Applications of Polydopamine in Implant Surface Modification

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There is great clinical demand for orthopedic and dental implant surface modification methods to prevent osseointegration failure and improve implant biological functions. Notably, dopamine (DA) can be polymerized to form polydopamine (PDA), which is similar to the adhesive proteins secreted by mussels, to form a stable bond between the bone surface and implants. Therefore, PDA has the potential to be used as an implant surface modification material with good hydrophilicity, roughness, morphology, mechanical strength, biocompatibility, antibacterial activity, cellular adhesion, and osteogenesis. In addition, PDA degradation releases DA into the surrounding microenvironment, which is found to play an important role in regulating DA receptors on both osteoblasts and osteoclasts during the bone remodeling process. Furthermore, the adhesion properties of PDA suggest its use as an intermediate layer in assisting other functional bone remodeling materials, such as nanoparticles, growth factors, peptides, and hydrogels, to form "dual modifications." The purpose of this review is to summarize the recent progress in research on PDA and its derivatives as orthopedic and dental implant surface modification materials and to analyze the multiple functions of PDA.

1. Introduction

Implants have been widely used as a predictable and successful treatment for patients who are edentulous or partially edentulous.[1] Recently, the number of implants used worldwide has been increasing each year.[2] Compared with other dental treatment modalities, tooth implants can be placed without preparing the adjacent teeth;[3] on the other hand, the masticatory function of the patients can be improved.[4] Thus, implants have attracted more attention and become more popular. However, the environment of the oral cavity is complex; implants not only need to be firmly fixed in the jaw in a bacterial and humid environment[5] but also suffer from occlusal force for decades.[6] Studies have found that the early failure rate of implant dentures is ≈1%–2% and that early failure occurs due to inadequate osseointegration and implant detachment a few months after implantation; the late failure rate of implants is ≈5%, and late failure often occurs due to the occurrence of peri-implantitis after implantation.[7] Thus, effective improvements in implant material performance are urgently necessary due to increasing clinical demand. The successful fixation of dental implants in the jaw is greatly dependent on the balance between bone remodeling and new bone formation.[8] An increasing number of studies have shown that implant material surface characteristics play a key role in regulating bone remodeling around implants.[9] Achieving efficient and stable osseointegration through implant surface modification is an important and promising technology. For example, surface modification with biofunctional and bioinspired materials has attracted more attention and has become a new driving force for meeting the requirements of tissue regeneration and implant surface modification.[10–15]

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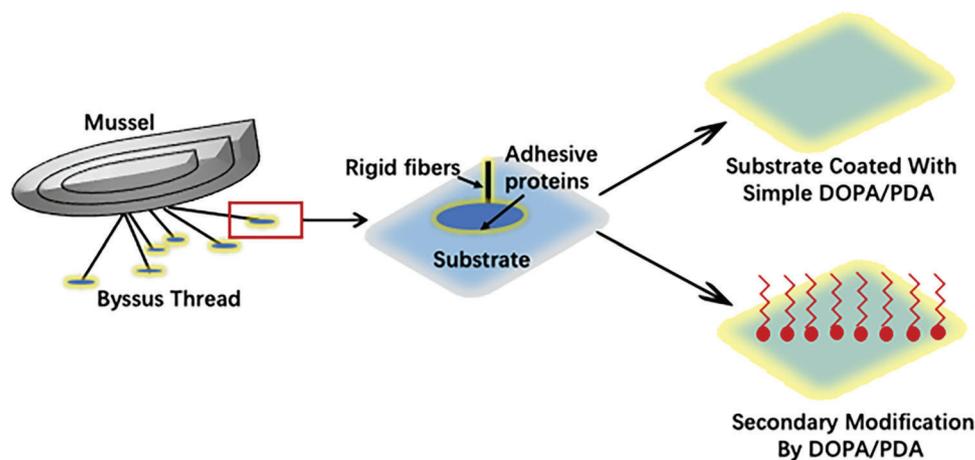Beijing 100081, P. R. China
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2. Polydopamine

Marine mussels can tightly attach to many different surfaces, such as rocks and ships, in seawater via secreted adhesive proteins.[16] The important component of its sticky glue is a group of proteins referred to as mussel adhesive proteins (MAPs), which are posttranslationally modified by the amino acid 3,4-dihydroxyphenol-*L*-alanine (*L*-DOPA).[17] As the precursor of dopamine (DA), *L*-DOPA can transform into DA under the action of decarboxylase.[18] Inspired by the ability of mussels and their adhesion proteins to adhere to wet material surfaces, Lee et al.[19] introduced a simple surface modification method in which substrate materials were immersed in an alkaline (pH

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Figure 1. Properties of mussel adhesive and applications of mussel-inspired substrate-modified materials.

= 8.5) DA solution. This solution was further polymerized to form a polydopamine (PDA) film around the substrate materials. The PDA deposition rate can be accelerated by oxygen. In addition to oxidation methods, different polymerization methods, such as ultraviolet irradiation, promotion and electrochemical methods, are also constantly being used.[20] Previous studies have shown that titanium surfaces modified by either L-DOPA or DA polymerization had enhanced surface wettability and osteoblast proliferation and differentiation promoting abilities with no significant differences.[21] Further research showed that this cell behavior could be regulated by the PDA redox process. Tan et al.[22] showed that the PDA redox process is a switching reaction between oxidized PDA and reduced PDA, involving an interconversion of coupled two-proton ($2H^+$) and two-electron ($2e^-$) processes. The redox-switchable reversible surface potential arises from the potential-tunable redox reaction of the phenolic and quinone groups on PDA. The quinone groups on PDA greatly enhanced osteoblast spreading and proliferation, while the phenolic groups enhanced osteoblast differentiation. Considering the effect of PDA on cell adhesion and differentiation, there are several merits of PDA application in orthopedic and dental implant surface modification. First, the preparation of coatings of DA and its derivatives does not require special equipment, the polymerized coating performance is stable, and polymerization can occur on the surfaces of a variety of substrate materials, such as metals, semiconductors, ceramics and synthetic polymers. Second, most of the clinical bone implant materials, such as titanium, have poor bioactivity. The properties of PDA effectively improve the biological inertness of implants, which is beneficial for osteointegration between the bone surface and implants. Third, the main degradation product of PDA is DA, which has good biocompatibility and has been proven to stimulate osteoblast differentiation and inhibit osteoclast differentiation by activating receptors on the cell membrane. Last but not least, PDA can also provide a platform for secondary implant modification, which exerts a dual effect on enhancing implant success (**Figure 1**). Therefore, in recent years, implant surface modification through this treatment method has been widely used.

