



Engineering surfaces of polymer-based medical implants for tissue repair and regeneration

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ABSTRACT

Polymer-based medical implants hold significant importance in modern healthcare due to their unique properties and versatile applications. Before implantation, tailoring the interfacial interactions between the implant and the biological tissues via the functional modification of implant surfaces is a vital step in addressing key challenges associated with implants while improving patient outcomes, such as reduced immune rejection, improved tissue integration, bioactive signaling, infection resistance, long-term stability, etc. In this review, we first introduce some typical polymeric materials used for medical implants, and then systematically illustrate various surface functionalization strategies of polymer-based medical implants, and finally provide a brief overview of the current challenges and future directions associated with highly efficient and universal implants' surface-functionalization strategies.

1. Introduction

Medical implants refer to active or non-active medical devices that are permanently or temporarily implanted in the human body to serve therapeutic or diagnostic purposes, including repair, replacement, or functional enhancement of human tissues or organs. There is a wide variety of materials used in medical implants, including metals, polymers, and bioceramics [1–3]. These materials each possess distinct characteristics, making them suitable for different implantation scenarios. Specifically, polymer-based medical implants have been widely used in tissue repair applications such as artificial blood vessels, covered stents, artificial joints, urinary catheters, absorbable sutures, and balloon catheters due to their excellent processability and biocompatibility. Dating back to the 1940s, polymethylmethacrylate (PMMA) was the first polymer material successfully implanted into the human body as orthodontic retainers, dentures, and dental restorations [4]. Subsequently, PMMA was widely adopted in neurosurgical practice for cranial reconstruction [5]. The success of PMMA marked the beginning of the modern era of polymer-based medical implants, and subsequently led to the development of revolutionary products such as polytetrafluoroethylene vascular grafts (1940s) [6], polyester vascular grafts (1950s) [7], polyethylene artificial joints (1960s) [8], polyvinyl chloride

catheter (1960s) [9], polyurethane pacemaker leads (1970s) [10], polyetheretherketone spinal implant (1990s) [11], and poly-L-lactide-caprolactone absorbable stents (2010s) [12]. With the global demography of aging and the rise in various chronic and sudden-onset diseases, the market demand for polymer-based medical implants continues to grow. Market statistics show that the global market size of medical-grade polymer materials was approximately 21.51 billion USD in 2023, and it is expected to reach 36.77 billion USD by 2030 [13].

Following implantation, the implant initially interacts with the host tissue through its surface. The interfacial interactions between the implant surface and surrounding tissues can trigger biochemical cascades, critically influencing biocompatibility and long-term functionality [14,15]. However, the majority of polymer implants are bio-inert, not only affecting their functionality but may also trigger long-term complications, such as adverse immune responses by nonspecific adsorption of proteins, infections by bacterial colonization, and repair failure due to the mechanical mismatch between the implant surface and tissue microenvironment. Therefore, engineering the implant surface with specific functionality (surface functionalization) plays a pivotal role in ensuring the biosafety and clinical efficacy of implants. Generally, the objectives of surface functionalization include: (1) Mitigating the foreign body response. Unmodified implant surfaces are prone to

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recognition as foreign substances by the immune system, leading to functional failure and adverse complications [16]; (2) Conferring bioactivity to implants. For instance, applying a bioactive coating treatment to the surface of artificial joints can promote the adhesion and growth of bone cells, thereby achieving enhanced osseointegration [17]; (3) Endowing the scaffold with drug-loading and sustained-release properties to exert its specific function, such as antimicrobial, anti-fibrosis, or anti-inflammation performances; (4) Enhancing the functional lifespan of the implants. For example, modifying the surface of cardiovascular stents with anti-thrombogenic capability not only reduces patients' health risks but also eliminates the need for frequent replacements caused by degraded stent performance [18]. In summary, applying specific surface modifications to implants to endow them with multiple functionalities can significantly improve implant performance, reduce complications, promote patient recovery, and serve as a critical strategy for enhancing clinical efficacy.

A comprehensive review of surface functionalization strategies for polymeric implants will facilitate researchers' timely access to cutting-edge advancements in this field, provide the latest research progress in this field, and enable the design of customized surface-functionalized products as needed. Some earlier reviews and book chapters, such as "Surface Modification of Polymeric Biomaterials" in *Biomaterials Surface Science* [19], have provided valuable overviews of polymer surface modification techniques [20,21]. However, most of these works primarily deal with traditional physicochemical modification strategies and fundamental polymer surface properties. In contrast, this review focuses on the recent progress, predominantly within the past five years, in advanced surface engineering strategies for polymeric implants. Specifically, we highlight progress in biointerfacial interactions, bio-inspired design, stimuli-responsive coatings, and multifunctional hybrid interfaces, with particular attention to their potential in clinical translations (Fig. 1). Firstly, we provide an overview of common polymeric implant materials, their clinical applications, and surface characteristics. Subsequently, we systematically illustrate the recent progress in surface functionalization methodologies, emphasizing the necessity of universal surface functionalization and exploring cutting-edge directions for achieving 'customizable functionalization' of implant surfaces, highlighting emerging technologies that enhance surface

adaptability, bioactivity, and durability to meet diverse clinical demands. Furthermore, we discuss the potential of dynamic, intelligent, and patient-specific implant systems, which offer promising avenues for future medical applications.

2. Polymer implants overview

Polymer-based implants primarily consist of synthetic polymers demonstrating excellent biocompatibility, ease of processing, and tailorable mechanical properties. Currently, more than 17 types of polymer materials have been clinically implemented as the main components of implants for restoration in various medical scenarios (Fig. 2), including surgical sutures, artificial blood vessels, artificial joints, and tissue engineering scaffolds (Table 1). Based on differences in chemical structures, these polymers can be broadly categorized as follows: polyolefins, polytetrafluoroethylene, biodegradable polyesters, polyurethanes, polyetheretherketone, polyacrylics, and hydrogel. In this section, seven types of polymer implants most widely used in clinical applications, including polyether ether ketone (PEEK), polytetrafluoroethylene (PTFE), polyurethane (PU), polyvinyl chloride (PVC), silicone-based polydimethylsiloxane (PDMS), poly(L-lactide-co-ε-caprolactone) (PLCL), and polylactic acid (PLA) will be introduced, highlighting their surface properties and application occasions.

2.1. Polyetheretherketone (PEEK)

PEEK is a semi-crystalline high-performance thermoplastic composed of repeating aromatic ether ketone units. It is typically synthesized via a nucleophilic substitution reaction, produced by the polycondensation of 4,4'-difluorobenzophenone with a salt of resorcinol under high temperature, high vacuum, and in a polar solvent such as diphenyl sulfone [43]. The abundance of aromatic ring structures in its molecular chains confers PEEK with exceptional rigidity and stability [44]. The combination of flexible ether bonds and carbonyl bonds provides segmental mobility, thereby balancing inherent stiffness while maintaining outstanding mechanical strength. The achievement of this structural characteristic depends on precise synthesis processes. The raw material purity, polymerization temperature, and post-treatment methods determine the purity, molecular weight, and chain uniformity of PEEK [45]. Impurities in raw materials or inadequate temperature control have been shown to cause molecular weight heterogeneity and a broad molecular weight dispersion. This phenomenon not only directly diminishes the mechanical properties of the material, making it inappropriate for long-term use in weight-bearing implants, but also increases surface roughness, thereby elevating the risk of bacterial adhesion. Due to its remarkable qualities attained through controlled synthesis, PEEK has been widely adopted in multiple clinical specialties since obtaining FDA approval for medical implants in 1999 [46–48]. In orthopedic applications, PEEK's elastic modulus (3–4 GPa) closely matches that of cortical bone (7–30 GPa), effectively reducing stress-shielding phenomena [49]. This modulus compatibility makes it ideal for spinal cages and arthroplasty components [50]. For neurosurgical applications, PEEK exhibits near-radiolucency (radiolucency similar to soft tissue, with only 10–20 Hounsfield units difference) and MRI compatibility, making it particularly valuable for cranial reconstruction [51]. In dental implantology, PEEK's exceptional wear resistance and tooth-like aesthetics have promoted its use in abutments and provisional restorations [52].

Nevertheless, the inherent hydrophobicity and chemical inertness of PEEK substantially impair protein adsorption and cellular attachment, frequently causing inadequate osseointegration and/or biofilm-associated infections that may culminate in implant failure [46,53,54]. Clinical studies demonstrate that untreated PEEK implants exhibit a 5-year osseointegration failure rate ranging from 15 % to 20 % [55]. Recent advances in surface engineering strategies have significantly improved the osteoinduction and antibacterial properties of PEEK

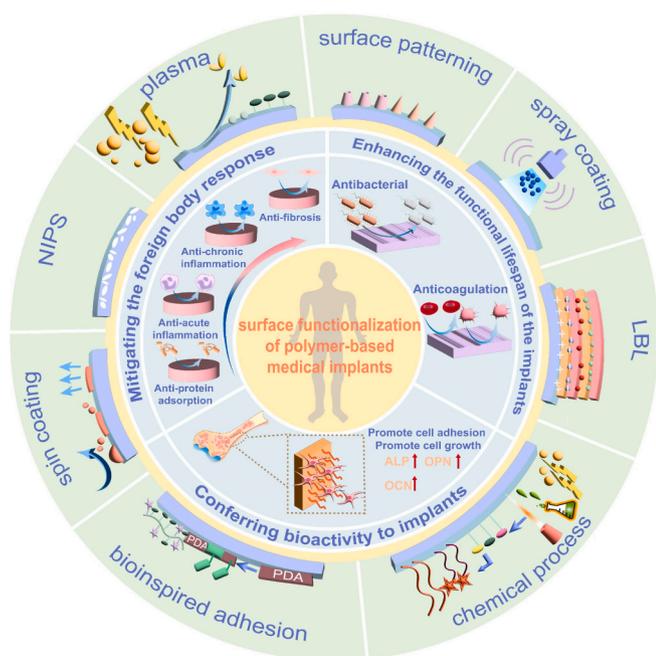


Fig. 1. Emerging approaches of surface functionalization of medical implants for various applications in tissue repair and regeneration.

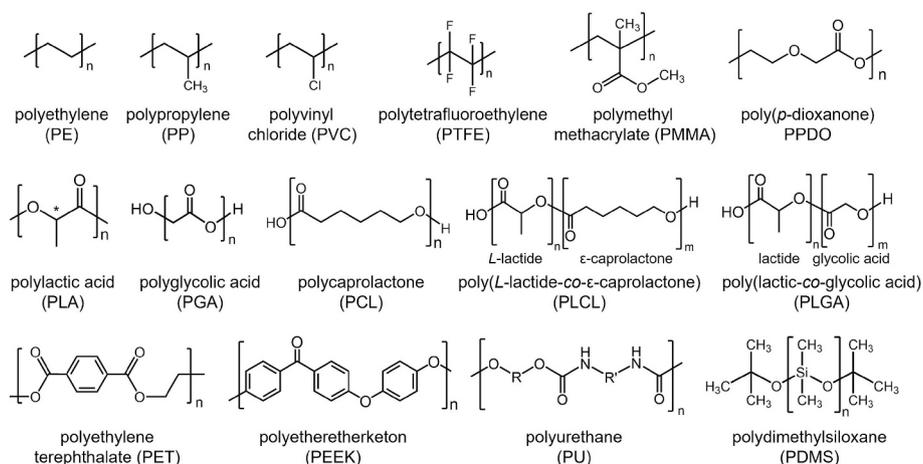


Fig. 2. Chemical structures of typical polymers for medical implants.

Table 1

Typical polymers in the fabrication of medical implants for clinical applications.

Types of medical polymers	Advantages	Disadvantages	Application	Refs.
PDMS	Excellent mechanical flexibility and chemical stability	Surface hydrophobicity leading to biofouling, fibrous encapsulation	Breast prosthesis, artificial joint spacer, catheter	[22]
Ultra-High Molecular Weight Polyethylene	Biocompatibility, low coefficient of friction, high impact resistance and toughness	Wear particles trigger osteolysis, poor thermal stability	Artificial joint liners, spinal implants	[23,24]
PMMA	Excellent biocompatibility, injectability and mechanical strength	Biological inertness, exothermic reaction burns surrounding tissues	Bone cement, dental fillings, artificial lenses	[25]
PTFE	Excellent biocompatibility, chemical stability, and flexibility	Biological inertness	Artificial blood vessels, heart patches	[26]
PEEK	Excellent mechanical and physicochemical tolerance	Biological inertness, poor osteoinduction	Spinal fusion devices, dental implants, cranial prosthetic plates	[27]
PU	Excellent elasticity and flexibility, controllable degradation properties	Surface easily calcified, potential toxicity of long-term degradation products	Artificial heart valves, artificial blood vessels	[28]
PET	Excellent biocompatibility, mechanical properties	Biological inertness	Artificial blood vessels, artificial ligament	[29,30]
Polypropylene	Excellent biocompatibility, mechanical properties, ease of processing, low cost	Surface inertness	Hernia repair mesh, non-absorbable sutures	[31]
PVC	Adjustable flexibility	Plasticizer migration problems, lack of biocompatibility, limited mechanical properties	Catheter	[32]
PLA	Biodegradability and biocompatibility	Rapid decay of mechanical properties	Absorbable bone nails/plates	[33]
Polyglycolic acid (PGA)	Rapid degradation and absorption, biocompatibility	Excessive degradation rate, acidic degradation products induce localized inflammatory responses	Absorbable Suture	[34]
Polycaprolactone (PCL)	Superior flexibility and toughness, excellent biocompatibility, ideal material for drug slow-release carriers	Acidic degradation products induce localized inflammatory responses	Sutures, soft tissue repair implants	[35]
PLCL	Excellent mechanical properties and biocompatibility, controlled degradation rate, high machinability	Lack of bioactivity	Absorbable sutures, biodegradable stents	[36]
poly(lactic-co-glycolic acid) (PLGA)	Controlled degradation rate, excellent biocompatibility and safety, high machinability	Low mechanical strength, degradation rate influenced by the environment	Absorbable sutures, biodegradable stents	[37,38]
Poly(p-dioxanone)	Excellent biodegradability, biocompatibility, bioabsorbability	Easily hydrolyzed, poor thermal stability	Absorbable Suture	[39]
Hyaluronic acid hydrogel	Excellent biocompatibility, degradability, and functional modifiability	Limited mechanical properties, uncontrolled degradation, and insufficient long-term stability	Facial fillers, artificial vitreous substitutes	[40]
Polyvinyl alcohol hydrogel	Excellent biocompatibility, tunable mechanical properties, and 3D printing suitability	Limited mechanical properties, insufficient long-term stability	Cartilage implant	[41,42]

implants. To improve these problems, researchers have developed a variety of surface modification methods. For instance, the infiltration of hydroxyapatite into PEEK by physical laser actuation has been shown to induce a hydrophilic transformation in the treated PEEK surface [56]. Another study proposed a strategy to modify the surface of 3D-printed PEEK implants to address the limited osseointegration capability of PEEK implants and their susceptibility to bacterial colonization. The hydrophilicity of the PEEK surface was achieved by subjecting the

surface to oxygen plasma treatment, and then hyperbranched poly-L-lysine (HBPL) was modified onto the surface by physical adsorption and chemical grafting, respectively. HBPL contains α -PL and ϵ -PL units. ϵ -PL has been shown to disrupt microbial cell membranes, thereby playing an antimicrobial role, while α -PL has been demonstrated to promote osteointegration by regulating cell adhesion and differentiation through electrostatic interaction [57].

