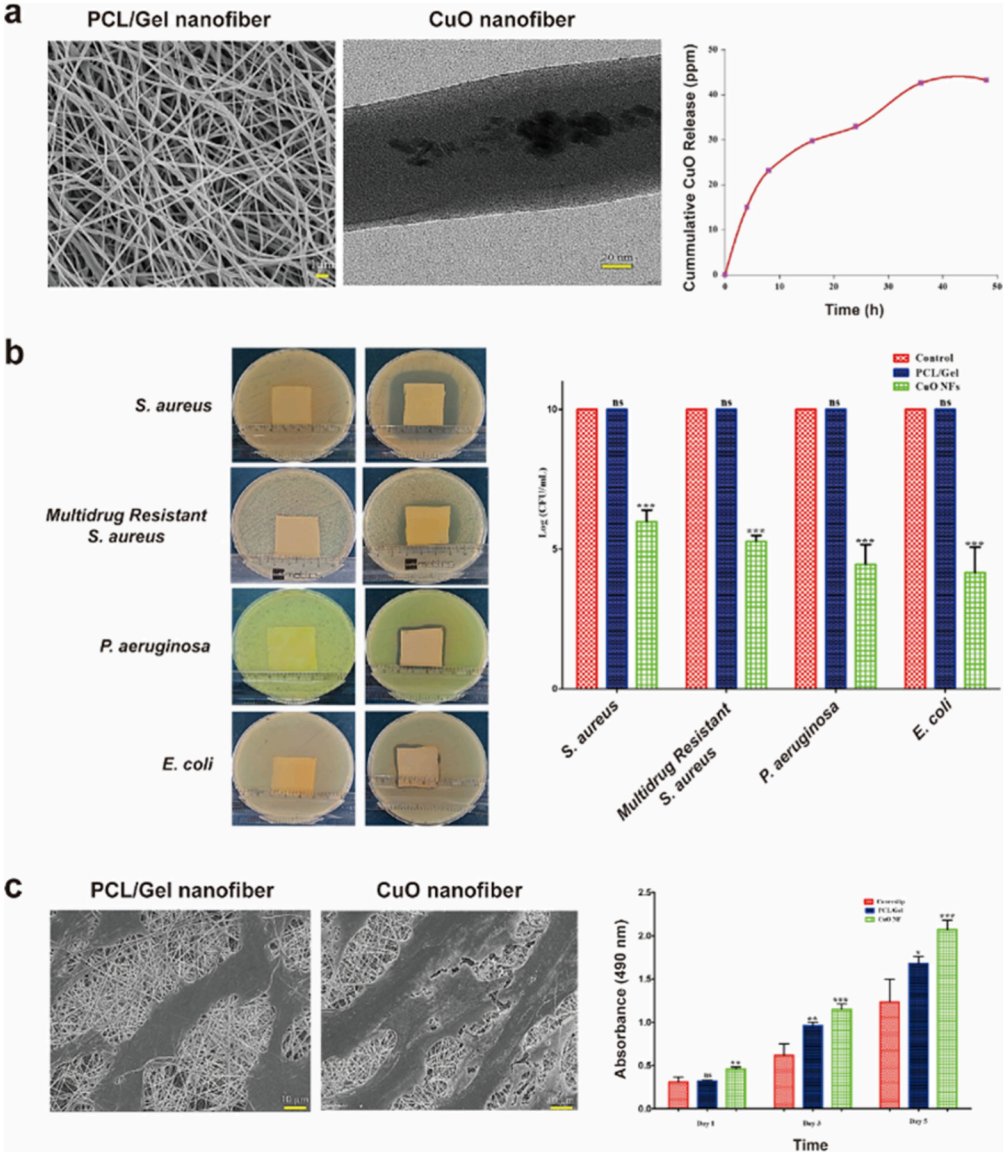

Figure 5. (a) SEM images of the PCL/gel nanofiber and CuO nanofiber. Drug release of CuO nanofiber. (b) Antibacterial profile of PCL/gel and CuO nanofiber. (c) FESEM image of fibroblast cells cocultured with CuO nanofiber. The proliferation of fibroblast incubated with PCL/gel and CuO nanofiber was assessed. Reproduced with permission from 63. Copyright 2021 Elsevier.