3. Properties of Polydopamine

PDA coating provides a general surface modification strategy for orthopedic and dental implants (metallic, inorganic, and organic surfaces) and is expected to improve implant wettability, roughness, morphology, mechanical strength, biocompatibility, antibacterial activity, cellular adhesion and osteogenesis.

3.1. Wettability

Wettability is an important surface property influenced by the surface energy and morphology of the substrate. Compared with hydrophobic surfaces, hydrophilic surfaces exhibit stronger adhesion abilities for cellular attachment and growth.[23] The hydrophilic property of PDA is mainly due to the presence of polar functional groups and various methods of codeposition, which could also be used to address the insufficient hydrophilicity of PDA.[24] When a titanium surface was modified by PDA coating, its water contact angle (WCA) decreased from the original value of 68.6° to 48.4°, indicating that its hydrophilicity was improved.[25] In 2007, Lee reported that the typical WCA of PDA coatings is between 40° and 60°.[19] Since PDA coatings are hydrophilic, the surface wettability of a substrate is well-hydrophilic after PDA coating, whether the substrate is hydrophilic or hydrophobic.[26] Wettability can greatly influence cell behavior; after PDA coating, it was found that surface wettability and chemistry had greater effects on osteoblastic differentiation than surface roughness.[27]

3.2. Roughness and Morphology

Xi et al.[28] reported that the membranes of porous polymers became smoother after poly(3,4-dihydroxyphenylalanine) coating. Conversely, poly(L-lactide-co-caprolactone)film surfaces transitioned from smooth to rough. After PDA modification, the surface roughness of the materials increased, and the surface morphologies also changed. Kim et al. reported that after L-DOPA coating, the roughness of a titanium disc increased, as

observed by atomic force microscopy (AFM).[29] The increased surface roughness could be explained by the polymerized DA being deposited on the surface or the unpolymerized DA particles adhering to the surface of the material through $\pi-\pi$ bonds or van der Waals forces.[30] Although the PDA/L-DOPA coating did not change the bulk surface properties of the substrate,[19] this coating often changed the substrate color from the color of the bulk substrate to dark brown.[31] Wang et al.[31] developed a new wound dressing by coating PDA on an Antheraea pernyi silk fibroin (AF) film. After DA self-polymerization for 8 or 16 h on the AF film, a PDA-AF (PAF) film was produced. The appearance of the PAF film changed from its original transparency to a brown color. AFM studies also indicated that the PDA nanoparticles were aggregated on the substrate, which led to a rougher surface than that of the control group. In addition, the longer coating time increased the PDA nanoparticle size and the film roughness.

3.3. Mechanical Strength

An ideal bone scaffold is expected to have a mechanical strength comparable to that of natural cortical bone.[32] Recently, technological improvements have enabled the development of electrospun collagen and hydroxyapatite nanocomposite scaffolds for bone regeneration, but the lack of mechanical strength remains a major issue. Lee et al.[33] developed a hydroxyapatite collagen calcium silicate-polydopamine (HCCS-PDA) biomaterial to repair critical size bone defects; they found that the flexural strength of HCCS-PDA was higher than that of HCCS after PDA modification. Ghorbani et al.[28] found that the tensile strength and Young's modulus of polyvinyl alcohol /polyurethane -polyaniline matrices with PDA were increased, which is indicative of the potential of application processes in bone tissue engineering.

3.4. Biocompatibility

Biocompatibility is a crucial characteristic of materials, especially biomaterials. PDA, which is a common natural substance for humans and other life forms, has an excellent biocompatibility which makes it a promising candidate for biomedical applications. According to reports by Ku et al., PDA is an inert material that is nontoxic to many different types of cells (i.e., osteoblasts, fibroblasts, neurons and endothelial cells) in vitro.[34] This is consistent with the results reported by Li et al., which showed that PDA-modified bioceramic scaffolds enhanced the adhesion and proliferation of adipose-derived mesenchymal stem cells (MSCs).[35] Furthermore, Hong et al.[36] found that a PDA coating reduced the expression of inflammatory response factors on poly-L-lactic acid surfaces in vivo. Several other experiments similarly confirmed the excellent biocompatibility of PDA. For example, Tavakoli et al. found that PDA@ZnO nanoparticles exhibited nontoxic effects on human cells and significantly promoted cell survival compared to ZnO nanoparticles without modification.[37] Another long-term in vivo toxicology study of dopamine-melanin colloidal nanospheres (Dpa-melanin CNSs) showed that there were no significant changes in behavior or in the results of routine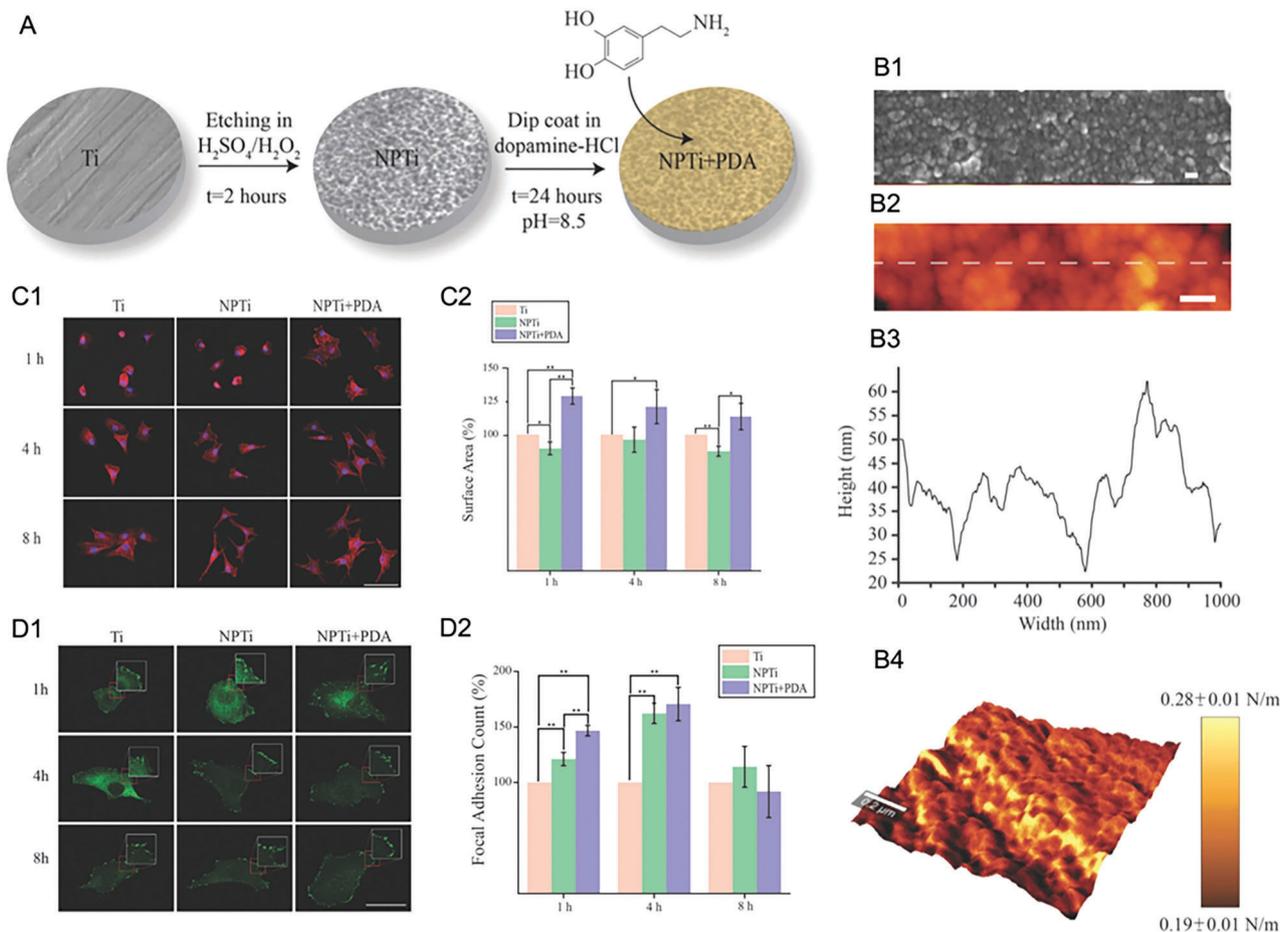 blood tests or other organ histopathological examinations after the intravenous injection of a single dose of Dpa-melanin CNSs.[38]

