

REVIEW

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Recent progress in side-chain amino acid-based polymers: synthesis, self-assembly, and emerging biomedical applications

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Side-chain amino acid-based polymers (SCAAPs), as a class of functional polymeric materials constructed from natural amino acids or their derivatives, have garnered significant attention in recent years in the fields of materials science and biomedicine. Their unique structural designability, excellent biocompatibility, and “smart” responsive properties make them an ideal platform for biomedical applications. This review systematically summarizes the synthetic strategies of SCAAPs, covering the rational design of amino acid-based monomers and their controlled polymerization through typical techniques (including reversible addition–fragmentation chain transfer polymerization, photoinduced electron/energy transfer–reversible addition–fragmentation chain transfer polymerization, atom transfer radical polymerization, ring-opening metathesis polymerization, and activated ester substitution). Additionally, this review delves into the self-assembly behavior and multi-responsiveness (temperature, pH, and ionic responsiveness) of these polymers, revealing the mechanisms by which they form nanostructures driven by noncovalent forces such as hydrophobic interactions and hydrogen bonding. Finally, this review highlights recent progress in biomedical applications of SCAAPs, encompassing anticancer therapy, antimicrobial treatment, biosensing, tissue engineering scaffolds, and antifouling coatings. By integrating perspectives from chemical synthesis, materials science, and biology, this review aims to provide a theoretical foundation and technical reference for further research and application of SCAAPs.

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1. Introduction

As an important class of biomaterials, amino acid-based polymers have garnered widespread attention in the biomedical field in recent years due to their excellent biocompatibility, biodegradability, and significant potential for functional group modification.^{1–3} Amino acid-based polymers are polymers composed of amino acids or their derivatives as basic structural units linked through covalent bonds, and they can be synthesized through various methods, such as condensation reactions and active ring-opening reactions. Based on the position of the structural units within the polymer backbone, amino acid-based polymers can be classified into main-chain and side-chain types. When amino acid structural units are linked repetitively *via* amide bonds (peptide bonds) to form the polymer backbone, the resulting materials (such as traditional

poly(amino acids), peptides, or peptidomimetic materials) are referred to as main-chain amino acid-based polymers.⁴ In contrast, polymers in which the polymer backbone consists of non-amino acid synthetic macromolecules (such as polyacrylates, polystyrene, or poly-norbornene), and amino acids or their derivatives are covalently attached to the backbone as side chains, are referred to as side-chain amino acid-based polymers (SCAAPs).⁵

Compared to main-chain amino acid-based polymers, SCAAPs exhibit numerous unique advantages. First, their main chains are typically composed of synthetic polymers lacking peptide bonds, making many of them less susceptible to protease-mediated backbone cleavage and, depending on the backbone and linker chemistry, more stable under physiological conditions and endowing them with higher chemical stability, which confers superior conformational stability and structural durability to the materials. Second, various functional groups can be introduced into the side chains as needed, allowing flexible control over the polymer's hydrophilicity, lipophilicity, charge properties, and functional group density, thereby providing greater design freedom.⁶ Furthermore, the

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incorporation of bioactive molecules into the side chains enables multifunctionality.² Based on these characteristics, SCAAPs possess more diverse chemical functions and superior physical properties, enabling them to demonstrate enhanced structural stability and functional reliability in complex physiological environments (such as blood and the extracellular matrix). Consequently, SCAAPs exhibit tremendous application potential in biomedical fields such as drug delivery, biosensing, and tissue engineering.^{1,3,4}

Although several reviews have summarized progress in side-chain amino acid-based polymers, most have focused on selected aspects rather than providing a comprehensive overview of their molecular design, synthesis, assembly behavior, responsiveness, and biomedical applications. For instance, De *et al.* have illustrated the self-assembly properties of side-chain amino acid-based polymers and their utility in drug or gene delivery, antimicrobial applications, and antifouling coatings.⁷ Nevertheless, the synthetic strategies for SCAAPs have been continuously refined and developed, encompassing controlled/living polymerization techniques (such as RAFT, PET-RAFT, ATRP, and ROMP) as well as activated ester methods.^{4,8} Concurrently, in terms of structural design, SCAAPs have advanced from simple linear polymers to highly structured architectures such as brush-like, hyperbranched, dendritic, and star-shaped polymers.⁶ Therefore, this review systematically summarizes recent advances in the monomer

design and synthesis of SCAAPs, discusses their self-assembly behavior and stimuli responsiveness, and highlights their biomedical applications in antitumor therapy, antimicrobial treatment, biosensing, tissue engineering, and antifouling coatings.

It is foreseeable that, with the continuous advancement of polymerization methodologies, precision molecular modification techniques, and multi-scale characterization approaches, SCAAPs will play an increasingly central role at the interface of materials science and biomedicine, opening new ideas and pathways for the design and application of next-generation functional polymer materials (Fig. 1).

2. Synthetic strategies for SCAAPs

2.1. Monomer design

In the synthesis of SCAAPs, the core of monomer design lies in balancing controlled polymerization with side-chain functionality through functional group protection and deprotection strategies. The synthesis of polymers with functional side chains from amino acid monomers often requires the introduction of polymerizable groups while protecting reactive amino acid functionalities when necessary. Unsaturated acyl groups (such as acryloyl or methacryloyl groups) can be introduced into the amino group of an amino acid to yield the

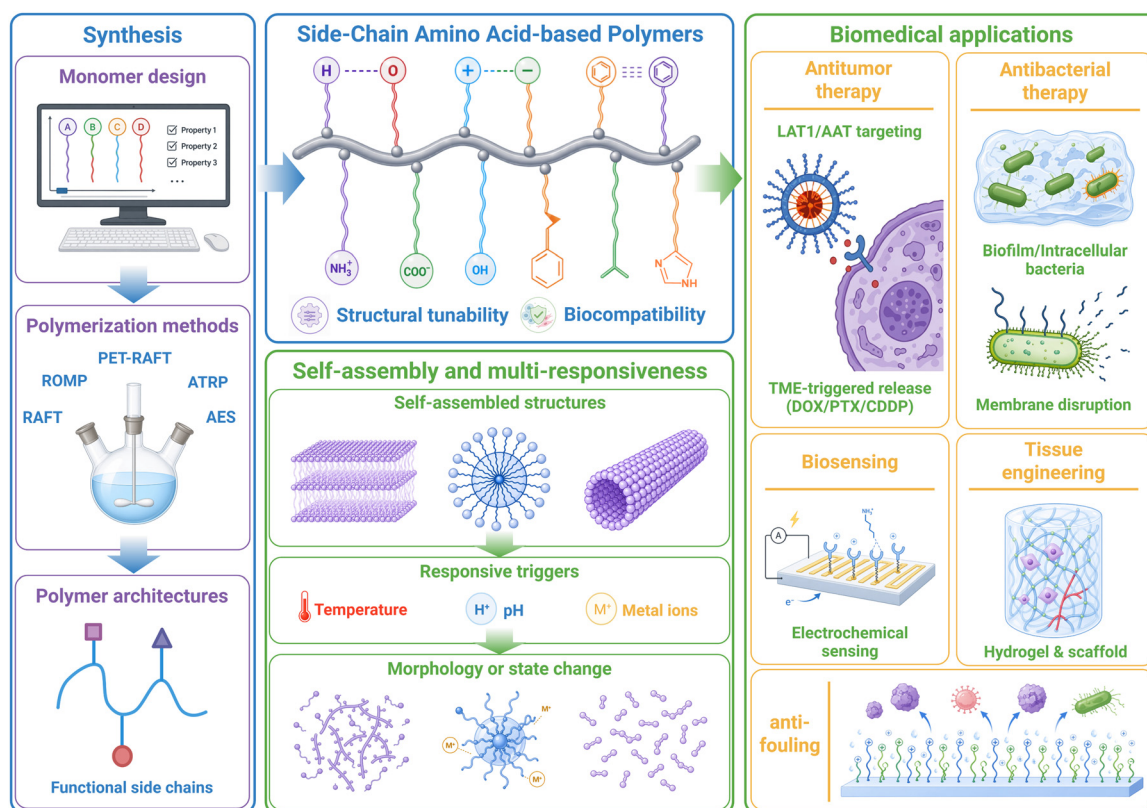


Fig. 1 Overview of the synthesis, self-assembly, multi-responsiveness, and biomedical applications of SCAAPs. Created using BioRender. Jason, X. (2026) <https://BioRender.com/3yao2no>.

corresponding acrylamide or methacrylamide monomers, or unsaturated groups can be grafted onto the carboxyl group to yield acrylate monomers. For example, Mays *et al.* used acryloyl β -alanine as a monomer and successfully synthesized polymers with a dispersity ranging from 1.13 to 1.25 *via* atom transfer radical polymerization (ATRP).⁹ During monomer preparation, protective group strategies are often employed to prevent side reactions triggered by amino acid functional groups. For example, the ϵ -amino group of lysine is protected using the NH-Boc protected strategy, and the γ -carboxyl group of glutamic acid can be protected as a benzyl ester.¹⁰ The functional group protection strategy ensures the smooth polymerization of active groups, while the activity of functional side chains (such as amino or carboxyl groups) can be restored post-polymerization through deprotection. In addition, there are studies on the direct polymerization of unprotected functional monomers. For example, Wang *et al.* reported that amino acid acrylamide monomers containing free carboxyl groups could be polymerized in methanol without carboxyl protection, successfully yielding functionalized homopolymers and diblock copolymers.¹¹

Furthermore, the design of cyclic backbone monomers is another key approach for constructing high-performance SCAAPs. In ring-opening metathesis polymerization (ROMP), norbornenes or oxanorbornenes, which possess high ring strain, are typically used as polymerization-driving carriers.^{12–14} Designers have modularly coupled various amino acid residues to the side chains of the bicyclic scaffold *via* ester or amide bonds, thereby preparing monomers with high structural regularity. This design ingeniously exploits the Grubbs catalyst's high tolerance for polar groups (such as amino acid side chains), enabling the monomers to retain the configurational integrity of the amino acid chiral centers during polymerization.^{12,14–16} On the other hand, monomer design is not limited to monomers that directly incorporate amino acid structures; it also includes activated ester precursor monomers for post-polymerization modification. Monomer designs represented by pentafluorophenyl methacrylate (PFPMa) pre-incorporate a pentafluorophenyl ester group that is relatively stable toward water but highly reactive toward primary amines.^{17,18} The advantage of this design approach lies in the fact that it postpones the complex incorporation of amino acids until after polymerization. By following a “polymerize-first, functionalize-later” pathway, it effectively avoids polymerization challenges caused by differences in solubility or functional group interference among various amino acid side chains. Furthermore, monomer design for photoinduced electron/energy transfer-reversible addition-fragmentation chain transfer (PET-RAFT) polymerization has further expanded the scope of application for unprotected monomers. Due to the mild reaction characteristics of PET-RAFT under visible light and at room temperature, monomer design can reduce reliance on complex protective groups. For example, even unprotected dicarboxylic acid amino acid monomers can undergo highly efficient polymerization directly in protic solvents such as methanol. This approach not only simplifies the synthetic steps but also avoids potential damage to heat-sensitive biological moieties (such as peptides, proteins,

or thiol-carbonyl-thiol end groups) caused by deprotection conditions involving strong acids and high temperatures.^{11,19}

Taken together, the monomer design of SCAAPs has evolved from the traditional “protection-polymerization-deprotection” model toward a diversified approach encompassing modular scaffold design (such as norbornene derivatives), activated ester precursor design (such as activated ester monomers), and direct polymerization with tolerance (such as unprotected multifunctional monomers), laying the foundation for the precise regulation of polymer topological structures and biological functions.

2.2. RAFT polymerization

RAFT polymerization has become a core strategy for constructing SCAAPs due to its excellent functional group tolerance. RAFT polymerization enables the direct polymerization of amino acid monomers with polar or charged side chains in conventional solvents or even in aqueous systems without the need for cumbersome protection/deprotection steps. In aqueous systems, precise control of pH and reaction conditions can effectively suppress side reactions such as the hydrolysis of the chain transfer agents (CTAs) and amide hydrolysis triggered by amino acid side chains.^{5,20} Furthermore, the thio-carbonyl groups retained at the ends of RAFT-polymerized chains confer macro-chain-transfer agents (Macro-CTAs) activity to the polymers, facilitating the design of SCAAPs with complex topological structures (*e.g.*, block, star, and hyperbranched).⁶ For example, Wang *et al.* utilized a one-pot iterative RAFT polymerization to synthesize proline-based multi-block copolymers with precisely controlled sequences and high monomer conversion rates (>98%). By altering the sequence arrangement, they were able to precisely regulate the polymers' phase separation behavior and low critical solution temperature (LCST).²¹ Addressing the potential cytotoxicity of CTAs' end-groups (such as dithiobenzoate) that is of widespread concern in biomedical applications, current studies indicate that using biocompatible trithiocarbonate-based CTAs or cleaving the end-groups *via* mild methods such as amination or radical-induced reduction can mitigate or reduce potential end-group-related cytotoxicity.²² Overall, RAFT technology provides a highly flexible platform for the precise synthesis and functionalization of SCAAPs.

