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Review

Multifaceted Materials for Enhanced Osteogenesis and Antimicrobial Properties on Bioplastic Polyetheretherketone Surfaces: A Review

Ziyang Bai,[▽] Yifan Zhao,[▽] Chenying Cui,[▽] Jingyu Yan, Danlei Qin, Jiahui Tong, Hongyi Peng, Yingyu Liu, Lingxiang Sun, Xiuping Wu,* Bing Li,* and Xia Li*

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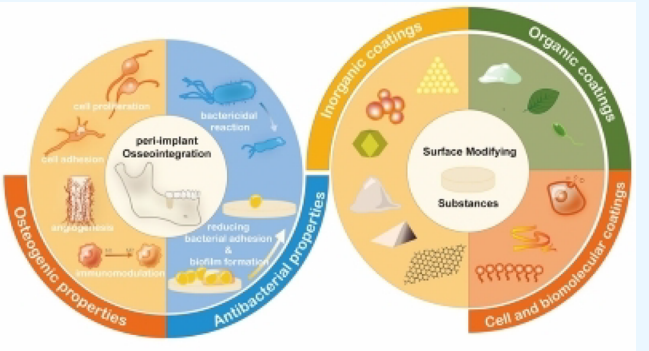
ABSTRACT: Implant-associated infections and the increasing number of bone implants loosening and falling off after implantation have become urgent global challenges, hence the need for intelligent alternative solutions to combat implant loosening and falling off. The application of polyetheretherketone (PEEK) in biomedical and medical therapy has aroused great interest, especially because its elastic modulus close to bone provides an effective alternative to titanium implants, thereby preventing the possibility of bone implants loosening and falling off due to the mismatch of elastic modulus. In this Review, we provide a comprehensive overview of recent advances in surface modifications to prevent bone binding deficiency and bacterial infection after implantation of bone implants, starting with inorganics for surface modification, followed by organics that can effectively promote bone integration and antimicrobial action. In addition, surface modifications derived from cells and related products of biological activity have been proposed, and there is increasing evidence of clinical potential. Finally, the advantages and future challenges of surface strategies against medical associated poor osseointegration and infection are discussed, with promising prospects for developing novel osseointegration and antimicrobial PEEK materials.



1. INTRODUCTION

Bone tissue is a kind of tissue with natural regeneration ability, which can heal by itself in small injury sites, but when the critical size threshold is exceeded (usually >2 cm), bone defects are difficult to heal by themselves.[1−3] Trauma, degenerative diseases, birth defects, or surgical removal of tumors resulting in large bone defects or loss are inevitable clinical interventions to achieve complete healing and functional recovery.[4,5] Compared with autologous bone and allogeneic bone, synthetic bone materials have less damage to patients, lower risk of immune rejection, and lower risk of disease transmission related to donor materials. Therefore, they are regarded as excellent bone defect repair and bone implant materials and have been widely studied and applied.

The use of laboratory-made materials to repair lost or damaged bone was first reported in the early 19th century.[6] So far, many studies on metals and their composites, bioactive glass, and polymers used in bone implants have been widely carried out. Metals and their composites, such as stainless steel, cobalt−chromium alloy, and titanium and their alloys, have been widely used in clinical bone implantation therapy due to their excellent load-bearing properties and stability.[7] However, anaphylaxis resulting from the metal implant and the release of metal particles may lead to inflammatory reactions around the implant, which could potentially affect the long-term efficacy. Furthermore, due to the mismatch in elastic modulus with bone and low fatigue strength, the metal implant fails to adequately promote healing of the surrounding bone, rendering it unsuitable for permanent implantation. Even though bioactive glasses demonstrate favorable biocompatibility and notable long-term bone integration performance, their brittleness requires extra protection, and complex processing with limited adjustability hinders application in specialized bone repair cases.

Polyetheretherketone (PEEK) is a two-phase semicrystalline polymer with high mechanical strength, high temperature

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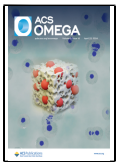

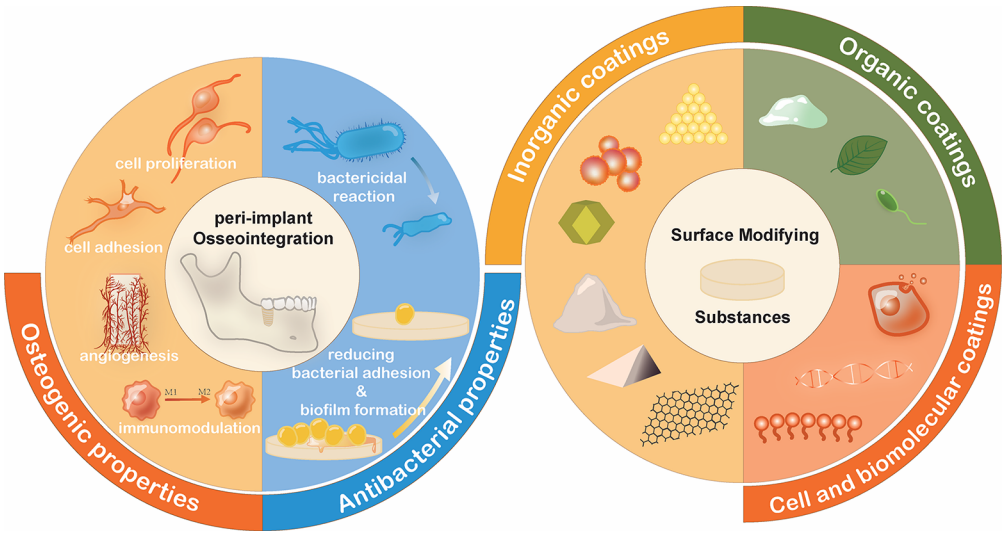

Figure 1. Review of strategies for enhancing osteogenic and antimicrobial properties with polyetheretherketone surface modification.

resistance, and fatigue resistance and does not affect magnetic resonance imaging. PEEK is chemically stable and can withstand all chemical agents, except 98% sulfuric acid. PEEK has strong wear resistance, produces fewer wear particles during implantation, avoids the release of harmful byproducts such as metal ions, and alleviates immune rejection.[8] The benzene ring in the molecular structure gives PEEK rigidity, while the ether bond allows enough toughness to make PEEK highly resistant to cyclic stresses. More importantly, the elastic modulus of PEEK (about 3 GPa) is comparable to that of human bone (3−17 GPa), so it can effectively alleviate the "stress occlusion" problem at the surgical site and reduce the risk of osteoporosis.[9] PEEK was authorized by the US Food and Drug Administration (FDA) as an implantable biomaterial in the late 1990s[10] and has been successfully used in spinal fusion, dental implants, and skull reconstruction.[11−15]

The main disadvantage of PEEK as an implant is the highly hydrophobic nature of the material,[16] resulting in its biological inactivity. After implantation, the surface of the implant has difficulty adhering to cells, resulting in poor bone integration and weak antibacterial performance. These factors significantly impede its clinical application to a large extent.[17] The development of surface engineering provides the possibility of the further development of PEEK as a bioactive implant. Through surface modification engineering, PEEK can be endowed with a variety of biological functions without compromising its mechanical strength, which will help to further promote the use of PEEK in bone implantation. In order to accelerate the application of PEEK in the field of bone implantation, many reviews have examined the research reports of its modification. Several reviews have focused on physical modifications that can enhance PEEK surface properties,[18] but most of them only focus on some details, such as improved performance of modified PEEK.[19] We currently have only a partial and incomplete understanding of the osteogenic and antimicrobial improvement of PEEK surface modification by biologically active materials. The purpose of this Review is to summarize the research progress of PEEK surface modification substances and to review the effects of inorganic, organic, cell, and growth factor (GF) modifications on osteogenesis or antibacterial activity of PEEK-based implants (Figure 1). The research direction of PEEK modified by different substances was prospected, which provided reference for the research of PEEK-based implant materials.

2. SURFACE MODIFICATION SUBSTANCE COATINGS

Surface modification substances, or surface active substances, are a series of substances that can be loaded on the surface of PEEK bone implants and help to improve the ecological relationship between bone implants and surrounding bone after implantation surgery. These substances participate in an important part of life activities, can promote cell adhesion, proliferation, and osteogenic differentiation around PEEK bone implants, and inhibit bacterial infection and immune regulation. Ultimately, it facilitates better osteogenic bonding between PEEK and the surrounding bone tissue. According to its substance classification, it can be divided into inorganic substances, organic substances, and cells and their biomolecules.

Among them, inorganic materials were the first to be explored in the surface modification of bone implants, with the most complete mechanism and the most complex function. However, the selection of the appropriate dose and the toxicity of the dose are difficult to avoid,[32,33] which affects the popularization of its application in the activities of complex organisms. The application of organic bioactive substances in the clinic and research is gradually spreading; its excellent performance in clinical and biological experiments makes it gradually enter the public view, but its involved mechanism remains to be further explored by researchers. Cells and their biomolecules are a new class of bioactive substances, which have exploration value in the modification of PEEK surfaces (Table 1). Based on such substances, we may be able to study a class of composite surface modification methods to regulate biological behavior.

2.1. Inorganic Coatings. *2.1.1. Zinc and Zinc Containing Compound Coatings.* Zinc (Zn) is an essential trace element in the human body. It enters the cell in the form of zinc ions (Zn^{2+}), activates the cAMP-PKA pathway, and triggers intracellular calcium ion (Ca^{2+})[34] response to promote bone formation by promoting alkaline phosphatase (ALP) activity, extracellular matrix (ECM) mineralization, and expression of osteogenic genes. More importantly, it has good antibacterial potential through the production of reactive oxygen species

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Table 1. Materials and Their Contributions to the Promotion of Bone Formation and the Enhancement of Antibacterial Properties on PEEK Surfaces along with Potential Mechanisms