3.5. Antibacterial Properties

Bacterial infections are believed to be the main cause of implanted device failure.[39] Many antimicrobial materials with safe and controllable antibacterial properties have been developed. PDA exhibits potential antibacterial effects due to its photothermal conversion and hydrogen peroxide formation abilities.[40,41] In addition, PDA has an abundance of catechols and amine structures that could be applied in the loading of different antibacterial composite materials.[42] PDA also exhibits a contact-active antibacterial effect due to its chelation of ions or proteins and an electrostatic effect by destroying the bacterial cell membrane.[43] Su et al. found that roughened PDA coatings on different substrates, without any other antibacterial agents, exhibited markedly enhanced antibacterial activities against gram-positive *Staphylococcus aureus* (*S. aureus*) and gram-negative *Escherichia coli* (*E. coli*) and Pseudomonas aeruginosa.[44] In addition, many studies have investigated whether PDA has a high photothermal conversion capacity due to the self-polymerization of DA into DOPA-quinone and DOPA-indole.[45] Fan et al.[46] demonstrated that MagI-polyethylene glycol (PEG)@PDA NPs could effectively kill *E. coli* at a low temperature of ≈45 °C when exposed to near-infraredradiation, while native PDA NPs showed no bacterial killing ability. On the other hand, PDA is regarded as redox-active and can transfer electrons from endogenous extracellular regions toward O_2-rich regions to sustain reactive oxygen species (ROS) production.[47] For example, the intracellular ROS and antioxidative capability measurement results of Gao et al. showed that a titanium alloy modified with PDA and Ag nanoparticles (TiO_2-PDA-Ag) exhibited satisfactory antibiofilm activities.[48] Choi et al.[49] studied the antibacterial characteristics of PDA- and silver-coated Ti against S. mutans and P. gingivalis; they also identified that the progression of S. mutans and P. gingivalis was retarded by coating PDA and silver on Ti. Although the antibacterial effect of PDA has been widely explored, there are still some challenges (i.e., the antibacterial ability of PDA is relatively mild, which makes it difficult for PDA-incorporated materials to meet more stringent antibacterial requirements) that need to be overcome.[47]

3.6. Cellular Adhesion Properties

The adhesive property of PDA is mainly due to its catechol group, which plays a vital role in adhesion. Additionally, the binding interactions between PDA and substrates can be categorized into covalent and noncovalent binding. Covalent binding occurs on surfaces containing amine and/or thiol groups via Michael addition and/or Schiff base reactions. On the other hand, noncovalent binding between PDA and substrates involves $\pi-\pi$ stacking and metal chelation or coordination.[50] For example, Li et al.[51] showed that PDA coating can significantly promote the adhesion of MC3T3-E1 cells on 3D-printed porous Ti-6Al-4 V scaffolds and effectively promote early osteogenesis. In another study, a PDA film was deposited on nanoporous titanium. As shown in

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Figure 2. PDA enhanced MG-63 human osteoblastic cells adhesion and proliferation. A) schematic diagram of PDA coating on implants. B1) SEM and B2) AFM images of the PDA coating, (B3) AFM line scan and B4) DPFM-AFM image showing the stiffness and topography overlay for the PDA coating. C1) Fluorescence images and C2) area (expressed as percentage increase/decrease in respect to bare titanium) of MG-63 osteoblastic cells adhering on Ti, NPTi, and NPTi + PDA surfaces at 1, 4, and 8 h. D1) Fluorescence images and D2) Number of focal adhesion complexes of focal adhesion complexes at short intervals. Reproduced under the terms of the Creative Commons Attribution License (CC-BY).[15] Copyright 2016, Royal Society of Chemistry.