randomly oriented filamentous 3D structure with an average diameter of 427 ± 149 nm. The elasticity modulus and fibrous tensile strength of the PP-pDA-Ag-COL scaffold were well maintained after silver and collagen modifications. PP-pDA-Ag and PP-pDA-Ag-COL scaffolds exhibited significantly more robust antibacterial capability than PP-pDA after 24 h incubation with *S. aureus* and *Streptococcus mutans*. PP-pDA-Ag-COL scaffolds showed enhanced MC3T3 cell adhesion with the highest β1 integrin expression. In an alveolar bone defects mouse model, the PP-pDA-Ag-COL scaffold improved alveolar bone regeneration by 31.8% and reduced microbial growth of periodontitis for 6 weeks. Micro CT showed a decreasing distance between alveolar bone ridges and cemento−enamel junction (CE junction) with an implantation with the PP-pDA-Ag-COL scaffold. The PP membrane of PP-pDA-Ag-COL was beneficial to periodontal tissue regeneration, and the efficacy could be further enhanced by Ag/COL modifications. Furthermore, the bone volume of PP-pDA-Ag-COL was significantly enhanced, and the bone mineral density was maintained to a comparable level with control groups.

2.2.4. Magnetic NPs-Incorporated Materials. The coating of magnetic NPs on the surface of polymeric scaffolds can reinforce surface roughness and produce magnetic stimuli. With the increased roughness of scaffolds, bone stem cells are more prone to adhering to the surface and accelerating osteoconductive and osteoinductive effects for bone defect healing. However, the magnetic NPs might hinder adipose-derived mesenchymal stem cells (ADSCs) from developing into adipogenic lineage. Mohammadnejad et al. synthesized superparamagnetic iron oxide NPs (15−30 nm) by coprecipitation and then used a PCL/Col I nanocomposite scaffold to entrap magnetic NPs. After being isolated from rat adipose tissue, the ADSCs were loaded onto PCL/Type I collagen (Col I)/magnetic NPs scaffolds with/without osteogenic media.[70]

To assess the early-stage bone cell differentiation, ALP activity was set as an indicator for osteoinduction capacity of

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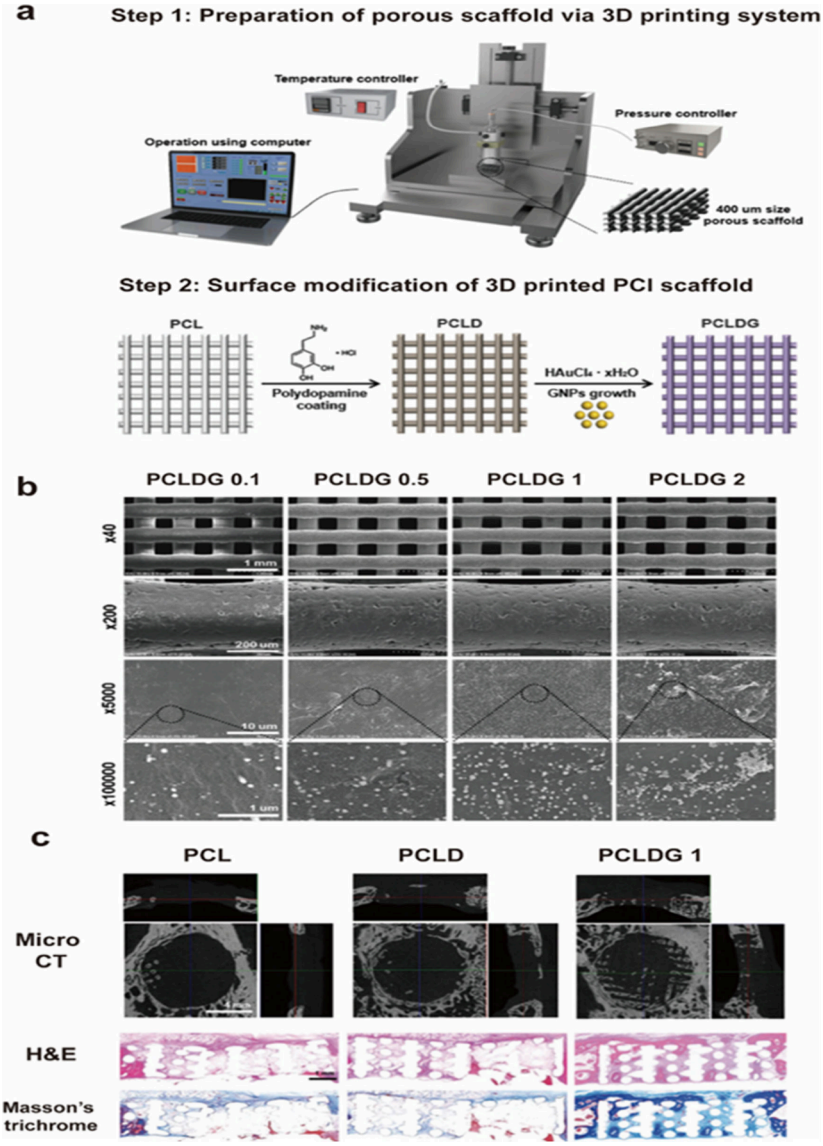