	components		performance			
no.	PEEK: enhancing attachment	multifaceted materials	osteogenesis	antibacterial and anti-infection	animal model	ref
1	acrylic acid (AA)	Zn^{2+}	**MC3T3-E1:** Zn is released locally, promoting cell proliferation and differentiation, ALP activity, bone matrix mineralization and expression of osteoblast-related genes (OCN, BSP).	Zn plays electrostatic adsorption to bacteria contact and prevents the synthesis of bacterial genetic material. ***S. aureus*:** about 62.31%	none	20
2	PDA	Mn and Ag^{+}	**MC3T3-E1:** increased expression of osteogenic genes, ALP activity, and mineralization. Ag^{+} release was controlled and did not affect biocompatibility and osteogenic activity.	Ag^{+} inhibited the formation of bacterial biofilm. ***S. aureus*:** 90.32% ***E. coli*:** 84.42%	rats lateral femoral condyle bone defect model	21
3	PDA	Cu^{II}	**rBMSC:** Cu^{II} can improve the osteogenic ability. **HUVECs:** Cu-10 exhibited the best angiogenic ability **RAW264.7:** Cu induces M1 transformation and does not lead to excessive or chronic inflammation, instead enhancing the healing process.	The direct contact and release of Cu^{II} promotes the polarization of M1-type macrophages, activates host immune defense, and thus inhibits bacterial growth and clears biofilm. **MRSA:** about 78.34% in Cu-10	rat femur MARS infection bone defect implantation model; mouse air pouch model	22
4	sulfonated PEEK and PDA and silk	$SrCO_3$	**RAW246.7:** The cells adhere well to the materials.	Silk proteins adsorb gentamicin, enabling the early, slow release of antibiotics around the implant. ***S. aureus* and *E. coli*:** close to 100%	SD rat femur defect model; mice back subcutaneous implant model	23
		gentamicin (GS)	**hBMSCs:** With the increase of strontium content on the surface of the material, the upregulation of osteogenic gene expression also increased.			
5	sulfonated PEEK	Ni	**HUVEC:** Ni promotes angiogenesis by creating an anoxic environment and effectively promotes vascularization in in vivo and in vitro experiments.	none	rabbit femoral condyle implantation model	23
		HA	**MC3T3-E1:** HA coating can properly inhibit the release of Ni ion and induce the increase of cell osteoblast to differentiation.			
6	inductively coupled plasma-enhanced chemical vapor deposition (ICPECVD)	Si_3N_4	**rBMSCs:** Si^{+} is released to form a weakly alkaline environment that facilitates cell proliferation and subsequent cell differentiation. The loading of Si^3N^4 forms a coating with a graded nanostructure that promotes cell adhesion and diffusion by providing more cell adhesion sites.	The graded nanostructured surface and the weakly alkaline microenvironment formed by Si^{+} release work inhibit bacterial attachment and growth. ***S. aureus*:** 92.2% ***E. coli*:** 86.7%	none	23
7	none	black phosphorus (BP)	**MC3T3:** BP slowly releases PO_4^{3-}, promoting the formation of calcium phosphate minerals, which is conducive to bone formation, and the cationic nature of CS attracts glycosaminoglycans (GAG) through electrostatic interactions, which retain and concentrate growth factors by colonizing cells.	CS has a slight antibacterial effect. Under NIR, BP/DOX produces ROS, which leads to lipid peroxidation of the bacterial cell membrane and damage of bacterial DNA. ***S. aureus*:** 85.61 ± 6.04% (42% of CS) ***E. coli*:** 91.07 ± 6.00% (46% of CS)	the BALB/c nude mice model; the rat distal femoral condyle defect model	24
		doxorubicin hydrochloride (DOX)				
		chitosan(CS)				
	PDA	osthole (Ost)	**rBMSCs:** Ost nanoparticles enhanced the expression of osteogenic genes, and their morphology was maintained under the protection of PDA.	Ber can interfere with bacterial DNA replication and protein synthesis. ***S. aureus* and *S. epidermidis*:** close to 100%	SD rat femur defect model	25
	silk fibroin (SF)	berberine (Ber)				
	SPEEK					
8	diamond-like carbon (DLC)	ALN	**RAW264.7:** Osteoclast differentiation of macrophages was significantly downregulated.	none	SD rat femur defect model	26
	N_2 PIII treatment	osteogenic growth peptide (OGP)	**BMSCs:** Increased cell proliferation, ALP activity, ECM mineralization, and upregulation of osteogenic genes.			

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Table 1. continued

no.	components: PEEK: enhancing attachment	components: multifaceted materials	performance: osteogenesis	performance: antibacterial and anti-infection	animal model	ref
9	DOPA	antimicrobial peptide (AMP)	**BM-MSCs:** In vitro bone calcification and upregulation of osteogenic genes were OGP dependent.	AMP impinges on the bacterial cell wall and induces bacterial lysis.	*S. aureus* infected SD rat femur defect model	27
	zylcyclooctyne (DBCO)	OGP		***S. aureus* and *E. coli*:** about 77.00%		
10	tannic acid (TA)	BMSC-derived Exos	**RAW264.7:** Exos negatively regulates the NF-κB pathway through miRNA, regulating the polarization of macrophage M2, and promotes bone formation.	none	SD rat air-pouch model and femur defect model	28
	SPEEK		**rBMSC:** Exos contains multiple types of noncoding RNAs that induce osteogenic differentiation of BMSC by activating MAPK and PI3K/Akt.			
11	mesoporous bioactive glass nanoparticles (MBGNs)	miRNA	**RAW264.7:** miRNA inhibits the activation of pro-inflammatory factor gene NFκB in vivo by decreasing the expression of phosphorylated IκB (p-IκB).	none	SD rat air-pouch model and femur defect model	29
	tannic acid (TA)		**rBMSC:** miR-21a-5p promotes osteogenic differentiation through targeted downregulation of PTEN through the pAKT/pGSK3β/beta-catenin signaling pathway, and inhibits osteoclast differentiation through SKP2.43,44.			
12	ethylenediamine (EDA)	chondroitin sulfate (CS)	**HUVEC:** Sr^{2+} promotes angiogenesis.	none	SD rat femur defect model	30
	SPEEK	Sr	**MC3T3-E1:** CS has anti-inflammatory activity and, together with Sr and EDA, improves calcification and osteogenic differentiation of osteoblasts.			
13	none	liposomes Dex/Mino	**hMSCs:** Liposomes loaded with Dex released poorly water-soluble Dex into the surrounding tissue environment and promoted the osteogenic differentiation of hMSCs.	Mino interfers with the synthesis of bacterial proteins. ***S. mutans*:** about 97.40% ***P. gingivalis*:** about 93.99%	C57BL/6 mouse subcutaneous foreign body reaction; beagle femur defect models	31

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(ROS) and its destructive interaction with bacterial membranes.[35]

Zhang et al.[20] developed a modified PEEK surface by constructing a layer of acrylic acid (AA) polymer coating loaded with Zn^{2+} through a combination of plasma-induced graft polymerization and a chemical immersion technique. The AA coating significantly increased the hydrophilicity of PEEK and efficiently loaded and released Zn^{2+}. In vitro cell culture using MC3T3-E1 preosteoblasts demonstrated that the released Zn^{2+} from PEEK-AA-Zn promoted cell proliferation and elevated gene expression levels of ALP, osteocalcin (OCN), and bone sialoprotein (BSP). Additionally, antibacterial tests showed that PEEK-AA-Zn effectively inhibited the proliferation of *Staphylococcus aureus* (*S. aureus*). These results indicate that the combination of grafting polymerization and Zn^{2+} doping endows PEEK with good osteogenic and antibacterial activity.

The researchers were not satisfied with simply loading Zn^{2+} onto PEEK, and they developed metal−organic frameworks (MOFs) based on nanoscale Zn^{2+}. Zeolitic imidazolate framework-8 (ZIF-8) is a common emerging porous solid material consisting of a Zn^{2+} cluster tetrahedron and 2-methylimidazole (2-Melm) organic ligand. It has been shown to have superior osteogenic properties and antibacterial activity[36,37] and can achieve photothermal therapeutic effects under infrared light.[38]

Chen et al.[39] developed a polydopamine(PDA)-wrapped ZIF-8 coating on sulfonated PEEK (SPEEK). The coating allows for controlled release of Zn^{2+} and exhibits a strong photothermal capacity under near-infrared (NIR) irradiation. In vitro antibacterial experiments showed that the coating had 100% bactericidal efficiency against *S. aureus* and *Escherichia coli* (*E. coli*) under NIR. Without NIR, the ZIF-8/PDA-functionalized substrate demonstrated good biocompatibility and enhanced osteogenic activities.

To mitigate cell damage resulting from phototherapy, Deng et al.[40] created a heterostructured coating on a PEEK implant, consisting of simvastatin (SIM)-laden MOFs. The coating significantly enhanced cytocompatibility and osteogenic differentiation through various osteogenic mechanisms, including Zn^{2+} therapy, SIM drug therapy, and surface micro/nano-topological stimulation. Under NIR light, the coating produced singlet oxygen ($^1O_2$) and local hyperthermia, while also accelerating the release of Zn^{2+} ions. The coating effectively eradicated both Gram-positive and Gram-negative bacteria through the synergy of photothermal and photodynamic effects and the accelerated delivery of Zn^{2+} ions. In a rat femur defect model, the heterostructured coating demonstrated superior osteogenicity, osseointegration, and controllable disinfection using NIR light. In this experiment, the surface design of Zn^{2+} showed a synergistic effect of promoting bone bonding when combined with SIM and showed a synergistic effect of benefiting photothermal antibacterial therapy when combined with PDA. This shows that the simple use of Zn^{2+} surface modified PEEK still has drawbacks, and other substances are needed to better improve its bone implantation effect and reduce toxicity.

2.1.2. Silver Coatings. Silver ion (Ag^+) is a broad-spectrum antibacterial agent, which can inhibit both Gram-positive and Gram-negative bacteria.[43] Silver (Ag)-doped coatings have good biocompatibility and show toxicity to mammalian cells only at high concentrations.[44]

Lee et al.[45] synthesized silver nanoparticles (AgNPs) with an average size of 32 nm and coated a PEEK polymeric substrate with 0.5% AgNPs using an epoxy resin lining. Scanning electron microscopy and atomic force microscopy confirmed the uniform deposition of AgNPs onto the PEEK specimens. The antibacterial activity of the coated specimens was tested against *Porphyromonas gingivalis* (*P. gingivalis*), revealing a significant inhibition zone of 22.5 mm and an antibacterial rate of 83.47%. These results suggest that the 0.5% Ag-PEEK coating possesses potential antibacterial properties for implant applications, making it an effective approach for combating bacterial growth on the surface of medical implants.

By cultivating MG-63 cells on the surface of Ag-modified PEEK, Deng et al.[46] verified that Ag had little effect on cell proliferation within a certain concentration and inhibited cell proliferation with the increase of concentration.

Ag^+ shows good antibacterial activity, but in order to pursue the bone-binding effect of PEEK as a bone implant, multisubstance modification strategies should also be considered. Yu et al.[47] enriched Ag^+ on the surface of PEEK, which formed a carboxymethyl chitosan (CMC) membrane in spin coating and modified bone forming peptide (BFP). The obtained surfaces showed good antibacterial activity against both Gram-negative and Gram-positive bacteria and increased the bioactivity of promoting cell proliferation and osteogenic differentiation.

2.1.3. Titanium and Titanium Oxide Coatings. Titanium (Ti) is recognized as a nontoxic metal in the world and is often used in orthopedic implants. It has good biocompatibility and osteogenic activity and can improve the biological activity of the PEEK surface.[48]

Liu et al.[49] coated Ti on the surface of a PEEK cage using vacuum plasma spraying. In vitro cellular behavior experiments, skeleton staining, and the MTS assay demonstrated that MC3T3-E1 cells exhibited good spreading and growth on the surface of Ti-PEEK cages, while also showing upregulated bone-forming activity. In a sheep cervical spine fusion test, Ti-PEEK implants demonstrated a significant increase in new bone formation at 12 weeks, suggesting an improved osteointegration ability.

Changes in the physical and chemical surface states can also alter the biological behavior of PEEK implants. Xian et al.[50] modified the surface of PEEK by depositing a nanogranular-structured anatase titanium dioxide (TiO_2) coating. In vitro cell culture tests demonstrated that the modified PEEK showed improved adhesion and proliferation of fibroblast and osteoblast cells, reduced inflammatory reaction in macrophages by suppressing tumor necrosis factor-α (TNF-α) expression, and enhanced antibacterial activity against *S. aureus* and *Streptococcus mutans* (*S. mutans*). This shows the nanoparticle structure of TiO_2 not only through the substance itself but also by improving the surface properties and surface energy of PEEK.

Another form is the solgel derived TiO_2. Shimizu et al.[51] modified the surface of PEEK using a solgel derived TiO_2 coating. Through in vivo and in vitro experiments, it was concluded that acid post-treatment after sol−gel-derived TiO_2 coating significantly improved the bone adhesion ability of the PEEK surface.