Figure 2, compared to the smooth and nanoporous titanium, the PDA coated titanium induced the enhanced adhesion and proliferation of MG63 cells by regulating focal adhesions and RhoA, which is an important protein involved in cytoskeleton contractility.[52] Similarly, Ma et al. found that a sandblasted and acid-etched (SLA) titanium surface modified by a simple L-DOPA coating could promote the early cell adhesion, proliferation and differentiation of human bone marrow mesenchymal stem cells (hBMSCs); in the experiment, microarray analysis revealed that genes participating in focal adhesion were upregulated on the L-DOPA-coated surfaces.[53]
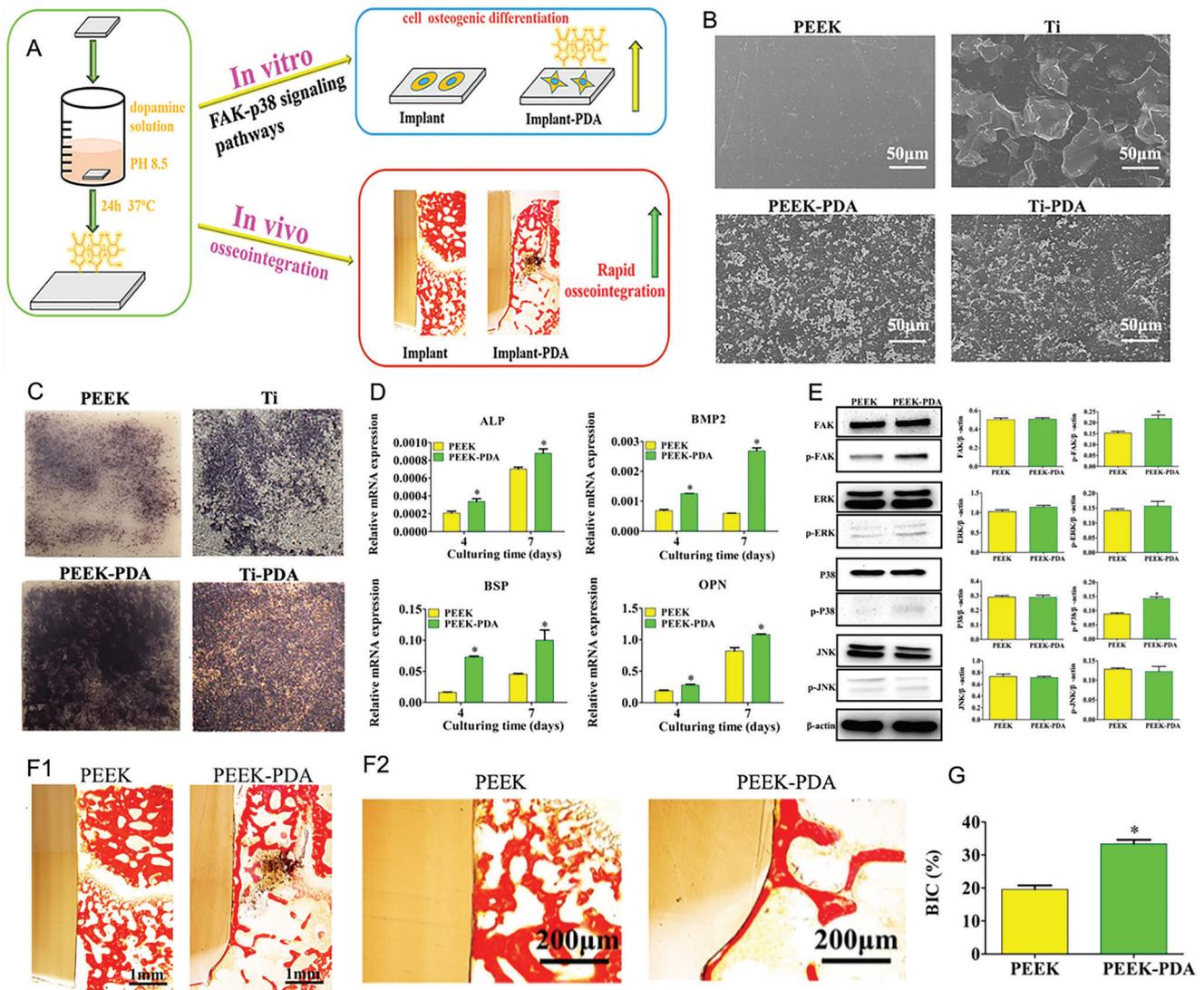
In addition to titanium substrates, other materials modified with PDA also demonstrated favorable cellular attachment and proliferation. Wang et al.[54] found that different substrate materials (Ti, polyetheretherketone (PEEK), and hydroxyapatite (HA)) modified by PDA could promote BMSC adhesion, proliferation and differentiation through focal adhesion kinase (FAK) and p38 signaling pathways; the expression of FAK and osteogenic genes was significantly increased in this study. Rim et al.[55] functionalized poly(L-lactide) (PLLA) fibers coated with polydopamine (PD-PLLA), which promoted the attachment, proliferation and

osteogenic differentiation of hMSCs by upregulating osteogenic gene expression and alkaline phosphatase (ALP) activity. In addition, Xu et al. showed that akermanite (AKT) bioceramics modified with PDA coatings could enhance the attachment, proliferation, and alkaline phosphate activity of MC3T3 cells on the AKT bioceramics.[56] Pacelli et al.[57] applied PDA as a bioactive layer that could improve the surface and biological properties of GG-based hydrogels. Human adipose-derived stem cells (hASCs) on the PDA-coated GG-hydrogels showed increased proliferation, adhesion and gene expression of focal adhesion and cytoskeletal genes.

In conclusion, these studies provide deeper insight into the in vitro cellular response to PDA by focusing on cell–PDA interactions, which could reaffirm the potential of this polymer as a functional modification material for bone tissue engineering applications.

3.7. Osteogenesis Properties

The osteogenic properties of PDA could be enhanced by increasing osteoblast adhesion with its functional groups. Studies have

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Figure 3. PDA enhanced osteogenic differentiation and osseointegration for implants. A) schematic diagram of PDA coating on implants. B) SEM images showed PEEK and Ti coating with PDA. C) The ALP staining images of BMSCs seeded on the different specimens at day 7. D) Real-time PCR analysis of osteogenic differentiation genes of BMSCs after culturing for 4 and 7 days on PEEK and PEEK-PDA samples. E) Western blot experiments showed the expression of FAK, p-FAK, and MAPK signaling pathways proteins of BMSCs cultured for 48 h on PEEK and PEEK-PDA samples. F1) Histological section images and F2) high magnification of the in vivo osseointegration of PEEK and PEEK-PDA. G) Histomorphometry analysis of BIC percentage of PEEK and PEEK-PDA implants. Reproduced with permission.[54] Copyright 2019, American Chemical Society.

also reported that PDA coatings have good effects on promoting bone formation in vivo. **Figure 3** showed Wang et al.[54] applied PEEK implants modified with PDA coatings in a rat femoral condyle model. After 4 weeks, histological observations indicated that this simple PDA coating could promote the formation of new bone around the implant and increase the rate of implant osseointegration (bone–implant contact, BIC). In another study, titanium implants modified with L-DOPA, zoledronic acid (ZA) and L-DOPA+ZA were applied in an osteoporotic rat femoral condyle model. The results showed that both the L-DOPA and L-DOPA+ZA treatment groups could promote the formation of new bone around the implants and the rate of implant osseointegration; in addition, the results of an mRNA transcriptome chip analysis of the bone tissue around the implants showed that the

coating improved osseointegration. The improved osseointegration mechanism may be related to the inhibition of the expression of key factors in the osteoclast differentiation signaling pathway. Although the effect of the L-DOPA coating was less significant than that of the L-DOPA+ZA coating of the positive control group, this simple coating preparation method was found to be safe and convenient for promoting implant osseointegration in patients with osteoporosis.[58]

Recently, research has shown that PDA can also be used to modulate the immune microenvironment to induce bone regeneration by affecting the surface potential of implants. Li et al.[59] applied PDA on a Ti surface to decrease its surface potential. The resulting lower negative surface potential favored a higher electronic repulsion between the surface and bone marrow-derived

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Table 1. DA receptors on bone remodeling-related cells.