2.2. Polytetrafluoroethylene (PTFE)

PTFE is a fully fluorinated linear polymer, characterized by a molecular structure comprising a carbon backbone enveloped by a densely packed shell of fluorine atoms. PTFE demonstrates exceptional chemical inertness and thermal stability (continuous service temperature up to 260 °C), stemming from the strong C—F bond (bond energy ~485 kJ/mol) [58,59]. The synthesis of PTFE can be performed via two approaches: suspension polymerization and emulsion polymerization, both of which involve polymerizing tetrafluoroethylene monomers under high temperature and pressure [60]. The polymerization temperature significantly affects the length of the polymer chains. Increased temperatures have been demonstrated to diminish molecular weight, hence lowering tensile strength and creep resistance. The rigorous regulation of reaction pressure and monomer purity is directly associated with molecular chain uniformity, which is essential for achieving a highly crystalline microstructure, imparting to PTFE an extremely low coefficient of friction, outstanding heat resistance, and non-melting properties [61]. In emulsion polymerization systems, the choice of emulsifiers and subsequent sintering operations may accurately control the material's hierarchical pore structure, which is essential for the preparation of expanded polytetrafluoroethylene (ePTFE) [62]. Thus, controlling the synthesis process enables the precise design of molecular weight, crystallinity, and pore shape. These unique properties enable medical-grade PTFE to meet diverse clinical demands, making it widely used in medical applications today. They are frequently utilized to fabricate artificial blood vessels, which are employed in vascular bypass surgery to supplant defective blood vessels [63,64]. Moreover, PTFE membranes serve as pericardial patches for myocardial repair and congenital defect closure [65]. Catheters fabricated from ePTFE are essential for angiographic, interventional, and drainage procedures [66]. Finally, in joint replacement surgeries, they are employed as joint surface coatings or spacer materials to mitigate joint wear [67]. However, the inherent inertness of PTFE surfaces impedes endothelialization and compromises drug-loading capacity, thereby restricting its clinical applicability [68,69]. Moreover, biofilm-associated infections on PTFE implants remain a major clinical challenge. In the past decades, various surface modification strategies have been developed to functionalize PTFE, aiming to overcome its inherent limitations and broaden its clinical utility. Yu et al. developed an ECM-coating strategy to functionalize PTFE surfaces [70]. By employing poly(dopamine) (PDA)/polyethyleneimine (PEI) co-deposition to mitigate its inherent bio-inertness, they concurrently integrated heparin and ECM coatings, achieving synergistic enhancement of endothelialization with concurrent suppression of smooth muscle cell proliferation. In another study, Zhang et al. designed a drug-eluting PTFE catheter via coating the impenem/cilastatin sodium-loaded dendritic mesoporous silica nanoparticle to achieve localized antimicrobial delivery and anticoagulant effects. This dual-functional system significantly reduced the incidence of bacterial infections by >90 % and thrombotic complications associated with intravascular catheterization [66].

2.3. Polyurethane (PU)

PU is a class of block copolymers produced via polyaddition reactions involving diisocyanates, polyols, and chain extenders. Bulk, solution, and emulsion polymerization are among the multiple methods available for synthesizing PU [71]. This polymer is characterized by the random arrangement of soft (typically polyether/polyester) and hard (containing urethane linkages) segments [72]. Due to the thermodynamic incompatibility between these segments, PUs spontaneously form microphase-separated structures consisting of soft and hard domains in the condensed state [73]. This microphase morphology plays a decisive role in determining the macroscopic properties of the material: the soft segments impart elasticity and high elongation, while the hard segments act as physical cross-linking sites through hydrogen bonding, thereby

providing mechanical strength, modulus, and creep resistance [74–77]. A narrow molecular weight distribution generally favors ordered packing and uniform aggregation of the hard segments, further enhancing microphase separation and mechanical stability. Precise regulation of monomer composition and reaction parameters allows for tunable microstructure and performance of PU, rendering it a critical material in diverse medical applications [78,79]. Since its inaugural application in fracture repair during the 1950s, research on PU's medical implementations has progressively advanced. Nowadays, medical-grade PU has been widely applied in the manufacturing of diverse medical implants [80,81]. For example, intra-aortic balloon pumps catheters fabricated from polyether-based PUs demonstrate superior clinical compliance, achieving flexural modulus values within the range of 10–20 MPa. However, the hydrophobicity of the PU surface renders it susceptible to nonspecific protein adsorption and platelet adhesion, triggering coagulation and immune cascade reactions, which can lead to clinical complications such as thrombosis and inflammation [82–84]. Moreover, unmodified PU surfaces lack the inherent bioactivity required for directing cellular responses and tissue integration [85]. Therefore, surface engineering strategies that confer targeted bioactivities are critical for enhancing PU's biocompatibility and ensuring implant longevity in physiological environments. Numerous bioactive moieties, including therapeutic drugs, broad-spectrum antimicrobials, antithrombotic agents, and tissue-specific biomolecules, have been incorporated onto PU surfaces to endow multifunctionality [86–89]. For instance, PU surface modified with a ternary coating system comprising photosensitizer BDP-6, hyaluronic acid, and gelatin exhibited 99 % inactivation efficiency against methicillin-resistant *Staphylococcus aureus* (MRSA), *E. coli*, and vancomycin-resistant *Enterococcus faecium* [90]. In this design, the photosensitizer BDP-6 not only facilitated photothermal conversion and ROS generation under 808 nm near-infrared light, enabling synergistic antibacterial effects, but also formed covalent Schiff base linkages with gelatin through its aldehyde groups, thereby ensuring coating stability and durability. In another study, Zwitterionic polymer brush-modified PU surfaces demonstrated reduced adsorption of fibrinogen, bovine serum albumin (BSA), or platelets by 70 %, 88 %, 80 %, respectively, vs. pristine PU [84].

2.4. Polyvinyl chloride (PVC)

PVC is a linear thermoplastic polymer synthesized via free-radical polymerization of vinyl chloride monomers [91]. The stereoregularity of the polymer chains significantly influences the formation and distribution of crystalline regions, which in turn affect the surface polarity and the diffusion–migration behavior of plasticizers within the matrix [92,93]. Due to its adjustable flexibility, biocompatibility, transparency, and low cost, medical-grade PVC has been widely used in flexible medical products such as infusion bags, hemodialysis tubing, urinary catheters, and endotracheal tubes [94,95]. However, the intrinsic hydrophobicity of PVC surfaces tends to promote nonspecific protein adsorption, leading to thrombin generation and complement activation, thereby compromising its hemocompatibility [96]. Moreover, to maintain the mechanical flexibility of PVC medical products, 40 wt% of plasticizers (e.g., DEHP) is typically incorporated. In systems with lower stereoregularity, these plasticizers exhibit a higher tendency to migrate toward the surface, resulting in surface tackiness, mechanical degradation, and a pronounced decline in hemocompatibility. Moreover, leaching of plasticizers such as DEHP has raised significant concerns due to their potential cytotoxic and endocrine-disrupting effects in patients [97,98]. To solve the above problems, Lin et al. developed a carboxybetaine copolymer (PCB) surface modification system that can convert hydrophobic PVC surfaces to highly hydrophilic surfaces with high-performance anti-fouling properties (average protein adsorption <5.0 ng/cm²), which effectively prevented platelet activation and complement activation. Furthermore, the PCB coating demonstrated a significant capacity to curtail DEHP leaching by nearly 90 %, in comparison

with uncoated PVC pipes [99]. Beyond this approach, other innovative modification strategies have demonstrated considerable potential in recent years. For instance, the chemical grafting of riboflavin onto PVC surfaces has been shown to in situ eradicate *Pseudomonas aeruginosa* biofilms and lentiviruses [100]. Amphiphilic hydrogel coatings constructed from polycarboxybetaine microgel and poly(sulfobetaine) (pSB) bonded to PVC substrates through a chain entanglement network demonstrated significant inhibition of fibrinogen, platelets, L929 cells, and bacterial adhesion [101]. Through the innovative combination of surface engineering and materials, medical-grade PVC is gradually overcoming the limitations of plasticizers and chemical inertness, and advancing toward safer and smarter next-generation medical implants.

2.5. Polydimethylsiloxane (PDMS)

PDMS is an organosilicon polymer characterized by a siloxane (Si—O) backbone with terminal hydrophobic methyl groups along the polymer chain [102]. It is commonly synthesized via ring-opening polymerization (ROP) of cyclic siloxanes [103]. By precisely controlling the catalyst type, reaction temperature, polymerization time, and end-capping agents, high-molecular-weight PDMS prepolymers with narrow molecular weight distributions can be obtained. Upon cross-linking, these prepolymers form densely entangled and highly elastic network structures, exhibiting enhanced tensile and tear strength [104]. Owing to the remarkable flexibility of its molecular chains (characterized by a low glass transition temperature, $T_g \approx -120^\circ\text{C}$), and the extent of cross-linking can be tuned to yield a broad spectrum of elasticity [105], allowing it to emulate the mechanical behavior of soft tissues ranging from fat (elastic modulus ≈ 1 kPa), to cartilage (elastic modulus ≈ 1 MPa). PDMS serves critical roles in biomedical engineering, enabling innovations such as flexible neural conduits for nerve repair, organ-mimicking microfluidic chips for precision medicine, and biocompatible dressings for burn recovery. Its adaptability spans reconstructive surgery, trauma care [106], and advanced devices [107,108]. This versatility positions PDMS as a unique biomaterial combining proven safety with multifunctional performance. The surface of PDMS exhibits pronounced hydrophobicity, with a static water contact angle typically ranging from 100° to 120° , primarily ascribed to the low surface energy of outward-oriented methyl groups [109,110]. Higher molecular weight or crosslinking density can suppress chain mobility and surface reorganization, thereby contributing to a more durable and stable hydrophobic surface [111]. However, this hydrophobicity promotes nonspecific protein adsorption, initiating undesirable cell attachment and fibrotic encapsulation. To address this limitation, multiple surface modification approaches have been established. For instance, plasma activation enables grafting of PEG or amphiphilic ionic polymers onto PDMS surfaces, improving hydrophilicity to promote cell adhesion or reduce biofouling [112,113]. Nevertheless, the clinical utility of these modifications is hindered by their limited long-term stability. Prolonged implantation can induce host foreign body responses due to chronic protein adsorption. This may lead to fibrous encapsulation and, in severe cases, capsular contracture, a significant complication in medical implants [114–116]. The advent of effective solutions necessitates an emphasis on the modulation of material-biological interfaces to enhance the host response through surface modifications.

2.6. Polylactic acid (PLA)

PLA is a renewable aliphatic polyester which could be synthesized either by ROP of lactide or polycondensation of lactic acid. The ROP process yields high-molecular-weight PLA with a narrow molecular weight distribution, resulting in excellent tensile strength, rigidity, and toughness [117]. In contrast, direct polycondensation generally results in lower molecular weight products with brittle mechanical properties due to the limitations imposed by the reaction equilibrium. More

crucially, lactic acid monomers exist as two enantiomers, L- and D-, and the polymerization configuration directly determines the stereostructure and properties of PLA [118]. The stereoregular PLLA (L-polymer) and PDLA (D-polymer) have highly ordered chain structures that can form stable crystalline regions, resulting in high crystallinity (30%–40%), elevated melting points (170 – 183°C), superior mechanical strength, and slower degradation rates. When PLLA and PDLA are mixed in an equal ratio, they form stereocomplex crystals, which further increase the melting point to about 230°C , significantly enhancing the thermal stability and mechanical performance of PLA. In contrast, PDLLA (random copolymer of D- and L-lactide) has an irregular structure, which hinders crystallization and leads to a lower melting point (120 – 130°C), reduced mechanical strength, and an increased degradation rate due to the larger intermolecular gaps in the amorphous region, which facilitate easier water absorption [119–122]. These structural characteristics render PLA an optimal implant applicable in many areas, like orthopedics, dentistry, and neurosurgery for bone defect repairs, fixation devices, and drug delivery systems. As a medical implant, the lactic acid generated by PLA degradation can be completely metabolized through the tricarboxylic acid cycle, with the final products being CO_2 and H_2O , with no toxic residues [123]. By adjusting crystallinity, differentiated mechanical properties can be achieved. Among PLA variants, poly(L-lactic acid) (PLLA), characterized by high crystallinity, superior mechanical strength, and the slowest degradation rate, has been approved by the FDA for long-term clinical implants requiring mechanical support, such as absorbable bone screws and cardiovascular stents [124,125]. These implants provide temporary assistance for bone repair or cardiovascular support and gradually degrade over time, eliminating the need for secondary surgical removal and minimizing patient trauma [126]. However, PLA's surface properties pose clinical challenges. Its surface hydrophobicity and lack of cell-signaling recognition sites often result in low cell affinity, manifesting as poor cell adhesion [127,128]. Additionally, the inherent inflammatory responses to PLA implants are a consequence of the foreign body reaction triggered upon implantation, which is sustained throughout the degradation process. The acidic microenvironment created by lactic acid release, along with the presence of low-molecular-weight degradation fragments, provides persistent stimuli that can lead to complications such as thrombosis, restenosis, and fibrosis [121,129,130]. Consequently, surface modification strategies are essential to improve PLA's biocompatibility and expand its biomedical utility, transforming it from a passive mechanical scaffold into a smart implant capable of integrating therapeutic and bio-regulatory functions.

2.7. Poly(L-lactide-co- ϵ -caprolactone) (PLCL)

PLCL is typically synthesized via ring-opening copolymerization of L-lactide (L-LA) and ϵ -caprolactone (ϵ -CL), and its molecular architecture and macroscopic properties are strongly dependent on synthesis conditions. The monomer feed ratio plays a decisive role in determining the copolymer's microstructure and crystallization behavior. Increasing the L-LA content leads to higher chain rigidity, crystallinity, and tensile modulus, whereas a higher ϵ -CL fraction enhances chain flexibility and elasticity [131,132]. The distinguishing feature of PLCL compared to the previously mentioned synthetic polymers is its biodegradability, and the degradation rate can be finely tuned from several months to several years by varying the L-LA/ ϵ -CL ratio [133]. In addition, PLCL exhibits favorable mechanical properties, which can satisfy the mechanical requirements of diverse tissue repairs [134]. In the clinic, PLCL has been extensively applied as absorbable sutures, which exhibit superior flexibility and knot strength. These sutures can undergo complete in vivo degradation, eliminating the need for secondary removal procedures. In tissue engineering, PLCL scaffolds can support three-dimensional cell proliferation and guide tissue regeneration through controlled porosity and pore size. Furthermore, PLCL can be fabricated into balloons or coronary occluders that possess strength and elasticity, thereby guiding

soft tissue remodeling and regeneration [135,136]. However, like most other synthetic polymers, PLCL exhibits limited intrinsic bioactivity, hampering direct cell-material interactions [137]. Therefore, significant research efforts have focused on surface engineering strategies to enhance PLCL's bioactivity [138,139].

2.8. Other potential polymers for biomedical implants

In addition to traditional materials like PEEK, PU, and PTFE, a new generation of high-performance polymeric materials has recently emerged. Due to their unique chemical structures and functional properties, these materials are propelling advancements in implant design. Instead of entirely substituting existing polymers, the objective is to address intrinsic limitations such as biological inertness, mechanical incompatibility, and unpredictable degradation, thereby providing enhanced solutions for clinical applications.

For high-performance and long-term implants, emerging polymers designed for specific tissue repair requirements are progressively overcoming the limitations of traditional materials. For instance, polyetheretherketone (PEEK), a member of the polyaryletherketone (PAEK) family, has attracted increasing attention owing to its superior osseointegration capability and excellent compatibility with 3D printing [140]. Compared to PEEK, PEKK possesses a lower crystallinity and tunable microscale surface roughness, both of which promote osteoblast adhesion and proliferation, making it an ideal candidate for personalized craniofacial implants and intervertebral fusion devices [141–143]. The increasing need for resilient implants in soft or dynamically loaded tissues has prompted the development of novel high-performance elastomers for hard-tissue repair. Recent studies have reported an ultra-tough bio-based furan polyurethane elastomer synthesized using bio-derived furan dicarboxylate as the core monomer, thereby eliminating reliance on petroleum-based feedstocks [144]. While maintaining high elasticity, this material exhibits strength and toughness several times greater than those of conventional thermoplastic polyurethane (TPU), presenting a prospective avenue for next-generation sustainable biomedical implants, including artificial ligaments.

In the realm of functional and smart-responsive materials, research focus has shifted from “biological inertness” to “active regulation”. Conventional materials like PU and polyethylene terephthalate (PET) offer fundamental hemocompatibility but demonstrate restricted antithrombotic efficacy. To address this, researchers have developed covalently modified thermoset polymers incorporating both anticoagulant and antiplatelet functional groups into their backbone, producing a bulk material with inherent antithrombotic activity [145]. Unlike conventional surface coatings, this material can serve directly as the matrix of cardiovascular implants (e.g., artificial blood vessels), where the synergistic molecular interactions effectively inhibit thrombin generation and platelet activation, significantly enhancing blood compatibility. Meanwhile, stimulus-responsive shape memory polymers (SMPs) have emerged as an important focus in the development of intelligent biomaterials. These systems, including polyurethane- and polycaprolactone-based SMPs, can revert to their pre-programmed configuration in response to body temperature or physiological fluids, and can also provide remote, spatiotemporally regulated actuation via near-infrared (NIR) stimulation [146]. Their potential for minimally invasive and adaptive implantable devices has been increasingly recognized, despite the fact that clinical translation still confronts challenges, such as optimizing photothermal conversion efficiency, tissue penetration depth, and long-term biosafety [147,148].