Due to the stable chemical properties of TiO_2, it often plays a role in cell contact, rather than indirect contact in the form of ions released into the surrounding environment of the material, so the biosecurity problem caused by the release of metal ions

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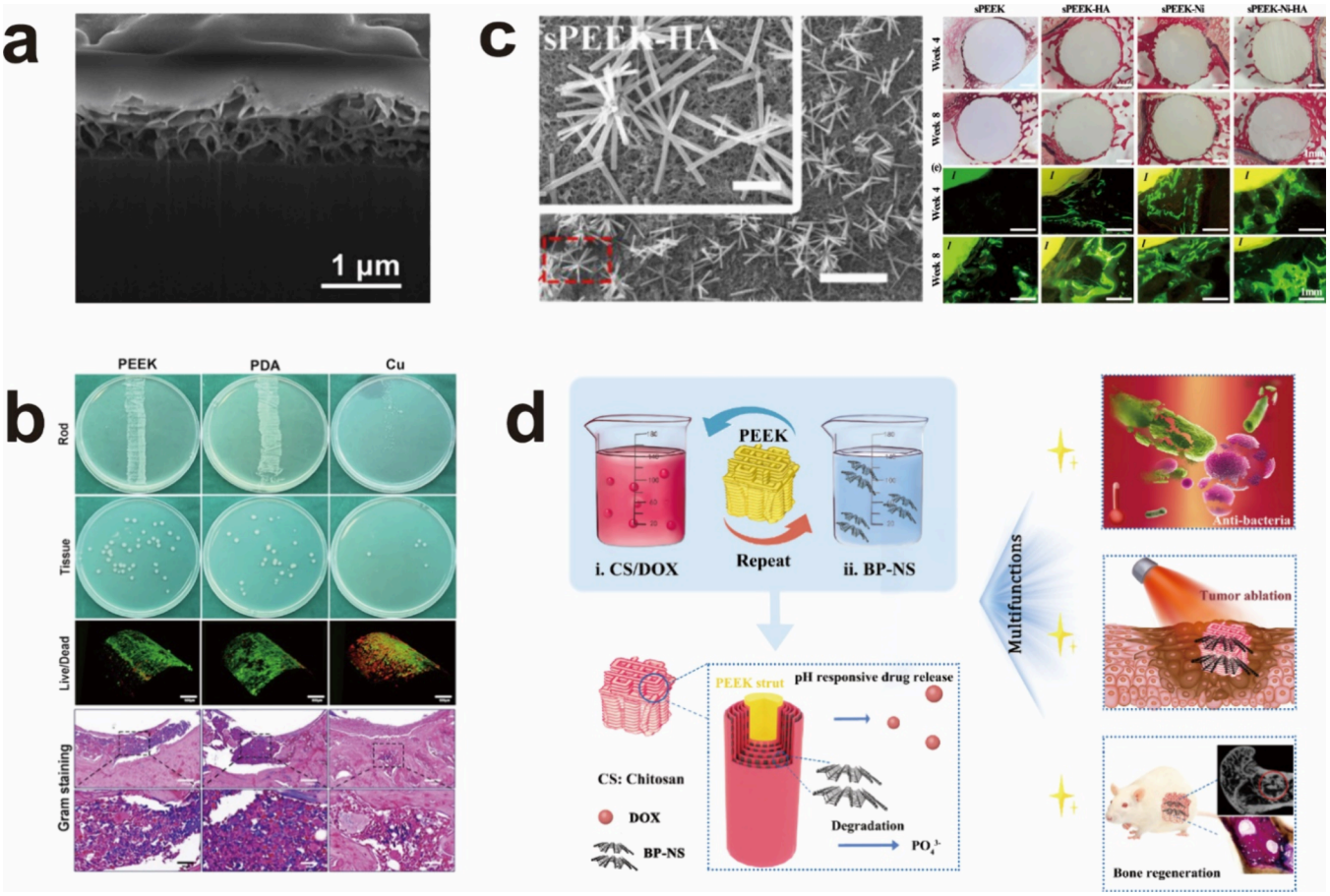

Figure 2. Surface modification strategies of inorganic substances. (a) Inorganic substances increase the contact area of the PEEK surface. SEM image of the cross-section of the amorphous magnesium phosphate (AMP) coated PEEK sample.[41] Copyright 2017 Elsevier. (b)The surface antibacterial ability of Cu-coated PEEK was improved, and the proportion of dead bacteria on the surface was increased.[22] Copyright 2022 Elsevier. (c) The surface osteogenic properties and bone-binding properties of PEEK loaded with hydroxyapatite (HA) were enhanced.[42] Copyright 2020 American Chemical Society. (d) Black phosphorus (BP) is helpful to the antibacterial properties of PEEK surface and tumor ablation properties under the photothermal effect and enhances the bone regeneration properties.[24] Copyright 2022 Elsevier.

is avoided. For metals such as Ti, the friction loss of wear particles involved in the implantation process should be considered so as to reduce the inflammatory response caused by wear particles and the potential risk of implant failure.

2.1.4. Magnesium and Magnesium Salt Coatings. Magnesium (Mg) is a biodegradable,[52−55] antibacterial material.[56−58]

Yu et al.[59] used vapor deposition to coat PEEK with high purity magnesium. After the mixture was soaked for 21 days, the Mg coating degraded and gradually peeled off the PEEK surface. The study found that the degradation of the magnesium coating can strongly kill *S. aureus*, and the antibacterial rate reaches 99%.

Many studies have found that Mg^{2+} can promote angiogenesis[60] and bone formation.[61−63]

Wei et al.[64] activated the 3D-printed porous PEEK using a PDA coating chelated with magnesium ions (Mg^{2+}). In vitro experiments demonstrated that the activated surface promoted cell proliferation, adhesion, osteoblast differentiation, and mineralization, while the released Mg^{2+} stimulated angiogenesis and the formation of osteogenic vessels. In vivo evaluation in rabbit femoral condyles showed that the porous PEEK scaffolds with the PDA coating facilitated vascular and bone ingrowth with the released Mg^{2+} accelerating early bone integration.

Magnesium salts also have good biocompatibility, and crystalline compounds such as guanite ($NH_4MgPO_4{\cdot}6H_2O$) have made rapid progress in bone physiology research.[65] Ren et al.[41] developed an osseointegrable amorphous magnesium phosphate (AMP) coating on the PEEK surface using microwave energy. The AMP coatings showed no cytotoxic effects and enhanced biological activity in vitro, promoting the formation of new bones and bone integration (Figure 2a).

2.1.5. Copper Coatings. Copper (Cu)[66,67] is a trace element in the human body and has excellent biological properties.

Liu et al.[68] prepared a fixed layer of copper nanoparticles by magnetron sputtering on the surface of SPEEK. In vitro antibacterial and immune experiments showed that Cu-SPEEK could play an ideal bactericidal effect on methicillin-resistant *Staphylococcus aureus* (MRSA) through structural and metallic mechanisms. At the same time, macrophages cultured on Cu-SPEEK can be activated and polarized into proinflammatory phenotypes while improving the phagocytic capacity of MRSA. The in vivo infection model proved that the incorporation of Cu-SPEEK had superior antibacterial activity.

This indicates that Cu can not only create an anti-infection environment on the surface of the material but also regulate its immunomodulatory function and drive macrophages to polarize toward M1 phenotype.[69,70]

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Experiments have shown that Cu has not only immunoregulatory properties but also osteogenic and tissue regeneration properties.[71,72] Cu can also promote angiogenesis, thus contributing to bone regeneration.[73]

Lyu et al.[22] incorporated copper into the PDA coating on PEEK surfaces. The resulting PDA-Cu^{II} coated PEEK surfaces demonstrated enhanced abilities in osteogenesis, angiogenesis, and antibiosis. Additionally, they exhibited immunomodulatory effects that enhanced macrophage-mediated osteogenesis and antibacterial activity. In both the mouse air pouch model and rat implant-associated osteomyelitis model, the PDA-Cu^{II} coated PEEK surfaces induced a mild and necessary inflammatory response, showcasing excellent antibacterial ability and superior osseointegration. These findings highlight the potential of the Cu coated PEEK surfaces for improving bone regeneration and preventing bacterial infections in biomedical applications (Figure 2b).

How to control the release concentration and release periods of Cu^{2+} is also a consideration for PEEK surface design. Yan et al.[74] developed a pH-responsive coating on porous PEEK by codepositing PDA and copper-citrate nanoclusters. In in vitro experiments, the PDA coating released high doses of copper and citrate at lower pH values, resulting in increased intracellular copper content, enhanced production of ROS, and severe damage to proteins, leading to the killing of 93% of planktonic bacteria and the eradication of adherent bacteria. At pH 7.4, the release of copper and citrate exhibited slow and sustained behavior, synergistically promoting the vascular formation potential and osteodifferentiation of adipose-derived mesenchymal stem cells (Ad-MSCs). In rabbit tibial implant models, micro-CT evaluation and histological analysis consistently showed that Cu coating increased new bone formation near coated PEEK implants and improved bone−implant interface integration. This result was confirmed to be related to the synergistic effect of citric acid, which promotes twice the flow of copper into the cells, not only enhancing the bacteria's killing ability but also promoting bone regeneration in the implant.

2.1.6. Calcium Salt Coatings. Ca^{2+} is one of the most abundant inorganic elements in the human body and is mainly distributed in bone and teeth. It can stimulate the response of osteoblasts and promote the osteogenic ability by enhancing the osteogenic of bone cells. Calcium carbonate ($CaCO_3$), as a Ca^{2+} donor, has been widely used in bone tissue engineering, biosensors, and drug carriers.[75−77]

Du et al.[78] coated electrically conductive PEEK/graphene nanocomposites (P/G) with a bioactive $CaCO_3$ coating containing AgNPs by electrophoretic deposition (EPD) of pumped CO_2. Through characterization, it was confirmed that $CaCO_3$ improved the surface coating with a smaller crystallinity and stronger hydrophilicity. In in vitro experiments, engineered PEEK showed excellent biocompatibility and improved cell diffusion and proliferation. In theory, $CaCO_3$ nanomaterial can decompose into Ca^{2+} and CO_2 when it comes into contact with the acidic environment after implantation in bone, thus consuming H^+ and alleviating infection and inflammation. However, excessive loading can produce CO_2 gas and interfere with the secretion of osteogenic factors and hydroxyapatite (HA) mineralization in surrounding cells. This explains why an appropriate concentration of $CaCO_3$ nanoparticle surface loading enhances bone binding and infection resistance around PEEK materials.

Calcium phosphate (CaP) is another form of compound that releases Ca ions. Human bones contain about 70% of the mineral CaP, and CaP nanoparticles are highly biocompatible and biodegradable due to their chemical similarity to hard human tissues such as bone and teeth.[79]

Shi et al.[80] developed a modified PEEK surface with an interface consisting of collagen and CaP, mimicking the characteristics of natural bone tissues in terms of composition and porous structure. In vitro evaluations showed that the modified PEEK surface promoted gene and protein expression related to osteogenesis thanks to its unique surface morphologies. In vivo experiments using BALB/c mice ectopic osteogenesis models demonstrated significantly enhanced osteogenesis effects with the modified PEEK substrates. This indicates that the coating of CaP contributes to the formation of PEEK surface morphology, thereby enhancing the cell adhesion, mineralized deposition, implant-bone bonding, and bone integration on the surface of the material.