Target cell	Receptors	Main function	Reference
Osteoblast-like cells	D1R–D5R	DA promotes cell differentiation via D1R activation	[61, 68–70]
Osteoclast-like cells	D1R–D5R	DA inhibits cell differentiation via D2R activation	[69, 70–74]
Endothelial cells	D1R, D2R, D4R	DA inhibits cell secretion of VEGF via D2R activation	[75]
Monocytes/Macrophages	D1R, D2R	DA inhibits cell inflammation via D1R agonist	[76, 77]
Dendritic cells	D1R, D2R, D5R	DA inhibits cell inflammation via D2R antagonist	[78, 79]

monocytes (BMDMs). This electronic repulsion induced the expression of integrin $\beta 1$ and integrin $\beta 3$ in the cell membrane and further upregulated the expression of adhesion-related genes. They also found that PDA surface modification tended to polarize BMDMs toward an anti-inflammatory phenotype (M2) by inhibiting the PI3K-Akt-mTOR signaling axis. This phenotype further induced the osteogenic differentiation of osteoblasts.
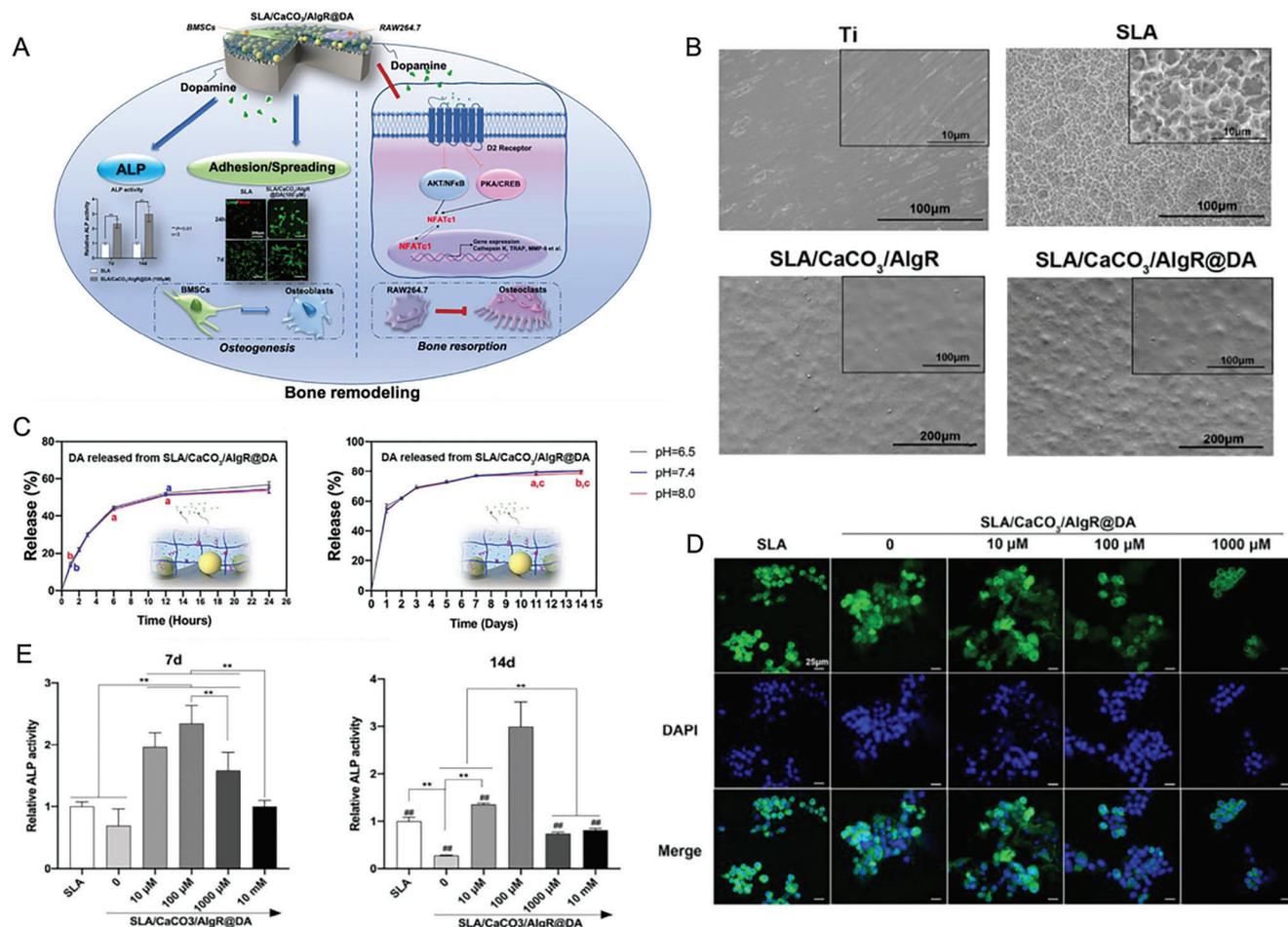
4. DA Release from PDA in Regulating Bone Remodeling

Compared to what is known about PDA formation kinetics and mechanisms, little is known about PDA degradation.[60] Several studies have previously demonstrated that free DA monomers can be detected in the space surrounding PDA.[61] To attain better physical and chemical properties, most researchers have used 150–500 µM DA to form PDA; therefore, a micromolar amount of DA can be expected to be released into the microenvironment around a PDA insertion site.[61–65] Caron et al. studied a DA transporter (DAT) knockdown mouse model with which the relationship between DA and bone remodeling was revealed.[66,67] The DAT is an important determinant of DA signaling activity as it is responsible for the rapid uptake of released DA into presynaptic terminals, which effectively removes extracellular DA and terminates its signaling. DAT disruption results in defects in bone structure and integrity, suggesting that DA signal transduction is involved in the regulation of bone mass.