2.3. PET-RAFT polymerization

Although traditional RAFT polymerization has demonstrated excellent compatibility and structural customization capabilities in the synthesis of SCAAPs, its reliance on thermal or conventional chemical initiation often limits the precise spatiotemporal control of the polymerization process, and high-temperature conditions may damage heat-sensitive bio-functional groups. To overcome these limitations, the development of PET-RAFT polymerization technology in recent years has provided a new approach for the synthesis of SCAAPs. PET-RAFT polymerization has garnered significant attention due to its mild reaction conditions and high polymerization efficiency. It utilizes photocatalysts (transition metal complexes, organic dyes, chlorophyll and bacterial chlorophyll, porphyrin compounds, *etc.*) to

generate excited states, which undergo electron or energy transfer with thiocarbonylthio RAFT CTAs, thereby generating active radical chains.¹⁹ Compared to conventional RAFT polymerization, PET-RAFT polymerization employs milder conditions, allowing polymerization to occur at room temperature under visible light to yield polymers with narrow molecular weight distributions and controllable molecular weights. This avoids the damage caused by high temperatures to heat-sensitive functional groups (such as accelerated hydrolysis of terminal thiocarbonyl groups, amination side reactions triggered by unprotected amino groups, thermal cleavage of thiol and disulfide bonds, and deactivation of heat-sensitive conjugates such as coupled peptides and proteins).^{9,11} Secondly, PET-RAFT polymerization offers spatiotemporal controllability; by switching the light source, polymerization can be initiated and paused, allowing precise control over the polymerization process to regulate the chain length and structure, which is particularly advantageous for synthesizing polymers requiring stepwise monomer addition.¹⁰ Finally, PET-RAFT polymerization exhibits high compatibility with functional groups. The lower visible light energy reduces side reactions involving sensitive functional groups, and the photoinitiation system demonstrates good tolerance to oxygen, allowing polymerization in relatively open systems under certain conditions and simplifying deoxygenation procedures. For example, Wang *et al.* successfully applied PET-RAFT to the polymerization of amino acid monomers. Under mild conditions, they successfully polymerized a variety of pre-synthesized amino acid monomers, constructing a series of polymer libraries with controllable molecular weights and low polydispersity. Interestingly, in the PET-RAFT polymerization system, unprotected dicarboxylic acid monomers can also be directly polymerized in methanol, avoiding cumbersome protection and deprotection processes, which demonstrates the unique advantages of this method.¹¹ Of course, PET-RAFT also has certain limitations. For example, the introduction of a photocatalyst may result in its residual presence in the product, posing a potential threat to the material's biocompatibility and physicochemical properties. Additionally, the polymerization reaction mechanism is relatively complex, involving multiple excitation and electron transfer pathways, requiring strict control of the catalyst and reaction conditions to ensure controlled polymerization.¹⁹ Overall, PET-RAFT polymerization combines the controllability of photochemistry with the compatibility of RAFT for functional groups, demonstrating great potential in the synthesis of SCAAPs. It enables mild conditions and precise control that are difficult to achieve using traditional methods, opening new avenues for the synthesis of functional polymers.

2.4. ATRP

ATRP is another important method of controlled radical polymerization and has also been applied to the polymerization of amino acid-derived monomers.²³ ATRP typically employs transition metal (such as Cu(I)) catalysts and halogenated alkane initiators to achieve controlled chain growth through a reversible transfer mechanism between active and dormant species. Compared to RAFT polymerization, ATRP imposes stricter

requirements on reaction conditions and functional group compatibility, as certain functional groups (such as amino and carboxyl groups) can coordinate with the metal catalyst, thereby disrupting the dynamic equilibrium between the active and dormant species. Therefore, when polymerizing amino acid-based monomers using this method, it is often necessary to protect sensitive groups and select appropriate solvents to optimize the activity and solubility of the metal catalyst. For example, carboxyl groups typically need to be converted into esters (such as methyl or ethyl esters) to shield their coordinating ability, thereby reducing interference with the activity of the metal catalyst.¹⁰ Nevertheless, there are reports of successful synthesis of amino acid-functionalized polymers *via* ATRP. For example, the team led by Mays initiated the polymerization of acryloyl- β -alanine (an amino acid monomer containing a free carboxyl group) using various water-soluble initiators under ambient aqueous conditions (20 °C) using a CuBr/2,2'-bipyridine catalytic system, yielding polymers with high yields and narrow molecular weight distributions.⁹ This study demonstrates that even when the monomer carries hydrophilic or acidic groups, ATRP can still achieve a controlled molecular weight and narrow molecular weight distribution under appropriate conditions. Furthermore, amino acid-derived monomers often contain polar groups and have limited solubility in organic solvents, and their amide groups may induce metal complexation, leading to side reactions such as deactivation or nucleophilic substitution; consequently, there are relatively few reports on the ATRP polymerization of amino acid-based monomers in organic media.²³ To overcome these challenges, various modified ATRP techniques have been reported. For example, under air conditions, using enzymes as macromolecular initiators and *in situ* aqueous activators generated by electron transfer for atom transfer radical polymerization, uniform and stable polymer-protein conjugates were prepared, demonstrating the feasibility of the improved ATRP system in complex biomolecular environments.^{24,25} In summary, ATRP is feasible for the preparation of amino acid polymers, but experimental conditions must be optimized to account for the characteristics of amino acid side-chain functional groups. One of its advantages is the provision of reactive chain termini, facilitating further chain extension or modification. At the same time, the diversity of ATRP catalyst systems (*e.g.*, different ligands and metals) offers possibilities for adapting to various functional groups. With the development of ATRP catalytic systems, the applicability to amino acid monomers is expected to improve further.

2.5. ROMP

ROMP, with its excellent functional group tolerance and controllable reactivity, has become one of the key strategies for the preparation of SCAAPs.¹⁴ Compared to traditional radical polymerization or condensation reactions, ROMP can proceed efficiently under mild conditions, enabling precise control over the molecular weight, degree of polymerization, and dispersity, thereby providing a reliable approach for constructing complex peptidomimetic biomacromolecules.¹² The ROMP strategy

primarily utilizes the high ring strain of norbornene or oxanorbornene as the driving force for polymerization, coupling various amino acid residues to the side chains of the bicyclic skeleton *via* ester or amide bonds.²⁵ Grubbs-type ruthenium catalysts generally exhibit high tolerance toward polar functionalities and sterically demanding monomers; therefore, ROMP of amino acid-functionalized norbornene derivatives can often proceed under relatively mild conditions in common organic solvents such as dichloromethane (DCM) or tetrahydrofuran (THF), although dry and inert conditions are typically used to ensure reproducibility and control. This mild polymerization environment effectively preserves the configuration of the chiral centers in the side-chain amino acids and the structural integrity of bioactive groups.²⁵ The core synthetic advantage of ROMP lies in its excellent ability to control topological structures. Since side reactions such as chain transfer and termination are significantly suppressed, ROMP enables the convenient preparation of multi-block copolymers with well-defined side-chain amino acid block ratios *via* sequential feeding.¹⁴ Furthermore, in combination with macro-monomer strategies or the “grafting-through” method, ROMP has been widely used to construct amino acid- and peptide-based brush polymers with high side-chain steric hindrance and high grafting density.^{13,16} For example, Wang *et al.* recently developed HYbrid DegRAding Copolymers (HYDRACs) through graft-through ROMP of norbornenyl-peptide monomers. By statistically copolymerizing peptide-based target-binding motifs with degron-containing norbornene monomers, they obtained proteomimetic peptide brush copolymers with tunable side-chain stoichiometry and multivalent payload display. This study further showed that the globular peptide-brush architecture could improve proteolytic resistance and cellular uptake while enabling targeted degradation of disease-relevant proteins such as MYC and KRAS.²⁶ In another recent study, Mesfin *et al.* reported Keap1-targeting protein-like polymers (PLPs) based on peptide-brush polymer design. The multivalent peptide side chains of these PLPs mimic the Nrf2-binding domain, engage the Keap1/Nrf2 protein–protein interaction, activate cytoprotective Nrf2 signaling, and exhibit therapeutic potential in a myocardial infarction model.²⁷ These recent examples indicate that ROMP-derived peptide brush polymers are not only synthetic models for high-density side-chain amino acid architectures but also functional proteomimetic platforms with enhanced stability, intracellular bioactivity, and translational biomedical potential. This dense molecular brush structure not only confers unique spatial and physical rigidity to the polymer but also constructs multivalent recognition units on its surface, demonstrating immense application potential in the design of targeted drug delivery carriers and biointerface materials.

Overall, ROMP provides a robust and efficient chemical platform for the customized synthesis of SCAAPs.¹² Through the modular design of norbornene derivatives and the synergistic effect of Grubbs catalysts, this method successfully overcomes the synthetic barriers posed by the polarity and steric hindrance of amino acid side chains in conventional

polymerization, laying an important foundation for the development of novel biomedical materials with excellent biocompatibility and precise molecular architecture.^{13,16}

2.6. Activated ester substitution

When constructing structurally well-defined and functionally diverse SCAAPs, post-polymerization modification strategies based on active parent polymers, particularly the activated ester substitution method, have demonstrated significant synthetic advantages. The core of this method lies in first preparing a backbone polymer containing highly reactive ester groups, followed by the introduction of amino acid functional units *via* nucleophilic substitution reactions. Among these, activated ester monomers, such as pentafluorophenyl methacrylate (PFPMA), serve as ideal scaffolds for constructing SCAAP libraries due to the high reactivity of the pentafluorophenyl ester group toward primary amines and relative stability toward water. The poly(pentafluorophenyl methacrylate) (PPFPMA) precursor prepared *via* RAFT polymerization maintains a narrow molecular weight distribution and a predefined degree of polymerization ($M_n = 33\,900\text{ g mol}^{-1}$). Under mild reaction conditions (typically at room temperature and without the need for complex catalytic systems), the PPFPMA scaffold can undergo efficient amidation reactions with various amino acids, peptide segments, or their derivatives bearing free amino groups, enabling modular functionalization of the side chains. This “polymerize-then-functionalize” activated ester approach effectively circumvents the issues of solubility differences and functional group interference that different side-chain amino acid monomers may face during direct polymerization, greatly simplifying the construction process of complex SCAAP libraries. Studies have shown that this substitution reaction typically achieves near-quantitative conversion in polar non-protonic solvents, thereby ensuring the precision of the resulting amino acid polymer components and batch-to-batch stability, providing a powerful chemical tool for the development of biomimetic functional materials with specific biosensing capabilities or stimulus responsiveness.¹⁷ Furthermore, when combined with controlled radical techniques such as RAFT polymerization, the activated ester method can be further utilized to prepare structurally more complex block or star-shaped amino acid copolymers, which hold broad application prospects in the fields of drug delivery carriers and biointerface modification.¹⁸

In summary, there are various methods for synthesizing amino acid-based functional polymers, each with its own characteristics and advantages. These range from precise control of monomer design to functional group protection and deprotection during the polymerization process. Methods such as RAFT, PET-RAFT, ATRP, ROMP, and activated ester substitution provide powerful tools for the precise design and preparation of functional polymers. These methods not only allow for the regulation of the polymer molecular weight, structure, and function but also preserve the functional side chains of amino acids under mild conditions, endowing the polymers with unique biological functions and application potential.

2.7. Comparison between SCAAPs and *N*-carboxyanhydride ring-opening polymerization (NCA-ROP)-derived poly(amino acids)

Although SCAAPs and NCA-ROP-derived poly(amino acids) are both constructed from amino acid building blocks, they differ fundamentally in molecular architecture, synthetic logic, degradation behavior, and biomedical applicability. NCA-ROP is a classical and powerful method for preparing synthetic polypeptides or poly(amino acid)s, in which amino acid residues are incorporated directly into the polymer backbone through repeated peptide or amide bonds. Therefore, NCA-ROP-derived polymers possess backbone structures closely resembling those of natural peptides and proteins. This structural similarity endows them with excellent biocompatibility, bioactivity, biodegradability, and the ability to form ordered secondary structures such as α -helices and β -sheets, which are highly attractive for drug delivery, gene delivery, tissue engineering, antimicrobial materials, and biomimetic supramolecular assemblies. In particular, synthetic polypeptides prepared by NCA-ROP have been widely recognized as important biomaterials because their side-chain diversity and secondary-structure-forming ability enable the construction of micelles, vesicles, nucleic acid complexes, hydrogels, and other biomedical platforms.^{28–30}

By contrast, SCAAPs generally contain non-peptidic synthetic polymer backbones, such as polyacrylates, polyacrylamides, polystyrenes, or polynorbornenes, while amino acid or peptide motifs are introduced as pendant side chains. This side-chain architecture decouples the mechanical and degradation properties of the main chain from the biological functions of amino acid residues. As a result, SCAAPs offer several advantages in terms of molecular design. First, controlled/living polymerization methods such as RAFT, PET-RAFT, ATRP, ROMP, and activated ester substitution allow precise regulation of molecular weight, dispersity, block sequence, grafting density, and macromolecular topology. Second, the density, spatial distribution, and chemical identity of amino acid side chains can be flexibly adjusted without necessarily altering the polymer backbone. Third, because the main chains of many SCAAPs do not contain continuous peptide bonds, they are often less susceptible to protease-mediated backbone cleavage and may exhibit enhanced structural stability in complex physiological environments. These features make SCAAPs particularly suitable for applications requiring robust and tunable polymeric scaffolds, such as long-circulating drug carriers, antimicrobial polymers, biosensing interfaces, tissue-engineering scaffolds, and antifouling coatings.