Regarding biodegradable and regenerative materials, the research emphasis is shifting from passive degradability toward the active promotion of tissue regeneration. Emerging bioactive composites not only offer mechanical support but also modulate the regeneration microenvironment via their degradation products or surface interactions. For instance, magnesium-doped PLA composites incorporate micro- or nanoscale magnesium particles, which undergo controlled degradation,

consistently releasing Mg^{2+} ions, thereby activating TRPM7/PI3K signaling pathways to promote osteoblast recruitment, migration, and mineralization [149]. By customizing the particle size, content, and distribution of magnesium, researchers can achieve dynamic synchronization between material resorption and tissue regeneration through precise regulation of the degradation rate [150].

In summary, emerging biomedical polymers highlight the trend toward integrated structural-functional design. Despite persisting challenges related to long-term stability, scalable fabrication, and clinical translation, recent breakthroughs have established an important material basis for the advancement of precision and personalized medical applications.

3. Biointerfacial effects of implant surfaces

The biointerfacial effects of implant surfaces are fundamental to understanding how surface properties dictate biological responses upon implantation. When an implant is introduced into the body, its surface becomes the primary interface with host tissues, triggering a cascade of events that determine the success or failure of the implant. Surface characteristics such as wettability, topography, charge, and chemical composition directly influence protein adsorption, the initial step in the host response, thereby affecting subsequent cell behaviors including adhesion, migration, differentiation, and proliferation [151].

For instance, hydrophobic surfaces (e.g., unmodified PEEK or PDMS) promote non-specific protein adsorption, fibrinogen deposition, and platelet activation—potentially initiating thrombosis or foreign body reactions, whereas their hydrophilic counterparts (e.g., from plasma treatment or chemical grafting) enhance biocompatibility by favoring albumin adsorption [18,152]. For another, nanoscale topological features such as grooves or aligned fibers have been shown to guide cell orientation and enhance neurite growth in neural tissues, while microporous structures facilitate vascularization and cell infiltration by providing a larger surface area for protein adsorption and nutrient exchange [151,153]. Moreover, stiffness gradients on material surfaces can dictate stem cell fate. Specifically, softer substrates (0.1–1 kPa) promote neurogenic differentiation, while stiffer ones (10–50 kPa) favor osteogenesis, which is mediated by integrin-mediated focal adhesion formation and cytoskeletal reorganization [153]. Chemical modifications, such as the introduction of functional groups (e.g., amino, carboxyl, or hydroxyl groups), improve biocompatibility by modulating protein adsorption and reducing immune responses [154]. Advanced coating technologies, including plasma treatment, 3D printing, and self-assembly, enable the integration of multiple physicochemical cues to create biomimetic microenvironments that mimic the native extracellular matrix [154–156].

Beyond these static physicochemical attributes, the dynamic nature of the biointerface is increasingly recognized as a key determinant of long-term implant performance. Once implanted, the adsorbed protein layer is not static but continuously reorganizes over time (known as the “Vroman effect”), forming a dynamic protein corona that governs subsequent cell recognition and immune signaling [157–159]. Environmental factors such as pH, ionic strength, and enzymatic activity further modulate this evolving interface, highlighting the need for adaptive materials that can maintain a favorable biological identity under physiological conditions.

Therefore, a deep understanding of these biointerfacial effects is essential for designing next-generation polymeric biomaterials, where tailored, biomimicking surface properties enable precise control over biological responses. This shifts the paradigm from inert coatings to active biological dialogue, mitigating complications like infections, fibrosis and rejection while driving functional biointegration.

4. Surface functionalization strategies for polymer-based medical implants

Current surface functionalization strategies for medical polymer implants include traditional physical/chemical methods and emerging approaches mediated by bioinspired adhesion mechanisms. Each of these methods has distinct advantages and limitations, which will be systematically reviewed below.

4.1. Physical methods

Physical methods principally encompass techniques that achieve functionalized modification of the substrate surface in a non-covalent form, including spin/dip coating, plasma activation, micro/nano-patterning, non-solvent-induced phase separation, aerosol spraying, and layer-by-layer assembly (Fig. 3). These techniques enable precise control over surface topography (from nano- to microscale) and chemistry, allowing customization for specific clinical applications. Physical methods demonstrate relative simplicity and operational efficiency. Beyond their standalone applications, these techniques are frequently employed as pretreatment steps for subsequent chemical modification processes.

4.1.1. Spin/dip coating

Spin coating is a thin-film deposition technique wherein centrifugal force generated by high-speed substrate rotation enables uniform spreading of the coating solution while expelling excess material, thereby forming a nanoscale film on the surface [160]. This method requires rigorous parameter optimization, including solution concentration, rheological properties of the coating fluid, spinning duration, and curing conditions dependent on temperature/humidity - all of which critically determine the coating thickness uniformity, surface morphology, and functional performance of the resultant layers [161,162]. The functionalization process on the surface can be subdivided into three primary stages. Initially, the hydrodynamic stage occurs, during which centrifugal acceleration induces uniform solution spreading and shear reduces the viscosity of the polymer solution, thereby forming an initial liquid film. The second stage involves solvent volatilization, during which Marangoni convection counteracts thickness inhomogeneity during solvent depletion. When the solvent content reaches the critical value, the system undergoes a glass transition, triggering an abrupt viscosity increase that cures the film into its final morphology. The final stage involves the interfacial adhesion, wherein the adhesion of the coating is augmented through mechanical interlocking and chemical bonding. Lu et al. developed concentric annular coatings with thin centers and thick edges on intraocular lenses (IOLs) using a two-step spin coating process (Fig. 4A). By systematically optimizing rotational speeds and durations for spin-up/spin-down phases, they achieved precise control over coating thickness and uniformity. This parameter-driven approach enabled tailored surface modification of IOLs to meet functional requirements [163].

Dip coating is a simple and cost-effective liquid-phase deposition technique used to apply thin, uniform coatings on substrates by immersing them in a precursor solution and withdrawing them at a controlled speed. The liquid film forms through the combined effects of gravity, adhesion forces, and surface tension, and the coating is obtained

after drying [165]. The dip-coating technique for the precise fabrication of functional coatings comprises three fundamental processes: (1) Withdrawal process: According to the Landau-Levich equation, the film thickness is synergistically controlled by the solution viscosity and withdrawal speed, while capillary action drives the infiltration of the solution into porous structures; (2) Drying process: gradient evaporation of the solvent induces directional migration of solutes; (3) Interface bonding: Stable attachment is achieved via electrostatic adsorption, hydrogen bonding networks, or covalent crosslinking [166]. Given the structural complexity and harsh operational environments of medical implants, which demand coating materials with both facile processability and long-term stability, the dip-coating method demonstrates superior clinical applicability compared to spin-coating. For instance, Liu et al. employed a straightforward dip-coating approach to rapidly form a uniform and robust heparin solution, containing heparin sodium (HS)/silicone quaternary ammonium surfactant (DAC), coating on thermoplastic polyurethanes (TPUs) [164]. The HS/DAC complexes could adhere to the surfaces of medical implants of arbitrary shapes and types (Fig. 4B), maintaining stability without detachment for 30 days, effectively addressing catheter-related thrombosis and bloodstream infections (Fig. 4C&D). In another study, Lin et al. dip-coated medical-grade PVC tubes with PCB copolymers, followed by UV irradiation to achieve photo-crosslinking, which covalently immobilizes the polymer chains onto the PVC surface to address plasticizer leaching, platelet activation, and complement activation (Fig. 4E) [99].

In a short summary, both spin coating and dip coating are relatively simple to operate and can efficiently modify substrate surfaces, imparting specific properties to the materials. However, both methods also exhibit inherent limitations that constrain their applicability in advanced material engineering. For instance, Spin coating demonstrates poor adaptability to complex three-dimensional implants and experiences significant solution loss from substrate surfaces due to centrifugal forces during processing, resulting in low material utilization [167]. Additionally, this method typically produces thin coatings, which may fail to meet requirements for surface modifications demanding thicker layers to achieve specialized functionalities [168]. Dip coating faces challenges in precisely controlling coating uniformity, which potentially compromises the final product quality consistency [169]. During the post-coating drying stage, uneven solvent evaporation often induces defects such as cracks and bubbles in the coating surface. These imperfections may degrade critical performance metrics, including biocompatibility and corrosion resistance, and could even lead to coating delamination during use, ultimately jeopardizing the implant's service life and safety.

4.1.2. Plasma treatment

Plasma treatment entails applying a high-voltage electric field to gas molecules (e.g., argon, nitrogen, oxygen, ammonia, etc.) to produce a plasma that interacts with the surface of the substrate. This process induces modifications in the physical and chemical properties of the material's surface, including at least three key effects: (1) Generation of nanoscale surface roughness due to the bombardment of high-energy particles; (2) Introduction of reactive functional groups as a result of the interaction between active free radicals and the surface, which enhances the surface reactivity; and (3) Activation of the surface for subsequent deposition or grafting of organic compounds (such as polymers

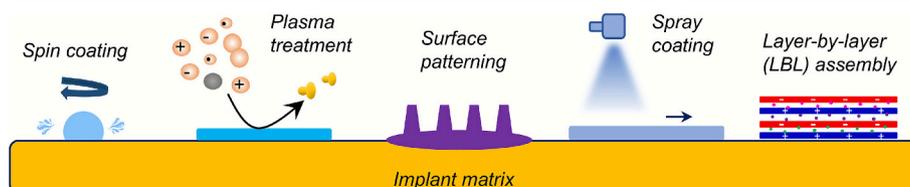


Fig. 3. Physical methods of surface functionalization of polymer implants.

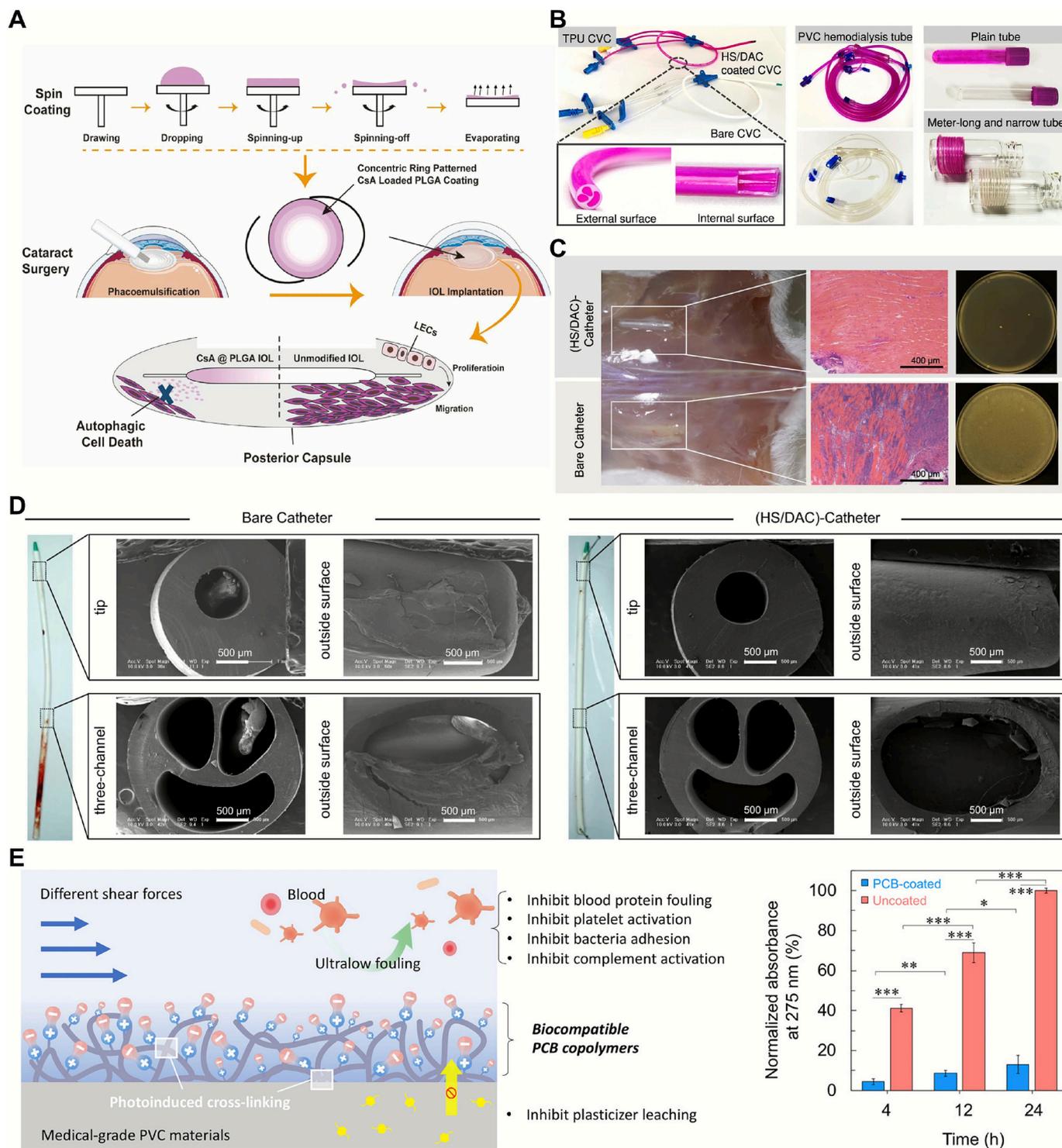


Fig. 4. Surface functionalization of medical implants based on the spin/dip coating method. (A) Schematic illustration of concentric ring polymer coating and coating modified IOL implantation for prevention of posterior capsular opacification by the spin-coating method. Reproduced with permission from ref. [163]. Copyright 2022, Elsevier Inc. (B) Preparation of HS/DAC coatings on different medical devices for the prevention of bacterial infections and thrombosis. (C) The antimicrobial performance of HS/DAC coating in vivo, including images of implant site infections, H&E staining, and colony counts. (D) Digital and SEM images showing thrombus formation on bare and HS/DAC-coated central venous catheters in an acute canine in vivo model. Reproduced with permission from ref. [164]. Copyright 2024, Springer Nature. (E) PCB-coated PVC pipe for antifouling and prevention of plasticizer migration. Reproduced with permission from ref. [99]. Copyright 2020, American Chemical Society.

or proteins). While plasma treatment itself does not directly deposit organic layers, it facilitates the attachment of such compounds in subsequent processes [170–174]. In general, plasma treatment of implants can significantly improve their surface wettability, adhesion, and

biocompatibility [175–177]. Furthermore, plasma treatment can serve as a pre-treatment step for surface functionalization, enabling the subsequent introduction of additional functional groups or biomolecules [178]. For instance, Song et al. described a method for creating a high-

density sulfobetaine amphiphilic polymer brush on the surface of the catheter with dopamine and sodium alginate as the intermediate layers [179]. The TPU catheter's surface was subjected to plasma treatment using a hydrogen and oxygen gas mixture, resulting in the introduction of hydroxyl groups to improve the adhesion of subsequent coatings. An intermediate layer composed of dopamine and sodium alginate was subsequently deposited on the surface (Fig. 5A). This step aimed to leverage the excellent adhesive properties of dopamine and the plentiful hydroxyl groups of sodium alginate to improve the grafting of the following polymer brushes (Fig. 5B). In another study, Chen et al. integrated surface sulfonation with low-temperature oxygen plasma treatment to enhance PEEK surface bioactivity. The last step of sulfonation involves the hydrothermal treatment in purpose of removing residual sulfuric acid and the embedded NaCl porogen while preserving the covalently attached sulfonic groups. This process was performed under high-temperature and high-pressure aqueous conditions, resulting in an interconnected porous architecture comprising macropores (100–200 μm) and submicron pores (0.5–10 μm) (Fig. 5C). Subsequent oxygen plasma treatment further refined the surface chemistry and significantly improved hydrophilicity without compromising the

hierarchical structure. Comparing with untreated or solely hydrothermally treated PEEK, the combined process markedly enhanced protein adsorption, cell adhesion, and spreading, thereby promoting osteogenic performance and osseointegration (Fig. 5D & E) [180]. In summary, plasma treatment has become one of the most widely adopted strategies for surface modification of polymer-based medical implants [176]. Nonetheless, the transient nature of plasma treatment effects remains a major challenge for its practical application. The treated surfaces often undergo an aging process, characterized by a progressive decrease in the efficacy of surface modification. This is most prominently demonstrated by a loss of hydrophilicity over time. The introduction of highly polar functional groups (such as -OH, -COOH, and -NH₂) onto the surface by plasma treatment leads to an immediate transition to a superhydrophilic state as a consequence of the increased surface energy. However, hydrophobic recovery is a phenomenon that results from the migration and reorientation of these polar groups within the polymer matrix over time [181,182]. Therefore, plasma treatment is often combined with other surface modification strategies to achieve more durable and stable functionalization.