DA, a neurotransmitter released by the central nervous system, has also been reported to regulate bone homeostasis and bone remodeling at micromolar or even lower concentrations, which might contribute to the effects of PDA.[74] Considering that both bone marrow and the peripheral sympathetic nervous system can store DA, bone cells expressing DA receptors for this neurotransmitter are thought to be involved in the underlying mechanism of these effects.[80,70] Currently, five subtypes of DA receptors (D1R, D2R, D3R, D4R, and D5R, encoded in humans by the DRD1, DRD2, DRD3, DRD4, and DRD5 genes, respectively) are known to mediate essentially all of the physiological functions of DA.[81,82] As members of the G protein-coupled receptor (GPCR) superfamily, DA receptors have a canonical seven-transmembrane structure and can signal through both G protein-dependent and G protein-independent mechanisms. Based on their coupling to either $G_{\alpha s \text{ or olf}}$ proteins or $G_{\alpha i/o}$ proteins to stimulate or inhibit the production of the second messenger (cAMP), respectively, DA receptors are divided into D1 receptors (D1R and D5R) and D2 receptors (D2R, D3R, and D4R).[83,84] In addition to DA neurons in bone marrow, DA receptors in osteoblast-like cells, osteoclast-like cells, immune cells, and vascular endothe-

lial cells have been previously detected (**Table 1**). These cells were previously reported to be involved in bone remodeling.

Compared to that between other cells in bone tissue, the balance between osteoblast-like cells and osteoclast-like cells is essential for the regulation of bone remodeling.[85,86] Regarding osteoblast-like cells, previous studies demonstrated that D1R–D5R were expressed on MC3T3-E1, an osteoblast precursor cell, and BMSCs.[80,87] In addition, it has been reported that activation of DA receptors by DA could increase the proliferation and adhesion of BMSCs via the integrin-focal adhesion kinase (Itg-FAK) signaling pathway.[61] Wang et al.[68] showed that DA enhanced BMSCs via the activation of D1R but not D2R and promoted the phosphorylation of ERK1/2. Zhu et al. further confirmed that the activation of D1R reduced dexamethasone (Dex)-induced bone loss by activating the ERK1/2 pathway in vivo.[88] For osteoclast-like cells, Hanami et al. reported that the activation of D2R, not D1R, inhibited the differentiation of RAW264.7 cells, the osteoclast precursor.[70] Wang et al. further confirmed that the activation of D2R decreased the phosphorylation of CREB and downregulated the expression of NFATc1, leading to the inhibition of RAW264.7 differentiation.[72,73] As shown in **Figure 4**, DA release from the implants has dual effect on both osteoblast and osteoclast differentiation. In addition to D1R activation, a G protein-independent mechanism was found to be involved in regulating osteoclast-like cell differentiation. Liu et al. demonstrated that the activation of D2R eliminated mammary tumor cell-induced osteoclast differentiation.[71] In vivo results showed that DA could alleviate the osteolytic lesions of mouse calvaria induced by titanium particles, and this protective effect was mainly mediated by the inhibition of osteoclastogenesis and inflammatory responses through the D2R pathway.[74] The above results showed that DA might influence both osteoblast-like cells and osteoclast-like cells. Additionally, DA has been reported to regulate angiogenesis, which is involved in vascularized bone regeneration. Vascular endothelial growth factor (VEGF), a potent cytokine expressed in several tissues, including bone, has critical roles in vasculogenesis. DA acts through D2R to induce the endocytosis of VEGF receptor 2, which is critical for promoting angiogenesis, thereby preventing VPF/VEGF binding, receptor phosphorylation, and subsequent signaling steps and further protecting against malignant tumors by antiangiogenic therapy.[75] Similarly, cabergoline, a specific D2R agonist, inhibited VEGF secretion in a dose-dependent manner to prevent ovarian hyperstimulation syndrome, and this effect could be eliminated by a D2 receptor antagonist.[89] In addition, the concept of osteoimmunology has been stressed in the regulation of bone remodeling. For example, osteoimmune interactions between immune cells and bone cells affect the functions of both cells.[90] DA can be con-

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Figure 4. Controlled release of dopamine coatings on titanium bidirectionally regulate osteoclastic and osteogenic response behaviors. A) Schematic diagram of the dual effect of DA releasing in osteoclastic-inhibition and osteogenic-stimulation. B) SEM images of DA coating on implants. C) DA release profile from implants at different pH value by HPLC. D) In situ immunofluorescence staining for NFATc1 on day 7. E) ALP activity of hBMSCs at implants surface with different DA concentration. Reproduced with permission.[73] Copyright 2021, Elsevier.

sidered as a connection between the nervous system and the immune system, but more evidence is urgently needed to elucidate the relationship between DA and osteoimmunity.[91]

The selection of DA receptors might influence the regulatory effect of DA on different cell functions. As DA is a nonselective receptor activator, the latest research has demonstrated the binding structure between DA and D1R and D2R. Compared to that of D2R, the DA-binding pocket of D1R was narrower. During binding, TM6 near the extracellular end of D1R moves 5.5 angstroms inward toward the transmembrane center, which may be the reason for the difference in the affinities of DA for the two receptors.[92] These results indicated that the DA concentration regulated receptor activation selection. In addition, the expression level of DA receptors affected receptor sensitivity to DA. Liu et al. reported that the ubiquity of KBTB6/KBTB7 promoted D2R degradation and decreased receptor activation sensitivity.[93] It was reported in similar studies that KLHL12 regulated D4R degradation.[94] Researchers further analyzed the structure of the KLHL family protein and suggested that the DA receptor desensitization mechanism was related to the KLHL family protein binding to both receptors and down-

stream β-arrestins, which led to receptor internalization and cascade signaling pathway elimination.[95] Additionally, DA receptor heteromerization is another possible factor affecting receptor activation. DA receptors are capable of forming homodimers, heterodimers, and higher-order oligomeric complexes, resulting in a change in the recognition, signaling, and pharmacology of individual protomers.[96] Previously, it was reported that a DA receptor could form heteromers with both other DA receptors and several GPCRs, including the N-methyl-D-aspartic acid receptor and adenosine receptor.[81,97,98] Interestingly, a recent study showed that after D1R-D2R heterodimer formation, DA selectively activated one receptor by inhibiting the other in a dose-dependent manner. A nanomolar concentration of DA inhibited D1R activation, and a micromolar concentration of DA inhibited D2R activation, which seems to reveal the relationship between DA concentration and DA receptor heteromerization that regulates the receptor activation selectivity.[99] Currently, the role of DA-selectively activated receptors in the regulation of bone remodeling remains unclear. An important limitation is that traditional technical methods cannot detect DA receptor activation at high spatiotemporal resolution. With the

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development of genetically encoded probes for monitoring the activation of DA receptors, the effect of DA monomers could be better elucidated in further research.[99–101] Thus, it can be inferred that various cells and factors are involved in the round-trip regulatory mechanism between biological signaling pathways and bone development.[102] As a neurotransmitter, DA can affect cellular functions via different receptors. With a new tool for detecting receptor activation at high spatiotemporal resolution, the regulation of bone mass by the DA network could be more thoroughly investigated in future research, which would further enhance the effects and safety of PDA application in bone tissue engineering.