Kokubo proposed that the essential requirement for the combination of artificial materials with living bone was to form bone apatite on the surface of living organisms when implanted in vivo, and the ion concentration of simulated body fluid (SBF) equivalent to human plasma could reproduce the formation process of apatite in vivo.[81]

Masamoto et al.[82] developed a surface treatment method on the PEEK surface by loading the "apatite precursor" (PrA), or SBF, through a simple cryogenic process. In animal models, mechanical testing, histology, and radiological analysis showed that PrA provides excellent bone-binding properties and bone conductivity to PEEK substrates in the early stages (weeks 4 and 8) and is extended to 16 weeks. Cell experiments confirmed that PrA on PEEK substrates did not produce cytotoxicity, but RT-qPCR showed that PrA treatment appeared to inhibit gene expression of integrin beta-1 and Alp after 7 days of culture. The authors suggest that there is an inconsistency between in vivo and in vitro biological activity, a difference that suggests that the formation of apatite does not always require activation of osteoblasts at a very early stage and that optimal conditions may differ at the cellular and organism levels.

The above studies show that different calcium compounds exhibit different bone-binding properties on the surface of bone implants and that the specific differences and the underlying principles still need to be further explored.

2.1.7. Manganese Coatings. As an essential trace element, manganese is related to maintaining the bone structure and regulating bone metabolism. Manganese can dose dependently activate human osteoblast integrins and enhance cell adhesion, proliferation, and diffusion.[83]

Yang et al.[84] prepared a manganese modification (PEEK-PDA-Mn) on the PEEK surface using PDA. In vitro cell experiments showed that Mn modification enhanced cell adhesion and diffusion and also enhanced peri-implant osteogenesis. In vivo, using a rat model of a femoral condyle defect, the results showed that Mn modification promoted bone tissue regeneration in the defect area.

At present, it has been proved that Mn exists in the form of Mn_2O_3, has catalytic activity, and can produce ROS to play an anti-Gram-negative bacteria effect. Mn_2O_3 films can act as a barrier to slow the release of manganese ions from the substrate to the external environment, thus avoiding toxicity to cells.[85]

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Although the surface of MN-modified PEEK has shown certain osseointegration effects, its antibacterial properties and composite methods still need to be further explored. Therefore, Yang et al.[21] employed a simple immersing method to modify the surface of PEEK with manganese (Mn) and Ag^+. The modified PEEK-PDA-Mn/Ag showed enhanced adhesion and distribution of MC3T3-E1 cells, favorable biosafety, osteogenic properties with increased expression of osteogenic genes, ALP activity, and mineralization as well as proven antibacterial capabilities against both *S. aureus* and *E. coli* in vitro. In a bone defect model in the lateral femoral condyle, PEEK-PDA-Mn/Ag demonstrated antibacterial properties and enhanced osseointegration in vivo. The above results reflect the osteogenic and antibacterial advantages of Mn and Ag^+ on PEEK surface modification.

2.1.8. Strontium and Strontium Salt Coatings. Strontium (Sr), as an important trace element in human body, is recognized for its dual role in bone metabolism and inhibition of osteoporosis bone resorption.[86−88] In addition, studies have shown that Sr can also trigger the secretion of VEGF,[89] an angiogenic growth factor responsible for regulating the angiogenesis process.

Wang et al.[90] loaded Sr and silicon (Si) onto the surface of PEEK implants using electron beam evaporation (EBE). In vitro experiments demonstrated that the Sr/Si ion-modified surface had a superior osteo-inductive effect on rat bone mesenchymal stem cells (rBMSCs) derived from ovariectomized rats. Additionally, the modified samples stimulated the migration and angiogenesis of human umbilical vein endothelial cells (HUVECs). Moreover, in an ovariectomy rat bone defect model, the modified surface exhibited faster bone formation, which was potentially attributed to the impact of endogenous MSC transformation and the promotion of endothelial cell angiogenic activity.

The adhesion of strontium ions to PEEK surfaces has also received attention. Using PDA as an intermediate, Sang et al.[23] embedded $SrCO_3$ nanoparticles into micropores on the surface of SPEEK to make the material release strontium ions stably. In in vivo experiments, the modified material showed not only good biocompatibility but also good cell adhesion. ALP, Alizarin Red staining, and PCR experiments verified the excellent bone formation properties of the material. In the SD rat femur defect model and BALB/c mice back subcutaneous implant model, the excellent osteogenic and antibacterial properties of the material were confirmed. Strontium fulminate is a compound commonly used to treat or prevent osteoporosis that promotes bone formation and inhibits bone resorption. It has been clinically used to treat osteoporosis and reduce vertebral morphological fractures in postmenopausal women.[91,92] Sun et al.[93] loaded different concentrations of strontium ranelate onto the surfaces of sulfonated 3D PEEK porous structures. In vitro cellular experiments demonstrated that the modified surface enhanced the adhesion of MC3T3-E1 cells and improved their activity in alkaline phosphatase, collagen secretion, and extracellular matrix mineralization deposition.

The synergistic effect of strontium ions and substances improves the antibacterial property. Wang et al.[94] coated ZnO and $Sr(OH)_2$ on PEEK. In vitro experiments demonstrated that the Zn&Sr-SPEEK implants released Zn^{2+} and Sr^{2+}, which synergistically inhibited pathogenic bacteria and promoted the activity of osteoblasts in a hyperglycemic environment. The implants effectively restored mitochondrial dynamic equilibrium and function by downregulating the Dynamin-related protein 1 (Drp1) gene, restoring mitochondrial membrane potential (MMP), and eliminating ROS, which ultimately enhanced osteogenicity in osteoblasts. In vivo evaluations using a diabetic rat femoral/tibia defect model confirmed that the ZnO and $Sr(OH)_2$ coatings significantly improved bone remodeling and osseointegration. This study provides a new orthopedic implant option for diabetic patients with mitochondrial regulatory abilities. Su et al.[95] developed bone implants with strontium-doped bioactive glass nanoparticle (Sr-BGN) modified PEEK surfaces. In in vitro experiments and in a BALB/c mouse subcutaneous implantation model, the engineered implant effectively destroyed the MRSA biofilm thanks to the antimicrobial properties of the PDA activated by NIR irradiation. The engineered implants have good cytocompatibility, and the released Sr ions inhibit the expression of inflammatory genes, creating a favorable environment for tissue repair after infection clearance.

2.1.9. Nickel and Nickel Hydroxide Coatings. Nickel (Ni) is a transition metal element that plays a crucial role in various essential physiological functions of the human body,[96,97] such as facilitating iron absorption, regulating glucose metabolism, synthesizing hormones, and improving bone strength. Insufficient nickel levels can lead to decreased dehydrogenase and aminotransferase activity along with reduced erythrocyte production, ultimately resulting in anemia.

Dong et al.[42] loaded HA nanoflowers and nickel hydroxide ($Ni(OH)_2$) nanoparticles onto the PEEK surface. The rational release of nickel ions (Ni^{2+}) significantly promoted the migration, tube formation, and angiogenic gene expression of HUVEC. In addition to angiogenesis, it showed enhanced cytocompatibility and osteogenesis in terms of cell proliferation, diffusion, alkaline phosphatase activity, matrix mineralization, and osteogenesis related gene secretion. In vivo evaluation confirmed that this dual decoration of nickel and HA nanoflower promoted bone remodeling/bone integration, thus significantly promoting osteogenic fixation of implants in vivo (Figure 2c). This is because Ni has the ability to induce the secretion of VEGF in vascular cells and promote vascular regeneration by creating an intracellular simulated hypoxia microenvironment.[98,99]

Some studies have also shown that Ni can have an inhibitory effect on certain bacteria. For example, Ni^{2+} can come into direct contact with bacteria, resulting in damage to bacterial cell membranes and the death of bacteria. Moreover, the heat treatment of the material can control the release of Ni^{2+}, thus significantly reducing the cytotoxicity caused by the release of metal ions.[100] Ni can also form compounds that achieve antibacterial function through peroxide-like activity, magnetic capture, and contact destruction.[101,102] However, the antibacterial effect of nickel may vary, depending on its concentration, bacterial species, and environmental conditions. The loading, release, and optimal antibacterial concentration of Ni on the PEEK surface needs to be further explored.

2.1.10. Tantalum Pentoxide Coatings. Tantalum (Ta) is a biocompatible metal with good biocompatibility[103] and excellent strength and corrosion resistance in acidic media.

Pang et al.[104] prepared a dense amorphous tantalum pentoxide (TP) coating on PEEK using vacuum evaporation and verified its surface biocompatibility.

In order to verify the bone bonding properties of PEEK materials modified by Ta, Lu et al.[105] injected tantalum ions into PEEK via plasma immersion ion implantation (PIII) to

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form Ta_2O_5 nanoparticles on the near surface. The results of nanoindentation show that the elastic modulus of the surface is close to that of the human cortical bone. In vitro cell experiments showed that modified PEEK could enhance the adhesion, proliferation, and osteogenic differentiation of rBMSC. In vivo experiments in rats confirmed that the histological analysis of osseointegration was significantly improved.

Tantalum oxide also has a photothermal effect. Wang et al.[106] fabricated black tantalic oxide (BTO) sub-microparticles on PEEK fibers to create fabrics for artificial ligaments. The PEEK with the BTO coating exhibited excellent photothermal performance, demonstrating antibacterial effects. The optimized surface facilitated the responses of the rBMSC and stimulated new bone formation, promoting ligament−bone healing. In the SD rat femur defect model, it showed enhanced osteogenic activity and photothermal antibacterial effect. The presence of oxygen vacancies and structure defects in BTO did not affect its surface properties and osteogenic activity but enhanced its photothermal antibacterial effect.

2.1.11. Hydroxyapatite Coatings. Hydroxyapatite (HA) consists of 18.5% P, 39% Ca, and 3.38% hydroxyl groups (OH) by weight. 50% of the bone weight is composed of HA, which has high biocompatibility and osteogenic activity.[107,108] The porous property of HA has high binding affinity for various pharmacological substances such as antibody fragments, enzymes, hormones, antibiotics, and steroids.[109−112] These properties increase the likelihood that HA will deliver pharmacological substances.

Lee et al.[113] prepared a uniform HA coating on the surface of PEEK by cold spraying. In cell experiments, HA-coated PEEK discs showed increased expression of osteoblast differentiation markers. In in vivo experiments, the implant bone combined with the surrounding condition improved.

How to improve the adhesion and stability of the HA-modified PEEK surface is the content of further exploration by researchers. Ferroni et al.[114] introduced methacrylated hyaluronic acid (MeHA)-HA hydrogel into the surface of a 3D-printed PEEK implant after its infiltration and UV photo-cross-linking to accelerate bone repair in vitro.

These studies confirmed the improved biocompatibility and bone integration of the PEEK surface after HA loading, which is conducive to its clinical application on the PEEK bone implant surface. However, whether the load of HA on the surface will reduce the mechanical strength of PEEK and whether it will shed debris during implantation and generate peri-implant inflammation and biomaterial implantation infection (BAI) remain to be verified.

Jang et al.[115] used radio frequency (RF) magnetron sputtering to coat PEEK/TiO_2 surfaces with HA. The results of hardness, tensile, compression, and scratch tests show that the mechanical strength of the composite structure is significantly improved. In addition, in vitro experiments showed that the HA surface coating did not affect the biocompatibility or osteogenic properties of the material. In vivo experiments, microcomputed tomography, and histological analysis confirmed novel bone formation and a high bone-to-implant contact ratio on HA-coated PEEK structures enhanced with TiO_2 nanoparticles.