From the synthetic perspective, NCA-ROP and SCAAP synthesis also show complementary advantages and limitations. NCA-ROP provides direct access to polypeptides with authentic peptide backbones and well-defined secondary structures. However, conventional NCA polymerization is often sensitive to moisture and impurities, and many protocols require rigorously anhydrous solvents, an inert atmosphere, or glovebox operation. In addition, the preparation of NCA monomers may require phosgene or phosgene derivatives, side-chain protection/deprotection, and careful purification, which can limit

functional-group tolerance and large-scale preparation.^{28–30} Recent advances, including fast organobase- or LiHMDS-initiated NCA polymerization, open-vessel polymerization, and moisture-tolerant synthesis of unprotected NCA monomers, have greatly improved the operational simplicity and scalability of NCA chemistry, but broad compatibility with highly reactive or multifunctional side chains remains an important consideration.^{10,31}

In comparison, SCAAPs can be synthesized through more diverse routes. For example, amino acid-derived vinyl monomers can be polymerized by RAFT, PET-RAFT, or ATRP; amino acid-functionalized norbornene derivatives can be polymerized by ROMP; and activated ester precursor polymers can be post-functionalized with amino acids or peptides under mild conditions. These strategies avoid some of the limitations associated with NCA monomer preparation and allow the construction of complex architectures, including block, star, hyperbranched, and brush-like polymers. Nevertheless, SCAAPs also have intrinsic limitations. Their non-peptidic backbones may reduce biodegradability and make metabolic clearance more dependent on the selected backbone and linker chemistry. In addition, although amino acid side chains can induce hydrogen bonding, chirality transfer, and stimuli responsiveness, SCAAPs usually cannot fully reproduce the continuous peptide-backbone-driven secondary structures of NCA-derived polypeptides. Residual catalysts, chain-transfer agents, or post-modification byproducts from controlled polymerization may also need to be carefully removed for biomedical use.

Therefore, SCAAPs and NCA-derived poly(amino acids) should not be regarded as competing systems but rather as complementary amino acid-based polymer platforms. NCA-ROP-derived polypeptides are particularly advantageous when biodegradability, protein-like backbones, and ordered secondary structures are required. In contrast, SCAAPs are more suitable when high structural stability, tunable side-chain functionality, diverse polymer topologies, and compatibility with conventional controlled polymerization methods are desired. The rational selection between these two platforms should be guided by the intended biomedical application, the required degradation profile, the desired level of biomimicry, and the need for architectural precision (Fig. 2).

3. Self-assembly and multi-stimuli responsiveness of SCAAPs

3.1. Side-chain-mediated self-assembly

The incorporation of natural amino acids or short peptide residues into the side chains of synthetic polymers provides an ideal platform for constructing biomimetic materials that combine the topological diversity of synthetic macromolecules with the precise multiscale structures of natural proteins.^{32,33} Many amphiphilic SCAAPs can spontaneously form ordered supramolecular architectures in aqueous media or selective organic solvents.³⁴ This self-assembly process not only greatly expands the morphological diversity of polymer materials but

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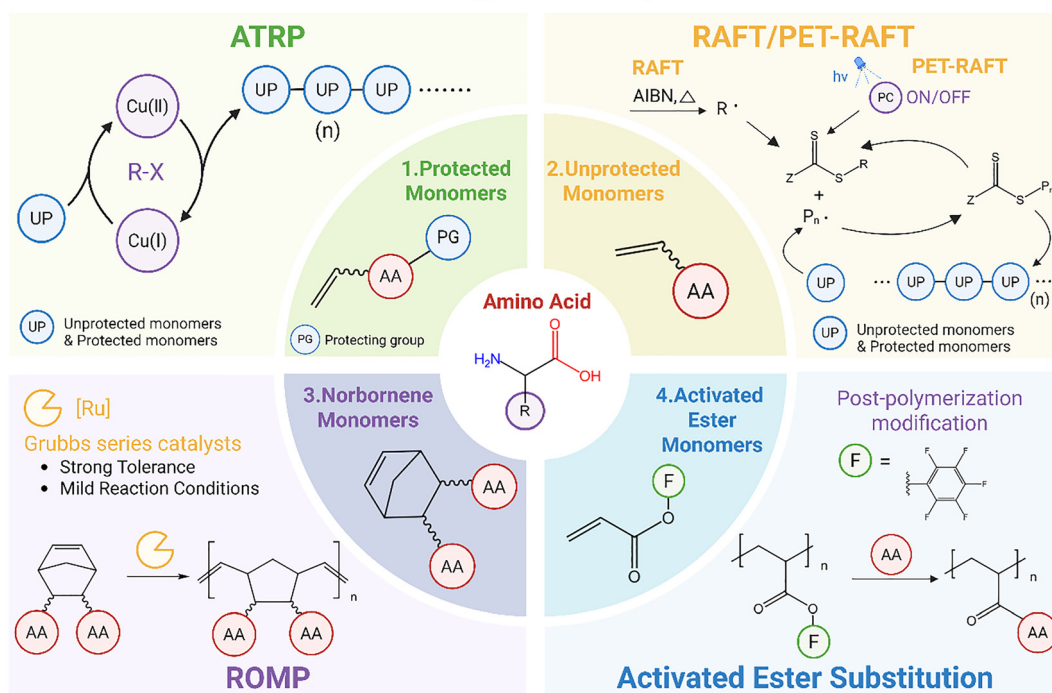


Fig. 2 Monomer design and polymerization strategies for SCAAPs. Schematic summarizes representative monomer platforms and synthetic routes for SCAAPs, including protected, unprotected, norbornene-functionalized, and activated ester monomers. Controlled polymerization methods, such as ATRP, RAFT/PET-RAFT, and ROMP, as well as activated ester substitution, enable the construction of SCAAPs with tunable side-chain functionality, molecular architecture, and biomedical potential. Created using BioRender. Jason, X. (2026) <https://BioRender.com/f54bubx>.

also enables the precise expression and amplification of molecular conformation and chiral characteristics at the mesoscale.³⁵ The following sections will systematically elucidate the self-assembly mechanisms of SCAAPs from three aspects: the driving forces of self-assembly, the laws of morphological evolution, and chiral transfer and multi-level helical superstructures.

3.1.1. Noncovalent driving forces. The self-assembly of SCAAPs is a thermodynamically controlled process, essentially driven by a synergistic network of multiple noncovalent interactions both within and between polymer chains. These interactions primarily include hydrogen bonds, hydrophobic interactions, π - π aromatic stacking, and electrostatic interactions.³⁵ Among these, intermolecular and intramolecular hydrogen bonds can play a dominant role in peptide-, amide-, or carboxyl-containing SCAAPs, often in synergy with hydrophobic, π - π , and electrostatic interactions in inducing and stabilizing supramolecular assemblies.³⁶ For example, side-chain oligopeptide fragments exhibit a strong tendency to form hydrogen bond arrays resembling β -sheets, thereby driving the close packing of polymer chains.³² At the same time, hydrophobic interactions drive the formation of the assembly core to minimize the interfacial free energy of the system. In addition to these hydrophobic driving forces, polymers containing phenylalanine side chains can engage in strong π - π stacking interactions between the aromatic rings, which further enhance the stability of the hydrophobic core.³⁷ Furthermore, the

ionization state of amino acid side chains makes their assembly behavior highly sensitive to environmental stimuli (such as pH).³⁸ For example, the protonation and deprotonation of pH-responsive amino acid side chains under different pH conditions directly alter the electrostatic repulsion and hydrogen bonding networks between molecules, thereby triggering the reorganization of the assembly structure.^{32,33}

3.1.2. Morphological evolution of self-assembled nanostructures. Based on the delicate balance of the aforementioned multiple driving forces, SCAAPs exhibit highly programmable morphological changes.³² According to the packing parameter theory, precise control of the supramolecular interfacial curvature can be achieved by systematically adjusting the ratio of hydrophilic to hydrophobic segments in amphiphilic block copolymers. For example, Wang *et al.* used PET-RAFT polymerization to precisely control the hydrophilic/hydrophobic ratios, revealing the dominant role of inter-carboxylate hydrogen bonding in the evolution of the self-assembly morphology. Specifically, as the proportion of hydrophilic PD segments increases, the assemblies sequentially transform from spherical to rod-like, fibrous, and finally layered structures. At the same time, this system exhibits excellent cargo loading efficiency (21.8–32.6%) for various drugs such as paclitaxel, doxorubicin, and cisplatin, which is primarily attributed to the synergistic effects of hydrophobic interactions and hydrogen bonding.³⁸ Furthermore, the design of specific amino acid side chains can induce even more complex topological

morphologies. For example, a copolymer composed of polyethylene oxide and short peptide side chains (PEO-*b*-poly(valine)) can assemble into thick-walled vesicles in solution and even form rare toroidal structures under specific hydrophilic–hydrophobic equilibrium conditions, primarily due to the strong β -sheet stacking of valine residues, which restricts the uniform closure of the vesicles.³⁷ Furthermore, even minor chemical modifications to the amino acid side chains can trigger dramatic morphological changes. For example, hydrolyzing the valine side chain on the polystyrene–acetylene backbone from its ester-protected form to a free carboxylic acid form significantly enhances the intermolecular hydrogen-bonding network and alters the chain's hydrophilicity, causing its primary assembly morphology in methanol to transform from discrete micellar pearls into high-aspect-ratio helical cables under the reported conditions.³²

3.1.3. Chiral transfer and hierarchical helical assemblies.

The remarkable aspect of SCAAP self-assembly lies in its ability to transmit stereochemical information across multiple spatial scales, that is, from the molecular chiral centers of amino acid side chains, through amplification into the conformational chirality of the polymer backbone, and ultimately evolving into macroscopic helical assemblies at the supramolecular level.³² At the molecular level, the asymmetric force field generated by the chiral amino acid side chains restricts the polymer backbone to adopt a specific monochiral helical conformation, thereby exhibiting a strong Cotton effect in circular dichroism (CD) spectroscopy.³³ At the mesoscopic level, when a poor solvent is added to the solution or the solvent evaporates, these independent helical chains further associate in a side-by-side manner through highly ordered hydrogen-bonding arrays between side chains, forming twisted fibers or supercoiled cables with well-defined macroscopic chirality. For example, polytriazine derivatives bearing L-phenylalanine side chains and exhibiting aggregation-induced emission (AIE) activity can self-assemble into luminescent left-handed helical fibers in the aggregated state. This multilevel chiral superstructure exhibits deep tunability toward external environments and host–guest interactions.³² On the one hand, by introducing chiral host–guest molecules (such as chiral cyclohexanediamine), the additives can form multiple strong hydrogen bonds with the carboxyl groups on the polymer side chains, exerting a multi-chiral asymmetric force field that promotes the transfer of chirality to the main chain and leads to tighter assembly of the helical fibers, thereby achieving significant amplification of the polymer's circularly polarized luminescence (CPL) and CD signals.³⁶ On the other hand, external stimuli such as strongly basic conditions promote the deprotonation of side-chain carboxyl groups, directly disrupting the interchain hydrogen bond network that maintains the helical superstructure. This disrupts the ordered helical assemblies and converts them into less ordered conformations. Changes in solution polarity (*e.g.*, switching from methanol to tetrahydrofuran) can similarly modulate the folded and extended states of polymer chains, thereby influencing the assembly pathways of higher-order helical morphologies.³²

In summary, the self-assembly of SCAAPs is a programmable thermodynamic process driven by the synergistic interaction of multiple noncovalent forces (particularly hydrogen bonding and hydrophobic interactions). This process not only enables the transition from simple geometric morphologies to complex topological structures through the regulation of hydrophilic–hydrophobic equilibrium or side-chain modification but also demonstrates the unique advantage of scaling molecular chirality across multiple length scales to form multi-level macroscopic helical superstructures. This self-assembly mechanism combines precise conformational expression, high morphological diversity, and responsiveness to environmental stimuli. It lays a solid theoretical and structural foundation for the development of novel smart biomimetic materials, highly efficient drug delivery carriers, and chiral optoelectronic materials. Such multiscale chiral architectures, which precisely amplify molecular stereochemistry into macroscopic helicity, are particularly attractive for developing chirality-responsive drug delivery vehicles and biomimetic surfaces capable of selective cell recognition.