Figure 6. (a) Schematic illustration of PCL−PDA scaffolds for bone tissue regeneration. (b) SEM images of PCLD scaffolds. (c) Micro CT, H&E, and Masson's trichrome staining images of newly formed bone around a PCL−PDA scaffold in a rabbit calvarial defect model. Reproduced with permission from ref 31. Copyright 2018 RCS.

the nanomagnetic scaffold. Researchers found that the ALP activity of magnetic NPs-incorporated scaffolds was more evident after 7 days when compared with the control group or PCL/Col I group. On days 7−21 , the enzyme activities of all groups were increased, and the maximum enzymatic levels were reached by magnetic nanoparticles cultivated with scaffold-seeded cells. Similar to ALP activity increase, calcium deposition and mineralization were observed in PCL/Col I and magnetic NPs-modified PCL/Col I scaffolds incubated with osteogenic cues-free media over days 7−21. With the aid of magnetic NPs, seeded ADSCs were able to migrate to the inner region of polymeric scaffolds and improve calcium deposition to reconstruct bone.

3. CONCLUSIONS AND FUTURE PROSPECTS

In this Review, we discuss the synthesis, polymerization, ionic reduction, biologically active properties, and recent progress of PCL, PDA, and metal-based materials in regenerative medicine. Various forms of materials and corresponding functions are presented in detail. PCL can serve as a porous and safe scaffold to adhere protein and cells, providing a 3D backbone for bone and tissue implant. When collectively functioning with PCL, PDA has an advantage in surface coating and main structure construction. In this way, PCL−PDA scaffolds are widely explored in bone repair, bone regeneration, wound healing, and tissue engineering. In addition to PCL−PDA scaffolds, metal ions bring more strength of antibacterial property and anti-inflammation into regenerative materials.

Despite promising advances in the development of the bioactive scaffolds being achieved, several unmet medical needs and clinic translational challenges are continuously presenting ahead of us. One obstacle is our limited understanding toward the material functioning mechanisms of action and the interactive cellular response. This difficulty requires the decoupling study of material properties, understanding the functions of each part, and their collective interactions. It is even harder when the requirements and

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functions of components are contradicted with each other. One such example can be found in good mechanical properties and stability requirement of the PCL scaffold and an appropriate degradation speed in neobone formation. Additionally, composite materials with various functions are synthesized under different conditions, which may complicate the processing methods and the stability of the scaffold. The exact polymerization mechanism of surface coating PDA is not fully elucidated; deeper study is needed for a wider application of PDA in different scaffolds. The majority of current research on PDA/metal nanoparticle-modified PCL-based scaffold and the corresponding impact on bone tissue regeneration is verified via in vitro and in vivo experiments. Deeper and more incisive research to better understand the underlying mechanisms of the PDA/metal nanoparticle-modified PCL-based scaffold and cell interactions and functions in vivo is beneficial for identifying clinical requirements and clarifying the role of the PDA/metal nanoparticle-modified PCL-based scaffold in the clinical stage. Therefore, it remains to be seen whether PDA/metal nanoparticle-modified PCL-based scaffolds meet the long-term safety and application needs in clinical regenerative medicine.

New directions of regenerative material investigations can be studied in the future: exploit new functionality by bottom-up strategy that combines chemistry, structure, size, and shape of a single component or building block to produce scaffolds with bioactive and responsive capability. Moreover, innovative synthesis and fabrication techniques are desired for bioactive materials at multiscale dimensions in bone tissue engineering. Improve mechanical and biological activity of the PCL scaffold by means of surface modifications and additive materials selection. Biotoxicity of metal ion release from bone and tissue regenerative scaffolds should be carefully considered and evaluated before translational applications. It is our hope to find a new balance of excellent functions, antibacterial properties, low infection rate, low immunogenicity, and biocompatibility in materials for bone and tissue engineering.

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Notes

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