The above studies prove that HA can improve the biological activity of the PEEK surface and promote bone integration through surface modification. Although the above experiments did not prove that HA on the PEEK surface has antibacterial activity, previous experiments have proved that sulfonated HA plays an antibacterial role by introducing a sulfonic acid group ($-SO_3H$) on its surface through adsorption of metal ions, creation of a negative electric environment, and destruction of biofilm and other mechanisms.[116] Moreover, doping antibacterial agents (such as Ag^+) into the crystal structure of hydroxyapatite or coating antibacterial coatings[117] on its surface can effectively improve the antibacterial performance of HA.

2.1.12. Silicon Coatings. Silicon is an essential element for healthy connective and skeletal tissue development and is concentrated in the mineralized front of growing bone.[118] Recent studies have confirmed that silicon and silicate can promote peri-implant osseous integration[119] through silicon deficiency and bone metabolic dysfunction,[120] ion doping[121] and bottom-up promotion of bone formation mediated by protein templates[122,123] and other pathways. In addition, studies have shown that locally released Si ions can provide a preferential microenvironment for bone induction of bone marrow mesenchymal stem cells in an osteoporosis environment and enhance angiogenic activity.[124,125]

Wen et al.[126] introduced a bioactive silicate coating on the PEEK surface by EBE technology and controlled the duration of EBE to fine-regulate the incorporated amount of silicon on the PEEK surface. In vitro experiments showed that the cell adhesion, proliferation, osteogenic gene expression, and protein detection results of PEEK implants coated with silicate were improved. In ovariectomized (OVX) rat femur implantation models, significant improvements in adhesion, spreading, osteogenesis, and differentiation of rBMSCS-OVX were observed in silicate coated samples. Among the surfaces of PEEK implants with different Si incorporation levels, the surface with medium incorporation levels had the best osteogenic effect in vitro, while the surface with medium incorporation levels had better bone integration in vivo. This may be related to the complex microenvironment in the body and the dilution effects of body fluids. More detailed inclusion criteria must be validated in larger animal models.

Si compounds such as silicon nitride (Si_3N_4) are also resistant to Gram-positive bacteria. Boschetto et al.[127] and Xu et al.[128] coated Si_3N_4 on the surface of PEEK. The functionalized surface can significantly promote the adhesion, proliferation, differentiation, and expression of osteogenic genes of rBMSCs, and in the antibacterial experiment, it showed stronger antibacterial activity. These effects may be related to the steady release of reactive nitrogen species (RNS) by Si_3N_4 in aqueous environments.

2.1.13. Black Phosphorus Coatings. Black phosphorus (BP) is a black metallic crystal formed by the conversion of white phosphorus under a high temperature and pressure. BP has low cytotoxicity, and the $^1O_2$ it produces can destroy the bacterial membrane of *S. aureus*, significantly improving the antibacterial performance of the polymer.[129]

Li et al.[130] deposited BP on the surface of carbon fiber reinforced (CFR)-PEEK. Mechanical experiment results showed that the abrasion resistance of modified PEEK is improved effectively, which may be due to the coating not being easy to oxidize. In in vitro experiments, modified PEEK showed an inhibition against *S. aureus* without cytotoxicity.

Black phosphorus nanosheet (BP-NS) is the first single element two-dimensional semiconductor material successfully prepared, which not only is widely used in the field of optoelectronics but also has good biocompatibility and other

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properties. In the environment of the human body, BPs can be degraded into nontoxic PO_4^{3-}, promoting bone regeneration in the body. Under NIR irradiation, it also exhibits strong photothermal therapy (PTT) effects,[131] and previous studies have shown that bactericidal ROS can be released during its degradation process.[132] Due to these excellent properties, BP-NS has been widely used in biomedical applications such as tissue generation, cancer/immunotherapy, bioimaging, and biosensing.[133]

He et al.[24] developed a layer-by-layer assembled BP-NS/doxorubicin hydrochloride (DOX)-chitosan(CS) composite coating on a 3D printed PEEK bone scaffold. The composite coating provided enhanced biocompatibility and increased the expression of osteogenesis-associated genes. The composite coating consisting of BP (as photothermal agents) and DOX-CS can enable bone tumor ablation through multimodal therapy combining on-demand laser induced heating and pH sensitive cancer drug release. The BP-NS released ROS to eradicate *E. coli* and *S. aureus*, addressing potential post-operation infections. Chitosan (CS), as a drug carrier, has a pH-regulated drug release effect, which may also help reduce direct exposure to ROS, thereby protecting osteoblasts. In the BALB/c nude mice model and the rat distal femoral condyle defect model, the coated scaffold demonstrated multifunctionality, including tumor inhibition, bacteria eradication, and bone regeneration (Figure 2d). The above experiments confirmed the possibility of BPs as an osteogenic antibacterial coating on the PEEK surface.

2.1.14. Graphene Oxide (GO) Coatings. Graphene oxide (GO) is an important graphene derivative, with a dense honeycomb structure of single-atom two-dimensional nanostructures with a large number of ROS functional groups, showing obvious antibacterial ability against Gram-negative and Gram-positive bacteria. The abundant chemical groups on its surface provide a large number of reaction sites, which can significantly improve the interaction with proteins[134,135] and contribute to the potential enhancement of osteogenic differentiation of stem cells.

Ouyang et al.[136] prepared GO on the SPEEK surface by dipping coating. The antibacterial tests showed that GO-SPEEK showed excellent inhibition against *E. coli*. In vitro cell experiments showed that the GO-SPEEK substrate could significantly accelerate the proliferation and osteogenic differentiation of osteoblast-like MG-63 cells.

Additionally, GO has a strong photothermal effect and excellent biocompatibility, which can be used for photothermal antibacterial activity and improving the surface biocompatibility of materials.[137,138] Wu et al.[139] prepared a novel GO based phototherapeutic agent, in which ferric oxide reduced glutaraldehyde modified GO. In such a study, when NIR is used, magnetic GO materials have the ability to capture and kill Gram-positive and -negative pathogens.

Li et al.[140] coated the surface of sulfonated CFR-PEEK composites with GO. The experimental results showed that the mechanical properties, bending strength, and compressive strength of modified PEEK are effectively improved. In vitro experiments showed that modified PEEK had improved biocompatibility, increased apatite deposition, and upregulated osteogenic gene expression. In vivo bone defect models confirmed that the GO modified PEEK showed better bone integration.

Wang et al.[141] assembled GO nanosheets with oligopeptides onto the surface of SPEEK. In in vivo and in vitro antibacterial experiments, the GO/PDA hybrid complex anchored on the SPEEK surface by $\pi-\pi$ stacking can produce synergistic photothermal/photodynamic therapeutic effects, resulting in powerful antibacterial phototherapy. After exposure to light for 10 min, both *S. aureus* and *E. coli* on the modified PEEK surface had film shrinkage. At the same time, modified PEEK implants showed enhanced cytocompatibility, alkaline phosphatase activity, calcium matrix deposition, expression of osteogenic genes, and in vivo bone integration and bone remodeling.

The above experiments on loading GO on the PEEK surface proved that the loading of GO improved the antibacterial properties of the PEEK surface and also promoted the bone binding on the implant surface.

Like GO, 2D titanium carbide (MXene) is a new class of two-dimensional materials with a graphene-like structure, consisting of transition metal carbides, nitrides, or carbon nitrides. It has a wide range of light absorption capacity from ultraviolet to near-infrared light and high photothermal conversion efficiency and can be used as photothermal nanopreparations for photothermal treatment and photodynamic treatment of material surfaces.[142] It can also carry positive drugs through strong electrostatic action, giving the surface composite properties of the material.

Du et al.[143] loaded MXene nanosheets on the surface of CFR-PEEK. In vitro results showed that PEEK surfaces loaded with MXene could effectively kill bacteria after 10 min of NIR irradiation at 808 nm. In addition, PEEK bone implants loaded with MXene showed good cytocompatibility and an excellent ability to promote bone formation.

Yin et al.[144] coated MXene nanosheets on sulfonated PEEK. In vitro experiments demonstrated that the multifunctional coatings effectively killed osteosarcoma cells through thermal ablation under NIR irradiation, utilizing the synergistic photothermal effects of MXene and PDA. At the same time, antibiotics are loaded on the surface to realize the synergistic effect of anti-Gram-negative bacteria and Gram-positive bacteria. The GO modified PEEK bone implant demonstrated osseous integration in a rat model of a femoral defect.

2.2. Organic Coatings. *2.2.1. Polymer Coatings.* Chitosan (CS) is a natural marine macromolecule with antimicrobial properties. It also has good biocompatibility and osseointegration properties. As an antibacterial material, CS is inherently active and efficient against a variety of bacteria, such as *E. coli* and *S. aureus*, as well as filamentous fungi and yeasts.[145]

Qiu et al.[146] coated the PEEK with a CS layer using a simple facile self-assembly method. The existence of CS not only boosted cell adhesion, proliferation, and expression of osteogenic genes but also endowed the implant with in vitro antibacterial activity against *Porphyromonas gingivalis* (*P. gingivalis*) and *S. mutans*, which are oral resident bacteria. This may be related to the fact that CS is similar to the natural ECM component glycosaminoglycan, creating a local microenvironment for cell growth,[147] and the positively charged CS molecules react with the negatively charged molecules on the surface of the bacteria, changing the permeability of the bacteria and inhibiting their metabolism, that is, bacterial death.[148]

However, when CS is grafted with other biomaterials, physical cross-linking usually does not provide it with sufficient structural stability and results in separation from other materials.[149] In order to overcome the above problems,