3.2. Multi-responsiveness

SCAAPs can integrate the excellent biocompatibility, chirality, and multi-level structure-forming ability of natural amino acids with the structural diversity of synthetic polymers. Due to the abundance of active functional groups on the amino acid side chains (such as carboxyl groups, primary amine groups, hydrophobic alkyl chains, and specific ligands), these polymer networks or assemblies can undergo highly sensitive conformational transitions or phase separations in response to external environmental stimuli, thereby exhibiting significant multi-stimulus responsiveness.^{17,39–44} Through precise molecular engineering of the hydrophilicity–hydrophobicity balance (HLB) of amino acid side chains, researchers have developed a series of polymer systems capable of intelligently responding to temperature, pH, and specific metal ions, demonstrating immense application potential in fields such as biofouling-resistant coatings, targeted drug and gene delivery, self-healing hydrogels, and the capture of heavy metals in the environment.^{40–42,44}

3.2.1. Temperature responsiveness. Temperature responsiveness (thermal responsiveness) is one of the core research directions in smart polymer materials. Due to the diversity and designability of their side-chain structures, SCAAPs have achieved a series of significant advancements in the field of temperature-responsive materials in recent years. The phase-transition behavior of SCAAPs primarily stems from the delicate dynamic balance between intramolecular and intermolecular hydrogen bonds and hydrophobic interactions. By modifying the hydrophilicity or hydrophobicity of amino acid side chains and introducing specific functional groups, their LCST or UCST can be tuned over a broad range by molecular design. For example, Higashi *et al.* conducted a detailed evaluation of the thermoresponsive behavior of vinyl polymers based on glycine, alanine, phenylalanine, and valine. The study found that due to thermally reversible hydrogen bonding involving the side-chain carboxyl groups, alanine-based polymers (PNAa) exhibited

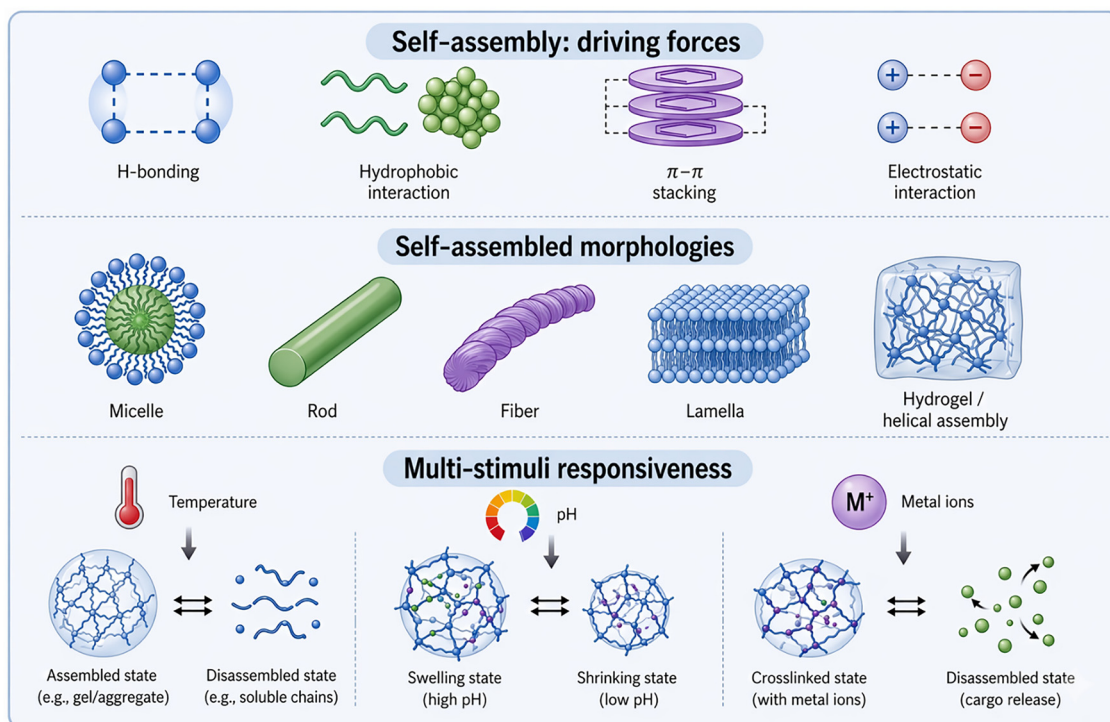


Fig. 3 Schematic illustration of the self-assembly of SCAAPs, including the main driving forces (hydrogen bonding, hydrophobic interaction, π - π stacking, and electrostatic interaction), representative self-assembled morphologies (micelle, rod, fiber, lamella, and hydrogel/helical assembly), and multi-stimuli responsiveness to temperature, pH, and metal ions.

distinct UCST behavior at low pH (pH < 2.0); however, upon methylation of the carboxyl groups (PNAAME), the system shifted to exhibiting an LCST of 18 °C due to the disruption of the hydrogen-bonding network and a significant increase in hydrophobicity.⁴⁰ Furthermore, to achieve control over the phase transition temperature, Bauri *et al.* prepared a random copolymer containing leucine derivatives and oligoglycol (MEO₂MA) *via* RAFT polymerization. Such copolymers with a helical conformation exhibit dual responsiveness, and their LCST can be flexibly controlled within the physiologically relevant temperature range of 26 °C to 74 °C by adjusting the proportion of hydrophobic amino acids in the copolymer.⁴⁴

3.2.2. pH responsiveness. In smart polymer materials, pH responsiveness (acid-base responsiveness) is also one of the most prominent research focuses. Because many amino acid side chains contain ionizable groups, appropriately designed SCAAPs can exhibit pH-responsive behavior. When the environmental pH changes, the protonation and deprotonation states of these groups directly alter the polymers' surface charge and solubility, thereby triggering structural transitions. De Breuck *et al.* developed a series of amino acid-derived anionic polyacrylamides with different alkyl side chains, all of which have side-chain carboxyl pK_a ranging from 4.8 to 5.5. In the slightly acidic intracellular environment, the degree of carboxyl deprotonation decreases, and the overall hydrophobicity of the polymer increases significantly, thereby effectively promoting its hydrophobic interactions with the cell membrane and endocytosis, providing a safe membrane-penetrating strategy

for intracellular delivery.¹⁷ On the other hand, polymers containing side chains with removed Boc protection typically exist in a cationic state in acidic or neutral media. The amphiphilic block copolymer (mPEG-*b*-P(H₂N-AA-EMA)) designed by Kumar *et al.* exhibits distinct pH responsiveness, as confirmed by the transition of the polymer solution from clear to turbid upon reaching specific phase-transition pH values (5.6, 6.4, 5.8, and 6.9). This pH-triggered assembly property has been demonstrated to be effective for encapsulating the hydrophobic drug doxorubicin, as well as for forming polymer-plasmid DNA (pDNA) complexes for efficient gene transfection.³⁹

3.2.3. Ion responsiveness. Due to the unique electronic structure of specific amino acid groups, SCAAPs possess strong metal coordination and chelation capabilities, opening new avenues for the development of ion-responsive materials. Adamowska *et al.* synthesized a smart hydrogel composed of pure amino acid derivatives, which exhibited excellent coordination and adsorption capabilities toward heavy metal ions in wastewater. When the concentration of absorbed heavy metal ions increases, the amino acid groups form stable stoichiometric complexes (1 : 1 or 1 : 2) with the metal ions, causing the polymer network to undergo rapid contraction and a sharp drop in swelling ratio. This macroscopic volume phase transition provides an intuitive response signal for water purification and heavy metal sensing.⁴² Meanwhile, Tang *et al.* introduced histidine into the side chains of linear polymers and constructed supramolecular metal gels through transient coordination with Ni²⁺. Rheological analysis and "sticker dissociation

diffusion spectroscopy (SDDS)" revealed that the histidine-nickel coordination bond exhibits a highly dynamic dissociation and binding process; this metal-ligand binding kinetics not only directly determines the viscoelasticity and relaxation time of the polymer network but also endows the material with self-regulation and self-healing capabilities under stress (Fig. 3).⁴¹

4. Biomedical applications of SCAAPs

SCAAPs have become an ideal platform for constructing advanced biomedical functional materials due to their excellent biocompatibility, designable side-chain chemistry, and rich biological functions. By introducing specific amino acid functional groups into the side chains, their physicochemical properties (such as charge, hydrophilicity/hydrophobicity, and stimulus responsiveness) and biological activities (such as target recognition, membrane interaction, and signal transduction) can be flexibly regulated, thereby adapting to complex physiological environments and application requirements. The following section highlights five core application areas of SCAAPs in the biomedical field. In anticancer therapy, they serve as smart nanodrug carriers, enabling specific targeted delivery and drug release responsive to the tumor microenvironment. In the field of anti-infection, they eliminate free-floating and intracellular bacteria and disrupt biofilms through multiple mechanisms, thereby helping to address drug-resistant infections. In biosensing, they construct high-performance recognition interfaces to enhance detection sensitivity and selectivity. In tissue engineering, they mimic the extracellular matrix microenvironment, dynamically regulate cell behavior, and promote tissue regeneration and repair. In the field of antifouling coatings, with their amphoteric ionic structure and strong hydration capacity, SCAAPs can form a dense hydrated layer on the material surface, effectively resisting the non-specific adsorption of proteins and the initial adhesion of microorganisms, thereby imparting long-lasting antifouling properties to the coating. These systematic studies demonstrate the broad prospects of SCAAPs, spanning from molecular design to biomedical applications.

4.1. Anticancer drug delivery and therapy

Due to their exceptional biocompatibility and the high programmability of their side-chain groups, SCAAPs have become an ideal platform for constructing intelligent nanodrug delivery systems for anticancer therapy. Through precise modification of the chemical structure of the side chains, efficient drug loading and programmed release can be achieved. Furthermore, the unique diversity of amino acid side chains endows the polymers with the ability to precisely regulate their conformation, charge distribution, and hydrophilicity/hydrophobicity under complex physiological conditions, thereby significantly enhancing drug penetration into the tumor microenvironment (TME) and improving targeting specificity. These characteristics make SCAAPs a crucial material for constructing efficient, safe, and intelligent anticancer drug delivery systems. SCAAPs demonstrate broad application prospects in the field of

anticancer therapy. Based on their functional mechanisms within therapeutic systems, their applications can be categorized into the following two types.

4.1.1. Amino acid transporter-mediated targeted delivery.

Tumor cell surfaces often overexpress specific types of amino acid transporters (LAT1, ASCT2, and ATB^{0,+}), providing highly promising new targets for targeted therapy. By introducing specific amino acids (methionine, glutamic acid, lysine, aspartic acid, *etc.*) into the polymer side chains, the affinity for tumor cell membrane transporters can be enhanced, enabling specific targeting and efficient drug delivery.⁴⁵ For example, Guo *et al.* synthesized a polymer with a sulfur-containing amino acid-like structure modified with a methionine side chain (PAsp(Met)), which specifically targets large amino acid transporter 1 (LAT1). Studies have shown that PAsp(Met) exhibits high-efficiency cell uptake mediated by LAT1 selectivity and can selectively accumulate at tumor sites in a peritoneal dissemination model. Because its side chains are closer to the structure of natural LAT1 substrates, it demonstrates stronger LAT1-mediated endocytosis in various cancer cell lines (SKOV3, BxPC3, and CT26). In the SKOV3-Luc peritoneal dissemination model, PAsp(Met) efficiently and selectively accumulated at the tumor site. When loaded with a photosensitizer, PAsp(Met) achieved significant tumor suppression upon light exposure without damaging normal tissues such as the liver (Fig. 4).⁴⁶

Further studies revealed that nanoparticles modified with polyglutamyl methacrylate (pGlnMA), which incorporates glutamine into its side chains, can achieve deep penetration into tumor tissues and efficient drug delivery by recognizing amino acid transporters (AATs) overexpressed on tumor cells.⁴⁷ Additionally, it has been reported that Li *et al.* prepared PLGA nanoparticles by conjugating glutamate with polyoxyethylene stearate as a targeting ligand; by targeting LAT1, which is overexpressed in cancer cells, they achieved efficient cellular uptake and significant cytotoxicity in HeLa and MCF-7 cells. The results indicate that LAT1-based targeted therapy can achieve cellular accumulation of the drug of interest and holds great potential for application in cancer treatment.⁴⁸

4.1.2. Tumor microenvironment-responsive drug release.

The TME typically exhibits specific physicochemical characteristics, such as reduced pH, increased reducing potential (high glutathione concentration), and the presence of specific enzymes. These differences can serve as triggers for designing stimulus-responsive drug delivery systems.^{49,50} By incorporating structural units sensitive to these stimuli into polymers, smart drug delivery systems can be developed to selectively release drugs at tumor sites while avoiding damage to normal tissues. A common strategy is to leverage the acidic pH characteristic of the TME to construct pH-responsive drug delivery systems. For example, block copolymers with a poly(methyl acrylate) backbone and tryptophan-introduced side chains stably encapsulate the hydrophobic anticancer drug doxorubicin (DOX) under physiological conditions (pH 7.4). However, in the acidic tumor environment (pH 5.5–3.0), the amino groups on the side chains undergo protonation, inducing micelle disassembly and enabling targeted drug release.