5. PDA Applications in Implant Surface Modification

Because of the properties of PDA and its DA-releasing ability, PDA surface modification has been successfully applied. Considering that the functional groups on PDA, such as phenol and amino groups, can be modified to graft other functional bone remodeling materials onto implant surfaces, PDA has also been used as an intermediate layer to achieve secondary modification. Currently, implant surface modification mainly consists of topographical modification or is used in combination with bioactive molecules.[103] Previous research has shown that PDA can change implant topology by bonding nanoparticles and hydrogels. In addition, PDA can also be directly coated with growth factors or peptides to enhance bone formation around implants.

5.1. PDA-Assisted Nanoparticle Modification

Nanoparticle-decorated substrates can induce cell behavior and tissue growth by forming micro/nanostructures on material surfaces.[104] In the study of Li et al., a PDA-assisted nanosilver/calcium phosphate (CaP) composite coating was prepared on the surfaces of TiO_2 nanotubes (TNTs) and effectively promoted the early adhesion, proliferation and osteogenic differentiation of osteoblast-like MG63 cells.[105] Similarly, Yu et al.[106] found that hydroxyapatite-functionalized nanoparticles of PDA (HA/nPDAs) on implant surfaces could effectively reduce the content of ROS in MC3T3-E1 cells and simultaneously promote the early adhesion, proliferation and differentiation of the cells. The thickness, composition and morphology of the HA/nPDA coating were controlled by adjusting the preparation conditions, such as the mineralization time and reactant concentration. The prepared coating could eliminate ROS and promote osteogenesis in an environment with normal and high ROS levels, which is expected to improve implant osseointegration, especially under the high-ROS conditions associated with diseases. Jia et al.[107] presented a strategy for applying hierarchical TiO_2/Ag coatings on Ti substrates by harnessing the adhesion and reactivity of PDA, and these coatings could protect the substrate from corrosion and enhance antibacterial properties and osteoblastic differentiation. Simple and safe functionalization strategies with PDA coatings could provide bedside solutions to the current challenges of orthopedic implants.

5.2. PDA-Assisted Hydrogel Modification

PDA modification is regarded as a promising strategy because it involves the use of in situ polymerization to create adhesive bioactive interfaces. The soft tissue integration of medical implants is one of the important factors in the prevention of bacterial infection and implantation failure. Dinh et al.[108] found that a gelatin hydrogel combined with PDA could well adhere to three model implant materials: aluminum, polymethyl methacrylate (PMMA) and titanium substrate. This enzyme-crosslinked gelatin hydrogel exhibited no cytotoxicity toward human dermal fibroblasts and enhanced cell adhesion and proliferation. This result indicates that the combination of PDA coating and gelatin hydrogel could be used to enhance the soft tissue bonding of medical implants.

5.3. PDA-Assisted Growth Factor Modification

To increase the biological activity of Ti implants, biological methods, including those involving growth factors, were designed to develop bioactive agents that can be released in a controlled manner from Ti surfaces. The cooperation of multiple growth factors not only increases the bioactivity of Ti surfaces but also enhances their respective functions.[109] Wu et al.[110] found that using PDA to load dual growth factors of BMP2 and bFGF to modify a titanium surface effectively promoted the proliferation, migration and differentiation of osteoblast-like cells MC3T3-E1 and vascular endothelial cells, suggesting that modification can play a role in the process of osteogenic differentiation and vascularization on orthopedic implant surfaces. Furthermore, a PDA coating was used to immobilize VEGF on a Ti-based biosubstitute without influencing the activity of VEGF.[111] Through the immobilization of BMP or other growth factors by PDA-assisted surface modification, the surface properties of substrates can be greatly improved, and material mineralization can also be enhanced.[60,112] Moreover, chitosan (CS) was anchored onto a porous poly(ϵ-caprolactone) surface via PDA, and the in vivo results showed that CS immobilization onto the scaffold surface could promote cranial bone formation.[113] Similarly, hASCs were seeded onto PDA-loaded BMP-2-modified PLGA scaffold materials that were implanted into mouse skull defects, which effectively promoted new bone formation at the bone defect sites.[114]

5.4. PDA-Assisted Peptide Modification

A short peptide sequence (Arg-Gly-Asp, RGD) composed of glycine, arginine and aspartic acid is a ubiquitous adhesive motif that is currently widely used for adhesion promotion. This RGD sequence plays an important role in bone formation and is present in several extracellular matrix (ECM) molecules, such as collagen, fibronectin, and osteonectin; the presence of this RGD peptide on the surfaces of biological materials can not only induce osteoblast adhesion and migration but also promote osteogenic gene expression.[115,116] In a previous study, Chien et al.[117] developed a "one-pot" deposition method based on DA polymerization. RGD polymers, hydroxyapatite nanoparticles (HAp), and bone morphogenic protein-2 (BMP-2) were

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Table 2. Effects of PDA modification on the biological functions of cells in vitro.

Substrate	Surface composition	Cell type	Adhesion	Proliferation	Differentiation	Antibacterial activity	Ref.
Ti-6Al-4V	pDOP/pTAN	RAW264.3		×	×		[126]
TNT	PDA+Ag+CaP	MG63	√	√	√	√	[105]
Ti	HA+nPDA	MC3T3-E1	√	√	√		[106]
Ti	MAO/Ag	MG63	√	√	√	√	[107]
Ti	PDA+bFGF+BMP-2	MC3T3-E1, HUVECs		√	√		[110]
Ti	PDOP-VEGF	HDMECs hMSCs	√	√	√		[111]
Ti-6Al-4V	PDA+RGD+nHAp+BMP2	hBMSCs, 3A6	√		√		[117]
PAP	DA+RGD+P24+HAp	rBMSCs	√	√	√		[118]
Ti	MAO+PDA+LL-37+POPC	rMSCs			√	√	[119]
Ti/Al/PMMA	PDA+gelatin hydrogel	hDFs	√	√			[108]
TNs	PDA+SiO$_2$	MC3T3-E1	√		√		[121]
3D rGO/PPY	PDA+Si	MC3T3-E1	√	√	√		[122]
Ti	PDA+Zn	MC3T3-E1	√			√	[123]
Ti	PDA+HA+LF	OB		√	√	√	[124]

PDA or pDOP: polydopamine; HDMECs: human dermal microvascular endothelial cells; PAP: poly(lactide-co-glycolide) (PLGA)-[Asp-PEG]n-scaffolds; RGD: (K)16GRGDSPC.