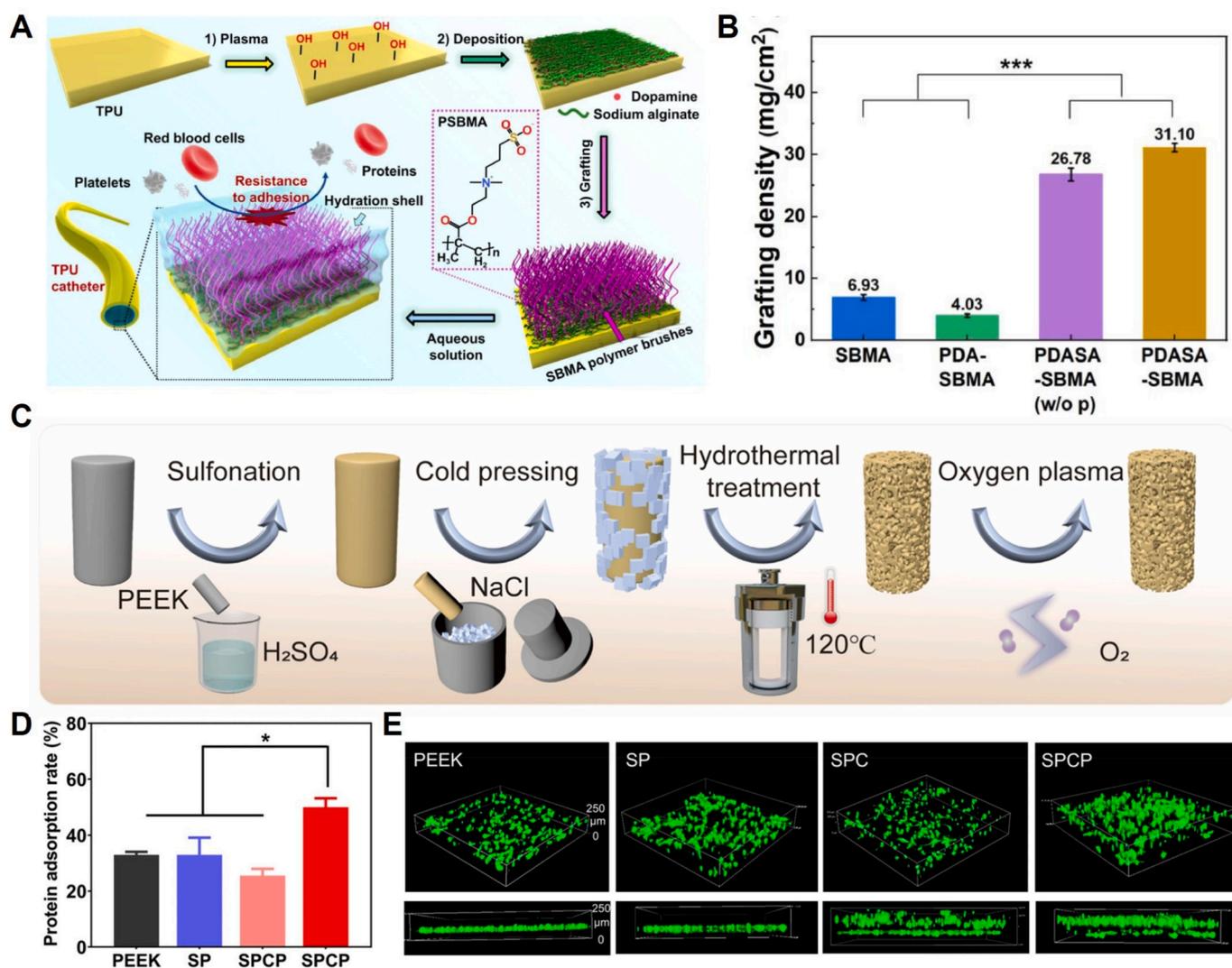


Fig. 5. Surface functionalization of implants based on the plasma treatment method. (A) Schematic of the process flow for constructing stable anti-adhesion and lubrication coatings on the TPU surfaces. (B) Grafting density of SBMA on the TPU surface under different modification methods. Reproduced with permission from ref. [179]. Copyright 2024, Elsevier Inc. (C) Schematic of PEEK surface preparation with 3D hierarchical porous structure. (D) Adsorption rates of proteins by PEEK with different surface treatments. (E) Three-dimensional and Z-directional CLSM images of BMSCs on different samples after 3 days of incubation. PEEK (unmodified), SP (sulfonated and hydrothermally treated), SPC (cold-pressed and hydrothermal treatment of SP), and SPCP (low-temperature oxygen plasma treatment of SPC). Reproduced with permission from ref. [180]. Copyright 2023, Springer Nature.

4.1.3. Surface patterning

Surface patterning is a surface modification method that employs techniques such as photolithography, etching, and high-precision 3D printing to create micrometer- or nanometer-scale topologies with specific geometries, sizes, and alignments on implant surfaces. Numerous studies have indicated that the topography of implant surfaces exerts profound effects on cellular behavior and tissue response [183–185]. Micro/nano-scale grooves, pillars, or lattice structures can guide cells to extend along specific directions and promote directional migration. Cells sense substrate stiffness and surface topography through integrins, activating relevant mechanotransduction signaling pathways to regulate gene expression [186]. Surface topography can also modulate the macrophage polarization and extracellular matrix deposition [187]. He et al. prepared PDMS substrates with different stiffnesses at MPa levels and surface topologies (stripe/dot arrays) to investigate the mechanisms by which the stiffness and surface topology of PDMS implants regulate

inflammatory responses of macrophages (Fig. 6A) [188]. Results showed that the stiffness dominated inflammation through the activation of the adhesion patch-MAPK/NF- κ B pathway, whereas surface topography exerted an inhibitory effect by restricting cell spreading only under low-stiffness conditions. The clinical design of PDMS implants is predicated on the principle of “stiffness first, topology second”, which posits that the stiffness of the material is preferentially matched to the mechanical environment of the implantation site.

Rational design of implant surface topological structures proves crucial for regulating host-implant interface reactions and enhancing long-term stability and functionality, representing a vital approach for developing next-generation, multifunctional implants. Furthermore, incorporating biomimetic micro/nanostructures onto the substrate surfaces not only endows implants with novel enhanced functionalities, e. g., antimicrobial and antifouling properties [190], but also facilitates the development of intelligent implant coatings integrating detection and

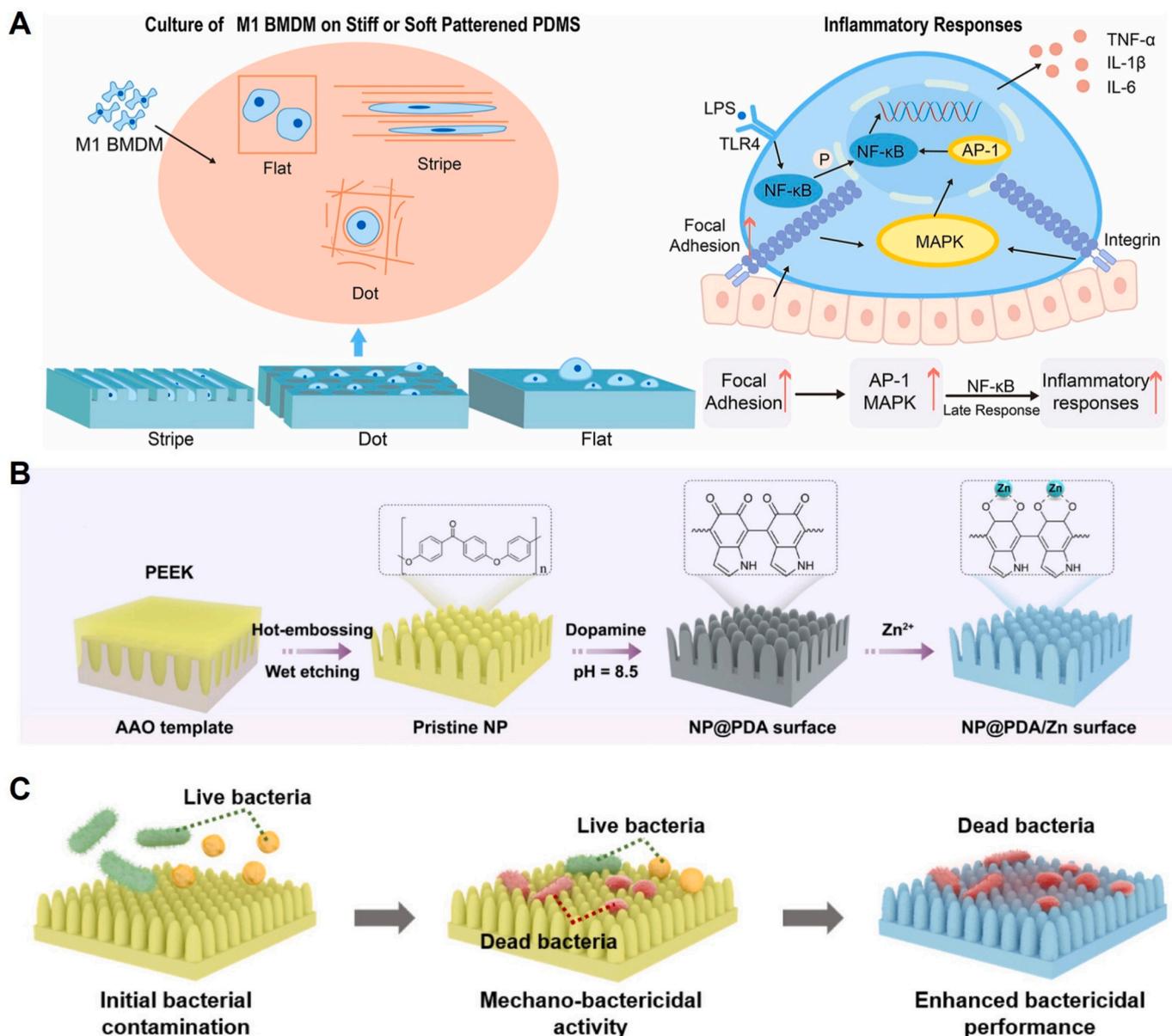


Fig. 6. Surface patterning modulates cell behavior, and biomimetic nanomicrostructures confer antimicrobial properties to the materials. (A) Stiffness and surface topology of PDMS implants competitively mediate inflammatory responses of macrophages. Reproduced with permission from ref. [188]. Copyright 2024, Elsevier Inc. (B) Schematic diagram of the NP@PDA/Zn preparation process. (C) Bactericidal mechanism of NP@PDA/Zn hybrid nanopillars and schematic illustration of the synergistic effect of mechano-bactericidal nanopillars and immobilized immunomodulatory Zn²⁺. Reproduced with permission from ref. [189]. Copyright 2024, American Chemical Society.

therapeutic modalities [191]. Inspired by the surface of insect wings, researchers prepared arrays of nanopillars with high aspect ratios on PEEK surfaces (Fig. 6B) [189]. Upon interaction with the surface of the nanopillars, bacterial cells experience a sustained physical effect originating from the mechanical tension of the nanopillars. This mechanical bactericidal mechanism synergizes with the chemical inhibition of Zn^{2+} in the system to achieve efficient antibacterial activity without relying on antibiotics (Fig. 6C).

In general, current research predominantly focuses on elucidating how different topographies influence cellular behaviors, such as cytoskeletal reorganization and signaling pathway activation, while systematic investigations into topography-based functionalization of implants remain limited. Additionally, some surface patterning techniques relying on high-precision equipment, e.g., electron beam lithography and focused ion beam, face challenges including high costs, complex processes, and substrate-dependent pattern fidelity, limiting

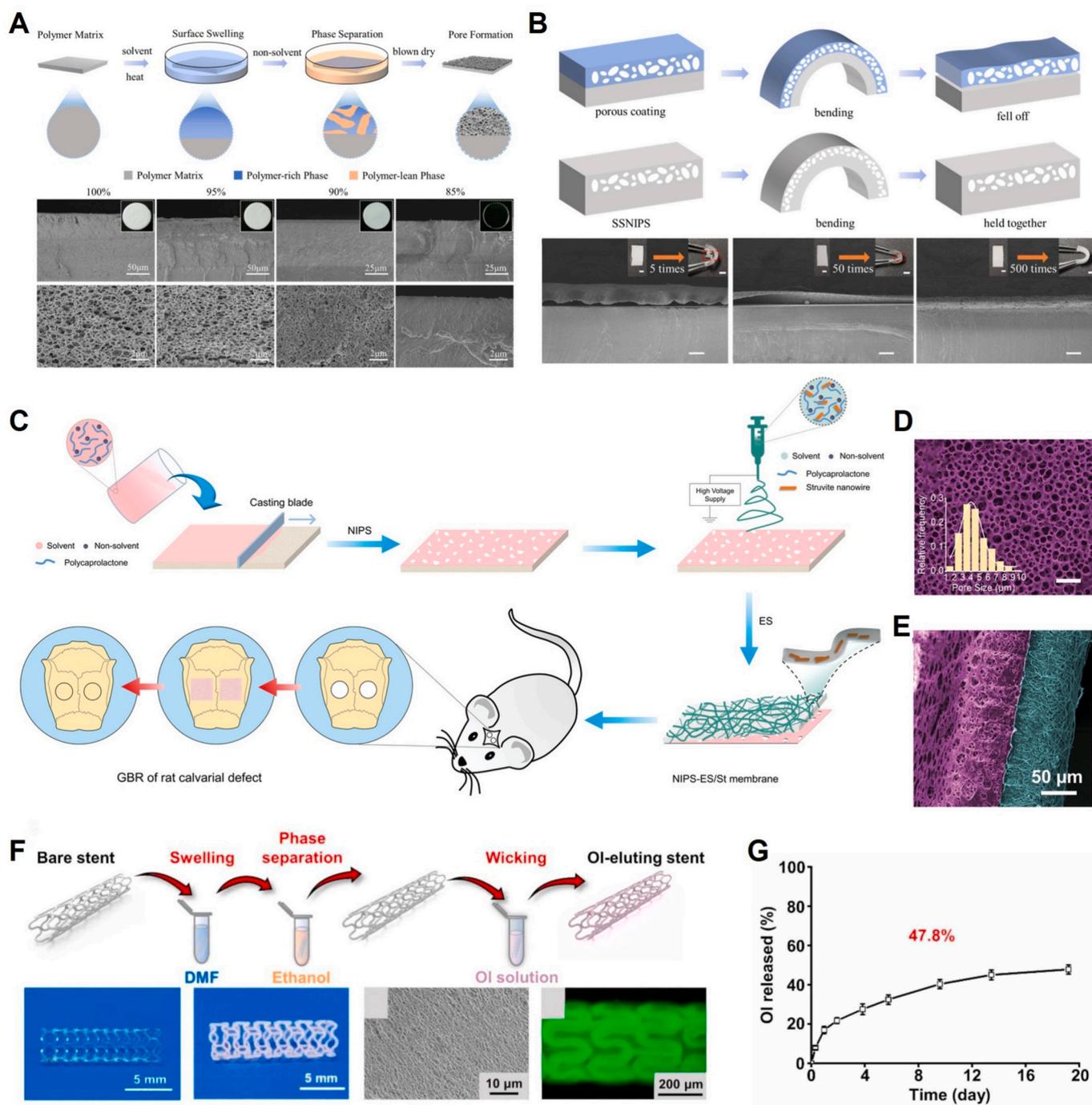


Fig. 7. Surface functionalization of implants based on the non-solvent induced phase separation method. (A) Schematic diagram of the porous surface fabrication process and SEM images of PMMA porous surfaces prepared from different solvents with cross sections at high and low magnification. (B) SEM images of SSNIPS porous surfaces on different substrates after bending. Reproduced with permission from ref. [195]. Copyright 2021, American Chemical Society. (C) Schematic of the preparation of polycaprolactone/ornithine nanowires and their application in rat cranial defects. (D) SEM image of the microporous layer and its pore size distribution. (E) Cross-sectional SEM image of the NIPS-ES/8 % St membrane. Reproduced with permission from ref. [196]. Copyright 2022, Wiley-VCH GmbH. (F) Fabrication of "spongy skin" and drug loading on porous cardiovascular scaffolds. (G) Release behavior of PLLA "spongy skin" loaded with 4-octyl itaconic acid ester over 20 days. Reproduced with permission from ref. [198]. Copyright 2023, Elsevier Inc.

their universal applicability.