Furthermore, the tryptophan segments possess fluorescence properties, enabling dual functionality as both drug carriers and biological probes, while also exhibiting good biocompatibility and stimulus responsiveness.⁵¹ Another study utilized RAFT polymerization to prepare a tyrosine- and polyethylene glycol methacrylate (PEGMA)-based amphiphilic diblock copolymer, constructing a delivery system with both pH and temperature responsiveness. This system can simultaneously load DOX and exhibit antibacterial activity against *Escherichia coli* (*E. coli*). Under physiological conditions, this system stably encapsulates DOX. Upon entering the weakly acidic tumor microenvironment, its responsive structural changes not only trigger the release of DOX but also increase its surface charge, thereby activating its antibacterial activity against *E. coli*. This combined strategy of integrating tumor chemotherapy with antimicrobial therapy offers a new approach for treating diseases such as colorectal cancer associated with dysbiosis.⁵²

Further research combines chemotherapy with gene therapy to establish a triple-synergistic antitumor platform. This platform is based on an amphiphilic copolymer (mPEG_n-b-P(Boc-AA-EMA)) composed of a hydrophilic polyethylene glycol segment and a hydrophobic Boc-protected amino acid segment, which self-assembles into micelles in water and efficiently encapsulates hydrophobic molecules such as DOX or Nile Red. *In vitro*, the Boc protecting group is removed chemically (TFA/DCM) and protonated under acidic pH conditions, promoting interaction with the negatively charged MCF-7 cell membrane and enhancing the micelle's cellular uptake efficiency. After deprotection, mPEG_n-b-P(H₂N-AA-EMA) forms polymer-DNA complexes with pDNA *via* electrostatic interactions. At a polymer/pDNA weight ratio of ≥ 2 , DNA electrophoretic migration is completely blocked, enabling stable gene loading and protection. This system exhibits good biocompatibility and possesses the ability to simultaneously achieve controlled drug release and gene transfection, providing strong

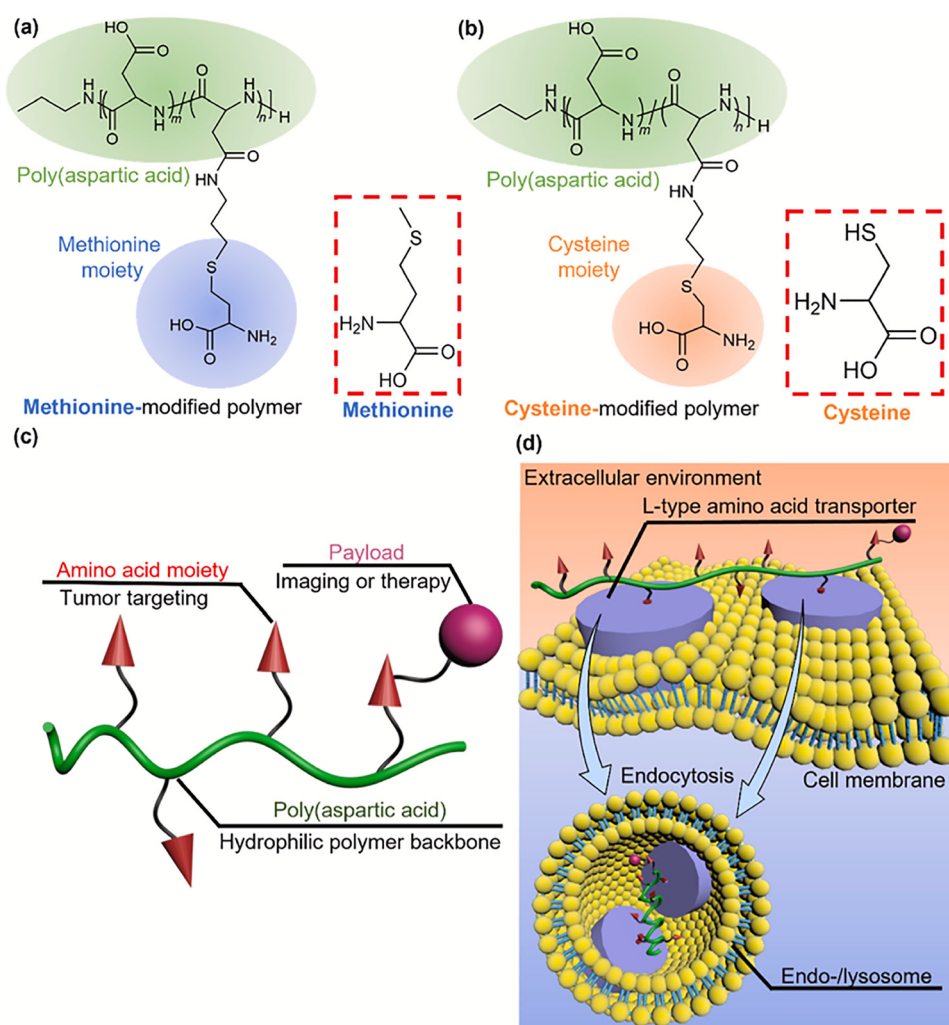


Fig. 4 Chemical structures of Met-modified polymers and a schematic illustration of LAT1 targeting. The chemical structures of (a) Met- and (b) Cys-modified polymers. (c) and (d) Schematic illustrations of an amino acid-modified polymer and its interaction with amino acid transporters on cells. The polymers are expected to multivalently interact with overexpressed amino acid transporters, followed by internalization *via* endocytosis.⁴⁶ Reproduced from ref. 46 with permission from Elsevier, copyright 2023.

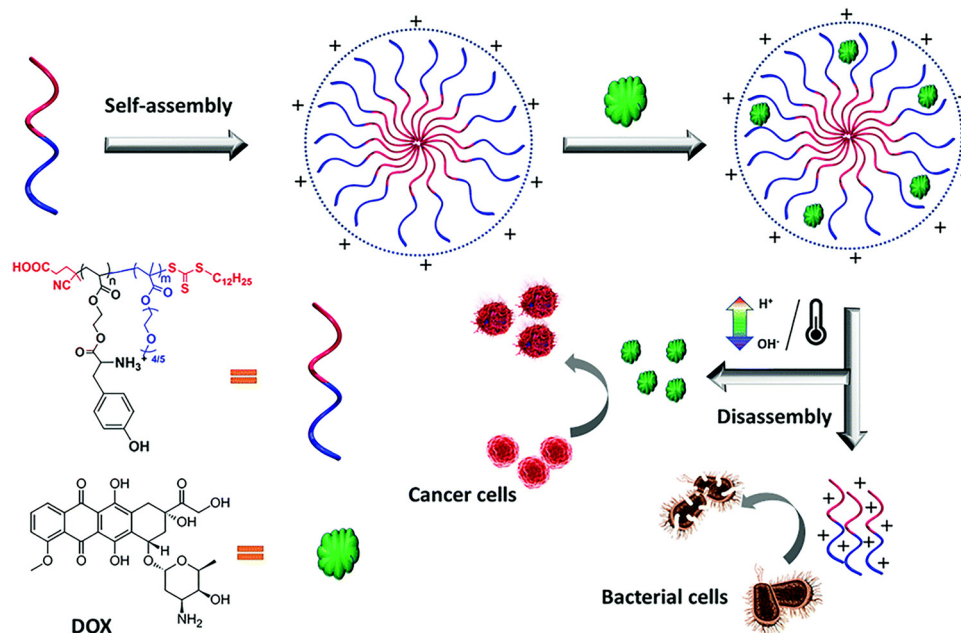


Fig. 5 Schematic representation of the self-assembly of cationic tyrosine-based copolymers in water, encapsulation of DOX, stimulus-responsive release, and the corresponding therapeutic effect.⁵² Reproduced from ref. 52 with permission from the Royal Society of Chemistry, copyright 2022.

support for the development of a smart synergistic chemo/gene co-delivery platform.³⁹

4.2. Antimicrobial therapy

SCAAPs have emerged as a cutting-edge strategy for combating complex bacterial infections due to their excellent biocompatibility, broad multi-target synergistic effects, and effective biofilm disruption capabilities. Addressing the three core challenges in clinical treatment, the spread of planktonic bacteria, intracellular bacterial parasitism, and biofilm barriers, SCAAPs demonstrate multidimensional mechanisms of action by precisely regulating the amphiphilic balance and surface charge density of their molecular chains. In the elimination of planktonic bacteria, SCAAPs primarily achieve mechanical membrane disruption through electrostatic-driven adsorption and the insertion of hydrophobic segments into the lipid bilayer. For intracellular and adherent bacteria, SCAAPs leverage their advantages as nanocarriers, utilizing ligand-mediated cascade targeting technology to cross host cell barriers and combining metabolic awakening strategies to reverse bacterial dormancy. For structurally complex biofilms, SCAAPs achieve depolymerization of the extracellular polymeric substance matrix and deep penetration killing through mimicking D-amino acid permeation or *in situ* photochemical conversion. The following sections will systematically elaborate on the research progress and clinical translation potential of SCAAPs in modern anti-infective therapy from three dimensions: the mechanism of killing planktonic bacteria, the precision delivery system for intracellular infections, and the targeted disruption strategies for biofilms.

4.2.1. Membrane-disruptive activity against planktonic bacteria. The mechanism by which SCAAPs kill planktonic bacteria primarily relies on the disruption of the cell membrane

or cell wall, involving two main processes: electrostatic adsorption and hydrophobic fragment insertion. Cationic groups on the polymer side chains (such as the amino group of lysine or the guanidino group of arginine) bind to negatively charged components on the bacterial surface (such as lipopolysaccharides in Gram-negative bacteria or teichoic acids in Gram-positive bacteria).⁵³ Subsequently, hydrophobic units introduced *via* the side chains (such as long-chain alkyl or aromatic groups) insert into the lipid bilayer, disrupting the phospholipid arrangement, leading to membrane perforation and cytoplasmic leakage.

Mukherjee *et al.* found that P(Leu-HEMA)₁₅, a homopolymer with methacrylate as the backbone and leucine introduced as the side chain, undergoes protonation of the side-chain amino groups under acidic conditions. P(Leu-HEMA)₁₅ binds to bacteria *via* electrostatic interactions; its hydrophobic groups penetrate the peptidoglycan layer, disrupting the inner membrane and causing cytoplasmic leakage, thereby inducing a morphological change in *Escherichia coli* (a Gram-negative bacterium) from rod-shaped to spherical. P(Leu-HEMA)₁₅ showed the minimum inhibitory concentration (MIC) of 60 $\mu\text{g mL}^{-1}$ under the reported conditions, indicating notable antibacterial activity. For *Bacillus subtilis* (a Gram-positive bacterium), P(Leu-HEMA)₁₅ interacts with the thick peptidoglycan layer (porous and loose) and the cell membrane, causing membrane fusion, the aggregation of lipid vesicles, and the collapse of the membrane surface, ultimately leading to bacterial death.⁵⁴ Li *et al.* prepared amphiphilic block copolymers with natural amino acid side chains (*e.g.*, Val, Ser, and Asp) grafted *via* amide bonds for the delivery of rifampicin (Rif). The results showed that by regulating the hydrogen bonding and hydrophobic interactions of SCAAPs, it is possible to precisely control the nanoparticle size (240.7–302.7 nm), drug loading

efficiency (9.57–19.76%), and drug release rate (49.6–69.7%), with an optimal MIC of 8.93 ng mL⁻¹ against methicillin-resistant *Staphylococcus aureus* (MRSA), significantly enhancing antimicrobial efficacy.⁵⁵

4.2.2. Targeted delivery for intracellular bacterial infections. In many chronic infections, bacteria do not exist solely in a planktonic state but reside within host cells, evading clearance by antibiotics and the immune system, leading to chronic infections, recurrence, and drug resistance. In recent years, SCAAPs have been extensively explored for addressing intracellular infections due to their structural design flexibility and drug delivery properties.