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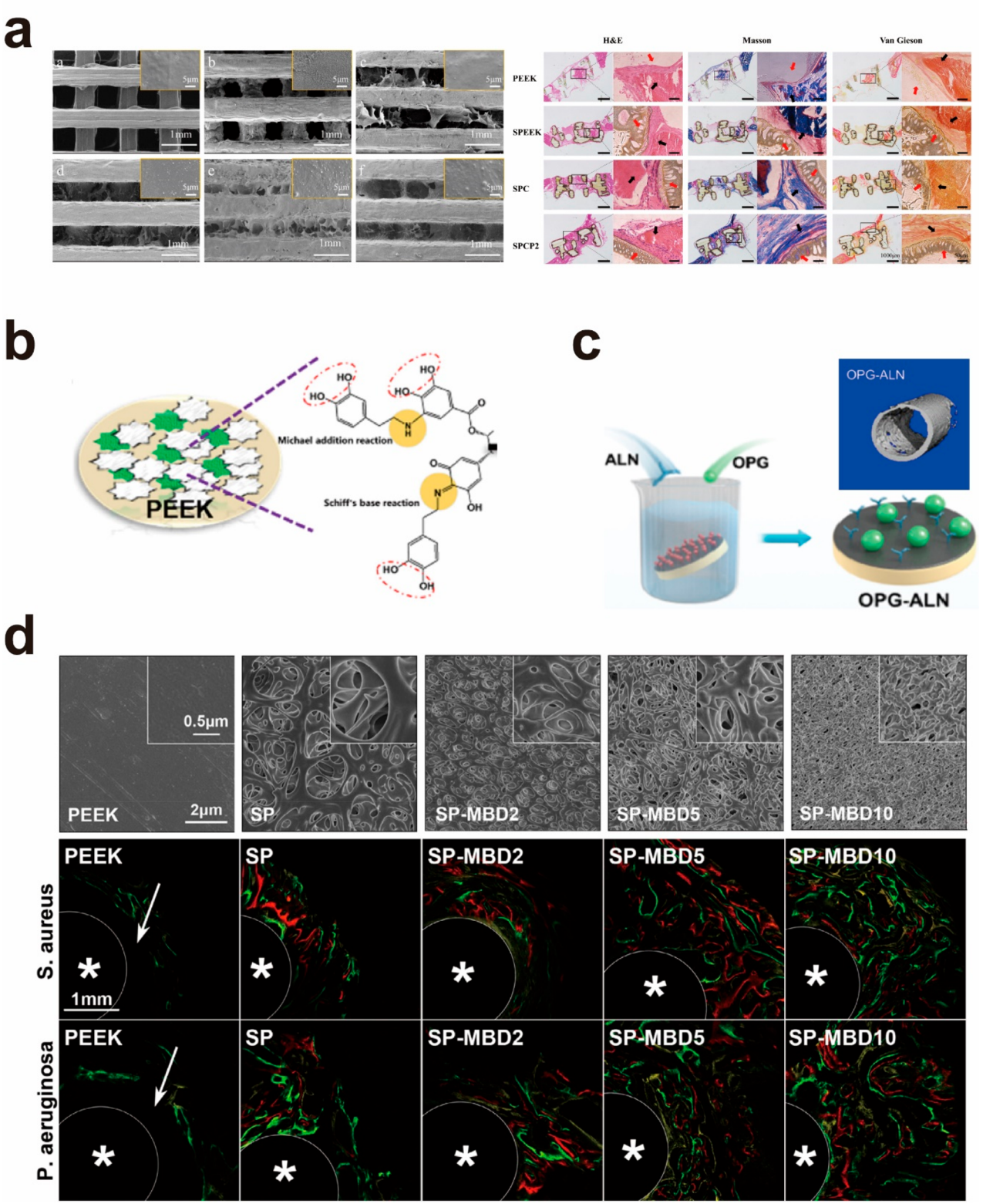

Figure 3. Surface modification strategies of organic compounds. (a) The polymer increased the contact area of the PEEK surface and enhanced the bone bonding ability of the PEEK surface.[150] Copyright 2022 Elsevier. (b) Epigallocatechin-3-gallate (EGCG), a Chinese herbal extract, was loaded on the PEEK surface.[155] Copyright 2023 Elsevier. (c) Loading of the osteoporosis drug alendronate (ALN) on the PEEK surface enhanced the surface osseous association.[26] Copyright 2022 Elsevier. (d) PEEK surfaces loaded with antimicrobial peptides showed good antimicrobial properties.[156] Copyright 2019 Elsevier.

methacrylic acid (MMA) was esterified and given photo-cross-linked grafting under ultraviolet irradiation.

Liu et al.[150] developed caprolactone-based shape memory alloy (CSMA)/polyhedral oligomeric silsesquioxane (POSS) nanocomposites on sulfonated 3D printed PEEK surfaces by

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UV-induced graft polymerization. Due to the presence of CSMA, the modified PEEK has improved surface properties, such as protein adsorption and apatite formation. In vitro and in vivo studies have shown that PEEK modified with CSMA/POSS nanocomposites has enhanced cell adhesion, proliferation, osteogenic differentiation, and osteogenic ability in rBMSCs and rat skull defect repair models (Figure 3a). This may be due to the fact that CSMA induces apatite deposition and improves osteogenic activity[151,152] by chelating Ca^{2+} while providing a local microenvironment for PEEK surface cells and cytokines.[153]

Dong et al.[154] decorated the surface of LCFR-PEEK with MOFs mediated by methacryloyl chitosan (MACS) hydrogels. In vitro experiments showed that modified LCFR-PEEK could regulate immune response, promote angiogenesis, and promote osteogenic differentiation. The subcutaneous implantation model in SD rats and the tibial defect model in rabbits further confirmed the superior immune regulation, angiogenesis, osteogenic differentiation, and bone integration capabilities of the implant.

The efficacy of these surface modifications is due to the pH-sensitive biomolecular release ability of the MACS hydrogels. It can be designed to release bioactive substances in the early stage of osseointegration (low pH), actively and accurately creating an immune microenvironment. In the later stage of osseointegration (normal pH is 7.4), the continuous long-term release of calcium is conducive to promoting bone−implant integration.

Poly(lactic-*co*-glycolic acid) (PLGA) is a kind of macromolecular material, which is widely used in pharmaceutical, medical engineering materials, and modern industrial fields. The degradation cycle of PLGA microspheres was about 9 weeks.[157]

Polyethylene glycol (PEG) is a type of biomedical substrate or lubricant. PLGA−PEG−PLGA can provide a controlled release in time and space for different types of therapeutic drugs.

Qi et al.[158] used PLGA−PEG−PLGA thermos-responsive hydrogels loaded with vancomycin on the surface of porous PEEK. It showed high inhibition rate against methicillin-resistant *S. aureus* in vitro. In vivo histological observation showed that PK had obvious bacteriostatic activity.

The addition of the polymer facilitates the rapid release of antimicrobials and sustained release of osteogenic drugs on the PEEK surface. Poly(vinyl alcohol) (PVA) is a water-soluble polymer with good hydrophilicity, chemical stability, biocompatibility, and bioadhesion and has been widely used as a drug delivery system and implantable artificial cartilage material.[159,160] It can be quickly dissolved in water, forming a stable colloidal performance between plastic and rubber. The rapid release of antibacterials in the early stage of implantation can be achieved by using PVA. The drug delivery system of PLGA nanoparticles is slow to release, which can control the drug release.

Yin et al.[144] used a cyclic freeze−thaw method to introduce drug-loaded PLGA nanoparticles and drug-loaded PVA gel into the surface of the sulfonated PEEK implant. The composite coating utilizes the swelling properties of PVA, and the gradual degradation of PLGA, which, respectively, load vancomycin hydrochloride (VA) and dexamethasone (Dex), enabled rapid release of antibacterial drugs and sustained release of osteogenic drugs. In vitro evaluations demonstrated effective antibacterial activity against *S. aureus* and promoted cell growth, adhesion, proliferation, and osteogenic differentiation.

2.2.2. Natural Extract Coatings. Natural extracts are substances derived from natural animal and plant extracts. Some of them come from animal collagen, such as gelatin. Some are derived from plants or herbs such as EUP from *Eucommia*. Some of them are widely used in the field of medicine and health as extracts,[161] and some play a therapeutic role as the main components of Chinese herbal medicine. The researchers applied natural extracts to the PEEK surface to help improve its peripheral bone-binding properties and antibacterial effects as bone implants.

Mehdizadeh Omrani et al.[162] modified PEEK's surface using oxygen plasma and gelatin. Gelatin is a macromolecular hydrophilic colloid derived from collagen with a structure similar to that of the ECM. The gelatin-coated PEEK surface showed increased wettability and supported greater cell attachment and proliferation. The addition of animal extract to the PEEK surface also showed antibacterial activity. Yang et al.[163] loaded sodium butyrate (SB), a fermentation product of the gut microbiota, onto the surface of sulfonated PEEK. On the surface of the experiment, modified PEEK enhanced the performance of macrophages, so as to play a good anti-*S. aureus* effect. In a rat model of femur infection, SB-loaded samples also showed significant osteogenesis in an infected environment.

The modification of plant extracts on the PEEK surface has also been extensively studied. Mao et al.[155] fabricated epigallocatechin-3-gallate (EGCG) coatings to PEEK. EGCG is a catechin monomer isolated from tea, which is the main component of tea polyphenols. It has various biological functions such as antioxidant, free radical scavenging, anti-inflammatory, antibacterial, etc.[164,165] The EGCG coating showed noncytotoxicity and promoted excellent cell adhesive and osteogenic effects in vitro. In vivo evaluation in a rabbit femoral condyle defect model demonstrated improved bone ingrowth (Figure 3b).

EUP is one of the main active ingredients of eucommia ulmoides (EU), a unique medicinal herb in China. It is mainly composed of six monosaccharides: glucose, fructose, mannose, fucose, galactose, and arabinose. It has multiple biological effects, such as immunomodulation and promoting bone integration.

Deng et al.[166] synthesized strontium EUP-Sr by linking *Eucommia* polysaccharides with strontium, which also has bone-immune function, and verified its anti-inflammatory and osteogenic effects. Mengdi et al.[167] coated EUP-Sr on the surface of PEEK. In vitro experiments showed that it could effectively promote the proliferation of MC3T3-E1 and showed obvious anti-inflammatory and osteogenic effects.

Osthole (Ost) extracted from *Cnidium* fruit can enhance osteogenic differentiation of osteoblasts by increasing the transcription factor Osterix through cAMP/CREB signal transduction.[168] Berberine (Ber) is an alkaloid contained in the rhizome of *Coptis chinensis*. Ber can effectively kill *Staphylococcus* by interfering with bacterial DNA replication and protein synthesis.[169] Sang et al.[25] loaded Ber onto a SPEEK surface. In vitro experiments showed that modified PEEK prevented *Staphylococcus* adhesion and growth and promoted osteoblast adhesion and osteogenic differentiation. Implantation experiments in rats also demonstrated the material's ability to promote bone formation and prevent endophytic bacterial infection.

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These studies suggest that natural extracts can improve the bacterial response and osteogenic effects around PEEK bone implants and contribute to the surrounding bone binding.

2.2.3. Synthetic Drug Coatings. In the clinical work of orthopedics and stomatology, some drugs used throughout the body are commonly used to treat osteoporosis, enhance the ecological balance of bone tissue, and protect bone health. These drugs bind specifically to active bone remodeling sites and reduce bone loss by inhibiting bone resorption and promoting bone formation. Loading this class of drugs on the PEEK surface is expected to regulate the surrounding environment of PEEK implants, enhance cell osteoblast differentiation, and strengthen bone binding around implants.

Alendronate (ALN) is an effective therapeutic agent for promoting bone formation and inhibiting bone resorption.[170,171] Studies have shown that ALN acts on BMSCs in a dose-dependent manner by activating ERK and JNK mediated pathways to stimulate osteogenic differentiation and inhibit lipogenic differentiation.[172]

Chen et al.[26] loaded ALN on the surface of PEEK. The surface introduction of bisphosphonates inhibits an acute inflammatory response, promotes the transformation of macrophages from M1 phenotype to M2 phenotype, downregulates osteoclast differentiation, enhances cell proliferation, ALP activity, and ECM mineralization, and upregulates in vitro osteogenesis related genes. In vivo experimental results also showed that the loading of bisphosphonates alleviated the inflammatory response of tissues surrounding PEEK bone implants and promoted bone−implant integration (Figure 3c).

Aspirin is a classic nonsteroidal anti-inflammatory drug (NSAID). NSAIDs have anti-inflammatory, antirheumatic, analgesic, and antipyretic effects.[173,174] Aspirin is widely used in the treatment of osteomyelitis, osteoarthritis, and various painful conditions.[175] The anti-inflammatory mechanism of aspirin is that it inactivates cyclooxygenase (COX), thereby inhibiting the conversion of free arachidonic acid oil into prostaglandins.[176] In the field of oral medicine, aspirin is used to treat periodontitis.[177] Therefore, the aspirin modification of PEEK surfaces can effectively inhibit the inflammatory response around bone implants.