4.1.4. Non-solvent induced phase separation

The non-solvent induced phase separation (NIPS) is a technique where the mutual diffusion between a solvent and a non-solvent induces the polymer substrate surface swelling and phase separation, ultimately forming an interconnected porous structure on the polymer substrate [192,193]. The NIPS process consists of three components: polymer, solvent, and non-solvent. Its core mechanism includes immersing a polymer solution into a non-solvent, where non-solvent infiltration drastically reduces polymer solubility. The differential diffusion rates between outward solvent migration and inward non-solvent penetration drive liquid-liquid phase separation, creating polymer-rich and polymer-lean phases [194–196]. However, this process is acutely sensitive to variations in process parameters: minor variations in solvent concentration can induce pore size deviations, while rapid phase separation tends to generate through-going finger-like pore defects that compromise the structural integrity [197]. Upon complete solvent displacement, the polymer phase solidifies into a hierarchically porous matrix. Nevertheless, residual organic solvents, such as methylene chloride, often persist beyond FDA-mandated safety thresholds, thereby posing biocompatibility concerns.

The in-situ fabrication of porous surfaces by NIPS overcomes the interfacial adhesion limitations of traditional coatings (Fig. 7A) [195]. The resulting porous surface maintained structural integrity even after 500 bending cycles (Fig. 7B). Furthermore, the tunable swelling and phase separation processes enabled flexible control over both the thickness and pore size of the porous structure, thereby establishing the groundwork for its application in diverse complex in vivo scenarios. Zhu et al. developed a multifunctional membrane for guided bone regeneration through the integration of two advanced fabrication techniques: a microporous substrate layer fabricated via NIPS with submicron-scale pore architecture control, and a surface-functionalized guanidine-doped nanowire layer deposited through electrospinning (Fig. 7C). The core role of NIPS is to form a “selective barrier”, which can not only block the invasion of non-osteogenic tissues but also provide migration channels for osteoblasts (Fig. 7D). The microporous structure provides mechanical support for subsequent electrospun layer deposition and ensures uniform coverage of the fiber layer (Fig. 7E). This dual-functional architecture realizes the efficient regulation of bone regeneration [196]. Leveraging the rapid capillary action of porous structures, Qian et al. engineered an ordered porous ‘sponge-like surface layer’ on polymer substrates (Fig. 7F), enabling controllable loading and sustained release of diverse drugs and bioactive molecules (Fig. 7G) [198]. Furthermore, the NIPS-based methodology demonstrates a broad material compatibility, including PMMA, TPU, PLA, and PLGA, offering a novel strategy for developing drug-device combination implants.

4.1.5. Spray coating

Spray coating technology is a technique that utilizes spraying apparatus to atomize a coating solution containing functional molecules for application onto the implant surface. Under the auxiliary action of acoustic or electric fields (e.g., ultrasonic spray or electrostatic spray), this technique enables the formation of thin and uniform coatings on implant surfaces, with coating uniformity exceeding 95 %. Currently, spray coating technology has been widely utilized for the surface functionalization of polymer implants, such as balloons, catheters, and vascular stents [199]. The integration of functional coatings comprising bioactive compounds, polymers, and medicines has significantly enhanced the biocompatibility and therapeutic effectiveness of these implants [200–202]. The surface functionalization mechanism of spray coating technology constitutes a multi-scale coordinated process [203–205]: At the macroscopic level, ultrasonic or electrostatic fields atomize the coating solution into micron-sized droplets, facilitating uniform substrate coverage through precise control over the process parameters. At the microscopic level, functional molecules adhere to the

substrate via non-covalent interfacial bonding, including electrostatic adsorption and hydrophobic interactions. Pre-treatment of the implant surface by plasma can enhance surface energy and markedly improve the wettability.

Recently, Wang et al. developed freeze-dried viscous hydrogel powders composed of poly(acrylic acid-co-3-(trimethoxysilyl)propyl methacrylate) crosslinked with chitosan, which were applied onto substrates using electrostatic spraying technique and rehydrated to form hydrogel coatings (Fig. 8A). This approach was demonstrated to enable the formation of smooth surfaces with tunable coating thickness on a broad range of materials, and strong adhesion was achieved through a three-step bonding mechanism involving electrostatic attraction, hydrogen bonding, and covalent bonding [204]. In other studies, ultrasonic spraying in combination with UV-triggered polymerization was employed to disperse precursor solutions containing various functional components onto the surface of the occluder. Subsequently, UV irradiation and heat treatment were utilized to form a dual-network coating characterized by electrostatic interactions and covalent bonding (Fig. 8B). The wetting capability of PEI, together with the uniform atomization characteristics of ultrasonic spraying, enables effective coatings on complex structures such as Nitinol frames and PET fabrics, ensuring complete surface coverage [200]. In another study, Wang et al. developed an industry-compatible hydrogel coating process for cardiovascular implants (Fig. 8C) [206]. The protocol combines plasma treatment with ultrasonic spray deposition, allowing for uniform coating application and strong adhesion of polycation-based hydrogel layers on microscale PLLA stents. In the work of Zhao et al., dopamine-modified oxidized dextran, caffeate prodrug, containing phenylboronic ester groups, and a macromolecular nitric oxide (NO) donor were dynamically self-crosslinked via Schiff base chemistry through ultrasonic spraying to form a gel. The coating material was atomized into uniform micro-droplets by high-frequency ultrasonic vibrations and precisely deposited on the surface of the vascular balloon, forming a mesh structure with dual dynamic covalent bonds (Schiff base and phenyl borate ester) (Fig. 8D) [199].

It should be noted, however, that surface functionalization based on ultrasonic spraying or electrostatic spraying exhibits several inherent limitations. Firstly, the spraying speed is somewhat slow, making it inappropriate for large-area implant coatings. Secondly, their operational principle relies on the atomized droplets, imposing stringent requirements on the fluid viscosity and surface tension. This limits compatibility with poorly atomizable functional molecules (e.g., high-MW polymers) or micron-sized particles. Thirdly, the ultrasonic spraying technology generates localized heat, making it inappropriate for temperature-sensitive bioactive coatings (e.g., protein-based formulations requiring storage at 2–8 °C).

4.1.6. Layer-by-layer assembly

The layer-by-layer (LBL) assembly method refers to a surface functionalization strategy utilizing certain interfacial physicochemical interactions. By alternatively depositing oppositely charged polyelectrolytes or functional molecules, it achieves the multilayer functionalization requirements of implant surfaces [207–210]. This method features simple operation, enables multilayer assembly, and allows independent control over the species, density, and content of biomolecules in each layer, thereby facilitating the adjustment and optimization of surface functionalities in multi-component modifications. Consequently, LBL assembly emerges as a promising approach for the surface functionalization of implants, requiring spatiotemporal-dependent functional modulation [211]. Electrostatic interactions, the predominant driving factor for assembly, establish a robust ionic bonding network by sequentially adsorbing positively charged polycations and negatively charged polyanions [212–214]. Zhang et al. constructed an LBL assembly from the positively charged PEI and the negatively charged choline phosphate (PC)-modified hyaluronic acid (HA). Unlike conventional LBL approaches that fabricate coatings with

driven LBL technique [213]. The IOL surface was precoated with positively charged PEI, and then glucose oxidase and horseradish peroxidase were co-immobilized in mesoporous silica nanoparticles to form an En@M catalytic platform. This platform was alternately deposited with negatively charged chitosan using electrostatic adsorption (Fig. 9A). This technique facilitates the precise and controllable assembly of the catalytic system through electrostatic driving, resulting in significant enhancements in enzyme loading and catalytic stability.

In addition to electrostatic interaction-induced LBL, other intermolecular forces such as π - π stacking, host-guest interactions, metal-organic coordination, and hydrophobic interactions can also contribute to the formation of LBL assembly [207,217,218]. For example, Feng et al. combined electrostatic LBL assembly with host-guest interactions to construct a hierarchically anticoagulant surface on PVC central venous catheters. In this strategy, multilayered polyelectrolyte films containing adamantane guest groups were sequentially assembled on the substrate. Subsequently, amino-functionalized β -cyclodextrin was introduced, whose hydrophobic cavities specifically encapsulated the adamantane moieties on the polycation side chains, forming stable host-guest inclusion complexes. On this anchoring layer, heparin was further grafted. As a result, the resulting coating integrated inert antifouling, active anticoagulant, and fibrinolytic functionalities into one system, markedly enhancing the hemocompatibility of the PVC surface (Fig. 9B) [207]. In another study, Huang et al. constructed an antioxidant and antimicrobial bifunctional system on the surface of PEEK through electrostatic interactions and hydrogen bonding interactions among tannic acid, gentamicin sulfate, and Pluronic F127 [219].

Nonetheless, relying solely on weak intermolecular interactions makes LBL assembly difficult to maintain stability in complex bodily fluid environments. To enhance stability under physiological conditions, hybrid assembly strategies have emerged by incorporating covalent bonds to create a synergistic interplay between physical interactions and chemical bonding [220,221]. In the work of Chen et al., the metal-phenolic networks (MPNs) assisted LBL self-assembly technique was employed, in which positively charged PEI and negatively charged HA were used as the polyelectrolytes for the electrostatic adsorption of the alternating deposition of the MPNs [215]. The MPNs, fabricated via the coordination of epigallocatechin gallate (EGCG) with Cu^{2+} , acted as an intermediate bridging layer. EGCG possesses abundant catechol and galloyl groups, and thus has a strong coordination affinity for Cu^{2+} . Moreover, the Cu^{2+} -EGCG complex can catalyze the generation of NO from endogenous substrates, which provides a key rationale for selecting this specific metal-phenolic combination as a functional coating component for cardiovascular stents. Through π - π stacking, hydrogen bonding, and covalent crosslinking between the quinone groups of EGCG and the amine groups of PEI, the resulting multilayer coating achieved enhanced structural stability and functional integration (Fig. 9C). Wan et al. developed a sandwich-structured coating using the LBL assembly approach. The system integrated epigallocatechin-3-gallate-tanshinone IIA sulfonate complexes (EGCG-TSS) within a polyelectrolyte layer composed of 3-aminophenylboronic acid-modified hyaluronic acid (HA-APBA) and carboxylate chitosan (CCS) [216]. The coating stability stems from the synergistic interplay of electrostatic attraction, hydrogen bonding, π - π stacking, and dynamic covalent boronate ester linkages, which collectively form a robust three-dimensional crosslinked network. Specifically, electrostatic interactions arise between the protonated amino groups of CCS and the negatively charged hydroxyl/carboxyl groups of EGCG-TSS and HA-APBA, respectively. Extensive hydrogen bonding among the three components, coupled with π - π stacking between the aromatic rings of EGCG-TSS and HA-APBA, further reinforced the network. Meanwhile, reversible boronate ester bonds formed between their ethylene glycol and boronic acid groups endow the structure with both integrity and adaptability (Fig. 9D). This strategy illustrates the potential of LBL assembly to achieve stable and multifunctional coatings. Similarly, other researchers have also employed naturally occurring and commercially available materials

(aminoglycosides, 5,6-dihydroxyindole, and formylphenylboronic acid) as building blocks to fabricate antimicrobial coatings through mussel-inspired polymerization and dynamic covalent chemistry, employing the LBL approach. Within these systems, aminoglycoside antibiotics are immobilized via reversible Schiff base and boronate ester linkages with formylphenylboronic acid and 5,6-dihydroxyindole, respectively. Under conditions simulating the mildly acidic microenvironment elicited by bacterial colonization, the pH-sensitive imine and boronate ester bonds undergo gradual hydrolysis, triggering controlled antibiotic release. This stimuli-responsive mechanism enables on-demand drug delivery while effectively mitigating the uncontrolled burst release commonly observed in conventional coatings [222]. Although LBL assembly has been extensively employed, the interlayer interactions are susceptible to interference from complex physiological environments (e.g., pH, ionic strength), resulting in compromised stability. Therefore, it is imperative to improve its performance through systematic design in the future.

In a short summary, different physical methods for surface functionalization possess unique advantages in terms of efficiency, functionality, and applicability ranges. Nevertheless, they all face inherent limitations in processing complexity, cost-effectiveness, or stability. In practical applications, these challenges are typically addressed through technical combinations, such as plasma activation followed by grafted coatings or the combination of patterned surfaces combined with drug spraying, to achieve durable, multifunctional composite modifications. Moreover, non-covalent functional coatings exhibit limited adhesion to the substrate surface. In the complex *in vivo* electrolyte environment, this inherent weakness poses a significant risk of coating detachment, thereby compromising their suitability for long-term biomedical applications.

4.2. Chemical methods

The chemical method of surface functionalization refers to anchoring functional groups or bioactive molecules to the implant surface through covalent bonds, thereby offering excellent durability. The chemical functionalization process primarily involves two essential steps (Fig. 10): First, reactive functional groups are introduced to the material's surface via pre-treatment; Second, bridging molecules, functional groups, or bioactive compounds are grafted to the substrate's surface through a series of post-modification procedures or polymerization reactions.

The prerequisite for chemical functionalization lies in possessing reactive functional groups on the surface. However, most polymer-based medical implants exhibit inert surfaces inherently deficient in reactive functional groups, making the direct covalent bonding of functional molecules unfeasible. To address this obstacle, surface activation strategies – including chemical etching, plasma treatment, and irradiation – are employed to introduce specific functional groups. The incorporation of particular functional groups, e.g., hydroxyl, amino, and carboxyl, onto the surfaces of polymer implants. The chemical etching method utilizes strong acids and bases to modify the surface, where localized cleavage of the polymer backbone generates certain functional groups [223,224]. For instance, Zheng et al. sulfonated PEEK using concentrated sulfuric acid prior to grafting chondroitin sulfate [225]. The sulfonation treatment activates the PEEK surface, which subsequently facilitates the introduction of EDA via a Schiff base reaction and the grafting of chondroitin sulfate via an amidation reaction. In another study, researchers coated TPU with a benzophenone (BP)-containing solution. Upon UV irradiation, photoactivated BP abstracts hydrogen atoms from the substrate, generating surface-bound radicals that initiate grafting of functional molecules [226]. Chemical etching offers simplicity but risks compromising mechanical integrity. Energetic particle/radiation-based methods (e.g., plasma, γ -irradiation) achieve efficient and versatile surface functionalization via radical generation [227,228], albeit requiring specialized equipment and offering limited penetration depth.

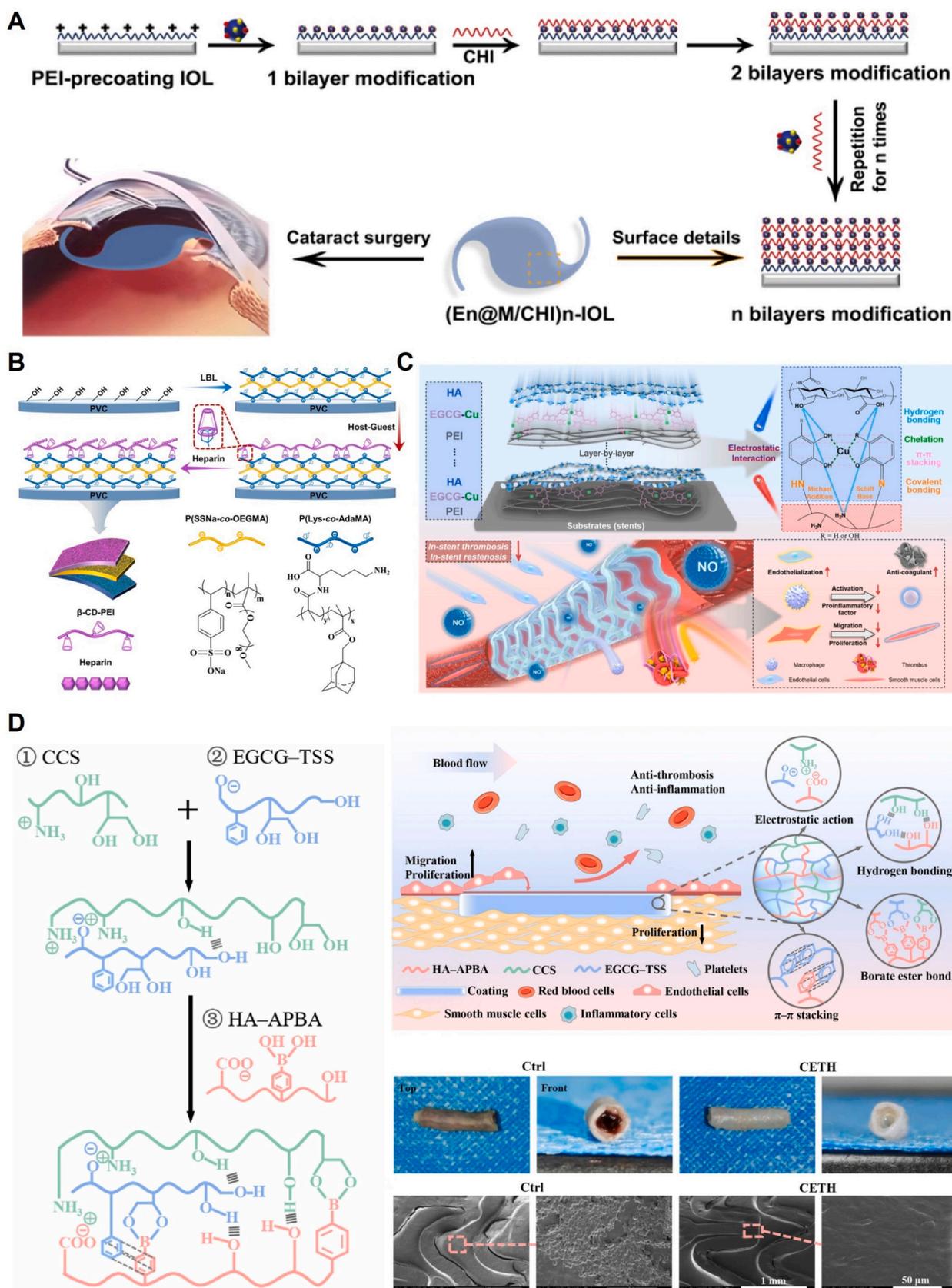


Fig. 9. Surface functionalization based on the layer-by-layer assembly method. (A) Construction of multilayer films on IOL by LBL self-assembly technique. Reproduced with permission from ref. [213]. Copyright 2025, Elsevier Inc. (B) Schematic of the preparation of the PVH coating. Reproduced with permission from ref. [207]. Copyright 2023, American Chemical Society. (C) Metal-phenolic network-assisted construction of multilayer analog endothelial coatings for vascular scaffolds. Reproduced with permission from ref. [215]. Copyright 2026, Elsevier Inc. (D) Preparation of sandwich-like CETH coatings on vascular scaffolds by LBL self-assembly technique. Reproduced with permission from ref. [216]. Copyright 2023, Elsevier Inc.