mixed in an alkaline DA solution, and then a titanium base material was immersed in the mixture. The results showed that RGD could enhance the adhesion of hBMSCs, and the incorporation of HAp and BMP2 promoted the osteogenic differentiation of hBMSCs, indicating that surface modification has great potential for promoting the osseointegration of orthopedic and dental implants. In addition, Pan et al.[118] used PDA modification to incorporate three types of biomolecules, that is, cell adhesion-promoting (K)16GRGDSPC peptides, HAps and osteoinductive BMP-2-derived P24 peptides, onto poly(lactide-co-glycolide) (PLGA)-[Asp-PEG]n scaffolds. The results demonstrated that the modification was noncytotoxic and significantly promoted cell adhesion, proliferation, osteodifferentiation, and mineralization in vitro. In addition, a PDA-assisted antibacterial peptide coating was designed to improve the properties of titanium. He et al.[119] treated native Ti substrates with microarc oxidation (MAO), followed by the application of a multilayer consisting of the cationic antimicrobial peptide LL-37, phospholipid (POPC) and PDA coating. They found that the antibacterial activities of the Ti surface against both *S. aureus* and *E. coli* bacteria were enhanced without influencing the cytocompatibility of the material toward MSCs and osteoblasts. These findings demonstrate a strategy for the development of antibacterial Ti-based implants. In addition, Lee et al.[60] isolated a short peptide of 15 amino acids derived from BMP-7 and named it a bone-forming peptide (bone-forming peptide 1, BFP1) and used PDA to adhere this peptide to PLGA. The scaffold was used for implantation in a critical-sized calvarial defect mouse model. Both the PDA treatment group and the BFP1-PDA treatment group showed improved new bone formation around the bone defect site. In another study, PLLA nanofibers with immobilized osteogenic growth peptide (OGP) were prepared by a PDA layer. The results from a critical skull bone defect model showed that PDA-assisted OGP treatment could significantly promote bone regeneration in bone defects.[120]

5.5. Other PDA-Assisted Modifications

PDA is also used to integrate other metallic materials or inorganic nonmetallic materials for bone growth or antibacterial modification. Silicon is an important trace element that regulates bone metabolism. Qiao et al.[121] used PDA-assisted modification to immobilize SiO$_2$ onto titanium dioxide nanotubes. In vitro experimental results showed that this modification could effectively promote cell attachment and ALP activity compared to those of the untreated group. Similarly, Wang et al.[122] carried out the PDA-assisted immobilization of strontium (Sr) onto a 3D reduced graphene oxide/polypyrrole (3D rGO/PPY) composite scaffold, and this 3D rGO/PPY/PDA/Sr scaffold could significantly promote the early adhesion, proliferation and osteogenic differentiation of MC3T3-E1 cells. On the other hand, Zn has attracted increasing attention because it can interfere with multiple bacteria-related activities. An ideal implant coating is expected to both promote osseointegration and inhibit microbial infection. In a recent study, Zn ions were immobilized on a Ti substrate via a PDA layer to prepare Ti-PDA-Zn coatings, which demonstrated good biocompatibility and antibacterial activities against both *S. aureus* and *E. coli*.[123] In addition, Shen et al.[124] attached a hydroxyapatite and lactoferrin multilayer structure (PDA-HA/LF) on a titanium matrix surface by PDA-assisted modification and found that the osteogenic and antibacterial properties of the substrate material surface were well balanced. They found that the above coating could inhibit the activity of bacteria (*S. aureus* and *E. coli*) and promote osteoblast proliferation and differentiation. In addition, hydroxyapatite/polyamide 66 (HA/P66) has been used clinically due to its good biocompatibility and biological activity, but studies have found that the osseointegration of HA/P66 implants often takes a long time. Therefore, to increase the osseointegration rate, researchers have developed a PDA-assisted biomimetic modification process for coating the HA/P66 substrate and found that the

Table 3. Summary of PDA application on different substances to promote bone formation and osseointegration in vivo.

Substrate	Surface composition	Animal model	Major conclusions	Ref.
Porous poly(ϵ-caprolactone) surface (PLC)	PDA+CS	Rat calvarial defect	Promoted cranial bone regeneration	[113]
PLGA	PDA+BMP2+ hADSCs	Mouse calvarial defect	Promoted new bone formation at the bone defect site	[114]
PLGA	PDA+ BFP1	Mouse calvarial defect	Significant improvements in the modified group	[60]
PLLA	PDA+OGP	Rat calvarial defect	Significantly promoted bone regeneration at the bone defect sites	[120]
HA/P66	PDA+HA	New Zealand white rabbit femoral condyles	More new bone formation around an HA/P66 scaffold that was coated with HA through PDA-assisted modification	[125]

CS: chitosan; BMP-2: bone morphogenetic protein-2; PLGA: poly(lactic-*co*-glycolic acid); PLLA: poly(L-lactic acid); OGP: osteogenic growth peptide; HA/P66: hydroxyapatite/polyamide 66.

resulting coating was very stable. The HA/P66 scaffold material modified with PDA and the HA coating was used for implantation in a rabbit femoral condyle model. After 8 weeks, micro-computed tomography (micro-CT) and hematoxylin-eosin (HE) staining showed that more new bone was formed on the material surface.[125]

Overall, the application of PDA in assisting other functional bone remodeling materials can also improve the biological properties of implant substrate materials. Here, we summarized the in vitro applications in **Table 2** and in vivo applications in **Table 3** as reviewed above

6. Conclusions and Perspectives

Here, we reviewed the application of biomaterials modified by PDA coatings in orthopedic and dental implant restoration. It was demonstrated that these coating are not only easy to prepare and obtain but also exhibit good biological effects and bone-promoting functions. They have attracted widespread attention from scholars and provide a versatile solution for implant surface modification. As an endogenous small molecule, DA has good biological safety. PDA coating modification can not only promote the adhesion, proliferation and differentiation of osteoblast-like cells but also inhibit the adhesion, proliferation and differentiation of osteoclasts. Previous in vivo studies of PDA coating modification were mostly conducted with healthy animal models, in which these coatings had obvious effects on promoting implant osseointegration; however, whether they are also effective in different disease states, such as those of diabetes and osteoporosis, still needs further research. Moreover, although PDA is widely used in surface modification studies as a promising biomaterial for clinical applications, the mechanisms by which DA receptor metabolism is regulated via downstream pathways in mesenchymal stem cells remain unclear. It is also important to clarify the process by which PDA is degraded in vivo and whether its products are harmful to patients. Finally, more attention should be given to PDA coating applications in osteoimmunity fields, as DA, a neurotransmitter and precursor of PDA, is present in our nervous system. In conclusion, the existing examples and applications demonstrate the medical potential of PDA for biomaterial surface modification.

Conflict of Interest

The authors declare no conflict of interest.

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