To eliminate intracellular bacteria, Feng *et al.* constructed cascade-targeting nanoparticles (Rif@FAM NPs) by introducing a D-amino acid analog (β -N-acryloyldi-D-alanine) as a side chain into the polymer backbone. The core of their antibacterial mechanism lies in the ability of this side chain to specifically bind to peptidoglycan in the bacterial cell wall. Upon uptake by macrophages, these nanoparticles responsively expose the D-amino acid side chain in an acidic environment, thereby escaping the lysosomes and precisely anchoring to methicillin-resistant MRSA within the cells, enabling *in situ* delivery of the antibiotic. This design allows for highly efficient targeting of intracellular bacteria. In terms of antimicrobial efficacy, Rif@FAM nanoparticles significantly reduced the number of colony-forming units (CFUs) within infected macrophages *in vitro* and demonstrated the best intracellular bacterial clearance in an *in vivo* peritonitis model.⁵⁶

Feng *et al.* designed dual-targeted SCAAP nanoparticles (Rif@FAM NPs) that achieve cascade targeting of macrophages and bacteria by introducing mannose (Man) and D-aminopropionic acid into the side chains. Rif@FAM NPs first selectively enter macrophages *via* the Man ligand, enhancing the intracellular accumulation of Rif. Subsequently, under acidic conditions, Man is shed, and the exposed D-aminopropionic acid binds to the peptidoglycan on the bacterial surface, precisely targeting *Staphylococcus aureus* (*S. aureus*) and enabling *in situ* drug release. Results show that this system exhibits approximately three-fold greater antibacterial efficacy against intracellular *S. aureus* compared to free Rif. In animal models, it significantly reduced intracellular bacterial load and inflammatory responses, validating the superiority of the SCAAP delivery system in eradicating intracellular bacteria (Fig. 6).⁵⁷

Zhao *et al.* co-loaded vancomycin (Van) and curcumin (Cur) to construct dual-targeted nanoparticles (Van + Cur@F(AM)NPs) based on poly(acryloyldiphenylalanine)-*block*-poly(acryloylaminoalanine-Man). By leveraging Man-mediated macrophage uptake and the peptidoglycan-anchoring properties of aminoalanine, Van + Cur@F(AM) NPs achieve precise delivery and synergistic release against intracellular MRSA. Compared to monotherapy, the dual-drug nanoparticles demonstrated stronger intracellular bactericidal effects both *in vitro* and *in vivo*. Furthermore, by regulating inflammatory factors such as IL-10, TNF- α , and IFN- γ , they promoted the polarization of macrophages toward the M1 phenotype, thereby further enhancing the antibacterial effect. This study indicates that SCAAPs can not only efficiently eliminate

drug-resistant intracellular bacteria but also modulate immune responses, demonstrating potential for clinical translation (Fig. 7).⁵⁸

Further research has revealed that intracellular surviving bacteria exist in a persistent state, and monotherapy is often limited in efficacy, frequently leading to antibiotic resistance or incomplete eradication. Yin *et al.* conducted a systematic review of the mechanisms of persistent bacterial formation, their ecological niches, and clearance strategies, emphasizing the importance of combining multiple mechanisms to combat drug-resistant bacteria. Through synergistic effects, this approach reduces the risk of resistance and significantly enhances therapeutic outcomes.⁵⁹ Persister bacteria, a phenotypically distinct subpopulation characterized by transient antibiotic tolerance and reversible metabolic dormancy, pose a significant challenge in treating chronic and recurrent infections.⁶⁰ Tackling this challenge, Yin *et al.* proposed a multifunctional polyamine-based platform, F(AM), for the effective eradication of intracellular persistent *S. aureus* through *in situ* antibiotic delivery. The F(AM) platform exhibits dual-targeting capabilities against macrophages and intracellular persistent *S. aureus*, effectively penetrating cellular barriers and enabling precise antibiotic delivery within the intracellular bacterial niche. By systematically summarizing strategies such as direct killing, metabolic reawakening, drug combination, and inhibition of persistence formation, the study specifically highlights that polyamino acid-based nanoparticles can overcome host cell barriers to achieve precise co-delivery of antibiotics and amino acids, directly acting on intracellular bacterial foci and reversing the persistent state by regulating central carbon metabolism, energy metabolism, and stress response pathways. These polymeric carriers are highly versatile and can be loaded with various amino acids and sugar molecules. This provides a powerful tool for studying drug combination therapy and the mechanisms of persistent bacterial clearance.⁶¹

Huang *et al.* designed a novel polyamino acid drug-loaded microsphere (FAlSbm@Rif) for the precise delivery of amino acids and antibiotics to intracellular persistent bacteria. FAlSbm@Rif utilizes Man receptor-mediated endocytosis to achieve cellular targeting. In the acidic intracellular environment, Man cleaves and, through an esterification reaction, anchors to the peptidoglycan of the bacterial cell wall, thereby achieving bacterial targeting. Through cascade targeting, Rif and amino acids are precisely released onto the bacterial surface, significantly increasing local drug and amino acid concentrations. The amino acids stimulate bacterial metabolism, forcing the dormant bacteria to exit their dormant state and enhancing the bactericidal effect of Rif against intracellular bacteria. *In vivo* experiments confirmed that the clearance rate of intracellular persister cells reached 99.78%, while that of extracellular persister cells was 99.01%, significantly higher than that in other treatment groups (Fig. 8).⁶²

4.2.3. Biofilm disruption and eradication. Biofilms consist of large numbers of bacteria and the extracellular matrix produced by the bacteria themselves. Aside from planktonic bacteria and intracellular bacteria, biofilms are also a major cause of antibiotic resistance and poor treatment outcomes.

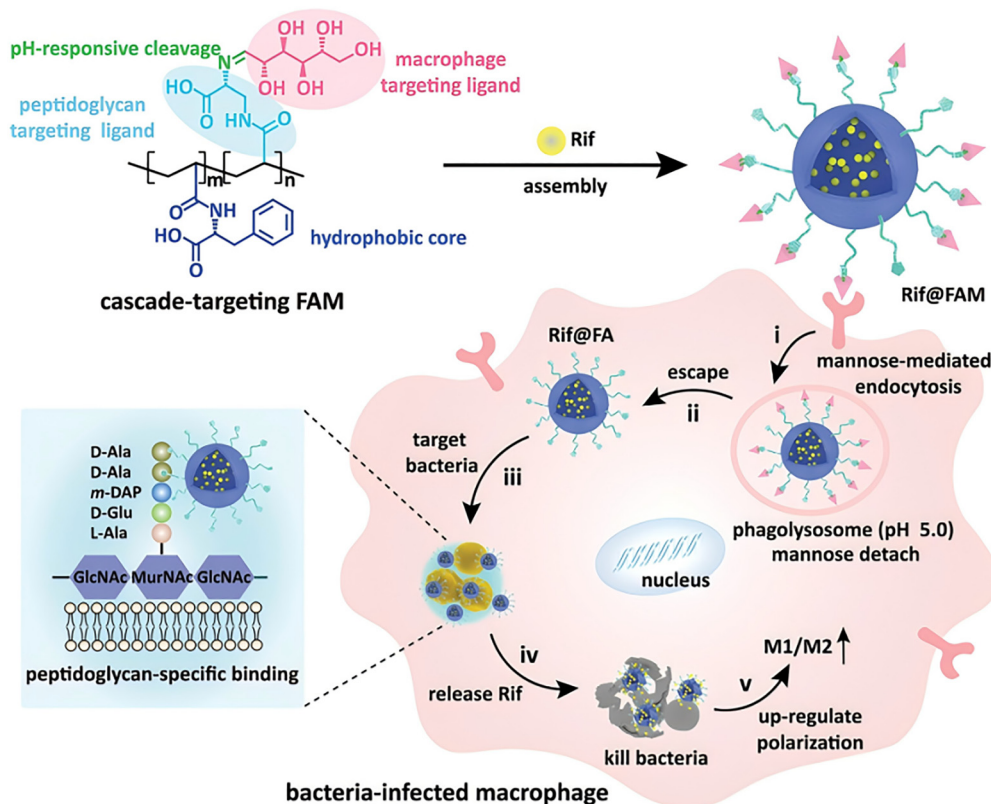


Fig. 6 The cascade-targeting SCAAP-based NPs (FAM) eliminate intracellular MRSA. Cascade-targeting FAM consists of 3 parts: (1) poly(α -N-acryloyl-phenylalanine) (PF) as the hydrophobic core; (2) poly(β -N-acryloyl-D-aminoalanine acid) (PA) as the bacteria targeting ligand; and (3) mannose as the macrophage targeting ligand. The cascade-targeting process of the DDS is divided into 5 steps: (i) Rif@FAM NPs selectively enter macrophages by mannose-mediated endocytosis; (ii) mannose is detached in acidic phagolysosomes via the dynamic Schiff base. The exposed D-aminoalanine moieties steer the resulting Rif@FA NPs to escape into the cytoplasm; (iii) Rif@FA NPs anchor the intracellular bacteria by peptidoglycan-specific binding; (iv) Rif@FA NPs release the Rif to kill intracellular bacteria; and (v) modulation of macrophage polarization.⁵⁷ Reproduced from ref. 57 with permission from the American Chemical Society, copyright 2024.

In addressing this challenge, SCAAPs have demonstrated exceptional biofilm-disrupting capabilities.

SCAAPs can specifically target the peptidoglycan in the bacterial cell wall, inserting and disrupting its biological structure. This not only directly causes the breakdown of the biofilm matrix but also significantly enhances the penetration and bactericidal efficacy of conventional antibiotics. For example, Wang *et al.* synthesized SCAAPs based on phenylalanine and alanine, loaded them with ciprofloxacin (Sit), and assembled them into (Sit@FA NPs). The study found that FA NPs, acting as exogenous D-amino acids, can be incorporated into bacterial peptidoglycan *via* PBP4-mediated integration. When Sit@FA NPs act on biofilms, the abundant D-alanine groups on their surface can efficiently bind to bacteria within the biofilm, inducing changes in the biofilm structural integrity and thereby leading to the disruption of the biofilm structure. Experimental results indicate that treatment with Sit@FA NPs reduced the number of *S. aureus* in the biofilm by 10^5 , with an eradication efficiency exceeding 90%. This drug delivery system, which simultaneously achieves biofilm disruption and antibiotic activity, demonstrates great potential for the effective treatment of biofilm infections (Fig. 9).⁵⁷

Bu *et al.* proposed a strategy for precise *in situ* phototherapy to eradicate refractory bacteria within biofilms. They synthesized DBP, a GSH-degradable phototherapeutic polymer, and encapsulated it within the amphiphilic thermosensitive azo polymer P3 *via* electrostatic interactions to obtain phototherapeutic nanoparticles (DA₃-NPs). D-Alanine was used as the key molecule to modulate the charge of P3, endowing DA₃-NPs with a neutral potential and peptidoglycan-anchoring properties, enabling them to effectively penetrate the extracellular matrix and target biofilms. In a wound biofilm infection model, laser irradiation (808 nm, 0.33 W cm⁻²) combined with DA₃-NPs eradicated 99.99% of the bacteria within the biofilm. In an implant biofilm infection model, a 96% biofilm clearance efficiency was achieved, with a bactericidal efficiency as high as 99.99%. As validated by *in vivo* wound biofilm infection and implant biofilm infection models, the developed phototherapy-based biofilm clearance strategy possesses strong internal bacterial targeting and killing capabilities, demonstrating excellent biofilm clearance and immunomodulating functions and providing a new approach for the treatment of biofilm infections caused by drug-resistant bacteria.⁶³

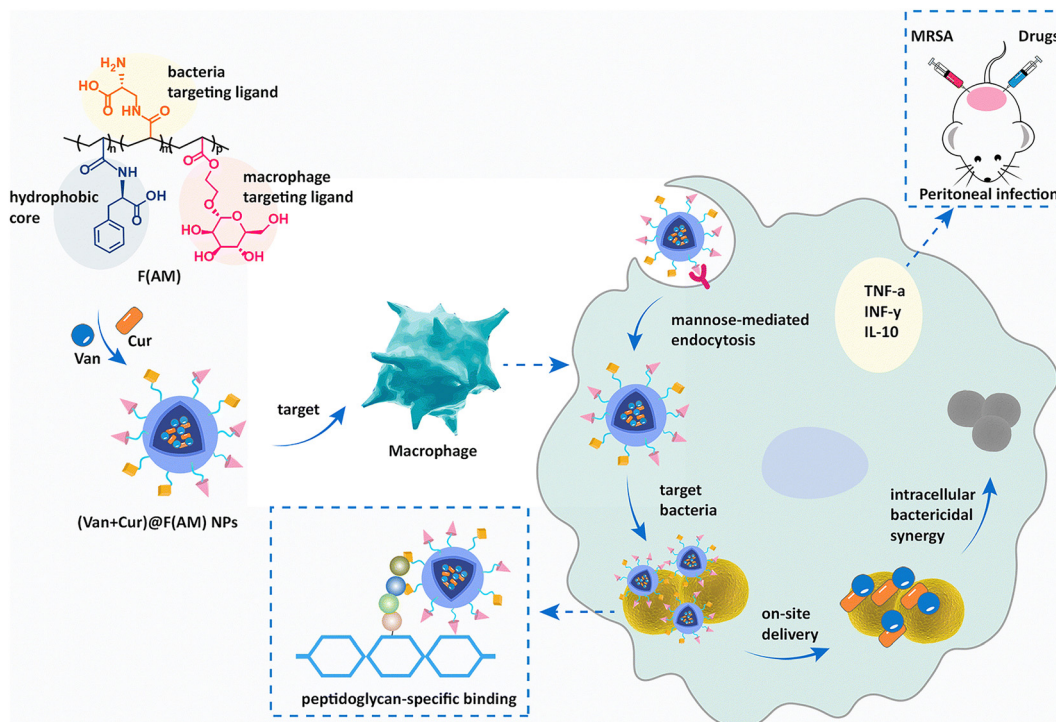


Fig. 7 Schematic diagram of the fabrication and intracellular bacteria elimination of (Van + Cur)@F(AM) NPs. Van and Cur can be successfully encapsulated in the DDS in a preset dose to form (Van + Cur)@F(AM) NPs. (Van + Cur)@F(AM) NPs exert an intracellular synergistic bactericidal effect via on-site delivery of the drug combination.⁵⁸ Reproduced from ref. 58 with permission from the Royal Society of Chemistry, copyright 2023.