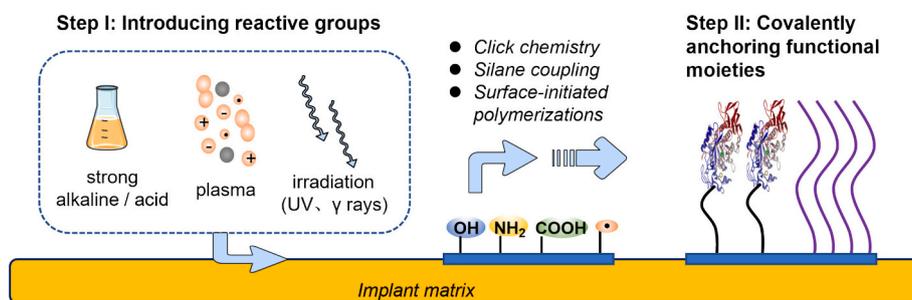


Fig. 10. Chemical approaches to surface functionalization of polymer-based medical implants.

Following the successful introduction of reactive functional groups, aqueous-phase and mild chemical reactions can be sequentially employed to graft bridging molecules, functional groups, or bioactive molecules to the substrate's surface. Common methodologies include Click chemistry [229] (e.g., cycloaddition reactions based on azide and alkynyl groups [27,230], thiol-ene coupling [231,232], Diels-Alder reactions, etc.), silane coupling [233,234], and surface-initiated polymerizations [200,235,236]. The Click chemistry demonstrates high specificity and can be operated under biocompatible conditions. However, it requires the pre-modification with orthogonal chemical groups, which is susceptible to interference from the surface heterogeneity. The silane coupling entails the attachment of functional molecules to the substrate surface via the hydrolysis of the silane coupling agent, such as (3-aminopropyl)triethoxysilane, (3-mercaptopropyl) trimethoxysilane, (3-Glycidioxypropyl)trimethoxysilane, et al. This method depends on hydroxyl-containing substrates and is prone to hydrolysis failure in the physiological environment. Surface-initiated polymerization involves a series of interfacial reaction steps: First, immobilizing initiators onto the surface; Second, activating initiators via exposure to heat, light, or other external stimuli to generate free radicals; Third, radical chain-growth polymerization of adjacent monomers to form polymer brushes. This method can generate high grafting density of polymers with tunable architectures. However, its multi-step workflow restricts the application expansion, and the polydispersity challenges in chain growth complicate the attainment of uniform polymer grafting.

As demonstrated by the above analysis, chemical methodologies enable precise molecular design, conferring the implant surface with specific functionalities, such as anti-infection properties and wound-healing promotion, while eliminating reliance on costly equipment. A representative example is the bioactive and conformal coating based on poly(p-xylylene), developed by Hao et al. [64]. In their design, an amine-functionalized poly(p-xylylene) was first deposited onto ePTFE via chemical vapor deposition, and then an antifouling PEG linker and the integrin-specific ligand LXW7 were sequentially grafted onto this surface (Fig. 11A). This strategy enabled spatiotemporal functional modulation of the implant surface: the PEG linker endowed the surface with antifouling and antiplatelet properties during the acute phase, while the high affinity of LXW7 facilitated early endothelial cell capture. Ultimately, the proliferation and differentiation of the adhered endothelial cells promoted complete endothelialization at the late stage (Fig. 11B). The LBL grafting strategy facilitates precise control over the density and content of each biomolecular layer. This coating showed excellent NO release performance and demonstrated high efficacy in inhibiting platelet adhesion/activation and suppressing the adhesion, proliferation, and migration of smooth muscle cells, while enhancing the adhesion, proliferation, and migration of endothelial cells. In another study, researchers constructed SCHSPEEK implants that mimic the fibrous structure of the periodontal ligament. These implants were prepared through a process of 3D printing and sulfonation of PEEK implants, followed by grafting acrylic acid-acrylamide hydrogels loaded with simvastatin and cefepime onto the surface of PEEK implants by light-curing technology (Fig. 11B). The results demonstrated that the

modification significantly enhanced the hydrophilicity, antimicrobial property (with an inhibition rate exceeding 90 %), and osteointegration ability of PEEK. In vivo experiments revealed that the amount of new bone production was 2.3 times higher than that of the unmodified group, and that the fibrous structure of the hydrogel could guide the orientation of cellular differentiation [237]. Zhang et al. employed a two-step photoinitiated polymerization technique to fabricate polymer brush coatings on stent surfaces for in-situ H₂S release (Fig. 11C) [238]. The coating incorporated both thiol-activated H₂S donors and RGD peptides to enhance endothelial cell attachment (Fig. 11D-E).

Despite these advancements, it is essential to recognize the inherent limitations of chemical grafting methods remain: (1) Insufficient or uneven distribution of functional groups directly compromises subsequent coupling efficiency; (2) Interfacial reactions are influenced by surface chemical composition, surface roughness, and the solution environment (pH, ionic strength), potentially leading to low grafting density or uneven distribution of functional molecules; (3) Specialized pretreatments and coupling strategies are required for different substrates, hindering the development of a “one-size-fits-all” approach.

4.3. Biomimetic surface engineering

Natural adhesives secreted by marine organisms such as mussels, sandcastle worms, and barnacles exhibit highly efficient adhesion in aquatic environments [239]. Inspired by this phenomenon, researchers have developed a series of surface functionalization strategies for implants in recent years. Through in-depth exploration of these adhesion mechanisms, it has been discovered that each type of natural adhesive possesses critical components responsible for adhesion. Leveraging advanced chemical synthesis or bioengineering techniques, scientists have successfully engineered biomimetic materials that replicate these key adhesive components to mediate the adhesion of functional molecules on material surfaces. Examples include mussel-inspired dopamine coatings [240–244], sandcastle worm adhesive protein-mimicking tripeptide adhesives [245,246], and barnacle cement protein cp19k-inspired adhesive peptides [247]. Among these, dopamine-mediated surface functionalization inspired by mussels has found the most extensive applications. Based on the modes of action, this method can be divided into three categories, which are described as follows.

4.3.1. PDA coating-mediated two-step grafting

First, dopamine undergoes self-polymerization under weakly alkaline conditions to form a PDA coating that adheres in situ to the substrate surface. This process exhibits three key features: (1) Universal substrate compatibility, enabling stable adhesion to diverse materials, including metals and polymers [248–250]; (2) Mild reaction conditions, typically conducted at room temperature [251,252]; (3) Abundant reactive functional groups in the PDA coating, primarily catechol and primary amine groups. Subsequently, functional molecules containing amino or sulfhydryl groups are covalently attached to the PDA coating surface via Michael addition and Schiff base reactions (Fig. 12A). This stepwise grafting approach provides a controllable and reliable pathway for

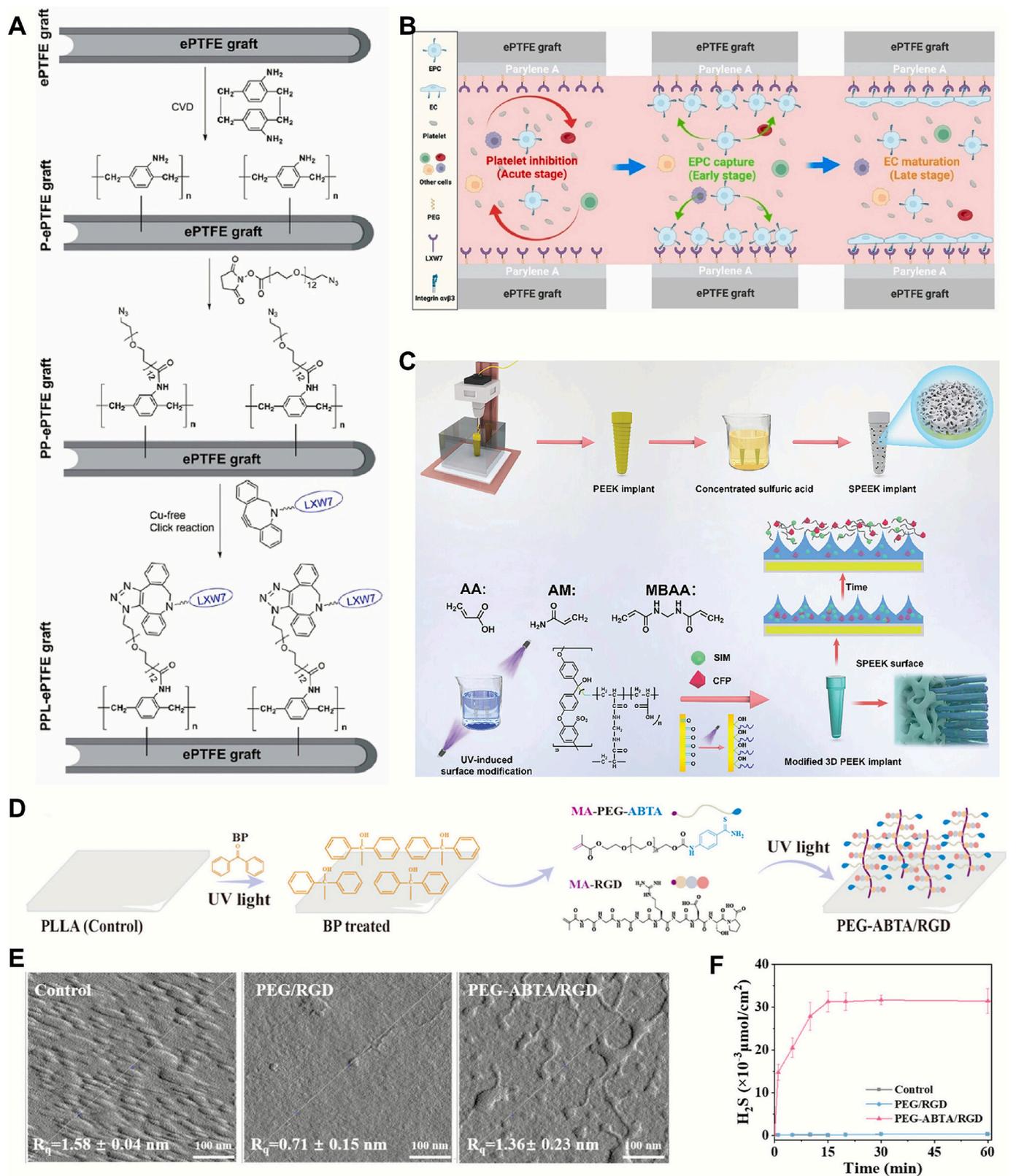


Fig. 11. Chemical-based surface functionalization. (A) The step-by-step process for PPL-ePTFE grafting. (B) Schematic diagram of the mechanism of action of PPL-ePTFE coating. Reproduced with permission from ref. [64]. Copyright 2023, Elsevier Inc. (C) Schematic diagram of the steps involved in the preparation of SCHSPEEK implants. Reproduced with permission from ref. [237]. Copyright 2024, Wiley-VCH GmbH. (D) Schematic of the preparation of H₂S-releasing polymer brush coatings. (E) AFM images of different samples. (F) H₂S release curves. Reprinted with permission. Reproduced with permission from ref. [238]. Copyright 2025, American Chemical Society.

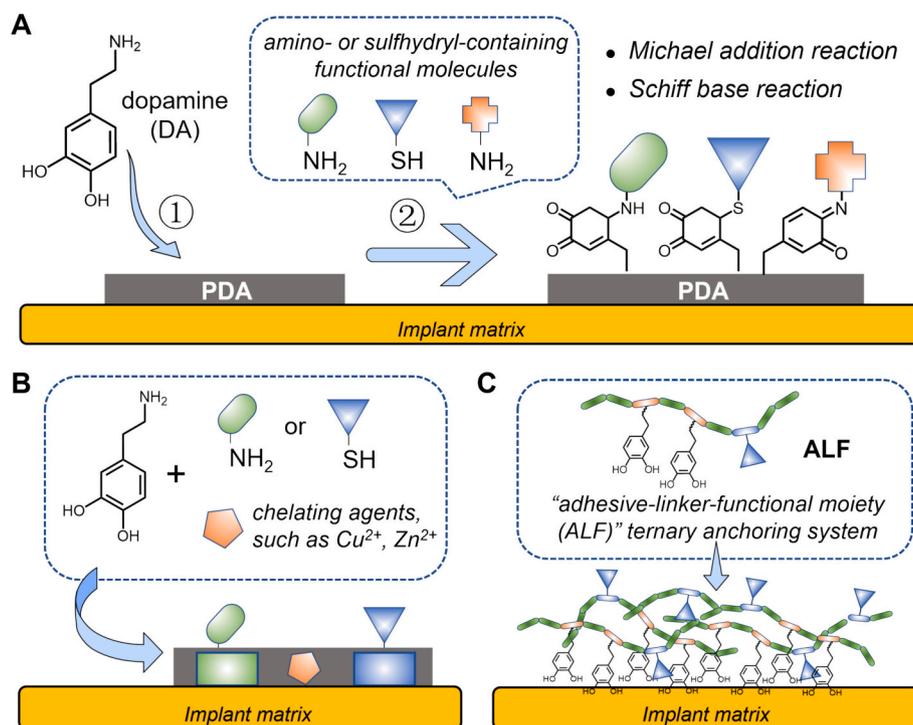


Fig. 12. Mussel-inspired surface functionalization strategies. (A) PDA coating-mediated two-step grafting; (B) One-pot co-deposition grafting method; (C) Single-step grafting based on the "adhesive-linker-functional moiety (ALF)" ternary anchoring system.

surface functionalization. For example, Wu et al. utilized the PDA bridge to conjugate with PEI through Michael addition and Schiff base reactions, obtaining an amino-rich coating surface [253]. Recombinant humanized type III collagen was then anchored onto the PDA/PEI coating via covalent bonding and electrostatic interactions. Unlike conventional drug-eluting stents that rely on antiproliferative agents such as sirolimus or rapamycin, this drug-independent collagen-based coating achieved multiple biological benefits, including reduced thrombosis risk, inhibition of restenosis, and promotion of in-situ endothelial regeneration (Fig. 13A). Li et al. pretreated the surface of degradable PLA scaffolds with amino-functionalized by co-deposition of PDA and PEI, and then utilized carboxybetaine acrylate-co-dopamine methacrylate copolymers containing catechol groups to form a mussel mimetic amphiphilic coating by Michael addition, Schiff base reaction, and cross-linking through π - π stacking and hydrogen bonding, which showed anticoagulant, anti-inflammatory, and anti-hyperplasia properties (Fig. 13B) [254]. In another study, Zhang et al. constructed a composite coating composed of polydopamine, lysine, and modified heparin on the surface of PVC tubes, a commonly used medical material (Fig. 13C) [255]. This composite coating significantly inhibited platelet adhesion and activation, extending the activated partial thromboplastin time by over 25 s. Moreover, the coating shows significant blood compatibility, with a hemolysis rate below 0.5 % and performs well in in-vitro blood circulation assessments (Fig. 13D). Extensive studies have shown that PDA can achieve efficient adhesion on various substrates, making it a universal strategy for surface modification of medical implants. However, biomolecule conjugation via Michael addition or Schiff base reactions may potentially impair the functionality of attached biomolecules by consuming their active sites, such as amino and sulfhydryl groups. Additionally, non-specific background adhesion refers to proteins or cells (e.g., immune cells) attaching to PDA-modified surfaces. This prolonged retention may promote sustained activation and amplified inflammatory signaling, ultimately contributing to chronic inflammation, foreign-body responses, and fibrosis [256,257].