Yu et al.[178] carried aspirin on the surface of sulfonated porous PEEK by immersion. The equipped porous PEEK has an enhanced osteogenic ability induced by immune regulation.

Antibiotics are considered the most effective drugs for treating bacterial infections and have successfully saved the lives of millions of infected patients worldwide. However, the disadvantages of systemic antibiotic use have led to the search for new solutions. Therefore, there is considerable concern about local administration of PEEK, which can achieve sufficient drug concentrations at the target infection site without increasing systemic toxicity, promising to improve antibiotic efficacy while reducing resistance.[179,180]

Gentamicin sulfate (GS), an antibiotic, is widely used in orthopedic surgery due to its broad-spectrum antibacterial action against a variety of strains.[181] Yan et al.[182] constructed a GS coating on a sulfonated PEEK surface. After treatment with this coating, the number of viable bacteria in the medium was reduced by 1/10, and the number of viable bacteria adhering to the coating was also reduced by 1/10. In addition, under physiological pH conditions, the modified PEEK surface structure is conducive to biocompatibility, cell adhesion, osteogenesis, and differentiation. As the pH decreases, the release of the antibiotic GS increases, triggering antibacterial action.

Moxifloxacin hydrochloride (MOX) is a novel 8-methoxyquinolone antibiotic with good broad-spectrum antibacterial activity and low cytotoxicity and has been widely used as a loaded antibiotic in local drug delivery systems.[183] In addition, studies have shown that MOX has higher bioavailability and bone tissue penetration than other typical first-line antibiotics such as vancomycin.[184,185]

Gao et al.[186] developed a modified PEEK surface by coating it with PDA and incorporating MOX and osteogenic growth peptide (OGP) for sustained release. In vitro experiments demonstrated that the modified surface not only significantly enhanced specific cell adhesion, proliferation, and osteogenicity compared to other groups but also had a durable and excellent antibacterial effect against *S. aureus* and *E. coli*. Importantly, using infected and noninfected rat tibia models confirmed the in vivo antimicrobial and osteogenesis abilities of SPD-MOX/OGP.

2.2.4. Peptide Coatings. Peptides, as important mediators of biological processes, have received extensive attention in the field of biomedicine due to their beneficial performance in titer, receptor selectivity, and low toxicity of metabolites.

Bone morphogenetic protein-2 (BMP-2) is a well-characterized growth factor that can induce osteoblast differentiation and bone formation.

Zhao et al.[187] coated the PEEK surface with azide-$DOPA_4$ and incorporated BMP-2p through bio-orthogonal reactions. The modified material had an increased surface roughness and hydrophilicity. In vitro, the modified material showed enhanced osteogenic induction of rat bone marrow mesenchymal stem cells. In vivo, the modified material exhibited higher new bone volume and density and better osseointegration in a rat bone defect model. Potentially, due to the $DOPA_4$@BMP-2p coating, osteogenesis was synergistically promoted with induced $Foxp^{3+}$ regulatory T cells.

Human hyaline protein (HVP), a peptide resistant to enzymatic degradation,[188] promotes cell surface glycosaminoglycan-mediated osteoblast adhesion.[189] Cassari et al.[190] decorated the surface of 3D-printed PEEK with adhesive peptides, HVP and D2HVP, through specific covalent bonds to improve their integration with host tissues. It demonstrated pH-sensitive biomolecule release capabilities. In vitro experiments revealed that both peptides promoted cell proliferation at 3 and 21 days, but D2HVP-functionalized PEEK demonstrated superior results, with increased proliferation, higher calcium deposition, and more elongated cell morphology.

BFP (Bone Morphogenetic Protein Interaction Network 7), derived from BMP-7, plays a significant role in the osteogenic differentiation of both human BMSCs and human induced pluripotent stem cells (hiPSCs).[191,192]

Vascular endothelial growth factor simulation peptide has been reported to have the same angiogenic activity as VEGF.[193]

He et al.[194] developed a multifunctional coating for sulfonated PEEK that combines two peptides, VMP and BFP. Fusion peptide engineered PEEK showed osteogenic and angiogenic activity. Bone integration and angiogenesis of modified PEEK were further demonstrated in a rabbit femur defect model.

Antimicrobial peptides (AMPs) are a class of amino acid sequences with broad spectrum and strong antimicrobial

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activity, which have positive charge and amphiphilic structure. Some of these are important components of innate immunity against pathogens in many organisms and can bind to negatively charged bacterial membranes through nonspecific electrostatic interactions, leading to cell death by destroying the bacterial membranes. In addition to directly killing bacteria, AMPs also have the dual role of eliminating biofilm and alleviating inflammatory response through immune regulation.[195,196]

Mouse β-defensin-14 (MBD-14) is a natural antimicrobial peptide that has chemotaxis against broad-spectrum leukocytes[197] and has similar broad-spectrum activity against Gram-positive and Gram-negative bacteria and multidrug resistant bacteria, fungi, and viruses.[197−199] Yuan et al.[156] modified mouse MBD-14 on a sulfonated PEEK surface. In vitro antibacterial experiments showed that modified PEEK was effective against *S. aureus* and *Pseudomonas aeruginosa*. In addition, the proliferation and osteogenic differentiation of rBMSCs on modified PEEK were also improved. In the infected rat femur model, modified PEEK enhanced the bone integration ability of the rat femur and successfully inhibited bacterial growth (Figure 3d).

In order to ensure that the surface of PEEK implants can not only resist infection but also promote bone tissue healing, Li et al.[27] designed a peptide engineering surface on the PEEK surface with both osteogenic properties and anti-infection advantages. When the ratio of click-chemically loaded OGP to AMP was 1:1, the surface showed the best synergistic effect of osteogenesis and anti-infection.

The use of peptides on PEEK surfaces still has many limitations, such as high development costs, and only low dose effective peptides have clinical translational potential. It is easily degraded and has a limited time to play a role in the body.[200] How to design and develop peptides with high titer and long action time to serve the bone implant industry is the prospect of expanding the application of peptides in the future.

2.3. Cell and Biomolecular Coatings. *2.3.1. Cells and Their Exosome Coatings.* The cell is the smallest unit of the organism that performs biological functions. Among them, mesenchymal stem cells (MSCS) have the potential to self-renew and multidifferentiate, making them useful for the regeneration and repair of bone, cartilage, muscle, bone marrow stroma, tendons, fat, and other connective tissues.[201,202]

Roskies et al.[203] adhered BMSC and adipose-derived stem cells (ADSCs) from rats to the surface of 3D-printed PEEK. The morphology of cells detected by SEM was similar to that of living fibroblasts attached to the surface of scaffolds and micropores, and the material surface showed good matrix mineralization. On the modified PEEK surface, the viability of ADSC and BMSC was good, and the bone differentiation rate of ADSC was higher than that of BMSC. This indicates that loading pluripotent stem cells onto the PEEK surface can induce the improvement of biological activity and enhance the play of surface biological functions. However, it should be considered that loading cell coating on the PEEK surface will bring about immunogenicity problems, and the next step should be to consider cell pretreatment and long-term detection.

However, the difficulty in obtaining a large number of mesenchymal stem cells makes it difficult to apply stem cell therapy to the clinic. The expansion of stem cells in vitro was associated with a loss of cell potency and phenotypic modification. The longer the incubation time of stem cells, the greater is the risk of contamination. Fortunately, studies have found that the therapeutic effect of direct stem cell replacement therapy is limited, and the therapeutic effect of mesenchymal stem cells is mainly played through the paracrine mechanism.[205] Through exocytosis, stem cells release exosomes (Exos), fusion bodies of the cell membrane with intracellular multivesicular bodies (MVBs).[206,207] As carriers of paracrine secretions, bone marrow mesenchymal stem cell-derived Exos contain a variety of biosignaling molecules, including proteins, lipids, and small RNAs, which are transferred to target cells to perform regulatory functions.[208−211]

Fan et al.[28] decorated BMSC-derived Exos onto tannic acid (TA) modified sulfonated PEEK. The Exos released slowly from SPEEK and were efficiently phagocytosed by cocultured cells, improving the biocompatibility of SPEEK. In vitro experiments demonstrated that Exos-loaded SPEEK promoted macrophage M2 polarization through the NF-κB pathway, enhancing BMSCs' osteogenic differentiation. In vivo assessments using a rat air-pouch model and rat femoral drilling model showed efficient macrophage M2 polarization, desirable new bone formation, and satisfactory osseointegration for Exos-loaded SPEEK.

In order to enrich the exosomal cargo and improve the targeting efficiency of Exos, the research is no longer limited to Exos themselves, and engineering Exos emerge. Engineering Exos are Exos generated by altering the parent cells or directly on the Exos by biochemical or physical processing.[212,213]

Ma et al.[214] cultured human mesenchymal stem cells (hMSCs) on nanotopological titanium surfaces to guide the ability of stem cells to adhere, proliferate, and differentiate. The Exos of hMSCs induced by nanomorphology were extracted, and the potential of the Exos to promote bone was verified by in vivo and in vitro experiments. This may be related to its involvement in the regulation of Ras, PI3K-AKT, and p53 signaling pathways, MAPK signaling, focal adhesion, mineral absorption, ECM−receptor interactions, and the cell cycle. The engineering Exos loaded on the surface of 3D-printed PEEK were observed to be uniformly distributed on the PEEK plate in vitro. In vivo, it was slowly released and absorbed after 7 days and significantly induced new bone formation after 12 weeks. Exosomes have great potential for PEEK surface applications, but it is undeniable that bioderived materials involve heterologous issues as they may be recognized by the host immune system and trigger an immune response. While enjoying its enhanced biological effect, we should also reduce the immunogenicity of engineered PEEK from the perspective of donor selection, purification, decontamination, and engineering modification.