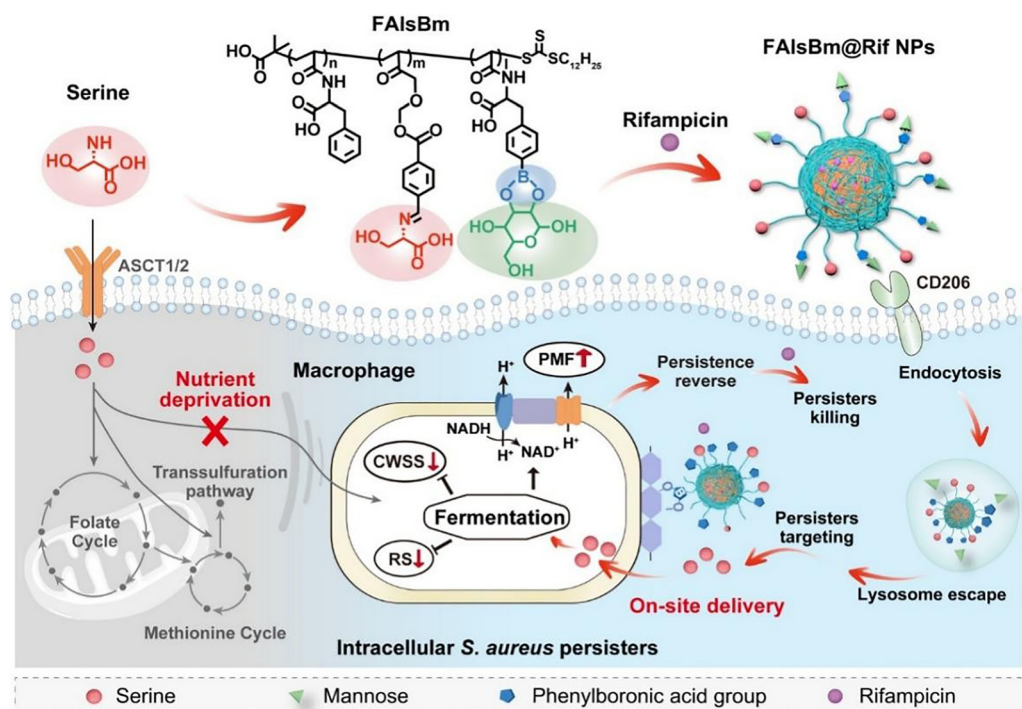


Fig. 8 Schematic illustration of intracellular *S. aureus* persister killing by FAlsBm@Rif NPs through on-site Ser and Rif delivery.⁶² Reproduced from ref. 62 with permission from the American Chemical Society, copyright 2025.

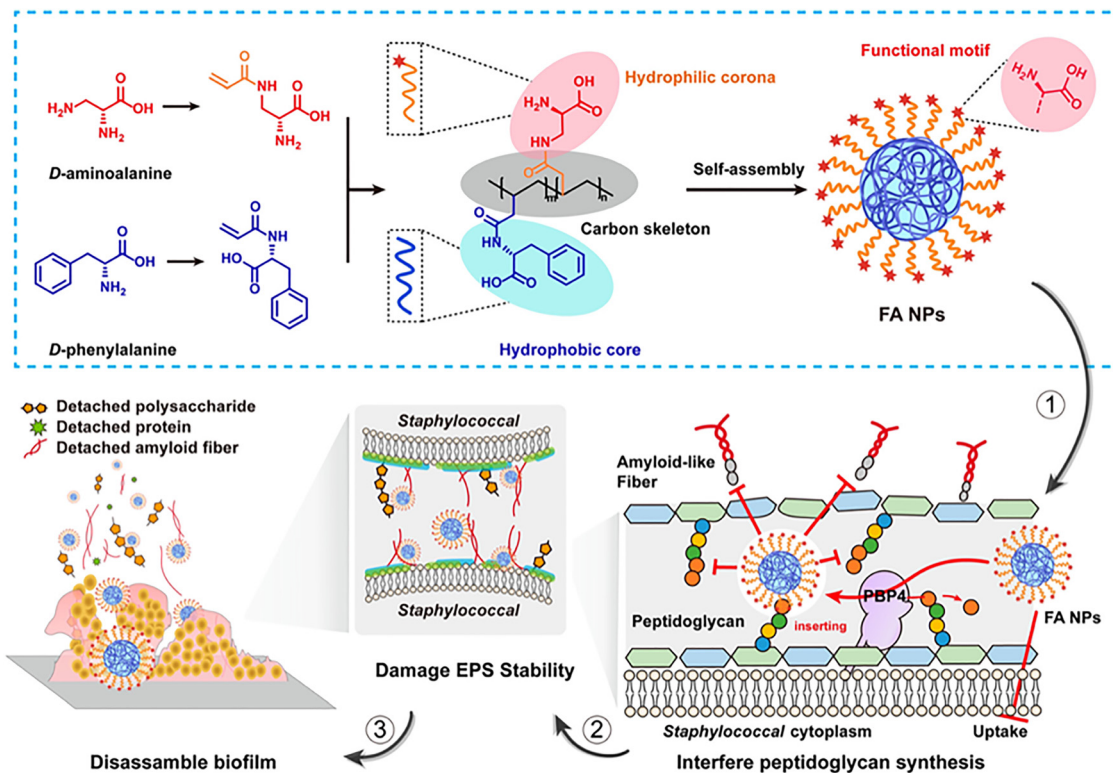


Fig. 9 Schematic illustration of the assembly process of FA NPs and the functional mechanism of biofilm disruption via interference with PG synthesis.⁵⁷ Reproduced from ref. 57 with permission from the American Chemical Society, copyright 2024.

4.3. Biosensing

SCAAPs, with their unique molecular recognition capabilities, biocompatible interface properties, and tunable signal transduction mechanisms, demonstrate immense application potential in electrochemical sensing, fluorescence detection, and environmental monitoring. By introducing specific amino acids into the polymer side chains, highly sensitive and selective detection of target analytes can be achieved. In recent years, significant progress has been made in the application of side-chain amino acid-derived polymers in biosensing, playing a crucial role in enhancing sensor performance and stability.

Kesik *et al.* reported a novel approach for preparing biosensors using conductive polymers containing side-chain amino acid fragments. An ethanol sensing system was prepared by grafting amino acid derivative fragments and dibenzofuran diimide derivatives onto the electrode surface. This system exhibits a fast response time (9 s), a wide linear range (0.17 mM to 4.25 mM), a low detection limit (0.28 mM), and high sensitivity ($12.52 \mu\text{A mM}^{-1} \text{cm}^{-2}$).⁶⁴ Chiarini *et al.* prepared polymers bearing various amino acid side chains and characterized their applications as sensing materials. By introducing different amino acids into the conjugated backbone, a flexible synthetic route allowed for the modulation of the materials' binding activity, molecular recognition, optoelectronic properties, and reactions upon exposure to metal ions. Subsequently, the luminescent sensing properties of the prepared materials toward metal ions were investigated. The results showed that all prepared materials exhibited high selectivity toward Hg(II)

ions, and compared to small-molecule analogs, signal amplification was observed in Hg(II) detection using the polymer compounds.⁶⁵ Nonspecific adsorption at optical sensing interfaces can be reduced by amphiphilic brushes formed from side-chain amino acids. Brush layers represented by polymethylacryloylserine (PSerMA) exhibit superior protein adsorption inhibition in whole blood compared to conventional PEG, thereby significantly reducing background signals in optical chips such as SPR.⁷ Side-chain amino acid polymers are commonly used to enhance the anti-fouling and stability of optical sensing interfaces. For example, polymeric brushes containing betaine-type amino acid side chains (such as PSerMA) have been shown to significantly inhibit protein adhesion in complex media such as whole blood, with anti-fouling performance comparable to that of traditional polyethylene glycol (PEG) brushes. Applying such anti-fouling coatings to optical sensing chips, such as surface plasmon resonance (SPR) devices, can reduce nonspecific background signals and improve detection accuracy.⁶⁶

In summary, polymers derived from side-chain amino acids offer multifaceted advantages in biosensors. Their excellent biocompatibility, abundant functionalization sites, and signal transduction capabilities make these materials an ideal choice for enhancing biosensor performance.

4.4. Tissue engineering

By introducing amino acids or their derivatives as side chains into synthetic polymers, SCAAPs ingeniously combine the

structural tunability of synthetic materials with the inherent biological activity of amino acids, thereby demonstrating powerful functional design flexibility in the field of biomaterials. The core objective of tissue engineering is to simulate the extracellular matrix (ECM) microenvironment using functionalized biomimetic materials to promote tissue regeneration and repair. By introducing amino acids into polymer side chains, it is possible not only to mimic the adhesion sites of the natural ECM but also to dynamically regulate the tissue repair process through responsive designs (such as pH or enzyme-triggered mechanisms). The following sections will illustrate how SCAAPs drive the development of high-performance smart biomaterials through their dynamic properties, biocompatibility, and functional tunability, focusing on two areas: hydrogels and biomimetic scaffolds.^{67–69}

4.4.1. Hydrogel-based platforms. Molecular design of side-chain functional groups endows polymers with the ability to precisely regulate cellular behavior, a mechanism that relies on the specific interactions between amino acid side chains and cell surface receptors.⁶⁷ Polymers containing phenylalanine (Phe) side chains mimic the fibrillar network structure of the ECM through hydrophobic interactions, thereby promoting axon outgrowth and synapse formation in neural stem cells. In a spinal cord injury model, polymers containing Phe residues effectively inhibited the excessive differentiation of astrocytes at the injury site by mimicking the hydrophobic fibrillar network of the ECM, thereby reducing glial scar formation and increasing nerve regeneration efficiency by approximately 40%.⁷⁰ Juriga *et al.* cross-linked polyaspartic acid (Pasp) using two amino acid derivatives, cystamine and lysine methyl ester. The hydrogel was obtained by a one-step cross-linking of the poly(succinimide) precursor followed by alkaline hydrolysis. By adjusting the ratio of cysteine to lysine methyl ester, the mechanical properties, redox responsiveness, biocompatibility, and drug release behavior of the hydrogels were controlled, demonstrating significant application potential in tissue engineering scaffolds and smart drug delivery.⁷¹ Fan and He *et al.* prepared a series of polyionic liquid hydrogels based on choline-amino acid ionic liquids and systematically investigated the effects of the amino acid type and chirality on the mechanical properties, antibacterial activity, conductivity, and biocompatibility of the hydrogels. The results demonstrate that the hydrogels exhibit excellent mechanical properties (tensile strength, toughness, and fatigue resistance), self-healing capability (>90%), broad-spectrum antibacterial activity (against *E. coli*, *S. aureus*, and *Cryptococcus neoformans*), conductivity, antioxidant properties, and biocompatibility (hemocompatibility, cell compatibility, and skin safety), making them suitable for electrostimulation-assisted wound healing and infection prevention (Fig. 10).^{72,73}

D'Souza *et al.* designed a hydrogel (L9-Ag) for use as a wound dressing. A non-natural amino acid (3'-pyridinyl-alanine, 3'-PyA) was introduced into the sequence of a non-peptide (L9) to form L9-Ag. L9-Ag, exhibits shear-thinning and rapid self-healing capabilities, can be administered *via* syringe, and adapts to wounds of various shapes. It demonstrates

significant growth-inhibitory effects against both Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria. By 'trapping' and 'slow-releasing' silver ions through the peptide sequence, a critical balance between antimicrobial activity and cytotoxicity is achieved.⁷⁴

4.4.2. Bioinspired scaffolds. SCAAPs demonstrate significant structural advantages in the construction of cell growth scaffolds. By adjusting the types of side-chain amino acids and the grafting density, precise tuning of the scaffold's mechanical strength, degradation kinetics, and surface charge density can be achieved. SCAAP-based biomimetic scaffolds not only provide robust physical support for cells but also mimic the charge distribution and structural characteristics of the natural ECM, creating a microenvironment conducive to cell growth and differentiation. Additionally, SCAAPs possess enzyme-responsive degradation properties; as tissues gradually heal, the scaffold material degrades in an orderly manner, thereby avoiding potential adverse effects associated with long-term residual material.⁶⁹

Through chemical modification, amino acids are introduced as side chains into non-protein backbones (such as polycarbonate or polyamide), constructing a series of highly bioactive pseudo-polyamides. By mimicking the natural bone matrix environment, these biomimetic scaffolds can promote osteoblast proliferation. Furthermore, leveraging their excellent anticoagulant properties and low immunogenicity, they can be used to prepare small-bore artificial vascular scaffolds or scaffold coatings, enabling efficient vascular reconstruction and re-endothelialization of the luminal wall.⁷⁵ Nichol *et al.* combined the flexibility of a polyphosphazene backbone with the hydrolysis sensitivity of amino acid esters. By protecting the carboxyl groups of L-alanine and L-phenylalanine, they obtained a series of amino acid alkyl ester hydrochlorides, which were then grafted onto a poly(dichlorophosphazene) backbone to prepare the final polymer material. Among these, phenylalanine-based polymers are considered ideal candidates for ligament/tendon scaffolds due to their slow degradation rate and good film-forming properties.⁷⁶ Rothmund *et al.* prepared a polyphosphazene-based degradable porous scaffold using glycine allyl ester as the side-chain amino acid derivative. The scaffold, prepared *via* thiol-ene photopolymerization, exhibits a connected pore structure and tunable degradation rate and is non-cytotoxic to adipose-derived stem cells. This work demonstrates that introducing amino acid derivatives into the polyphosphazene backbone is an effective strategy for achieving biofunctionalization and structural controllability of tissue engineering scaffolds.⁷⁷ The RGD (arginine-glycine-aspartic acid) tripeptide sequence in the ECM is a key signal mediating cell adhesion. Yassin *et al.* designed a novel three-dimensional porous biomimetic scaffold by covalently immobilizing the RGDC peptide (an RGD sequence followed by a cysteine residue, Cys) on the scaffold surface, effectively supporting the survival of human bone marrow mesenchymal stem cells (hBMSCs) and specifically inducing their differentiation into osteoblasts (by upregulating mRNA expression of early osteogenic markers such as alkaline phosphatase, as well as late osteogenic markers including osteocalcin and