4.3.2. One-pot co-deposition grafting method

Although effective, the conventional 'polymerization-then-grafting' strategy requires multi-step operations and often exhibits limited immobilization efficiency for functional molecules. To overcome these limitations, a one-pot co-deposition strategy mediated by PDA has been developed. In this approach, dopamine is pre-mixed with functional molecules containing thiol, amino, or metal-chelating groups and then co-incubated with the substrate (Fig. 12B). As the PDA layer forms, these molecules are simultaneously incorporated and covalently anchored within the PDA matrix through synergistic interactions, including π - π stacking, hydrogen bonding, Michael addition, and Schiff base reactions. Zhu et al. adopted the PDA-mediated one-pot co-deposition strategy to simultaneously immobilize layered double hydroxides loaded with dimethylolallylglycine and the natural antimicrobial agent eugenol onto the surface of PLLA scaffolds [258]. The early-stage contact-killing effect of eugenol achieved an inhibition rate of over 95 % against *S. aureus*, while the subsequent sustained release of dimethylolallylglycine and Mg^{2+} ions from the LDHs promoted angiogenesis and osteogenic differentiation (Fig. 14A). Li et al. proposed a surface modification strategy based on the biomimetic chemistry of mussel foot protein combined with functional molecules to construct an antimicrobial and antithrombotic coating for central venous catheters through a two-step method: In the first step, copper ions were covalently cross-linked by *ene*-functionalized dopamine and lysine, forming both covalent bonds and hydrogen bonds with the catheter surface via the catecholamine structure, resulting in the deposition of PDA/Lys/Cu coatings exhibiting antibacterial activity. In the second step, zwitterionic pSB was grafted onto the coating surface through free radical polymerization, thereby imparting lubricating and antifouling properties (Fig. 14B) [244]. Another representative work inspired by the insect cuticle hardening process combined mussel adhesion chemistry with metal coordination chemistry. A primary network was first constructed through chemical cross-linking of adhesive catechol and collagen, followed by zinc ions chelation via metal-phenolic coordination chemistry, creating a "metal-phenol-polyamine system" coating on the substrate surface (Fig. 14C) [259]. Although the one-pot co-deposition grafting method simplifies

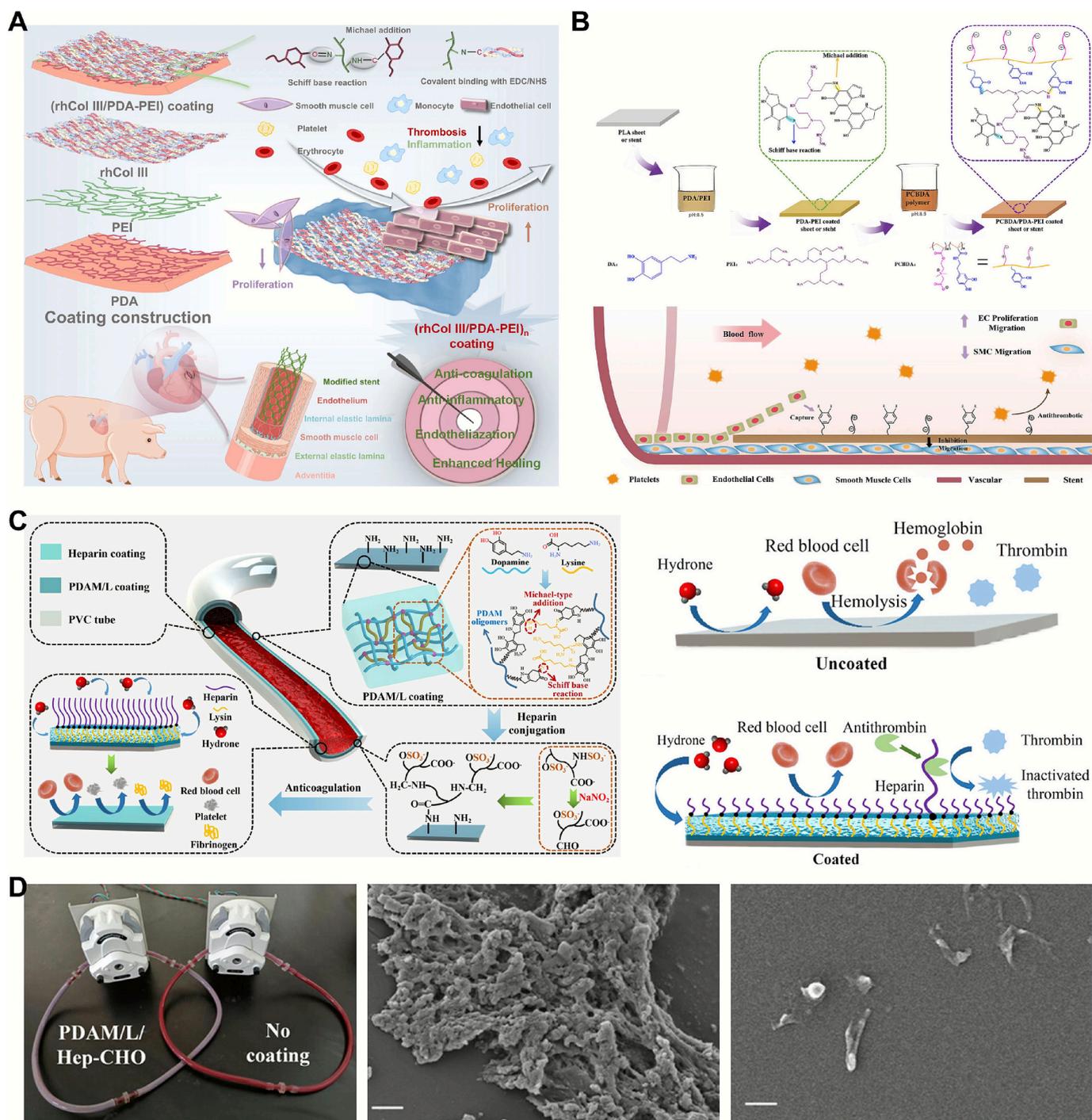


Fig. 13. Surface functionalization based on a two-step grafting method mediated by PDA coating. (A) Schematic representation of the preparation of multifunctional coatings for improving the properties of cardiovascular implants and their intrinsic interaction. Reproduced with permission from ref. [253]. Copyright 2024, Springer Nature. (B) Schematic diagram of PCBDA/PDA-PEI coating preparation on PLA substrate and the functioning of the coating. Reproduced with permission from ref. [254]. Copyright 2022, Elsevier Inc. (C) Schematic illustration of the preparation process and antithrombotic mechanism of PDAM/L/Hep-CHO coatings. (D) SEM images of uncoated and PDAM/L/Hep-CHO-coated tube surfaces after ex vivo blood circulation. Reproduced with permission from ref. [255]. Copyright 2023, American Chemical Society.

operation by eliminating intermediate processing steps in traditional two-step methods and shows broad applicability, functional molecules tend to be embedded within the coating during dopamine polymerization, making precise control over surface density and distribution of functional molecules challenging. Furthermore, this method still suffers from background adhesion issues similar to two-step methods, which may compromise functional molecule activity and clinical safety.

4.3.3. Single-step grafting based on the “adhesive-linker-functional moiety (ALF)” ternary anchoring system

Leveraging the bridging role of linkers, such as peptides or polymers, adhesive groups (e.g., catechol) and functional molecules can be coupled to form the ALF ternary anchoring system, which is able to be immobilized on the substrate surface via the single-step grafting without relying on PDA coating (Fig. 12C). Its core advantages lie in: (1) Direct binding to the substrate via adhesion groups, commonly catechol

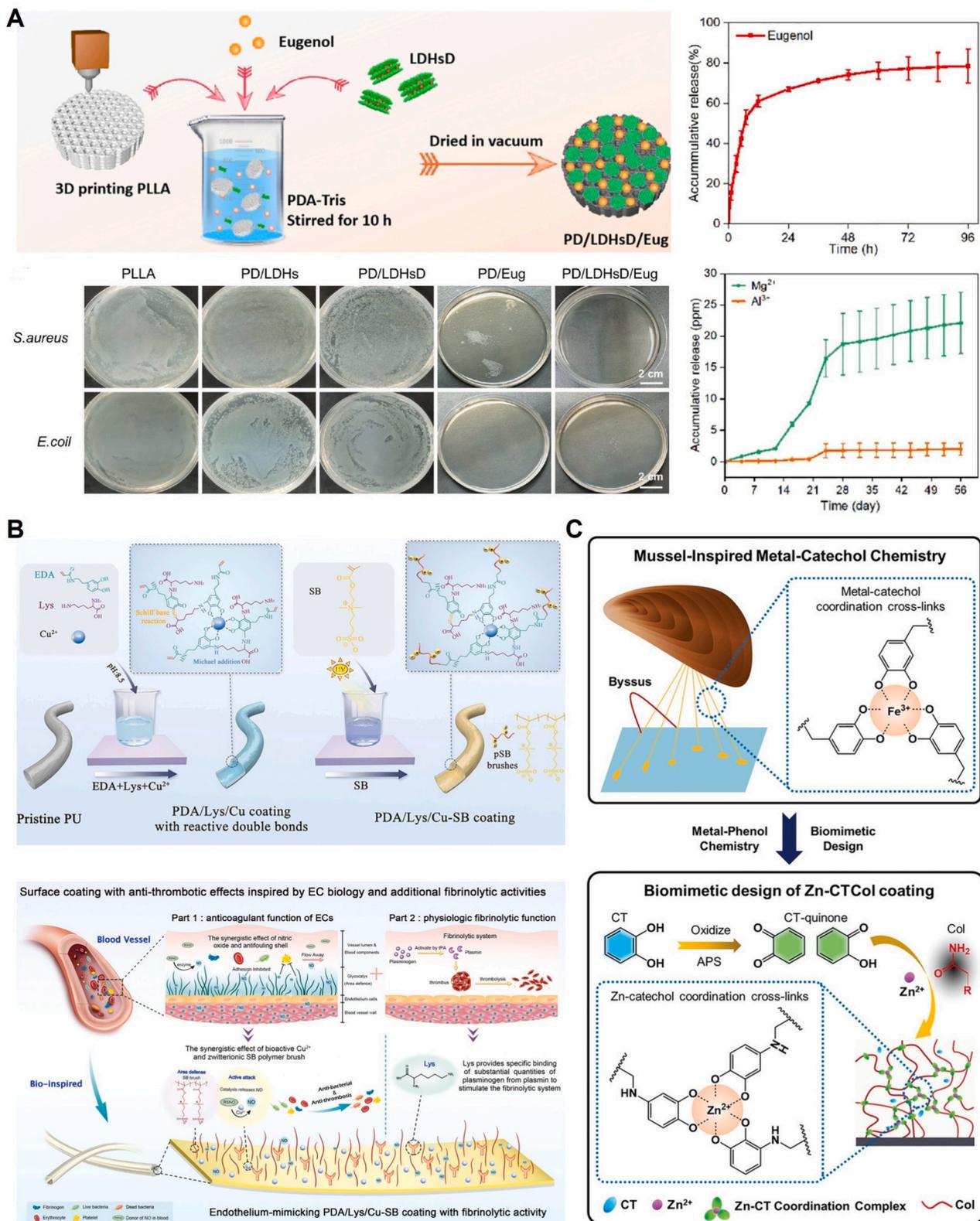


Fig. 14. Surface functionalization based on the one-pot co-precipitation grafting method. (A) Construction of multifunctional PLLA composite scaffolds utilizing spatiotemporal controlled release of DMOG and eugenol, which can play the roles of antimicrobial and promotion of osteogenesis and angiogenesis during cranial bone repair in vivo. Reproduced with permission from ref. [258]. Copyright 2025, American Chemical Society. (B) Construction of endothelium-mimicking PDA/Lys/Cu-SB coatings on commercial PU-based central venous catheters for antithrombotic and antimicrobial effects. Reproduced with permission from ref. [244]. Copyright 2023, Wiley-VCH GmbH. (C) Schematic representation of the mechanism of formation of Zn-CTCol armor inspired by the metal-phenol chemistry of mussel shell cuticle. Reproduced with permission from ref. [259]. Copyright 2024, Wiley-VCH GmbH.

inspired by mussel adhesion mechanisms; (2) Simultaneous bridging of functional molecules via linkers; (3) Dual benefits of eliminating the non-specific “background adhesion” inherent to PDA layers and simplifying operational procedures; (4) Significantly enhanced controllability over functional molecule activity and clinical safety. This design principle of ALF provides a highly flexible approach to the surface functionalization of medical implants, particularly suitable for complex clinical scenarios requiring precise control over surface functionalities.

In one study, researchers synthesized an ALF system based on a random terpolymers incorporating dopamine methacrylamide as the adhesion anchoring group, quaternized maleopimaric acid as the bactericidal component, and zwitterionic 2-methacryloyloxyethyl phosphatidylcholine as the antifouling component (Fig. 15A). They anchored this ALF system onto the surface of PDMS elastomers to construct a dual-functional antimicrobial coating, which displayed significant bactericidal effects against both Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*E. coli*, *P. aeruginosa*), effectively inhibiting the formation of pathogenic biofilms. In-vivo implantation models revealed that the coating effectively eradicated pathogenic biofilms and prevented host tissue damage and inflammation (Fig. 15B) [260]. In another study, Zhang et al. developed a polymeric ALF system integrating both “adhesive groups” (dopamine derivatives) and an “initiating interface” (bromoisobutyrate groups) [261]. A linear copolymer backbone was designed to incorporate N-(3,4-dihydroxyphenyl) ethyl methacrylamide, 2-methacryloyloxyethyl phosphorylcholine, and 2-(2-bromoisobutryl)ethyl methacrylamide, enabling one-step, activation-free self-assembly. The catechol groups ensured universal substrate adhesion, while the bromoisobutyrate moieties served as initiation sites for subsequent polymerization. Meanwhile, the phosphorylcholine segments enhanced hydrophilicity, antifouling performance, and interfacial stability. This synergistic design allowed rapid film formation within 3 min on diverse substrates, including complex catheter interiors. Subsequent SI-ATRP produced dense phosphorylcholine polymer brushes. The resulting coating maintained excellent stability under simulated blood flow for seven days, exhibiting nearly zero protein, platelet, and bacterial adhesion, with superior anticoagulant performance compared to commercial heparin coatings (Fig. 15C).

Overall, ALF-based surface functionalization represents a highly promising strategy for universal functionalization of substrate surfaces, while current research on the ternary anchoring system of ALF remains limited. In reported ALF systems, the “linkers” components primarily consist of linear macromolecules, with adhesive groups and functional molecules attached to the side chains of these linear structures. This molecular design has notable limitations: due to the influence of the coiled conformation of linear macromolecules in aqueous solutions, the spatially undifferentiated adhesive groups and functional molecules tend to interfere with one another. This interference not only reduces the anchoring efficiency of the adhesive groups to the substrate but may also hinder the subsequent coupling efficiency of functional molecules as a result of conformation shielding, potentially leading to functional inactivation.