In addition, MSC-derived Exos have been found to contain microRNAs related to cell activity and the regulation of biological activity. MiRNAs are endogenous noncoding RNA molecules composed of nucleotides that regulate the expression of related genes and proteins after transcription.[215]

By analyzing miRNA in Exos derived from BMSCs, Liu et al.[29] found that the expression of miR-21a-5p was the highest and was related to immune regulatory pathways. Therefore, they developed porous bioactive glass nanoparticles loaded with mir-21a-5p on PEEK surfaces (miR-21a-5p@T-MBGNs) to achieve controlled release of miRNA. The cocultured cells can engulf the miR-21a-5p@T-MBGNs that are slowly released in them. In in vitro experiments, modified PEEK

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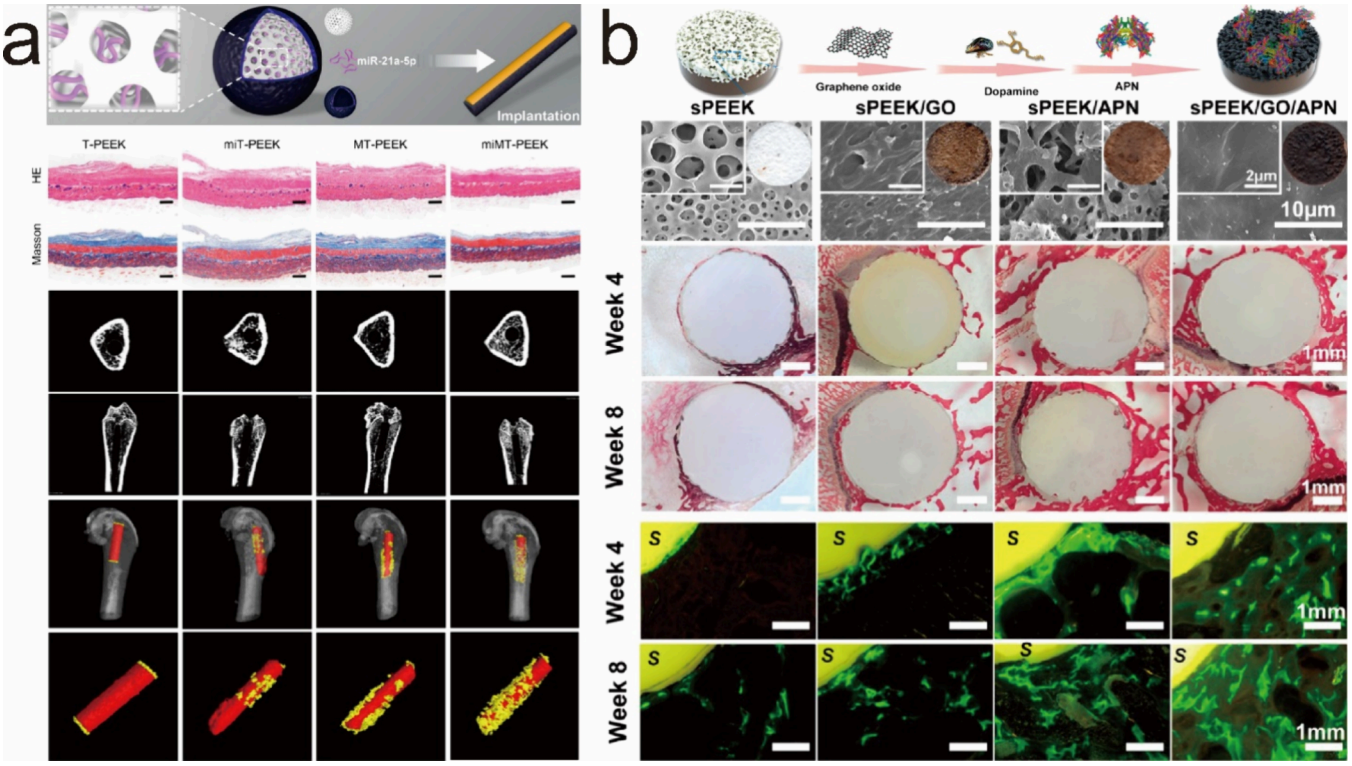

Figure 4. Surface modification strategies of organic compounds. (a) The loading of noncoding RNA on the PEEK surface contributed to immune regulation and enhanced peripheral bone binding around bone implants.[29] Copyright 2023 American Chemical Society. (b) Liposomes (APN) on the surface of PEEK promoted bone regeneration and osteounion around bone implants.[204] Copyright 2020 American Chemical Society.

enhanced macrophage M2 polarization through the NF-κB pathway and promoted BMSC osteogenic differentiation. In vivo experiments in a rat balloon model and rat femur drill hole model showed that macrophage M2 polarization was effective, new bone was formed, and bone binding was good (Figure 4a).

2.3.2. Biomolecular and Biofactor Coatings. PDA, or polydopamine, is a polymer of dopamine. It has a structure similar to that of mussel-derived peptides and strong adhesion properties; therefore, it is widely used for interfacial bonding. Research shows that it not only improves the adhesion effect of the interface but also helps to improve the biocompatibility of PEEK surface and enhances the load of metal particles,[21] drugs,[40] and proteins[182] on the PEEK surface. Studies have shown that mussel-derived peptide (Mfp-5) plays an antibacterial role by destroying bacterial membranes with a high lysine content. The mussel derived peptide DOPA produces hydrogen peroxide (H_2O_2), a powerful antibacterial agent, through the autoxidation reaction, which shows antibacterial activity.[216] Therefore, whether PDA also has similar antibacterial activity needs to be further verified in future studies.

Interleukin 4 (IL-4) is an immune-regulating cytokine secreted by immune cells. It plays an important role in regulating the balance of the T-helper (Th) cell subpopulation.[217] It is involved in regulating the bone-immune effect, and studies have found that its regulatory effect on macrophages controls subsequent angiogenesis.[218,219]

Zheng et al.[220] deposited IL-4 on PEEK. The coating promotes bone regeneration by alleviating acute inflammatory responses and promoting osteogenesis, while inhibiting osteoclast generation in osteoporosis conditions.

Chondroitin sulfate (CS) is a natural glycosaminoglycan that is widely present in human soft tissues and is one of the main components of the extracellular matrix. Studies have shown that CS has anti-inflammatory and osteogenic activities. Zheng et al.[30] loaded CS and Sr on the surface of PEEK. In in vitro experiments, it has been shown that the material can significantly promote cell adhesion and diffusion, improve osteogenic activity, and reduce inflammatory response. In the SD rat femur defect model, the modified material group showed better bone integration performance than did the unmodified material.

Adiponectin (APN) is one of the most abundant adipokines secreted by adipocytes. It is a protein hormone, whose basic biological function can maintain energy homeostasis and regulate glucose metabolism and fatty acid oxidation. Currently, many studies have shown that APN can serve as an active bone inducer to promote osteogenic activity and to induce bone formation within the conductor. Deng et al.[204] constructed a photoresponsive bone-promoting coating containing APN protein on sulfonated PEEK. In in vitro experiments, functionalized PEEK showed excellent cytocompatibility and in vitro osteogenic ability in cell proliferation, spreading, alkaline phosphatase activity, extracellular matrix calcification, and bone related gene expression and showed photothermal bactericidal ability. In vivo evaluation using a rabbit femur defect model confirmed that the multifunctional coating significantly promoted bone regeneration and bone integration (Figure 4b).

An et al.[221] constructed a HA hydrogel coating loaded with platelet-rich plasma (PRP) and nerve growth factor (NGF) on the surface of SPEEK. PRP is an autologous platelet concentrate in which the α-plasmid secretes a variety of

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growth factors. They synergistically promote the regeneration and repair of cells and substrates in damaged tissues, vascular regeneration, and bone tissue repair and regeneration.[222] NGF is a peptide growth factor that preregulates the proliferation and differentiation of neuronal and non-neuronal cells. NGF has been shown to be widely expressed in bone healing, and as a neurotrophin (NT), it may promote blood vessel formation by enhancing the expression of vascular endothelial growth factor.[223] In vitro and SD rat models of tibial defect confirmed that modified PEEK has a good ability to promote bone formation and angiogenesis.

The above experiments show that PEEK surface modified biological factors can help enhance related biological functions and have the advantages of small biosafety risks and strong titer. However, its stability and action time on the PEEK surface need to be further investigated.

2.3.3. Liposome Coatings. Liposomes, bilayer vesicles spontaneously formed by phospholipids in water, are a type of nano drug formulation that can carry, deliver, and slowly release some bioactive molecules into the cytoplasm. Within the vesicles of liposomes, a hydrophilic environment is suitable for encapsulating highly water-soluble drugs and gene fragments. The middle of the bilayer, where the tail of the molecule is located, is a suitable location for storing lipid soluble drugs.

Xu et al.[31] used Dex and minocycline supported liposomes (Dex/Mino liposomes) on PEEK surfaces. An in vitro study confirmed that the Dex/Mino liposome modified PEEK surface has good stability and cell compatibility. Compared with naked PEEK, improved osteogenic differentiation of human mesenchymal stem cells was found on the functional surface under bone-induced and bone conduction conditions due to the release of liposome Dex. An in vivo bacteriostatic test confirmed that Mino released from the functionalized surface has an effective antibacterial effect. Furthermore, subcutaneous foreign body responses and beagle femur implantation models confirmed the enhanced anti-inflammatory and osteointegration properties of functionalized PEEK. Therefore, the liposome has the potential to be an excellent drug carrier on the surface of PEEK bone implants.

3. CONCLUSION

We present the latest technologies in a series of material strategies for PEEK surface modification. The research described in this paper focuses on PEEK surface modification for anti-infection and osteogenic promotion, gradually validated through practical experiments. It lays the foundation for loading surface materials and enhancing biological activity, including but not limited to metal materials, glass ceramic materials, and biodegradable biomaterials. PEEK possesses inherent advantages in bone implantation due to its favorable elastic modulus matching with bone tissue, chemical stability, and X-ray transmission capabilities, among others. However, the field of PEEK bone implantation is still in its early stages, and the surface bioinactivity hinders the performance of its biological functions. Ongoing research on loading inorganic and organic matter, cells, and biomolecular coatings continuously introduces new materials for biomaterial researchers to apply in PEEK surface modification. Inorganic coatings are often released and play a role in the form of ions, while excessive ion concentration will hinder normal physiological activities and even lead to body poisoning. The optimal concentration and loading form of inorganic substances are problems that need to be explored on different surfaces. There are also problems in selecting the optimal concentration and designing the biological function program for organic coatings. For cell and biomolecular coatings, there is often a risk of an immune response and infection from alien biomaterials.

As research on PEEK surface loading deepens, the role of a single substance is gradually marginalized, paving the way for the possibility of designing surface modifications based on composite and synergistic biological development principles. While current experiments often independently verify the effects of a single molecule or substance, the human body undergoes countless interacting reactions. Thus, there is a clear need for responsive PEEK surfaces capable of addressing these compounded effects. In future applications of responsive PEEK biology and even clinical work, bone implantation remains the most common area. The elastic modulus, similar to that of bone, can effectively reduce bone resorption caused by the stress−concentration around the PEEK implant. Chemical stability ensures that the chemical properties of the surface remain unchanged after disinfection. X-ray transmission enables timely detection of peripheral inflammation after PEEK implantation, but it is challenging to inspect and locate it after surgery due to the lack of X-ray radiation resistance. Surface inertia needs to provide a modified solution, and the coordinated loading of inorganic matter, organic matter, cells, and biomolecules makes it possible for PEEK surfaces to exhibit biological activity. In future studies, addressing how to control the release of different substances at the required physiological and pathological stages, releasing the appropriate concentration of substances, designing synergistic effects between different modified substances rather than antagonistic effects, preparing personalized modification strategies for patients with different underlying diseases and physical conditions, and designing the convenient implementation of economical and applicable PEEK surface modification materials are the challenges facing scientific researchers.

AUTHOR INFORMATION

Corresponding Authors

Xia Li − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*; Email: lixia6881@163.com

Bing Li − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*; orcid.org/0000-0002-9410-733X; Email: 1975@163.com

Xiuping Wu − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*; Email: 77wxp@163.com

Authors

Ziyang Bai − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*

Yifan Zhao − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi*

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Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China

Chenying Cui − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*

Jingyu Yan − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*

Danlei Qin − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*

Jiahui Tong − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*

Hongyi Peng − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*

Yingyu Liu − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*

Lingxiang Sun − *Shanxi Medical University School and Hospital of Stomatology, Taiyuan, Shanxi 030001, China; Shanxi Province Key Laboratory of Oral Diseases Prevention and New Materials, Taiyuan, Shanxi 030001, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c00923

Author Contributions

[▽]Z.Y.B., Y.F.Z., and C.Y.C. contributed equally to this work. Z.Y.B, Y.F.Z., and C.Y.C. drafted the original manuscript and visualized the data. J.Y.Y., D.L.Q., J.H.T., H.Y.P., Y.Y.L., and L.X.S. provided suggestions and revised this Review. All authors have read and agreed to the published version of the manuscript.

Notes

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