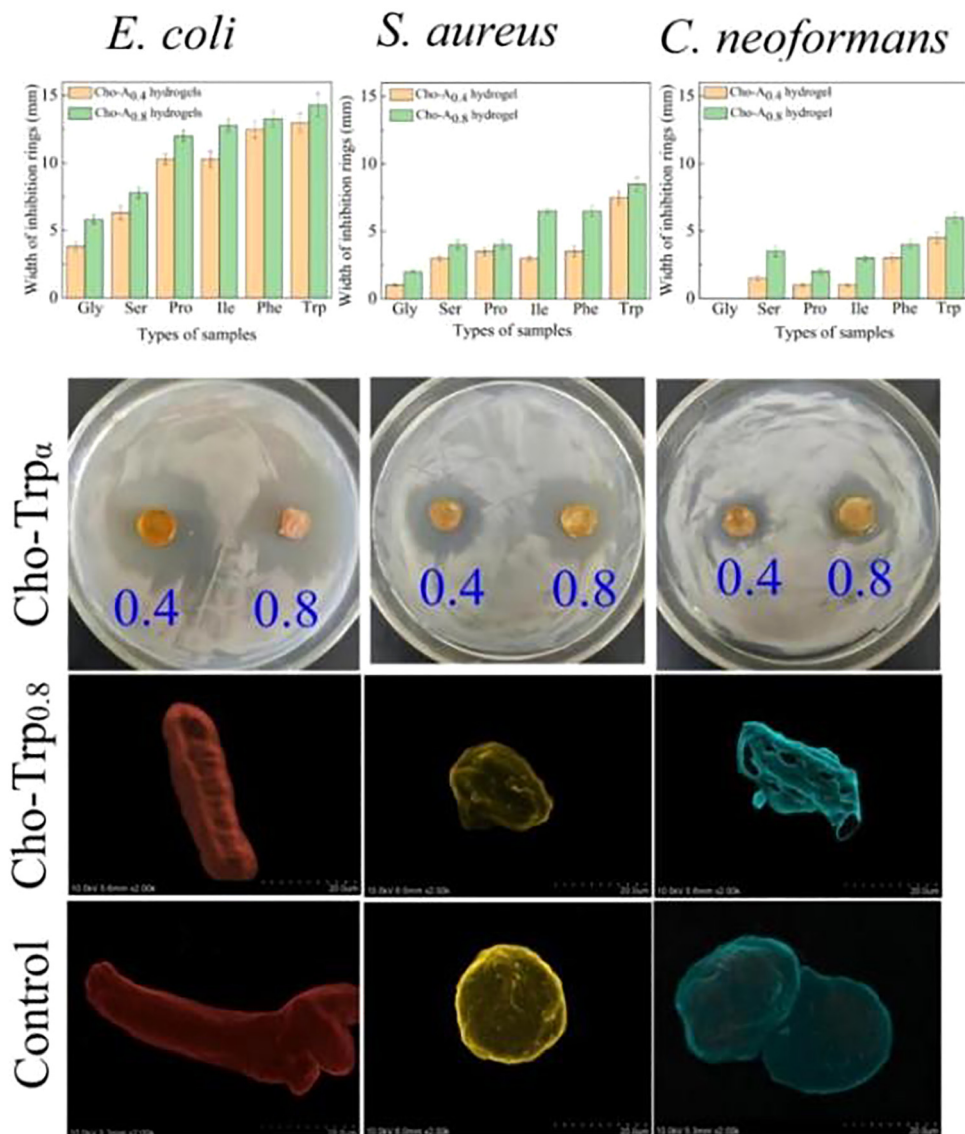


Fig. 10 The width of inhibition rings, photographs of the inhibition zone of hydrogels against *E. coli*, *S. aureus*, and *Cryptococcus neoformans*, as well as the microscopic morphologies of *E. coli*, *S. aureus*, and *Cryptococcus neoformans* cultured on the surface of hydrogels for 4 h (note: Gly, Ser, Pro, Ile, Phe and Trp refer to the corresponding Cho-A α hydrogels, respectively).⁷³ Reproduced from ref. 73 with permission from Elsevier, copyright 2022.

osteopontin).⁷⁸ Furthermore, in cartilage repair, arginine-modified polyetheramide (Arg-PEA) promotes the proliferation and differentiation of chondrocytes due to its enhanced cell adhesion properties and suitable mechanical properties, thereby aiding in the repair and reconstruction of cartilage tissue.^{68,69}

4.5. Antifouling coatings

Mohammad *et al.* prepared a novel amphiphilic triblock copolymer (PHisMAM-*b*-PB-*b*-PHisMAM) composed of L-histidine (amphoteric electrolyte) and butadiene (hydrophobic segment). This novel biohybrid exhibits dual pH- and temperature-responsiveness and can significantly reduce protein adsorption. With significant advantages such as ease of synthesis, handling, recovery, and reusability, as well as the absence of protected groups, it holds broad application potential in the

field of anti-fouling treatment.⁷⁹ Wang *et al.* utilized L-lysine, L-glutamic acid, and L-tyrosine as initiators to perform the ring-opening polymerization of ϵ -caprolactone, preparing a biodegradable polyurethane coating loaded with the natural anti-fouling agent butenolide (BU). The results indicate that amino acid modification significantly enhanced the coating's hydrophilicity, hydrolytic degradation rate, and adhesion to the substrate, thereby optimizing the controlled release behavior of BU; among these, the tyrosine-modified polyurethane exhibited the highest hydrophilicity and the fastest degradation and BU release rates due to the steric effects of the benzene ring side chains, while the glutamic acid-modified product possessed the optimal mechanical strength. Anti-fouling tests confirmed that the coating's anti-fouling efficacy results from the synergistic effect of the polymer matrix's self-polishing action and the

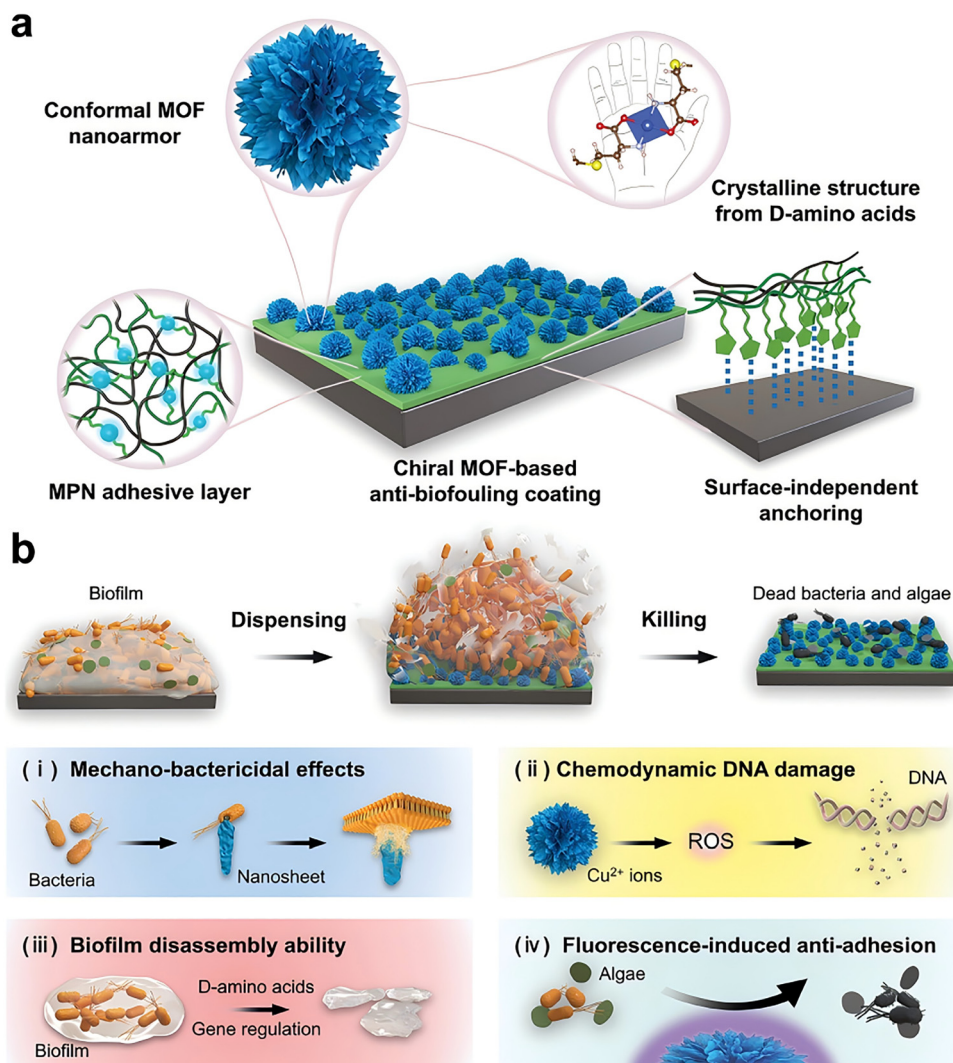


Fig. 11 Schematic illustration of the chiral MOF-based anti-biofouling coating. (a) The well-organized microstructure of the as-prepared coating with surface-independent anchoring ability constructed from an amorphous MPN layer and crystalline chiral MOFs. (b) The synergistic “dispense-then-kill” anti-biofouling mechanism encompasses four protection modes: (i) mechano-bactericidal effects, (ii) chemodynamic DNA damage, (iii) biofilm disassembly ability, and (iv) fluorescence-induced anti-adhesion.⁸¹ Reproduced from ref. 81 with permission from Wiley-VCH, copyright 2024.

sustained release of the anti-fouling agent. This work provides an effective strategy for regulating the structure–property relationship of polymers to develop high-performance, environmentally friendly smart marine anti-fouling coatings.⁸⁰ A chiral coating was constructed by directly incorporating D-amino acids as organic ligands into MOFs, thereby achieving a synergistic anti-fouling mechanism based on “dispersion followed by elimination.” This coating continuously releases D-amino acid signaling molecules to induce biofilm dissociation, while synergizing with the bactericidal action of Cu^{2+} ions. Data show that it can inhibit biofilm formation by up to 5.6 log CFU against various bacteria and further enhance the removal of mature biofilms by an additional 0.9–1.6 log CFU. Transcriptomic analysis confirms that the D-amino acid side chains significantly downregulate gene expression associated with bacterial adhesion, fimbriae synthesis, and quorum sensing, thereby driving biofilm disaggregation (Fig. 11).⁸¹

5. Conclusions and future directions

Through continuous innovation in synthetic methods, SCAAPs have achieved precise control over their molecular weight distribution, sequence regularity, and topological structure, providing accurate molecular substrates for functional applications. Their intrinsic multi-stimulus responsiveness and ordered self-assembly behavior not only deepen our understanding of the interaction mechanisms at the material–biological interface but also drive the clinical translation of smart polymers in precision medicine scenarios such as active tumor targeting and synergistic antimicrobial therapy. In the biomedical field, SCAAPs demonstrate high customizability: in anti-cancer applications, the use of endogenous amino acid transporter-mediated uptake mechanisms and tumor micro-environment-triggered release strategies has significantly enhanced the targeting specificity and systemic safety of drug

delivery systems; in antimicrobial applications, by mimicking the cationic/hydrophobic amphiphilic structure of natural antimicrobial peptides, they achieve highly efficient membrane disruption and biofilm degradation against multidrug-resistant bacteria; in biosensing and tissue engineering, their excellent biocompatibility and functional tunability provide critical support for constructing highly sensitive detection platforms and biomimetic ECMs. Looking ahead, although SCAAPs hold great potential in the field of precision medicine, key challenges that urgently require breakthroughs in this field include (i) precisely regulating degradation kinetics under complex physiological conditions, an effort that is being advanced by designing stimuli-responsive backbone linkages (e.g., enzyme-cleavable or redox-sensitive bonds) and by developing computational models to predict *in vivo* degradation profiles; (ii) reducing potential immunogenicity, which is being mitigated through the use of endogenous amino acid building blocks, PEGylation alternatives, and the rational design of biomimetic surfaces that avoid immune recognition; and (iii) achieving large-scale production of high-performance polymers, where recent progress in flow chemistry and automated solid-phase peptide synthesis offers scalable pathways to well-defined SCAAPs with narrow dispersity.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included, and no new data were generated or analyzed as part of this review.

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