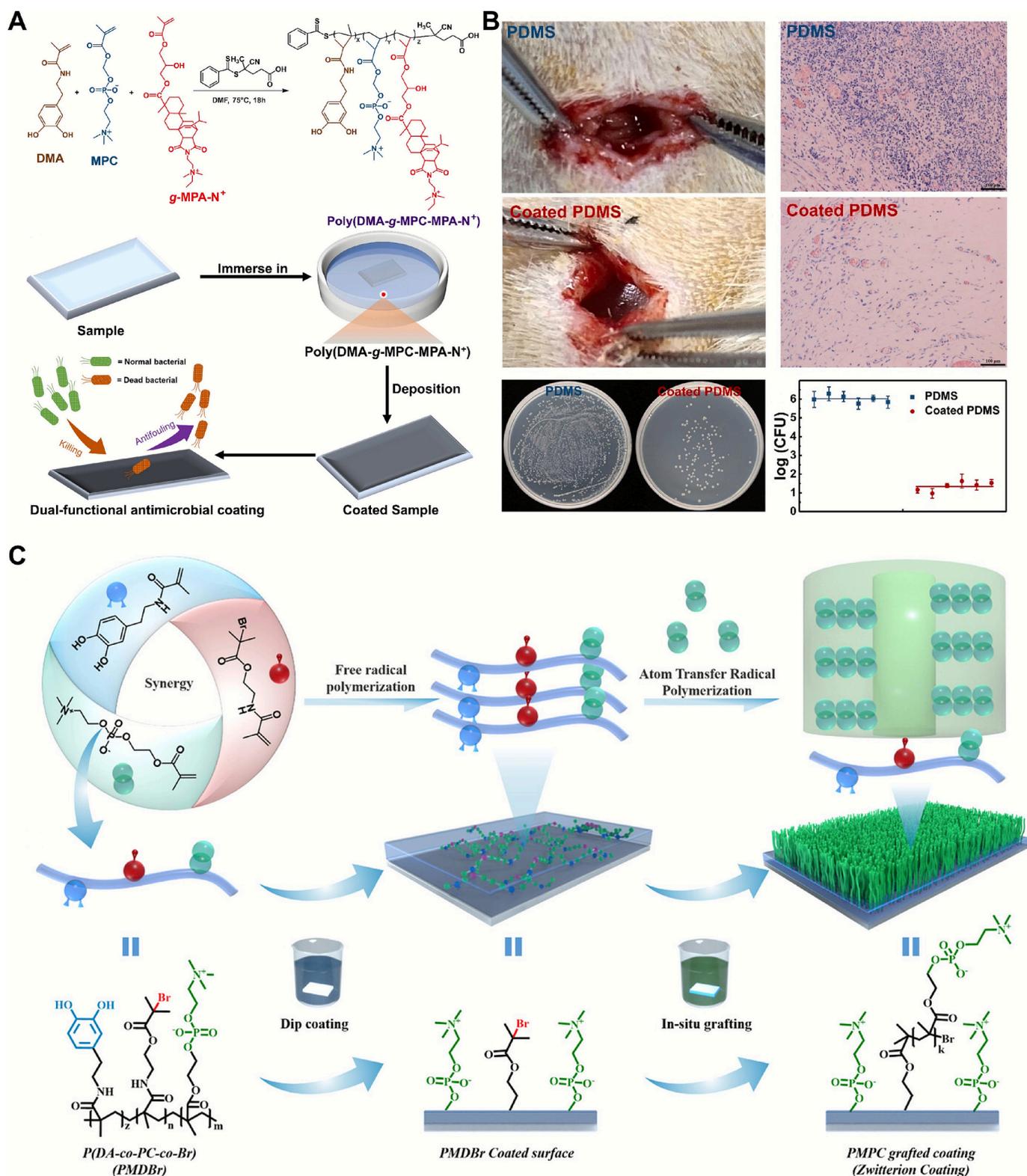
5. Drug-eluting coatings: chemical mechanisms and release kinetics control

Drug-eluting coatings represent a pivotal innovation in biomaterial science, enabling precise localized delivery of therapeutic agents such as antiproliferative drugs, antibiotics, growth factors, or genetic fragments to enhance implant functionality, improve biocompatibility, and minimize systemic toxicity [262]. The design of these coatings hinges on a multidisciplinary integration of material chemistry, drug loading methodologies, and release kinetics, all critically influenced by physiological conditions [263].

Coating materials are broadly categorized into synthetic polymers (e.g., PLGA, PVA, PCL), natural polymers (e.g., gelatin, chitosan, alginate),

and inorganic carriers (e.g., hydroxyapatite, mesoporous silica), each presenting unique advantages and challenges in biodegradability and drug interactions [263]. For instance, PLGA degradation rates can be tuned from weeks to months by adjusting the lactic-to-glycolic acid ratio (e.g., 50:50 to 85:15), allowing alignment with specific therapeutic windows [264]. In contrast, mesoporous silica leverages nanopores (2–10 nm) and silanol group interactions for high drug loading, though burst release effects necessitate mitigation via surface capping strategies like degradable polymer seals [265,266]. Drug loading techniques span a wide variety of methods, from physical blending (e.g., solvent evaporation, electrospinning) to chemical techniques such as LBL assembly and in situ polymerization. LBL is particularly advantageous for fabricating nanoscale multilayered structures, which can facilitate the sequential release of multiple drugs, offering enhanced therapeutic effects, especially in cases requiring combination therapies [218,267,268]. However, conventional methods like dip or spray coating often grapple with uneven drug distribution and loading efficiency issues, underscoring the need for optimizing processing parameters like temperature and solvent selection [269].

For drug-eluting polymeric coatings, the release kinetics are typically governed by diffusion-controlled, degradation-controlled, or stimulus-responsive mechanisms [270–273]. Diffusion-controlled release is governed by Fickian or non-Fickian models, where the drug is released through the coating by diffusion, a process modulated by coating porosity, thickness, and the size of the drug molecule [274]. For example, Tian’s research team developed a PTB@SA hybrid protein nanomembrane coating on silicone rubber catheters [275]. This was achieved by inducing the denaturation and aggregation of BSA using TCEP (tris(2-carboxyethyl)phosphine), followed by doping with sodium alginate (SA) (Fig. 16A). The high toughness nanomembrane was formed through electrostatic interactions and hydrogen bonding between SA and PTB. Rapamycin, an anti-fibrosis drug, was encapsulated as solid particles within the coating’s reservoir. Upon exposure to bodily fluids, the drug dissolved and diffused through natural channels in the PTB@SA hybrid nanomembrane, following a concentration gradient (Fig. 16B). The hydrogen bonding between SA and PTB reduced the swelling rate and water permeability of the membrane, while the membrane’s high toughness prevented leakage, achieving a stable, sustained release over 30 days. In degradation-controlled release, drugs are gradually released as the polymer matrix undergoes hydrolysis or enzymatic cleavage (such as ester bond breakdown). This mechanism is particularly sensitive to microenvironmental factors like pH and enzyme activity. This often results in nonlinear release profiles, which may exhibit an initial burst release followed by a more sustained release phase. Recent studies have reported the development of hydrogels with precisely programmable drug release profiles (Fig. 16C) [276]. These hydrogels are designed to prevent the initial burst release of the drug while maintaining their mechanical properties, thereby aligning the drug release with the optimal therapeutic timeline for the target disease. Stimulus-responsive coatings are an exciting area of development, where the release of the drug is triggered by specific environmental cues such as pH, temperature, redox potential, or enzymatic activity [277–279]. For example, pH-sensitive polymers can be designed to swell in tumor microenvironments (pH 6.5–7.0) to accelerate release, and disulfide bonds cleave under high ROS for targeted delivery [280,281]. Xu et al. successfully developed a Hes@PDA-PLLA biomimetic oriented fiber patch, where the immune-modulatory molecule hesperidin (Hes) is loaded onto a PDA coating [282]. Upon implantation, the decrease in pH induced by the inflammatory microenvironment disrupts the molecular interactions between PDA and Hes, thereby accelerating the on-demand release of Hes. Additionally, the topological structure of the oriented fibers, in combination with the immune-modulatory effect, synergistically alleviates immune rejection, inhibits fibrous capsule formation, and promotes cartilage regeneration (Fig. 16D). These coatings have the potential for high precision in controlled release, particularly for targeted therapies. However, challenges remain in optimizing these



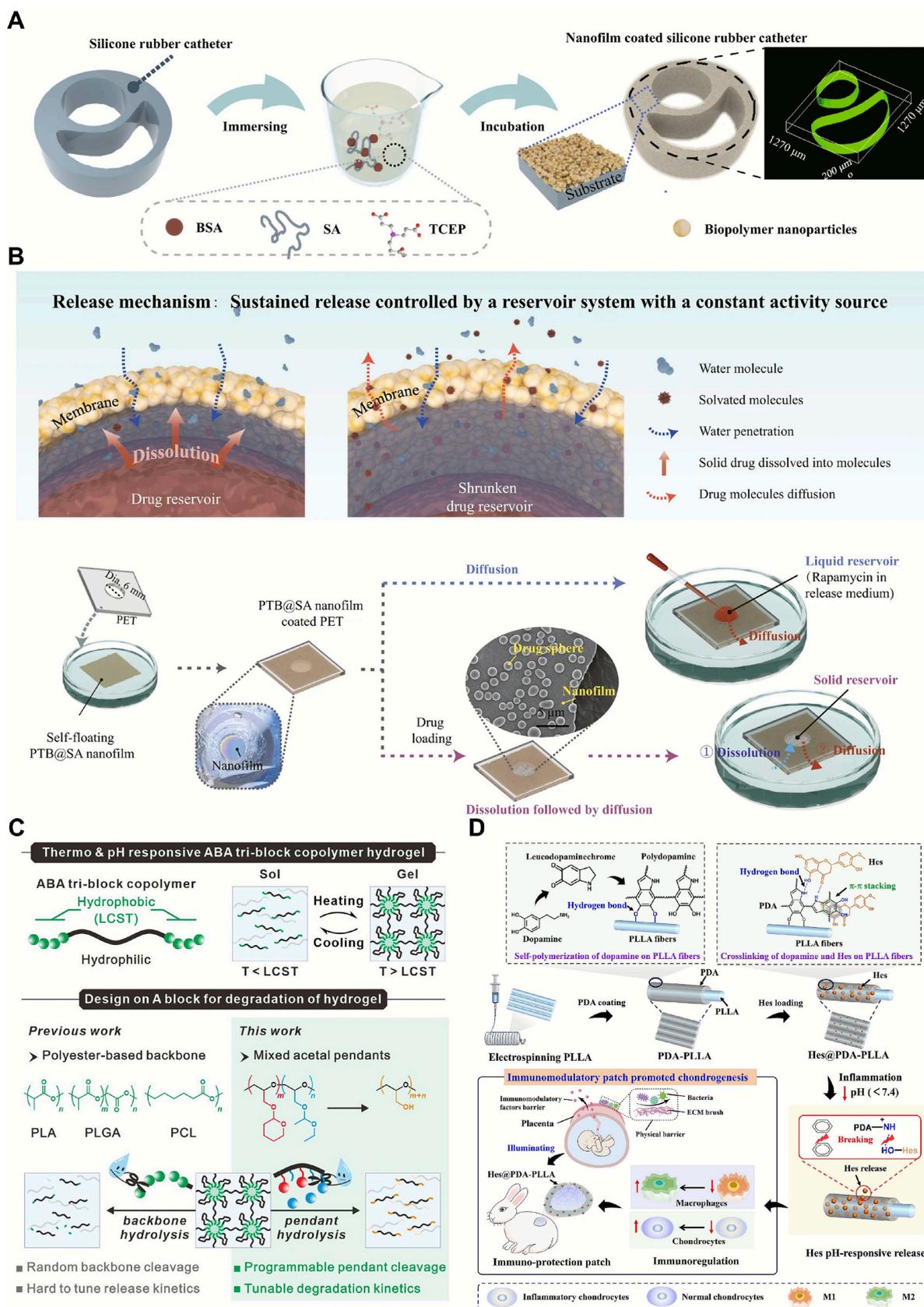


Fig. 16. Drug-eluting coatings for medical implants. (A) Schematic diagram of preparing hybrid nanomembranes on silicone rubber tubing. (B) Mechanisms of drug release from a reservoir-type system. Reproduced with permission from ref. [275]. Copyright 2023, Springer Nature. (C) ABA-type triblock copolymer hydrogel systems exhibit thermal and pH responsiveness (top figure) and a comparison of degradation mechanisms between polyester-based main chains and ABA-type triblock copolymers (bottom figure). Reproduced with permission from ref. [276]. Copyright 2024, American Chemical Society. (D) Schematic diagram of Hes@PDA-PLLA preparation and its immunomodulatory effects on cartilage formation. Reproduced with permission from ref. [282]. Copyright 2025, Elsevier Inc.

coatings to ensure precise triggering and minimize potential biosafety concerns, including unintended side effects or non-specific activation.

Future directions in drug-eluting coatings emphasize several promising areas, including multi-drug sequential release systems, in situ crosslinked coatings for interfacial stability, and the integration of machine learning to predict drug release behaviors and enhance personalized medicine [283–286]. Multi-drug release systems hold great potential for combination therapies, where different drugs can be released sequentially to maximize therapeutic efficacy.

6. Summary and outlook

Polymer-based medical implants have been widely applied in orthopedics, cardiovascular medicine, soft tissue repair, and other fields, accounting for approximately 15 %–20 % of the global medical device market [287]. Despite their widespread use, several critical challenges persist in clinical practice. These include long-term inflammatory responses arising from suboptimal biocompatibility [288], the contradiction between mechanical properties and biological functions (e.g., PEEK's lack of osteoblastic activity) [289], infection risk from bacterial biofilms [290], late-stage failure resulting from oxidative degradation of materials, and difficulties in meeting the requirements of personalized and intelligent medicine.

Surface functionalization of polymeric implants carries profound scientific and clinical significance. Precise surface modification strategies can finely tune the interfacial interactions between materials and biological systems, thereby mitigating adverse immune reactions such as inflammation, fibrous capsule formation, and foreign body responses. Critically, tailoring surface chemistry and structure to specific clinical requirements can endow functionalized implants with targeted bioactivities, such as antibacterial, antithrombogenic, and osteoinductive properties. From a materials engineering perspective, advanced modification techniques including micro/nanostructuring, chemical grafting and bioinspired coatings enhance the durability (e.g., wear resistance, oxidative stability, anti-aging performance), while preserving the mechanical integrity of the substrate. Moreover, integrating surface functionalization with precision medicine offers promising pathways toward intelligent, responsive, and patient-specific implant systems.

While biomaterial surface/interface engineering holds great promise for advancing tissue regeneration and clinical applications, it also presents challenges that warrant further exploration. The well-documented interplay between surface properties (e.g., topography, stiffness, and chemistry) and cellular responses reveals that nanoscale roughness enhances osseointegration in bone implants, while elasticity-matching substrates improve soft tissue regeneration. However, limitations persist, including the long-term stability and biodegradability of surface modifications in dynamic in-vivo environments [151]. Despite their simplicity, physical methods like spin coating and plasma treatment often suffer from poor adhesion and transient effects. Similarly, surface micro-nanostructures and patterning must overcome inherent durability issues like wear and aging, even as they successfully maintain the substrate's mechanical integrity. For biomolecule conjugation, well-established coatings like polydopamine, although convenient, often exhibit low grafting efficiency, poor uniformity, and potential cell-inhibiting effect [291].

To achieve real-time adaptation of biomaterial surfaces to dynamic physiological environments, future work should focus on the development of intelligent control systems with personalized responsiveness. This can be realized through advanced strategies like bio-orthogonal reactions or stimulus-responsive (e.g., pH, temperature) coatings [154]. In addition, the development of a universal, modular surface functionalization platform is imperative for the cost-effective performance enhancement of various medical polymer implants. A highly promising future approach involves developing a convenient and universally applicable surface functionalization method compatible with diverse polymer substrates. This method should offer modularly

customizable functionalities, enabling cost-efficient performance upgrades without altering manufacturing processes. However, current surface functionalization methods, whether physical or chemical, are typically confined to specific substrates or applications, thus lacking universal applicability. The biomimetic 'adhesive group-linker-functional moiety' (ALF) ternary anchoring system has shown great potential in providing substrate-independent surface functionalization. Nevertheless, significant challenges remain, including spatial interference between adhesive groups and functional molecules, as well as restricted customization capabilities. Both of these factors hinder successful clinical translation. Therefore, achieving effective spatial isolation between adhesive groups and functional molecules in the ALF system is critical for realizing customizable surface functionalization, marking a key direction for the development of next-generation ALF-based universal surface functionalization materials for medical implants. Future research should also prioritize the development of dynamic, multifunctional interfaces. Integrating artificial intelligence and machine learning for targeted predictive material design [154,292], could enable personalized medicine approaches. For instance, machine learning-assisted models predicting release curves can guide the design of multi-drug sequential release systems, enhancing personalized precision therapy [280].

To advance toward clinical translation, large-scale in vivo studies are required to validate safety and efficacy, particularly regarding immune compatibility and tissue integration. To overcome translational barriers between the laboratory and clinical practice, interdisciplinary collaboration among material scientists, biologists, and clinicians is essential. By prioritizing biocompatibility, scalability, and personalization, surface functionalization will not only enhance the performance of existing implants but also enable groundbreaking applications in regenerative medicine and beyond, ultimately improving patient outcomes and reducing healthcare burdens.

CRediT authorship contribution statement

Haodan Luo: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Xiaobo Liu:** Writing – original draft, Investigation, Data curation. **Xiaoyue Chen:** Formal analysis, Data curation. **Zuo Pu:** Writing – original draft, Project administration, Investigation, Funding acquisition. **Zhaojun Jia:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Data curation, Conceptualization. **Jun Yue:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

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Data availability

No data was used for the research described in the article.

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